

Rates of Adverse Events With Hydrogel and Silicone Hydrogel Daily Disposable Lenses in a Large Postmarket Surveillance Registry: The TEMPO Registry

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Submitted: August 29, 2014
Accepted: December 18, 2014

Citation: Chalmers RL, Hickson-Curran SB, Keay L, Gleason WJ, Albright R. Rates of adverse events with hydrogel and silicone hydrogel daily disposable lenses in a large postmarket surveillance registry: the TEMPO registry. *Invest Ophthalmol Vis Sci.* 2015;56:654-663. DOI:10.1167/iovs.14-15582

PURPOSE. To report annualized adverse events (AEs) including corneal infiltrative events (CIEs) with use of silicone hydrogel (SiHyDD) and hydrogel daily disposable (HydDD) soft contact lenses (SCLs) in the 1•DAY ACUVUE TruEye or 1•DAY ACUVUE MOIST Performance Overview (TEMPO) Registry (NCT01467557).

METHODS. Annualized incidence of symptomatic daily disposable (DD)-related AEs was calculated from 3064 surveys from 1171 subjects (601 SiHyDD and 570 HydDD, 31.8 ± 13.5 years, 68% female) during 1 year. Three independent experts adjudicated potential AE cases. Demographics were compared between wearers with and without AEs.

RESULTS. The registry tracked 960.3 years of lens wear: SiHyDD 489.4 years and HydDD 470.9 years. In that period, the 601 SiHyDD wearers reported eight AEs with office visits (1.6%/y; 2 CIEs, 0.4%/y), eight (1.6%/y) without office visits, and four AEs unrelated to SCLs (0.8%/y) (SiHyDD wearers with AEs; 44.8 ± 12.5 years; 75% female). The 570 HydDD wearers reported three AEs with office visits (0.6%/y; no CIEs), five without office visits (1.1%/y), and one non-SCL-related AE (0.2%/y) (HydDD wearers with AEs; 26.3 ± 8.0 years; 100% female). These CIE rates are significantly lower than the lowest estimate of 3.3% from prior studies. Wearers with SiHyDD-related AEs were significantly older than unaffected wearers ($P = 0.02$), but not for HydDD-related AEs.

CONCLUSIONS. The CIE rates of 0.4% and 0% with these DD lenses are significantly lower than rates reported with reusable SCLs (3%–4%/y), indicating improved safety outcomes with these DD lenses. Compared to unaffected wearers, SiHyDD lens wearers with AEs requiring clinical visits were significantly older. (ClinicalTrials.gov number, NCT01467557.)

Keywords: daily disposable contact lenses, adverse events, corneal infiltrates, registry, postmarket surveillance

Soft contact lens wear can be accompanied by a number of complications ranging from self-limiting conditions to rare cases of microbial keratitis (MK).^{1,2} Among them are corneal infiltrative events (CIEs), defined as a noninfectious infiltration of white blood cells into the avascular corneal stroma, often with accompanying hyperemia; these require differential diagnosis from infectious MK.² Those CIEs related to soft contact lens (SCL) wear are among the most important clinical complications encountered during SCL wear. In 2010 in the United States, it was estimated that there were approximately 32,013 nonsevere and 17,248 severe cases of CIEs, with an estimated cost of between \$1003 and \$1496 per incident, respectively.³ These inflammatory episodes typically drive clinical visits and pharmacologic treatment before they resolve and may discourage SCL wearers and prescribers alike due to the inconvenience and discomfort associated with them.⁴

In the last decade, the annualized incidence of symptomatic CIEs in safety studies was reported as 3.3%/y in a postmarket

surveillance registry of patients attempting 30-night continuous wear in North America^{5,6}; 4.0%/y in a retrospective chart review of mostly daily wear (DW)⁷; 3.4% for Hyd extended wear (EW) and 7.2% for SiHy EW (rates converted from eye-years to patient-years)⁸; 5.0% in a prospective study of DW of SiHy lenses⁹ and 10.7% in a smaller UK prospective study that included many neophyte wearers.¹⁰ In these studies, the rate fluctuated depending on study design and setting, with prospective designs with frequent clinical visits reporting more asymptomatic CIEs of lower severity.¹¹

There are many factors that have been associated with higher risk of CIEs with modern SCLs, including EW, associated with between 2× and 4× higher risk^{7,12-15}; bioburden on the eyelid (5× higher)⁹; a history of prior CIEs (7× higher) or corneal scars (4× higher)¹⁶; patient age < 25 years^{5,7,16,17} or > 50 years⁵; smoking¹⁸; 3× higher with use of a multipurpose lens care system compared with hydrogen peroxide⁷; and use of silicone hydrogel lenses (approximately 2×).^{7,13} Factors that may be ameliorated by single-use daily disposable (DD) lenses

compared to reusable lenses are 5.4× higher risk due to infrequent lens storage case replacement,¹⁹ 6.4× higher risk with poor case hygiene,¹⁹ bioburden on the SCL,¹⁸ and bioburden of the SCL storage case.^{20–22} Compared to use of reusable contact lenses, DD lenses were associated with a 12.5× lower risk of CIEs when worn on a DW basis in a large US case-control study,¹³ but in an earlier UK case-control study, one brand was associated with a 2.7× increased risk of sterile keratitis (CIEs).¹⁵

In the United States, DD lenses have an increasing market share, with a trend from approximately 10% in 2006 to approximately 25% of all SCL fits from 2008 forward.²³ Efron and coworkers²³ have reported a wide disparity in the proportion of DD lenses being prescribed in different countries, with Norway reporting approximately 45% of new fits in DD compared to Canada with fewer than 10% in DD lens types.

