IMPORTANCE Demonstrating that endothelial cell loss following Descemet stripping automated endothelial keratoplasty (DSAEK) is independent of donor cornea preservation time (PT) could increase the pool of corneal tissue available for keratoplasty.

OBJECTIVE To determine whether endothelial cell loss 3 years after successful DSAEK is related to PT.

DESIGN, SETTING, AND PARTICIPANTS A multicenter, double-masked, randomized clinical trial included 40 clinical sites (70 surgeons) in the United States, with donor corneas provided by 23 US eye banks. A total of 945 eyes of 769 participants were included in the Cornea Preservation Time Study that had not experienced graft failure 3 years after DSAEK, performed primarily for Fuchs endothelial corneal dystrophy (96% of the cohort). The study was conducted from April 16, 2012, to June 5, 2017.

INTERVENTIONS DSAEK with random assignment of a donor cornea with PT of 0 to 7 days (0-7d PT) or 8 to 14 days (8-14d PT).

MAIN OUTCOMES AND MEASURES Endothelial cell density (ECD) at 3 years determined by a central image analysis reading center from clinical specular or confocal central endothelial images.

RESULTS Nine hundred forty-five eyes of 769 participants (median age, 70 years [range, 42-90 years], 60.8% women, 93.0% white) in the Cornea Preservation Time Study that had not experienced graft failure 3 years after DSAEK were included. At the initial eye bank tissue screening, mean (SD) central ECD was 2746 (297) cells/mm² in the 0-7d PT group (n = 485) and 2723 (284) cells/mm² in the 8-14d PT group (n = 460). At 3 years, the mean (SD) ECD decreased from baseline by 37% (21%) in the 0-7d PT group and 40% (22%) in the 8-14d PT group to 1722 (626) cells/mm² and 1642 (631) cells/mm², respectively (mean difference, 73 cells/mm²; 95% CI, 8-138 cells/mm²; \( P = .03 \)). When analyzed as a continuous variable (days), longer PT was associated with lower ECD (mean difference by days, 15 cells/mm²; 95% CI, 4-26 cells/mm²; \( P = .006 \)). Endothelial cell loss (ECL) was comparable from 4 to 13 days’ PT (n = 878; 36%-43% when tabulated by day). Available extension study ECD results at 4 years mirrored those at 3 years in the 203 eyes in the 0-7d PT group (mean [SD] ECD, 1620 [673] cells/mm² and mean [SD] ECL, 41% [23%]) and 209 eyes in the 8-14d PT group (mean [SD] ECD, 1537 [683] cells/mm² and mean [SD] ECL, 44% [23%]) (mean difference, 112 cells/mm²; 95% CI, 5-219 cells/mm²; \( P = .04 \)).

CONCLUSIONS AND RELEVANCE Although ECL 3 years after Descemet stripping automated endothelial keratoplasty is greater with longer PT, the effect of PT on ECL is comparable from 4 to 13 days’ PT.

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The corneal endothelium is critical for deturgescence of the corneal stroma with its barrier and pump functions. Although central endothelial cell density (ECD) decreases with age, it decreases at a higher rate with corneal conditions, such as Fuchs endothelial corneal dystrophy, and following cataract surgery. Failure of the corneal endothelium to recover from endothelial cell damage is due to its limited ability to divide. If central ECD falls below a critical level with an insufficient number of endothelial cells and their associated sodium-potassium adenosine triphosphatase pump sites to dehydrate the stroma, the cornea swells, vision decreases, and keratoplasty is then indicated. The Cornea Donor Study and its ancillary study, the Specular Microscopy Ancillary Study, which evaluated the effect of donor age on graft success and endothelial cell loss (ECL) following penetrating keratoplasty (PKP), demonstrated the importance of ECL in estimating long-term graft survival. Five years after PKP, graft success rates were similar with older and younger donor age, but ECL was greater with corneas from older donors compared with younger donors. This ECL difference at 5 years preceded a higher graft failure rate in the older donor age group by 10 years. In addition, ECD at 6 months, 1 year, and 5 years was associated at each time point with subsequent graft failure, irrespective of donor age.

