

Effect of Graft Attachment Status and Intraocular Pressure on Descemet Stripping Automated Endothelial Keratoplasty Outcomes in the Cornea Preservation Time Study



ANTHONY J. ALDAVE, MARK A. TERRY, LORETTA B. SZCZOTKA-FLYNN, WENDI LIANG, ALLISON R. AYALA, MAUREEN G. MAGUIRE, ROBERT C. O'BRIEN, BETH ANN BENETZ, JOHN E. BOKOSKY, STEVEN P. DUNN, THOMAS E. GILLETTE, KRISTIN M. HAMMERSMITH, DAVID R. HARDTEN, BENNIE H. JENG, MARC F. JONES, RICHARD L. LINDSTROM, KENNETH J. MAVERICK, VERINDER S. NIRANKARI, MATTHEW S. OLIVA, IRVING M. RABER, CHRISTOPHER J. RAPUANO, GEORGE O.D. ROSENWASSER, KEVIN W. ROSS, JOHN W. SEEDOR, NEDA SHAMIE, CHRISTOPHER G. STOEGER, SHACHAR TAUBER, WOODFORD S. VAN METER, DAVID D. VERDIER, AND JONATHAN H. LASS, ON BEHALF OF THE CORNEA PRESERVATION TIME STUDY GROUP

• **PURPOSE:** To examine the association of donor, recipient, and operative factors on graft dislocation after Descemet stripping automated endothelial keratoplasty (DSAEK) in the Cornea Preservation Time Study (CPTS) as well as the effects of graft dislocation and elevated IOP on graft success and endothelial cell density (ECD) 3 years postoperatively.

• **DESIGN:** Cohort study within a multi-center, double-masked, randomized clinical trial.

• **METHODS:** 1090 individuals (1330 study eyes), median age 70 years, undergoing DSAEK for Fuchs endothelial corneal dystrophy (94% of eyes) or pseudophakic or

AJO.com Supplemental Material available at AJO.com.
Accepted for publication Feb 22, 2019.

From the Stein Eye Institute, University of California, Los Angeles, Los Angeles, California, USA (A.J.A.); Devers Eye Institute, Portland, Oregon, USA (M.A.T.); Case Western Reserve University Department of Ophthalmology and Visual Sciences, University Hospitals Eye Institute, and the Cornea Image Analysis Reading Center, Cleveland, Ohio, USA (L.B.S-F., B.A.B., J.H.L.); Jaeb Center for Health Research, Tampa, Florida, USA (W.L., A.R.A., R.C.O.); Center for Preventive Ophthalmology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA (M.G.M.); Eye Care of San Diego, San Diego, California, USA (J.E.B.); Michigan Cornea Consultants, P.C., Southfield, Michigan, USA (S.P.D.); Eye Associates Northwest, Seattle, Washington, USA (T.E.G.); Wills Eye Hospital, Philadelphia, Pennsylvania, USA (K.M.H., C.J.R.); Minnesota Eye Consultants, Bloomington, Minnesota, USA (D.R.H., R.L.L.); University of California, San Francisco, San Francisco, California, USA (B.H.J.); Northeast Ohio Eye Surgeons, Kent, Ohio, USA (M.F.J.); Focal Point Vision, San Antonio, Texas, USA (K.J.M.); Eye Consultants of Maryland, Owings Mills, Maryland, USA (V.S.N.); Medical Eye Center, Medford, Oregon, USA (M.S.O.); Ophthalmic Partners of PA, P.C., Bala Cynwyd, Pennsylvania, USA (I.M.R.); Central Pennsylvania Eye Institute, Hershey, Pennsylvania, USA (G.O.D.R.); Eversight, Ann Arbor, Michigan, USA (K.W.R.); New York Eye and Ear Infirmary, New York, New York, USA (J.W.S.); Keck Medical Center of University of Southern California, Ophthalmology, Los Angeles, California, USA (N.S.); Lions VisionGift, Portland, Oregon, USA (C.G.S.); Mercy-St. John's Clinic, Springfield, Missouri, USA (S.T.); University of Kentucky Department of Ophthalmology, Lexington, Kentucky, USA (W.S.V.M.); and Verdier Eye Center, Grand Rapids, Michigan, USA (D.D.V.).