Postmarket surveillance of safety outcomes such as CIEs can be accomplished through passive or active methods. The 1990 Safe Medical Device Act of the U.S. Food and Drug Administration (FDA) outlines the legal requirements for postmarketing surveillance and passive adverse event (AE) reporting for medical devices like SCLs.²⁴ Postmarket surveillance is not typically required for CLs, but can be mandated under the FDA 522 guidelines.^{25,26} In recent history, active postmarketing surveillance was mandated for three manufacturers of CLs that carried an indication for 30 nights of continuous wear^{6,27} and for lenses that were used primarily by pediatric populations.²⁸ Occasionally, these mandates follow the publication of case reports from the literature indicating a safety concern during normal clinical use, as in the case of overnight orthokeratology.^{29–36} Manufacturers may also decide on their own to establish rates for safety outcomes, but for SCLs, no large voluntary postmarket surveillance study has been conducted in recent history.^{37,38}

The purpose of this study was to measure the incidence of CIEs and other AEs in a postmarket surveillance registry of wearers who had recently been fit with 1-DAY ACUVUE TruEye (SiHyDD) or 1-DAY ACUVUE MOIST (HydDD) DD lenses (Johnson & Johnson Vision Care, Inc., Jacksonville, FL, USA), the TEMPO Registry. The incidence of CIEs was compared to estimates of historical CIE rates for each lens brand.

METHODS

This study was approved by the following ethics committees: the Investigational Review Boards (IRBs) of New England College of Optometry (central IRB), Southern California College of Optometry, State University of New York College of Optometry, Nova Southeastern University School of Optometry, and Case Western University. This registry was conducted in compliance with the International Conference on Harmonization Good Clinical Practice E6 and the tenets of the Declaration of Helsinki and was registered at the clinicaltrials.gov website (NCT01467557). All site personnel were trained in protection of human subjects, and all subjects signed informed consents (or assent documents, if minors) prior to registration.

Study sites were selected based on geographic clusters and evidence of substantial usage of the DD lens brands being studied. An effort was made to represent a broad array of various health care settings where patients can have SCLs prescribed (e.g., practices in retail chains, privately owned eye care practices, and specialty medical clinics). Sites agreed to participate, and staff were trained in group meetings and on-site before registrations began.

Study Procedures

Eligible subjects were any new or experienced SCL wearers age 8 and older who had recently (within the last 2 weeks) been fit with either 1•DAY ACUVUE TruEye (naraflcon B = SiHyDD) or 1•DAY ACUVUE MOIST (etafilcon A = HydDD) spherical DD SCLs in both eyes and had purchased at least a 3-month supply of that brand of lenses. (Lenses could be purchased elsewhere and brought back to the registration site to complete the registration process.) Exclusion criteria were previous wear of either test lens if the participant was intending to enroll wearing that lens type in the registry, any concurrent participation in an unrelated research study, or employment of the participant or a family member by the recruiting site or Johnson & Johnson Vision Care, Inc.

Lens wearers were registered after they and their eye care practitioner had decided that one of these DD lenses was appropriate for them, lenses had been fit, and they had purchased at least a 3-month supply. After informed consent and/or assent, the eye care practitioner completed an electronic questionnaire for each subject that included specific history such as prior SCL power, prior CL and lens care product brands, and prior CL-related complications experienced by the subject. Experienced lens wearers then completed a branching electronic survey that queried past experience with their CLs, symptoms, motivations to wear, and overall opinion of their habitual CLs; new wearers completed the same survey minus questions about habitual CLs. All registered wearers completed Release of Medical Records forms and provided contact information for remote follow-up for later surveys. Parents of registered wearers under age 15 years were asked to complete parent questionnaires. During this study, subjects purchased all lenses that they wore. No lenses were given as compensation for participation in the study.

All later surveys were collected remotely via e-mail or telephone, with reminders sent to the wearers after approximately 2 weeks (days 10–30), 4 months (110–150 days), and 12 months (350–395 days). A question about having experienced a red or painful eye was asked at all the follow-up surveys, and a positive response triggered investigation of clinical records. Wearers who failed to respond to a survey were retained in the cohort until the next survey cycle, but were considered nonrespondents if they failed to complete all later surveys. Wearers who reported that they were no longer wearing test lenses were paid for that survey and exited from the study. Subjects could withdraw from the study at any time. Wearers were modestly compensated for completion of each survey.

Adjudication Process

The primary endpoint was an AE with an adjudicated diagnosis of a CIE according to the Cornea and Contact Lens Research Unit Adverse Events grading scheme.^{1,2} All potential AEs were identified via a registered wearer's positive responses to the question "Since we last contacted you, have you experienced a red or painful eye that required a visit to an eye doctor or emergency room?" Any potential AEs captured by an affirmative answer to this question were investigated first with the registering site and then with other treatment facilities reported by the registered wearer. (This process allowed for tracking wearers who sought care at a facility other than the registration site.) Redacted electronic images (FAX or PDF) of the complete AE-related clinical record were obtained and were sent to the adjudication committee (Table 1) at the end of the study for consensus adjudication of diagnosis and determination whether the event was likely SCL-related. This

TABLE 1. Adjudication Panel

John K.G. Dart MA, DM, FRCOphth Consultant ophthalmologist Moorfields Eye Hospital 162 City Road London EC1V 2PD United Kingdom	Lyndon Jones PhD, FCOptom, FAAO School of Optometry University of Waterloo 200 University Avenue Waterloo, Ontario N2L 3G1 Canada	Deborah F. Sweeney, BOptom, PhD, FAAO Associate Pro Vice-Chancellor Research University of Western Sydney Penrith, New South Wales 1797 Australia
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study method has been employed in previous FDA-mandated postmarket surveillance of SCLs.^{5,6}

Statistical Methods

Demographics, history, and patterns of lens use at registration were described and compared between the HydDD and SiHyDD cohorts using *t*-tests for continuous data and χ^2 tests for categorical data. Primary outcome AEs were symptomatic CL-related CIEs that required an office visit for management and were analyzed by lens type.