The Cornea Preservation Time Study (CPTS) was designed to determine whether the success of Descemet stripping automated endothelial keratoplasty (DSAEK) performed for corneal conditions associated with endothelial failure is related to donor cornea preservation time (PT). With the Cornea Donor Study and the results of studies examining ECL following DSAEK in mind, the determination of ECL and its association with PT following DSAEK was considered an important secondary outcome in designing the CPTS protocol. Particularly since there have been few clinical studies assessing the effect of PT on ECL following keratoplasty with hypothermic (2°C-8°C) storage solutions. None of these studies examined the clinical performance of these solutions for the full 14 days approved by the US Food and Drug Administration. This report complements the CPTS article examining the association between PT and graft success following DSAEK by describing the effect of PT on long-term ECL following this procedure.

Methods

Participants were enrolled at 40 clinical sites and donor corneas were provided by 23 eye banks across the United States. Enrolled CPTS participants were aged 42 to 90 years (median, 70 years) with a corneal disease associated with endothelial dysfunction, including Fuchs endothelial corneal dystrophy (94% of eyes) and pseudophakic or aphakic corneal edema (6% of eyes). Eyes were randomly assigned to receive a donor cornea with PT of 0 to 7 days (0-7d PT group) or 8 to 14 days (8-14d PT group); for participants with both eyes eligible, the first eye was assigned randomly to a PT group and the second eye was assigned to the other PT group. The 1330 eyes completing surgery with a CPTS-assigned cornea were considered the study eyes. These CPTS-assigned corneas were from donors aged 12 to 75 years (median age, 61 years) with a minimum eye bank–measured central ECD of 2300 cells/mm² and a median PT of 6 days in the 0-7d PT group and 11 days in the 8-14d PT group. Under specific authorization from the Eye Bank Association of America, clinical investigators and participants were masked to all characteristics of the donor cornea, except for storage solution (Optisol-GS; Bausch and Lomb or Life 4°C; Numedica), residual bed thickness following lamellar dissection, and observations captured during donor tissue preparation; no Eusol (Alchimia) was used. Preoperative management, surgical technique, and postoperative care, including prescription of medications, were provided according to each investigator’s routine. Only eyes classified as a graft success at 3 years, as defined in our companion article, and with analyzable 3-year specular or confocal microscopic images were included in the ECD analyses reported herein. The study was conducted from April 16, 2012, to June 5, 2017.

Details of the CPTS protocol have been published and are available in Supplement 2. The protocol was approved by institutional review boards governing each investigational site (Appendix 2 in Supplement 1), and individual participants gave written informed consent to participate in the study. Participants received financial compensation at each protocol visit.

Endothelial Imaging and Image Analysis

The Corneal Image Analysis Reading Center at Case Western Reserve University and University Hospitals Eye Institute (CIARC) in Cleveland, Ohio, served as the central reading center for endothelial image analysis to determine ECD and also was responsible for quality-control measures at the eye banks and clinical sites. Each specular or confocal microscope at eye banks and clinical sites used in the study underwent a pre-study external calibration determination and image quality assessment; at sites with multiple instruments, each was calibrated. This prestudy instrument certification was designed to ascertain the specific magnification and image quality for each instrument so that ECD could accurately be measured by the CIARC. In addition, any replacement microscope installed during the study was certified before use in the trial.
The eye banks used specular microscopes for endothelial imaging (HAI Laboratories Inc [n = 7]; Konan Medical Inc [n = 32]). A contact or noncontact microscope (Konan Medical Inc [n = 37]; Tomey Corporation USA [n = 4]) or confocal microscope (Nidek Inc [n = 16]) was used at the clinical sites. All eye bank and clinical site personnel capturing images were trained and certified to obtain good to excellent image quality according to the protocol related to endothelial imaging.