Inquiries to: Jonathan H. Lass, University Hospitals Cleveland Medical Center, 11100 Euclid Ave, Cleveland, OH 44106 USA; e-mail: jlascornea@gmail.com

aphakic corneal edema (6% of eyes). Recipient eyes receiving donor corneal tissue randomized by preservation time (PT) of 0-7 days (N = 675) or 8-14 days (N = 655) were monitored for early or late graft failure through 3 years. Donor, recipient, operative, and postoperative parameters were recorded including graft dislocation (GD), partial detachment, and pre- and post-operative IOP. Pre- and postoperative central donor ECD were determined by a central image analysis reading center. Proportional hazards, mixed effects, and logistic regression models estimated risk ratios and (99% confidence intervals).

• **RESULTS:** Three independent predictive factors for GD were identified: a history of donor diabetes (odds ratio [OR]: 2.29 [1.30, 4.02]), increased pre-lamellar dissection central corneal thickness (OR: 1.13 [1.01, 1.27] per 25 μ increase), and operative complications (OR: 2.97 [1.24, 7.11]). Among 104 (8%) eyes with GD, 30 (28.9%) developed primary donor or early failure and 5 (4.8%) developed late failure vs. 15 (1.2%; $P < .001$) and 29 (2.4%; $P = .04$), respectively, of 1226 eyes without GD. 24 (2%) of 1330 study eyes had early acutely elevated postoperative IOP that was associated with a higher risk of graft failure through 3 years (hazard ratio: 3.42 [1.01, 11.53]), but not with a lower mean 3-year ECD (mean difference 61 (-479, 601) cells/mm², $P = .77$). History of elevated postoperative IOP beyond 1 month was not significantly associated with 3-year graft success or ECD.

• **CONCLUSIONS:** Donor diabetes, increased donor corneal thickness, and intraoperative complications were associated with an increased risk of GD. Early acutely elevated postoperative IOP and GD significantly increased the risk for graft failure following DSAEK. (Am J Ophthalmol 2019;203: 78–88. © 2019 Elsevier Inc. All rights reserved.)

THE CORNEA PRESERVATION TIME STUDY (CPTS), designed to evaluate the association of preservation time (PT) with graft success and cell loss after

Descemet stripping automated endothelial keratoplasty (DSAEK),¹ has yielded data that are being used to identify these and many other associations with endothelial keratoplasty outcomes. In regard to PT, the observed difference in survival of donor corneas with a PT of ≤ 7 days compared with those with a PT of 8 to 14 days was primarily related to a higher incidence of primary donor and early graft failures in the 8- to 14-day PT group.² Further analysis revealed that the incidence of failure was the highest in the 12- to 14-day PT subgroup, but analyses were not performed to determine the underlying reasons for this observation.

We previously reported the donor, recipient, and operative factors associated with graft success 3 years after DSAEK.³ While donor factors, such as age, and graft factors, such as preoperative endothelial cell density (ECD) and graft diameter, were not found to have a significant impact on graft success, other factors, such as indication for surgery (Fuchs endothelial corneal dystrophy [FECD] vs pseudophakic/aphakic corneal edema [PACE]) did have a significant impact.^{3,4} When factors associated with an increased risk for primary donor or early graft failure other than PT were evaluated, a history of donor diabetes and the occurrence of operative complications were identified as significant, although the mechanism underlying donor diabetes' impact on graft failure remains speculative.³ To gain a greater understanding of the factors that influence the development of primary donor or early graft failure, the 3-year graft success rate, and ECD after DSAEK in the CPTS, we performed an analysis of early postoperative events including all degrees of graft malattachment (partial detachment and dislocation) as well as intraocular pressure (IOP) throughout the postoperative period.