Years of exposure to lens wear were calculated as the difference in days from the date of the registration visit to the last survey completed by each subject, divided by 365 d/y. Subjects who switched to the opposite test lens (for example, a HydDD subject who began to use the SiHyDD test lens on a later survey, and vice versa) had their time split evenly between the two lens types since the exact date that they switched from one lens to the other could not be established. Subjects who reported that they had switched to another lens type had only the time when they were still wearing the study lens included in the years of lens exposure. Subjects who missed the 2-week or 4-month surveys but who subsequently completed the 12-month survey were retained in the study. Data from subjects who reported they were no longer wearing study lenses or were entirely lost to follow-up after registration were not analyzed. All data from all other surveys were used in this analysis.

The annualized incidence rates of AEs were calculated by dividing the number of cases by the person-years of follow-up. Rates are reported by lens type and expressed as events per 100 subject-years of wear. A Poisson distribution was used to calculate the 95% confidence intervals and the log of years of follow-up used as an offset and site as a random effect. Primary outcome events were symptomatic, CL-related, and requiring an office visit for management and were analyzed by lens type. We estimated that we required a sample size of 1085 to measure an AE rate that is 35% lower than historical controls (approximately 4%)^{5,7,9} with a power of 80% and setting level of significance at 5%. To allow for dropout we aimed to recruit a maximum of 1260 wearers, with at least 500 in each lens type. All other potential AEs are described separately, and event rates have been compared to those found in other

studies.^{5,7,9} The effects of lens type, age, sex, experience in lens wear, and high refractive error were modeled and interactions were explored. All data summaries and statistical analyses were performed using SAS software Version 9.3 (SAS Institute, Cary, NC, USA).

RESULTS

Study Enrollment and Retention

The TEMPO Registry enrolled 1171 subjects (*n* = 601 SiHyDD and *n* = 570 HydDD) from 37 sites with 83 registering clinicians between November 2011 and August 2012; of these, 977 (83.4%) were experienced SCL wearers. Of the subjects enrolled, 965 subjects completed the study (82.4%). The study tracked AEs in 960.3 years of lens wear. Subject accountability is shown in Table 2. Two-week surveys were completed by 1073 registered wearers (91.6%); 1026 (87.6%) completed the 4-month survey and 965 (82.4%) completed the 12-month survey. In total, 4235 surveys were completed, as shown in Table 2 by treatment arm.

Observed Cohorts

The observed groups reflected the male/female mix of SCL wearers in the United States with one-third male wearers³⁹; HydDD wearers were 31.2% male and SiHyDD wearers were 33.4% male (*P* = 0.42). The HydDD cohort was statistically significantly younger compared to the SiHyDD cohort (mean 30.3 ± 12.9 years versus 33.2 ± 13.9 years, respectively, *P* = 0.0002, Fig. 1), and there were significantly more students in the HydDD cohort. The age range was from 8 to 76 years. Wearers were racially quite diverse (64.6% Caucasian, 10.2% Hispanic/Latino, 7.2% Chinese, 18% other races), and 29.2% were students.

Table 3 describes the habitual SCLs for experienced wearers, and Table 4 shows the prior CL-related complications that were known by the eye care practitioners.

At registration, the HydDD cohort had a significantly shorter history of lens use, with significantly more of them entering the TEMPO Registry as new wearers (20.7%) compared to the SiHyDD group (12.7%) of new wearers (*P* = 0.009, Fig. 2). Twenty-five percent (25.3%) of the SiHyDD wearers and 19.5%

TABLE 2. Subject Accountability

	SiHyDD Cohort	HydDD Cohort	Total
Enrolled	601, 100.0%	570, 100.0%	1171, 100.0%
2-week survey*	551, 91.7%	522, 91.6%	1073, 91.6%
4-month survey*	533, 88.7%	493, 86.5%	1026, 87.6%
12-month survey*	502, 83.5%	463, 81.2%	965, 82.4%
Not completed	99, 16.5%	107, 18.8%	206, 17.6%
Withdrawal by subject reported on survey	21, 3.5%	24, 4.2%	45, 3.8%
Lost to follow-up	78, 13.0%	83, 14.6%	161, 13.8%

* Includes 84 wearers who reported use of both lens types across three follow-up visits, split equally between treatment groups ("switched").