Following donor cornea procurement, eye banks obtained 1 to 3 initial specular images of the central donor cornea endothelium after their usual procedure of warming the donor tissue to room temperature and then determined ECD by their usual analysis method (referred to as screening ECD). This assessment was not standardized, since it was performed at a time when the eye bank did not yet know whether the donor cornea would be assigned to a CPTS recipient. If a donor cornea was assigned to the CPTS, eye banks also obtained 3 preoperative study images of the central endothelium either after lamellar dissection or, if the donor cornea was to be prepared by the surgeon, prior to shipment. Before preoperative images were obtained, the donor cornea was again allowed to warm to room temperature so that the best-quality images could be obtained. Postoperative specular or confocal microscopic images of the central corneal endothelium of the graft were obtained at 6 months and then 1, 2, and 3 years as long as a participant remained in follow-up without experiencing graft failure or undergoing regrafting. Sites were requested to retake images of poor technical quality when possible and were provided specific advice on quality improvement techniques. Images were also obtained at 4 and 5 years for participants who consented to extended observation.

ECD Determination
Preoperative donor and postoperative recipient images were evaluated for quality and ECD by the CIARC. Details of CIARC procedures have been previously described, including reader training and certification, image-quality grading, image calibration, variable frame analysis for ECD determination, and adjudication procedures for image-quality and ECD determination. Briefly, image quality was assessed as analyzable or nonanalyzable by 2 independent readers and determined by a third adjudicator (one of us, B.B.) when either reader found the quality to be nonanalyzable. The ECD of all analyzable images was independently determined by 2 readers using the variable frame analysis method. This method was selected for the CPTS so that the maximal number of available cells with clear centers and borders could be analyzed. If the ECDs determined by the 2 readers differed by 5.0% or more, a third independent determination of ECD was made by an adjudicator. Final ECD was the mean of all ECDs that were within 5% of each other. Readers were masked to all information about the donor corneas and study participants. Throughout the study, the CPTS Data Management and Analysis Center (Jaeb Center for Health Research, Tampa, Florida) selected eye bank and clinical images for additional masked image-quality grading and ECD determination to assess both intraobserver and interobserver variability (eTable 1 in Supplement 1).

Statistical Analysis
The eye bank-determined screening ECD was considered the baseline value for all analyses evaluating the effect of PT, including calculations of ECL, since the preoperative ECD was measured after the donor corneas had already been preserved either 0 to 7 days or 8 to 14 days. The primary analysis to assess the effect of PT on 3-year ECD was conducted with a mixed linear model adjusting for baseline ECD, corneal diagnosis, and potential confounders, including storage solution, preparation by eye bank vs surgeon, and accounting for correlated data from participants with 2 study eyes or 2 corneas from the same donor. Other potential confounders were evaluated but not included in the final model (recipient and donor age, recipient and donor race, presence of glaucoma, presence of corneal vessels, history of smoking, time from lamellar dissection to surgery, and donor rim culture result). Potential confounders from univariate models with were evaluated in a multivariate model, keeping factors with following a backward selection process. Random effects were modeled to account for correlated data from fellow eyes of the same participant and correlated data from fellow corneas of the same donors. Preplanned secondary analyses were performed treating PT as categorical (predefined categories of 0–4 days, 5–7 days, 8–11 days, and 12–14 days) and as a continuous variable (days from initial preservation to surgery). Sensitivity analyses were performed using multiple imputation to impute the missing or nonanalyzable 3-year ECD of participants with a surviving graft at 3 years. Statistical models accounting for selective dropout due to graft failure, previously applied to Cornea Donor Study PKP data, could not be used owing to the overall low failure rate.

In another preplanned analysis, a repeated-measures least squares regression longitudinal model was fit using all available images obtained at screening, 6 months, and 1, 2, and 3 years, adjusting for corneal diagnosis and correlated data as described above. Preservation time was evaluated as both continuous and categorical. Sensitivity analyses were performed using multiple imputation to impute ECD at all missing time points for participants with a surviving graft at 3 years, with similar results.

Analyses of 4-year image data paralleled the primary 3-year analysis for participants with a surviving graft at 4 years. There were too few 5-year images for meaningful statistical analyses. Statistical analyses were conducted using SAS software, version 94 (SAS Institute). All P values are 2-sided and considered significant at <.05.