METHODS

THE CPTS WAS ORIGINALLY DESIGNED AS A NONINFERIORITY clinical trial of 3-year graft success using corneal donor tissue preserved for 8 to 14 days compared with donor tissue preserved for 0 to 7 days.¹ Institutional review board approval was secured at each participating clinical site and eye bank as shown in [Supplemental Table 1](#) (Supplemental Material available at [AJO.com](#)), and all participants provided written informed consent. Study oversight was provided by an independent data and safety monitoring committee. The research adhered to the tenets of the Declaration of Helsinki. The protocol was registered and is publicly available at <https://clinicaltrials.gov/ct2/show/NCT01537393>.

Details of the CPTS methods and primary results have been previously published.^{1,2,5} Standard donor information was gathered and reported by 23 eye banks, all accredited by the Eye Bank Association of America. Donor corneas met current Eye Bank Association of America standards for DSAEK⁶ and met additional criteria

regarding donor age, death to preservation time, and quantity and quality of endothelial cells.¹

The study prospectively gathered and recorded data on multiple donor, recipient, and operative factors, all of which have been previously assessed for their impact on graft success and endothelial cell loss.^{3,4} Specifically, we recorded the following data on donors: age, gender, race, and history of diabetes (yes/no) determined from medical records and/or next of kin as in the Cornea Donor Study.^{7,8} For donor corneas, we recorded eye (OD or OS), procurement information (time to refrigeration and time to preservation), and tissue preparation details including thickness before lamellar dissection by either the eye bank or surgeon, postlamellar dissection storage solution (fresh or initial solution), observations noted during lamellar dissection, and postlamellar dissection donor lenticule thickness. Each eye bank obtained up to 3 central endothelial images before shipping for surgeon-prepared lenticules or after lamellar dissection by the eye bank ("preoperative") that were sent to a central reading center (Cornea Image Analysis Reading Center [Cleveland, OH]) for determination of ECD.

Participant inclusion criteria have been previously published.¹ Participants between 30 and 90 years of age who had endothelial dysfunction suitable for DSAEK were included but were excluded if they were at high risk for graft failure, including patients with tube shunts, uncontrolled glaucoma, anterior chamber intraocular lenses, and anterior synechiae >3 clock hours.^{1,2} If eligible, both eyes of a participant could be enrolled. We recorded the following data on recipients: preoperative diagnosis (including a history of corneal dystrophy), presence of diabetes, and relevant ocular history, including medications and previous glaucoma surgery (ie, trabeculectomy and laser trabeculoplasty). At baseline, each clinical site measured intraocular pressure using their standard routine. Operative details and complications were collected prospectively in predetermined categories, including unplanned vitreous loss, posterior capsule rupture, suprachoroidal hemorrhage, significant hyphema, inverted donor tissue, difficult unfolding and positioning without use of a positioning instrument, difficult unfolding and positioning with use of a positioning instrument, difficult air fill and retention in positioning, and donor extrusion with subsequent reinsertion. None of the aspects of the surgical procedures were regulated but most were tracked as previously published, including incision size and location, donor cornea diameter, donor cornea insertion method, corneal stab "venting" incisions, peripheral posterior host stromal scraping, air fill duration, other procedures (eg, cataract surgery), and trainee participation (eg, tissue preparation, donor cornea insertion, and positioning).¹⁻³ Examinations were scheduled at 1 day, 1 week, and at 1, 6, 12, 24, and 36 months postsurgery for all participants with postoperative care provided according to each investigator's standard practice.