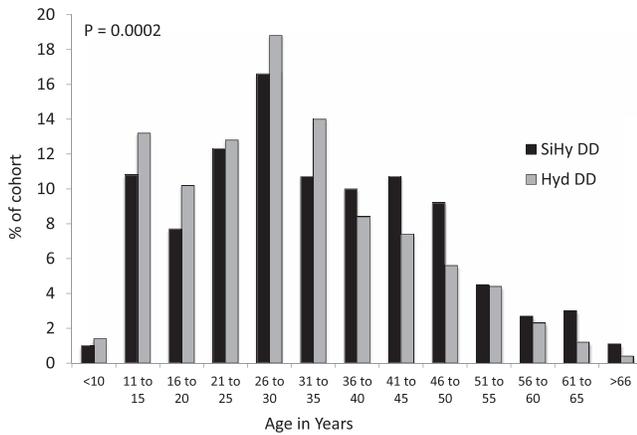


FIGURE 1. Frequency distribution of age for enrolled cohorts. Black bars: SiHyDD cohort; gray bars: HydDD cohort.

of the HydDD wearers reported swimming at least three times per week ($P = 0.50$), an activity that was queried due to the potential exposure to water that may increase the rate of AEs.

The HydDD cohort had a significantly higher self-report of previous red eye that caused a visit to the eye care practitioner or emergency room with prior CLs, with 19% citing that history compared to 11.5% of the SiHyDD cohort. The majority of these subjects wore their lenses 6 or 7 days per week (SiHyDD 70.7% and HydDD 64.8% $P = 0.016$ for entire days/week distribution). Approximately 75% reported using their lenses only on a daily wear basis, with no differences between cohorts, and only 3% reported wearing prior lenses 6 or 7 nights per week.

Years of Wear Tracked

The study tracked 960.3 years of DD lens wear: 489.4 years for the SiHyDD wearers and 470.8 years for the HydDD wearers. Each total included one half of 79.6 years, split equally between treatments. The totals also include 9.6 years for SiHyDD and 8.7 years for HydDD for wearers who were enrolled as one lens type but indicated wear of the other.

Misuse of Daily Disposables During Observation Period

The cohorts reported relatively high rates of noncompliance with use of DD lenses, and over time, levels of compliance diminished. Storage and reuse during the past 2 weeks was reported by 9.4% at 2 weeks, 12.7% at 4 months, and 16.6% at 12 months ($P = <0.0001$). Some EW during the past 2 weeks was reported by 14.3% at 2 weeks, 20.9% at 4 months, and 22.2% at 12 months ($P = <0.0001$). Noncompliance to daily replacement of lenses in the last 2 weeks was reported by 6.3% at 2 weeks, 10.0% at 4 months, and 14.5% at 12 months ($P < 0.0001$).

Incidence of Corneal Infiltrative Events

Table 5 shows enrollment, retention, and events with office visits reported by site, and Table 6 shows event rates, CL related or not, and how many were associated with an office visit. Table 7 gives details of each potential reported event with demographics and comments. One subject reported an event after having switched to a nonstudy lens, ACUVUE OASYS (Johnson & Johnson Vision Care, Inc.), and this event is not included in the totals.

TABLE 3. Habitual Contact Lens Details

	SiHyDD Cohort, $n = 525$ (%)	HydDD Cohort, $n = 452$ (%)
CL power, DS, right eye		
≤ -8.00	19 (3.6)	21 (4.6)
-7.75 to -7.00	24 (4.6)	11 (2.4)
-6.75 to -6.00	41 (7.8)	23 (5.1)
-5.75 to -5.00	43 (8.2)	46 (10.2)
-4.75 to -4.00	79 (15.0)	87 (19.2)
-3.75 to -3.00	102 (19.4)	97 (21.5)
-2.75 to -2.00	108 (20.6)	107 (23.7)
-1.75 to -1.00	104 (19.8)	109 (24.1)
-0.75 to 0.00	25 (4.8)	24 (5.3)
+0.25 to +1.00	12 (2.3)	7 (1.5)
+1.25 to +2.00	28 (5.3)	10 (2.2)
+2.25 to +3.00	11 (2.1)	14 (3.1)
$\geq +3.25$	15 (2.9)	14 (3.1)
Prior CL lens type habitual wearers		
Unknown	98 (18.7)	51 (8.9)
Reusable, hydrogel	29 (5.5)	40 (7.0)
Reusable, silicone hydrogel	227 (43.2)	247 (43.3)
DD, hydrogel	131 (24.9)	78 (13.7)
DD, silicone hydrogel	-	21 (3.7)
Other	40 (7.6)	15 (2.6)
Habitual lens care product		
Not needed, DD habitual CLs	177 (29.5)	122 (21.4)
None, new CL wearer	76 (12.6)	118 (20.7)
Using lens care	348 (57.9)	330 (57.9)
% of those using lens care		
Unknown	109 (31.3)	67 (20.3)
Multipurpose disinfecting solution	212 (60.9)	225 (68.2)
Hydrogen peroxide	27 (7.8)	38 (11.5)
Generic private label	6 (1.7)	16 (4.8)
Saline only	2 (0.6)	3 (0.9)
Other	7 (2.0)	19 (5.8)

DS, diopter sphere.

Regression analysis for all CL-related events ($n = 22$ with and without clinical visits) and CL-related events ($n = 11$) with clinical visits was not very illuminating due to the small number of events to consider⁴⁰ (Table 8). Extended wear (at the last survey or any survey) was not included in the models, as it was not reliably investigated at the time of the event, although none of the 11 cases with clinical visits and only one of the remaining 11 CL-related cases without office visits reported EW on any surveys during the study. The rate of CL-related events with office visits was low and not different between lens types (Table 6, 1.6%, 95% confidence interval [CI] 0.8-3.2 versus 0.6%, 95% CI 0.2-1.9). In all regression analyses there was no influence of lens type on risk of a CL-related event, though the 95% confidence intervals are very wide.