Results
Nine hundred forty-five eyes of 769 participants (median age, 70 years [range, 42–90 years], 60.8% women, 93.0% white) were included. Of the 675 study eyes undergoing DSAEK that were assigned to the 0–7d PT group and 655 assigned to the 8–14d PT group, 493 (73.0%) and 472 (72.1%) eyes, respectively, had a clear recipient stroma, functioning graft, and ECD images at 3 years. Of these 3-year image sets (3 images per set), 8 (1.6%) and 12 (2.5%) sets, respectively, were nonanalyzable.
owing to poor image quality or insufficient number of cells for analysis.22 Thus, the primary ECD analysis cohort included 485 eyes in the 0-7d PT group and the 460 eyes in the 8-14d PT group (Figure 1). The recipient and donor baseline characteristics of these eyes were similar to the characteristics of the full CPTS cohort (eTable 2 and eTable 3 in Supplement 1).

In the primary ECD analysis cohort, the initial mean (SD) eye bank screening ECD was 2746 (297) cells/mm² in the 0-7d PT group and 2723 (284) cells/mm² in the 8-14d PT group. Mean preoperative ECD (determined by CIARC) was 2745 (354) cells/mm² and 2764 (374) cells/mm², respectively.

At 3 years, mean (SD) ECL decreased from baseline by 37% (21%) in the 0-7d PT group and 40% (22%) in the 8-14d PT group, resulting in a mean (SD) 3-year ECD of 1722 (626) cells/mm² and 1642 (631) cells/mm², respectively (mean difference, 73 cells/mm²; 95% CI, 8-138 cells/mm²; \(P = .03\)). Analysis was adjusted for screening ECD, corneal diagnosis, and other confounding factors as described above (Table). Results were similar when 3-year ECD was imputed for the additional 68 and 48 eyes with graft success at 3 years, but without analyzable 3-year images (\(P = .02\)). In both PT groups, the majority of ECL occurred in the first 6 months after DSAEK (Figure 2A), with mean ECL of 24% (19%) in the 0-7d PT group and 26% (20%) in the 8-14d PT group at that time.

In preplanned secondary analyses, there was greater ECL with longer PT (\(P = .006\) treating PT as continuous [days] with mean difference by days, 15 cells/mm²; 95% CI, 4-26 cells/mm²).

Table. Three-Year ECD in Eyes With Graft Successa

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Eyesb</th>
<th>Screening ECD, Mean (SD)c</th>
<th>Preoperative ECD, Mean (SD)d</th>
<th>3-y ECD, Mean (SD)</th>
<th>ECL From Screening to 3 y, Mean (SD), %</th>
<th>(P) Value for 3-y ECD</th>
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<tr>
<td>0-7 d</td>
<td>485</td>
<td>2746 (297)</td>
<td>2745 (354)</td>
<td>1722 (626)</td>
<td>37 (21)</td>
<td>(P = .03)</td>
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<tr>
<td>8-14 d</td>
<td>460</td>
<td>2723 (284)</td>
<td>2764 (374)</td>
<td>1642 (631)</td>
<td>40 (22)</td>
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<td>0-4 d</td>
<td>122</td>
<td>2738 (302)</td>
<td>2691 (390)</td>
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<td>34 (21)</td>
<td>(P = .02)</td>
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<td>5-7 d</td>
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<td>1750 (621)</td>
<td>36 (21)</td>
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<td>2679 (310)</td>
<td>1596 (580)</td>
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<td>2587 (165)</td>
<td>2683 (317)</td>
<td>1311 (612)</td>
<td>49 (24)</td>
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</table>

Abbreviations: ECD, endothelial cell density; ECL, endothelial cell loss; PT, preservation time.

a All analyses (except analysis with imputation) included eyes with graft success and a gradable image at 3 years. Endothelial cell density reported as cells per square millimeter.

b Total of 945 eyes.

c Preoperative image ECD is missing for 15 eyes in each PT group, owing to imaging not done or not gradable.

d The final model for the primary analysis was a mixed linear model, adjusting for screening ECD and corneal diagnosis (predefined to include), as well as storage solution, preparation by eye bank vs surgeon, and accounting for correlated data from participants with 2 study eyes or 2 corneas from the same donor. Other potential confounders were evaluated but not included in the final model (recipient and donor age, recipient and donor race, presence of glaucoma, presence of corneal vessels, history of smoking, time from lamellar dissection to surgery, and donor rim culture result).

e The same primary analysis model was used, except PT subgroups were analyzed as categorical.

f The same primary analysis model was used, except PT was analyzed as continuous.