Donor attachment details were recorded through the first month of scheduled visits and for any unscheduled visits throughout the first 6 months. Specifically, donor positioning and location and extent of interface fluid were tracked, as well as the need for air injection and/or the need for external pressure or rolling maneuver with internal repositioning.^{9,10} Graft dislocation was defined as either: 1) total detachment of the graft (“total detachment”), as described in previous publications as a graft dislocation^{9,10}; or 2) an attached but decentered graft that required a surgically induced total detachment in order to reposition and reattach the graft accompanied by air injection (“graft repositioning”). All eyes with a partial detachment, characterized by the presence of interface fluid that did not require repositioning regardless of the need for air injection, were collectively analyzed under the category “interface fluid.” Because the use of various interventions (air injection and internal or external methods to reposition) varied among surgeons for a given malattachment, we chose to examine the relationship between the malattachment and graft failure rather than exploring the effect of interventions. This was a more inclusive approach because many of the malattachments (eg, interface fluid) were not necessarily followed by an intervention.

In addition, at the baseline and every postoperative visit, the study gathered information on topical and systemic medications (including corticosteroid usage but not type or dosage), and any study eye procedures since the previous visit (or history of glaucoma surgery at the baseline visit), allowing the collection of detailed information regarding glaucoma management. IOP measurement was required at all protocol visits, except the 1-day postoperative visit, using the surgeons’ routine methods. If IOP was measured on other visits per the surgeons’ preferences, it was recorded as well. Acute IOP events included any occurrence of IOP >40 mm Hg or paracentesis for pupillary block or angle closure in the first postoperative week. Other postoperative abnormal IOP events included any new glaucoma surgery, the addition of glaucoma medication, or any occurrence of IOP >25 mm Hg ≥1 month after surgery.

At each visit, the eye was also assessed for graft failure using the previously published CPTS definitions.¹ In brief, grafts were classified as failed if: 1) the study eye was regrafted for any reason; 2) the recipient cornea was cloudy or equivocally cloudy on the first postoperative day and did not clear within 8 weeks; or 3) the recipient cornea was initially clear postoperatively but became and remained cloudy for 90 days (late failure). A graft that failed during the first 8 postoperative weeks was further classified as a primary donor or early failure, depending on whether failure occurred in the absence or presence of operative complications, respectively.

Details of Cornea Image Analysis Reading Center procedures have been previously described, including reader training and certification, image quality grading, image calibration, variable frame analysis for ECD determination

by 2 independent readers, and adjudication procedures for ECD determination.^{1,5,11} Readers were masked to all information about the donor corneas, including PT. The analyzed images included the preoperative central endothelial images provided by the eye banks and 3 specular or confocal microscopic images of the central donor corneal endothelium obtained and provided by the investigators at 6 months and at 1, 2, and 3 years postoperatively as long as a participant remained in follow-up without graft failure or a regraft.

- **STATISTICAL ANALYSIS:** Selected candidate predictive factors for graft dislocation included eye bank observations, donor history of diabetes, operative complications, and prelamellar dissection donor cornea and postlamellar dissection donor lenticule thickness. The effect of each factor on graft dislocation was evaluated using logistic regression models. A base model included PT, recipient diagnosis, and random surgeon effect. Each factor was first evaluated using the base model. Factors associated with $P < .10$ were included in a multivariable backward model selection procedure.¹² To account for multiple comparisons, only factors with $P < .01$ were considered statistically significant and were retained in the final models. To provide more information, odds ratios adjusted for the factors in the final model were provided for each factor discarded during variable selection.

Data collected from protocol visits and unscheduled visits were included in the analyses of factors associated with graft success and ECD at 3 years. Variables of interest included graft dislocation, interface fluid, history of glaucoma at baseline, abnormal IOP ≥1 month postsurgery, and perioperative acutely elevated IOP. Cumulative probabilities of graft success at 3 years along with 99% confidence intervals were calculated using the Kaplan-Meier method. Cox proportional hazards regression models adjusted for PT, recipient diagnosis, donor history of diabetes, and operative complications were used to assess the association of these factors with 3 year graft failure, while mixed effects regression models adjusted for PT, preoperative ECD, recipient diagnosis, donor history of diabetes, and operative complications were used to assess the association of these factors with 3 year ECD. All models included surgeon as a random effect to accommodate the potential correlation in graft success among DSAEKs performed by the same surgeon. Analyses for the effect of graft malattachment and acute IOP events on graft failure included all study eyes in the CPTS (N = 1330), while analyses for the effect of history of glaucoma and elevated postoperative IOP at least 1 month after surgery were restricted to eyes at risk 1 month after DSAEK (n = 1277). Three-year ECD analysis was restricted to eyes with a functioning graft at 3 years and analyzable 3-year and preoperative endothelial images (n = 913).