Patient age was significantly related to development of an event with the 22 cases (with and without office visits, results not shown) and was apparent for the 11 cases with clinical visits but only after adjusting for lens and lens/age interaction (odds ratio [OR] 1.05, 95% CI 1.01-1.10). For every year older, there was a 5% increase in the risk of a CL-related AE requiring an office visit. Other factors, such as high lens power (Rx), lens wearing experience, and sex, were not significantly related to developing an event in the registry using either group of events.

TABLE 4. History of Prior CL-Related Complications Reported by Eye Care Practitioner at Registration

Responses	SiHyDD	HydDD	χ^2 P values†
	n = 501 (%) Habitual Wearers	n = 452 (%) Habitual Wearers	
Has this patient had a CL-related complication with any of their prior lenses of which you are aware?			
No	381 (76.1)	329 (72.8)	n.s.
Yes (if yes choose all that apply)	120 (24.0)	123 (27.2)	
1. CL-related dryness	78 (15.6)	50 (11.1)	P = 0.045
2. Allergic conjunctivitis	13 (2.6)	26 (5.7)	P = 0.021
3. Infiltrative conditions			
CL peripheral ulcer, CLPU	6 (1.2)	6 (1.3)	P = 0.018
CLARE, with/without infiltrates	2 (0.4)	10 (2.2)	
Infiltrative keratitis	2 (0.4)	5 (1.1)	
Toxic conj, soln hypersensitivity	0 (0)	3 (0.7)	
4. CL papillary conjunctivitis, CLPC	4 (0.8)	23 (5.1)	
5. Conjunctival injection	9 (1.8)	12 (2.6)	n.s.
6. Lid issues			
Blepharitis	3 (0.6)	5 (1.1)	n.s.
Hordeoleum	3 (0.6)	0 (0)	
Lid inflammation/contact dermatitis	1 (0.2)	0 (0)	
Meibomian gland dysfunction	2 (0.4)	2 (0.4)	
7. Microbial keratitis	6 (1.2)	8 (1.8)	n.s.
8. Corneal staining			
Asymptomatic corneal staining	2 (0.4)	2 (0.4)	n.s.
Symptomatic corneal staining	2 (0.4)	7 (1.5)	n.s.
9. Corneal abrasion	7 (1.4)	5 (1.1)	n.s.
Other infrequent events			
CL intolerance	4 (0.8)	2 (0.4)	n.s.
Viral conjunctivitis/Keratoconjunctivitis	1 (0.2)	2 (0.4)	n.s.
Herpes simplex keratitis	0 (0)	0 (0)	n.s.
Bacterial conj	0 (0)	4 (0.9)	n.s.
Superior epithelial arcuate lesion, SEAL	0 (0)	0 (0)	n.s.
Lens stuck, torn, inverted	0 (0)	0 (0)	n.s.
Microcystic edema	0 (0)	0 (0)	n.s.

CLPU, contact lens peripheral ulcer; CLARE, contact lens acute red eye; conj, conjunctivitis; soln, solution; n.s., nonsignificant.

* Missing data for 24 SiHyDD experienced wearers.

† P values from Fisher's exact test.

Figure 3 shows the CIE incidence and 95% confidence intervals compared to those of other large CIE studies in the United States. The incidence of CIEs in the current study is significantly lower than for any previously reported study with similar power.^{5,7}

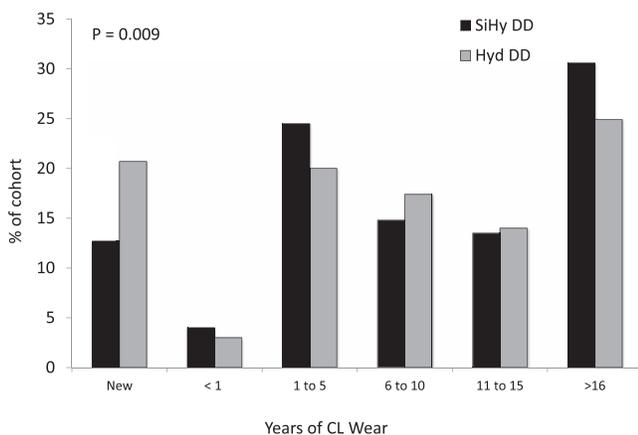


FIGURE 2. Frequency distribution years of CL wear for enrolled cohorts. Black bars: SiHyDD cohort; gray bars: HydDD cohort.

DISCUSSION

The annualized incidences of CIEs and other AEs are both significantly lower than in prior studies, even with ample representation of at-risk groups of younger (21.6% between 16 and 25 years) and older (9.7% older than 50 years) patients and noncompliant patients in our registry.^{5,7,17} This positive result with DD lenses was predicted in a previously reported case-control study that found 12.5× lower risk of CIEs with DD use compared to reusable lenses with daily wear,¹³ but in this prospective registry it is confirmed with a more rigorous methodology. The positive outcome also indicates that even when some wearers slip on the main best use habits with DD lenses (no EW, replacing with a new lens every day, and no storage and reuse), there was still a low rate of CIEs and other types of events with these lens brands. This suggests that these DD lenses are reasonably robust to imperfect patient practices.