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and $P = .02$ treating PT as 4 predefined subgroups (0-4, 5-7, 8-11, and 12-14 days) (Table, Figure 2B, Figure 3). Endothelial cell loss was comparable from 4 to 13 days’ PT ($n = 878$; 36%-43% when tabulated by day). In a longitudinal statistical model including all available images from baseline through 3 years, ECL was greater with longer PT ($P = .29$ comparing the 2 PT groups and $P = .005$ with PT as a continuous variable; $P = .22$ and $P = .004$, respectively, from multiple imputation sensitivity analysis).

Among participants with graft success and an analyzable image at 4 years (203 eyes in the 0-7d PT group and 209 eyes in the 8-14d PT group), mean (SD) ECD results at 4 years mirrored those at 3 years (ECD, 1620 [673] cells/mm² and 41% [23%] ECL) and 209 eyes in the 8-14d PT group (mean [SD] ECD, 1537 [683] cells/mm² and 44% [23%] ECL) (mean difference, 112 cells/mm², 95% CI, 5-219 cells/mm²; $P = .04$). (Table 4 in Supplement 1).

### Discussion

Results from the CPTS in our companion article indicated that PT up to 11 days can be expected to have little influence on graft success 3 years after DSAEK. Although there was statistically significant greater ECL with longer PT, this companion ECL study also supports the use of corneas with a PT up to 11 days, because there was little clinical difference in ECL over the 4- to 13-day PT range. The sample size was too small for a separate analysis of the effect of 3 days or fewer or 14-day PT on ECL.

There is limited literature on the effect of PT on ECL following keratoplasty using hypothermic 2°C to 8°C, chondroitin sulfate-based storage solutions with, to our knowledge, no randomized, masked studies. Bourne found a positive correlation between PT and ECL in 37 corneas 2 months after PKP for corneas stored in K-Sol, with the highest individual ECLs (>30%) occurring in donor corneas stored for at least 10 days. Terry et al found no correlation between PT and ECL within a limited range of PT in Optisol-GS (mean, 4 days; range, 1-8 days) in 362 eyes followed up after DSAEK for up to 2 years. Price and Price found no significant effect of donor death to surgery time (which includes time from death to preservation plus PT), ranging from 2 to 8 days with Optisol-GS storage, on ECL in 263 eyes after DSAEK at 2 years. In the Cornea Donor Study, median death to surgery time with Optisol-GS storage was only 4 days (25th and 75th percentiles 3 and 5 days, respectively) and no effect on ECL was noted. Life 4°C has shown better endothelial viability with storage up to 14 days compared with Optisol-GS in ex vivo studies. In a randomized clinical trial comparing the 2 solutions, ECL was comparable at 6 months; however, the full range of PT was not tested since PT was limited to a mean of 5 days and a maximum of 7 days. The CPTS could not examine any difference
Corneal Endothelial Cell Loss 3 Years After Keratoplasty

Original Investigation Research

Conclusions

Although there was a statistically significant association between greater ECL and longer PT in corneas that are clear 3 years after DSAEK, ECL was clinically similar among corneas stored for 4 to 13 days. With a higher frequency of graft failure in the 12- to 14-day PT group as reported in our companion article, the findings suggest that donor tissue with PT up to 11 days is suitable in terms of both graft success and ECL. Donor tissue stored for 12 to 14 days also may be considered suitable for logistical reasons, because the DSAEK success rate is high, irrespective of PT, although higher ECL in corneas that are clear at 3 years could portend a higher long-term failure rate.

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Author Contributions: Drs Lass and Ayala had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Lass, Benetz, Verdier, Szczotka-Flynn, Ayala, McCall, Ross, Kollman, Gal, Beck.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: All authors.

Critical revision of the manuscript for important intellectual content: All authors.

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Obtained funding: Lass, Ayala, Ross, Gal.

Administrative, technical, or material support: All authors.

Study supervision: Lass, Benetz, Szczotka-Flynn, Ayala, Gal, Beck.

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