Missing data were treated as a separate category for discrete factors, and a missing indicator was added for continuous factors. Continuous covariates were evaluated as continuous in all models. For the ease of interpretation,

TABLE 1. Effect of Donor, Recipient, and Operative Factors on Graft Dislocation

Risk Factors	N = 1330	Graft Dislocation, n (%)	Base Model, ^a OR (99% CI)	P Value	Multivariable Model, ^b OR (99% CI)	P Value
Factors included in the final multivariable model						
Preservation time subgroup, days				.005		.05
0-7	675	39 (6)	1.00		1.00	
8-14	655	65 (10)	1.81 (1.05–3.14)		1.55 (0.87–2.78)	
Recipient diagnosis				.58		.62
PACE (without FECD)	75	5 (7)	0.76 (0.21–2.75)		0.77 (0.20–2.94)	
FECD	1255	99 (8)	1.00		1.00	
Donor history of diabetes				<.001		<.001
No	973	57 (6)	1.00		1.00	
Yes	357	47 (13)	2.35 (1.35–4.08)		2.29 (1.30–4.02)	
Operative complications ^c				<.001		.001
No	1256	89 (7)	1.00		1.00	
Yes	74	15 (20)	3.36 (1.45–7.78)		2.97 (1.24–7.11)	
Prelamellar dissection donor corneal thickness (μ) ^d				.001		.004
<550	658	39 (6)	1.15 (1.03–1.28)		1.13 (1.01–1.27)	
≥550	629	61 (10)	per 25-μ increase		per 25-μ increase	
Factors not included in the final multivariable model						
Postlamellar dissection donor lenticule thickness (μ) ^e				.01		.19
<100	216	14 (6)	1.21 (0.99–1.49)		1.12 (0.89–1.40)	
100-<125	403	30 (7)	per 25-μ increase		per 25-μ increase	
125-<150	339	22 (6)				
≥150	305	31 (10)				
Any eye bank observations				.15		.22
No	795	59 (7)	1.00		1.00	
Yes	192	23 (12)	1.72 (0.82–3.61)		1.56 (0.73–3.34)	
Surgeon prepared tissue	343	22 (6)	0.94 (0.36–2.47)		0.78 (0.25–2.48)	

CI = confidence interval; DSAEK = Descemet stripping automated endothelial keratoplasty; FECD = Fuchs endothelial corneal dystrophy; OR = odds ratio; PACE = pseudophakic/aphakic corneal edema.

^aBase models adjusted for preservation time, recipient diagnosis, and random surgeon effect.

^bMultivariable model adjusted for preservation time, recipient diagnosis, and random surgeon effect. Donor history of diabetes, operative complications, and prelamellar dissection donor corneal thickness were retained in the final model via backward selection.

^cOperative complications include vitreous loss (unplanned), posterior capsule rupture, suprachoroidal hemorrhage, significant hyphema, inverted donor tissue, difficult unfolding and positioning without use of positioning hook, difficult unfolding and positioning with use of positioning hook, difficult air fill and retention in positioning, reinsertion of donor after extrusion, and other write-ins.

^dPrelamellar dissection donor corneal thickness is missing for 43 eyes. Eye bank determined by optical coherence tomography (586 eyes), ultrasonic pachymetry (337 eyes), specular microscopy (57 eyes), optical (7 eyes). Surgeon determined by ultrasonic pachymetry (299 eyes), nonultrasonic method (1 eye).