Rates of other AEs were also very low in this registry, although comparison to other studies depends on the study design. In a retrospective chart review that would primarily identify events severe enough to drive a visit, Wagner and coworkers⁴¹ found 522 AEs of various kinds that interrupted lens wear in 4662.5 years of wear, for an estimated annual rate of 11.2% for all types of AEs (including CIEs). Other prospective study designs with more frequent clinical visits

TABLE 5. Enrollment, Retention, and Events by Region

Region and Sites	Enrolled	Completed	Retention	CL-Related Event	Unrelated Event
Northern California					
A	70	57	81.40%	-	-
B	66	57	86.40%	-	-
C	52	45	86.50%	-	-
D	43	41	95.30%	-	-
E	34	29	85.30%	-	-
F	33	28	84.80%	-	-
Subtotal	298	257	86.20%		
Southern California					
A	65	54	83.10%	CL-related dryness	Conjunctivitis
B	26	21	80.80%	-	-
C	17	14	82.30%	-	-
D	12	8	66.70%	-	Subconjunctival hemorrhage
Subtotal	120	97	80.80%	-	
Florida					
A	48	41	85.4%	-	-
B	48	40	83.30%	-	-
C	33	27	81.80%	-	Allergic conjunctivitis
D	28	21	75.00%	Corneal edema	-
E	23	20	87.00%	-	-
F	22	19	86.40%	-	-
G	19	14	73.70%	-	Hordeolum
H	1	0	0.00%	-	-
Subtotal	222	182	82.00%		
Northeast					
A	63	50	79.40%	-	-
B	44	38	86.40%	-	-
C	22	16	72.70%	Contact lens peripheral ulcer, corneal abrasion	-
D	22	14	63.60%	-	-
E	21	19	90.50%	-	-
F	12	11	91.70%	-	-
G	10	9	90.00%	-	-
H	7	4	57.10%	-	-
I	3	3	100.00%	-	-
Subtotal	204	155	76.00%		
Midwest					
A	69	64	92.70%	Corneal erosion, CL-related dryness	-
B	48	42	87.50%	Infiltrative keratitis	-
C	33	28	84.80%	-	-
D	1	0	0.00%	-	-
Subtotal	151	134	88.70%		
Southeast/Southwest					
A	64	49	76.60%	Corneal abrasion	Corneal abrasion
B	39	35	89.70%	-	-
C	21	19	90.50%	Episcleritis, CL-related dryness	-
D	19	15	79.00%	-	-
E	17	14	82.30%	-	-
F	16	11	68.80%	Episcleritis	Conjunctivitis
Subtotal	176	143	81.30%		

report AE rates of 14.2%⁴² and 23%,¹⁴ for example. The 1.6%/y and 0.6%/y for the SiHyDD and HydDD cohorts in this study compare very favorably to low AE rates in earlier work by Solomon and coworkers⁴³ and represent a clinically important difference in problems encountered by the DD wearers in this registry.

Even with a paucity of events to analyze, this registry found that older age was independently associated with the development of a symptomatic AE requiring an office visit.

Older and younger age have been previously reported as a risk factor for CIEs with reusable SCLs.^{5,7,17} It is possible that older age may be a surrogate for another factor that was not explored in our analysis. However, we were limited by the lack of detail about circumstance at the time of the event and the small number of cases. Older age has been reported as a significant risk factor for worse outcomes in CL-related MK,⁴⁴ lending support for the hypothesis that there are changes in the ocular surface with age, which makes contact lens wearers more

TABLE 6. Annualized Rates of Adverse Events

Adverse Event Category	SiHyDD Cohort 489.4 Years (95% Confidence Interval)	HydDD Cohort 470.9 Years (95% Confidence Interval)
Corneal infiltrative events (included below)	0.4%, (0.1%-1.5%)	0%, (0.0%-0.6%)*
CL-related adverse events with office visit	1.6%, (0.8%-3.2%)	0.6%, (0.2%-1.9%)
Not CL-related adverse events with office visit	1.2%, (0.6%-2.7%)	0.2%, (0.04%-1.2%)
“Yes” to red eye question, but no office visit	1.2%, (0.6%-2.7%)	1.1%, (0.5%-2.5%)

* Method to calculate CI around “0” from Hanley and Lippman-Hand.⁵¹

vulnerable. In our study, a higher proportion of older wearers enrolled in the SiHyDD lens group (Fig. 1), possibly reflecting economic factors between young and older SCL wearers as the SiHyDD lenses carry higher cost.

The inherent weakness in any prospective study comes with subjects that are lost to follow-up; thus the retention rate in a study is a main quality measure. In this registry we had a known number of wearers and finished with a very successful retention of 82.3% of the enrolled wearers, 3.8% active withdrawals, and only 13.8% lost to follow-up. This rate of active withdrawals is extremely low, and more than likely a substantial number of wearers who discontinued use of these DD lenses are included in the group we are considering lost to follow-up. Even in 12-month studies in which CLs and supplies are provided free of charge, combined discontinuation and loss to follow-up rates between 32% and 36% have been reported.^{9,14,27} The TEMPO Registry’s retention at 82.3% is

TABLE 7. Details of All Potential Adverse Events

Age	Sex	CL Related?	Final Diagnosis	Comments
SiHy DD: CL-related events with office visit, <i>n</i> = 8				
60	M	Y	Infiltrative keratitis	Keratoconic with piggyback system
49	M	Y	Contact lens peripheral ulcer	
40	F	Y	Episcleritis	Wore lenses during colonoscopy
23	F	Y	Corneal edema	
55	F	Y	Corneal abrasion	
51	F	Y	Corneal abrasion	
49	F	Y	CL-related dryness	
31	F	Y	CL-related dryness	
SiHy DD: not CL-related events with office visit, <i>n</i> = 6				
41	F	N	Conjunctivitis type uncertain	Seen at weekend medical clinic
59	F	N	Conjunctivitis type uncertain	
49	F	N	Corneal abrasion	
30	F	N	Allergic conjunctivitis	
64	F	N	Subconjunctival hemorrhage	
40	M	N	Hordeolum	
SiHy DD: “Yes” to red eye question with no office visit, <i>n</i> = 6				
48	F	N	Makeup contamination	Self-limiting red eye from makeup
42	M	Y	CL-related red eye	E-mail: “My eyes did get red after wearing the CLs for a prolong [sic] period but not enough to seek medical help.”
11	M	N	Allergic conjunctivitis	E-mail: “Red eye was probably due to pollen allergy. Resolved in a few days, no real problem with lenses.”
64	F	N	No event	Error in completing survey
57	M	N	No event	Error in completing survey
27	F	N	No event	Error in completing survey
HydDD: CL-related events with office visit, <i>n</i> = 3				
27	F	Y	Episcleritis	
18	F	Y	Corneal erosion	
34	F	Y	CL-related dryness	
HydDD: Non-CL-related events with office visit, <i>n</i> = 1				
32	F	N	Conjunctivitis type uncertain	
HydDD: “Yes” to red eye question but no office visit, <i>n</i> = 5				
45	F	N	Allergic conjunctivitis	Wearer spoke with practitioner about allergy symptoms.
29	F	N	No event	Contacted study site, no office visits
18	M	N	No event	Error in completing survey
66	F	N	No event	Reported at registration visit
27	F	N	No event	
Nonstudy reusable lenses: CL-related events with office visit, <i>n</i> = 1				
53	F	Y	Contact lens peripheral ulcer/possible microbial keratitis	Wearer presented while wearing nonstudy CL brand (senofilcon A).

TABLE 8. Regression Analysis for CL-Related Events With Clinical Visits (n = 11)

Factors (Referent)	Univariate				Multivariate			
	Rate Ratio	Lower	Upper	P Value	Rate Ratio	Lower	Upper	P Value
DD lens (HydDD)	0.41	0.11	1.60	0.20	10.4	0.31	350.75	0.19
New wearer (experienced)	0.49	0.13	1.88	0.30				
High Rx (Rx < ±5.00 D)	0.76	0.20	2.88	0.69				
Age	1.03	0.99	1.08	0.07	1.05	1.01	1.10	0.03*
Sex (male)	0.49	0.11	2.22	0.35				
DD lens with age	0.91	0.81	1.02	0.10	0.91	0.81	1.02	0.10

D, diopter.

* indicates statistical significance

also slightly better than the 80% reported in a similarly designed study that was carried out a decade ago,^{5,6} most likely due to improved ability to contact wearers electronically and allow them to submit their responses online.

The registry encountered so few CIE events that our planned regression analysis to determine risk factors was not very fruitful. It is noteworthy that the subjects enrolled in the SiHyDD cohort were different than the HydDD cohort at the registration visit; they were older, had more CL experience, and included more subjects with CL-related dry eye at baseline, representing the types of patients whom practitioners selected for this relatively new lens modality. Some of these differences comprise a different risk profile for CIEs in the SiHyDD group and may account for the difference in AE rate for that cohort. Table 7 shows that 79% (11/14) of the wearers with clinical visits with AEs were older than 40 years of age in the SiHyDD group.⁴⁵ It has been hypothesized that the highest rate of severe complications (microbial keratitis) is found when a lens type is new to the market and used by “early adopters.” This was based on the observation that the risk profile of new products decreased once they were used more widely. The estimate for rate of complications with the SiHyDD product may be an overestimation; however, this cannot be inferred from our data. The very low rate of AEs in general and absence of CIEs with use of the HydDD product are extremely encouraging considering the larger proportion of wearers in their late teens and early 20s in that cohort. Young SCL wearers between 15 years and the mid-20s have been shown by a number of authors to carry higher risk of all AEs⁴¹ and CIEs

compared with other age groups, and the simpler DD care paradigm may help alleviate youth as a risk factor.^{5,7,13,16}

The advantages of DD lenses are many and are described thoroughly in a review by Cho and Boost.⁴⁶ In addition to being easy for wearers to use, the lack of need for cleaning and disinfection routines and lens storage cases very likely contributes to the low CIE rates found in this registry. Even though with improper use DD lenses can become contaminated,²² avoiding exposure to the lens storage case protects wearers from a high likelihood of bacterial contamination in the solution or biofilm on the case environment that may trigger CIE events.^{9,21,47–49} Avoiding the burden of cleaning and disinfecting SCLs properly should help patients use their SCLs the right way, resulting in improved safety outcomes.

Even with the easier paradigm offered by DD lenses, daily replacement frequency with better patient-reported compliance than with reusable lenses,⁵⁰ the slippage in best use habits increased with each survey after the registration visit. Wearers began to take matters into their own hands as the year progressed, and by the end of the year approximately one-fifth of the wearers were using DD lenses on an EW basis at least occasionally and one-seventh were sometimes failing to replace with a new lens and reused their DD lenses. This study with 37 registering sites participating offered a wide range of training and support to these lens wearers as they began to use these DD lenses, but the results indicate that some type of support independent of the prescribing site may be recommended to maintain best use habits in DD wearers. Eye care practitioner organizations and DD lens manufacturers should develop succinct messages to reinforce right use steps with experienced wearers as they begin to use DD lenses.

In conclusion, a decrease in the proportion of wearers who used their DD lenses properly (no EW, no lens reuse or overnight storage) between the 2-week and 4-month surveys points out the need for reinforcement of these instructions a few weeks after fitting with DD lenses. Eye care practitioners should make certain that the steps for proper use of DD lenses are clearly reinforced at each aftercare visit with strong, simple messaging that discourages overnight wear and reuse of DD lenses.

This postmarket surveillance registry provides encouraging and important real-life information on the safety outcomes with ordinary use of these DD lenses. The low rate of symptomatic AEs at 0.9%/y, and symptomatic CIEs in particular at 0.2%/y, should fuel wider use of these lens types in order to make the wearing experience safer and easier for the lens wearer and eye care practitioner alike. This could also result in a reduction of health-related spending due to SCL use.³ In particular, these results point to active prescribing for lens wearers aged 16 to 25 years and older than 50 years who are in higher-risk groups due to their demographics.^{5,7,13}

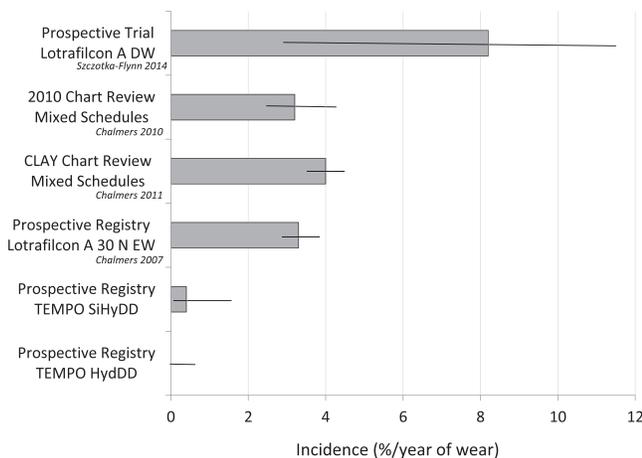


FIGURE 3. Annual incidence of CIEs for TEMPO registry and other recent studies. Error bars show 95% CI.

Acknowledgments

Supported by Johnson & Johnson Vision Care, Inc., Jacksonville, Florida.

The coordinating center was Foresight Regulatory Strategies, Inc., of Wilmington, Massachusetts. Data were managed by New England Survey Systems of Brookline, Massachusetts. The study team included Dawn Peer of Foresight Regulatory Strategies, Inc., and Elaine Anderson and Kate Connor of Johnson & Johnson Vision Care, Inc. Clinical sites included Site Principal Investigator (Subinvestigators):

Helen Abdal, OD, Linda Bennett, OD (Rebecca Maida, OD, Melanie Macbeth, OD); Virginia Bonoli, OD, Mitchell Cassell, OD (Sara Klibanoff, OD); John Todd Cornett, OD, Robert Davis, OD (Stephanie Davis, OD, Thuy-Lan Nguyen, OD); Aaron Evans, OD, James Flickner, OD (Christen Flickner, OD, Jennell Bockenstedt, OD); Kenneth Hall, OD (Cindy Szeto, OD, Maria Ha, OD, Tram Vu, OD); Bronson Hamada, OD (Amy Dinh, OD); James Hartzell, OD (Blane Brusen, OD); Nadine Jamal, OD (Jeffrey Cooper, OD, Vanessa Conenna, OD) Ashby Jones, OD PhD (Christine Brischer, OD); Jennifer Kao, OD (Grace Wong, OD, Trang Nguyen, OD); William Lay, OD (Kyla Cologgi, OD, Gregory Nixon, OD, Bradley Johnson, OD, Stacy Louise Stutler, OD, Carole Burns, OD, Amy Lay, OD); Steven Lowinger, OD (Michael Newman, OD); William Moscow, OD (Sharon Berger, OD, Jennifer Dattolo, OD); Dawn Lam, OD MSc (Timothy Edrington, OD MS, Eunice Myung Lee, OD, Annie Chang, OD, Justin Kwan, OD MS); Maureen O'Dwyer, OD, Lawrence Phillips, OD, Kathryn Richdale, OD PhD (Mitchell Dul, OD MS); Bradford Ripps, OD, David Ross, OD (Michael Bloom, OD, Robert Butterwick, OD, Matthew Mast, OD); Michael Rotberg, MD (Lisa Fox, OD); Judi Schaffer, OD, Jason Schwartz, OD, Lawrence Sider, OD (Jason Oganowski, OD); Sam Silverblatt, OD, Cindy Siu, OD (Carla Barnett, OD); Paul Super, OD (Catherine Barker, OD); Loretta B. Szczotka-Flynn, OD, PhD (Thomas Stokkermans, OD, MS, Sara Schoeck, OD); Nancy Eve Thomas, MD, Peter Van Hoven, OD (Nick Engle, OD); Heidi Wagner, OD, MPH (Andrea Janoff, OD, Perla Najman, OD, Eva Duchnowski, OD); Larry Wan, OD (Jeanie Tuan, OD, Stephanie Judkins, OD); Stephen Woo, OD, David Ziegler, OD (Chad Leffingwell, OD)

Disclosure: **R.L. Chalmers**, Johnson & Johnson Vision Care, Inc. (F, C), Alcon Research, Ltd. (C, R), CooperVision, Inc. (C); **S.B. Hickson-Curran**, Johnson & Johnson Vision Care, Inc. (E); **L. Keay**, None; **W.J. Gleason**, Johnson & Johnson Vision Care, Inc. (F, C), Alcon Research, Ltd. (C, R), CooperVision, Inc. (C); **R. Albright**, None

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