^ePostlamellar dissection donor lenticule thickness is missing for 67 eyes. Eye bank determined by optical coherence tomography (703 eyes), ultrasonic pachymetry (216 eyes), specular microscopy (58 eyes), optical (10 eyes). Surgeon determined by ultrasonic pachymetry (276 eyes).

continuous factors were categorized for display. All reported *P* values were 2-sided. Statistical analyses were conducted using SAS software (v 9.4; SAS Inc., Cary, NC).

RESULTS

• **GRAFT ATTACHMENT:** Eight percent (104/1330) of eyes had ≥1 graft dislocation by our definition during the postop-

erative period; among these, 18 were surgically induced total detachments in order to recenter the donor lenticule. Of these 104 eyes, 98 eyes had an air injection performed and 6 eyes did not. Of the 6 eyes that did not have an air injection, 5 were left free-floating until regrafted, whereas 1 eye had blunt trauma and was regrafted without a previous air injection attempt. One hundred fifty-two of the 1226 eyes (12%) without graft dislocation had ≥1 occurrence of interface fluid after surgery. Forty-one of these eyes (27%) had air injections, with 39 having 1 injection, 1 eye having 2

TABLE 2. Effect of Graft Dislocation (2 Groups) on 3-Year Graft Success

	N = 1330, n (%)	Failures		3-Year Cumulative Graft Success, % (99% CI)	3-Year Hazard Ratio (99% CI)	P Value ^a
		Primary Donor/Early, n (%)	Late, n (%)			
Graft dislocation						<.001
Yes (defined as total detachment or graft repositioning)	104 (8)	30 (28.9)	5 (4.8)	65.8 (52.1–76.4)	7.9 (4.1–15.3)	
No	1226 (92)	15 (1.2)	29 (2.4)	96.1 (94.3–97.4)	1.0	

CI = confidence interval.

^aModel adjusted for preservation time, recipient diagnosis, donor history of diabetes, operative complications, and surgeon effects.

injections, and 1 eye 3 injections; 17% (7/41) went on to fail by year 3. The remaining 111 of 152 eyes (73%) without dislocation but having interface fluid after surgery were simply followed for their interface fluid; 5% (5/111) failed by year 3. Overall, a total of 139 of the total group of 1330 eyes experienced ≥ 1 postoperative air injection for a rebubble rate of 10.5%.

The associations between predictive factors and graft dislocation are shown in Table 1. After accounting for PT and recipient diagnosis, a history of donor diabetes (OR 2.29 [99% CI 1.30–4.02]), greater central donor corneal thickness (before lamellar dissection; OR 1.13 [99% CI 1.01–1.27] for every 25- μ difference), and operative complications (OR 2.97 [99% CI 1.24–7.11]) were associated with a higher risk of graft dislocation. Donor lenticule thickness was included in the model selection procedure but was not statistically significant after adjusting for the factors included in the final model (ie, $P \geq .01$). Mean (standard deviation) prelamellar dissection donor thickness was 553 \pm 64 μ , while the postlamellar dissection donor lenticule thickness was 130 \pm 35 μ . Notably, there was only a weak correlation between the prelamellar dissection donor cornea and postlamellar dissection donor lenticule thickness (Spearman correlation 0.20; $P < .001$; Supplemental Figure 1 [Supplemental Material available at AJO.com]). Potential interaction effects between donor diabetes with pre/postlamellar dissection thickness as well as PT with pre/postlamellar dissection thickness were evaluated and not found to be significant (data not shown).

Twenty-nine percent (30/104) of eyes with graft dislocation developed primary donor or early failure and 4.8% (5/104) developed late failure, compared with 1.2% (15/1226; $P < .001$) and 2.4% (29/1226; $P = .04$) of eyes without graft dislocation, respectively. After accounting for donor history of diabetes, PT, recipient diagnosis, operative complications, and surgeon, eyes with graft dislocation had an increased risk for failure through 3 years compared with eyes without graft dislocation (hazard ratio 7.9 [99% CI 4.1–15.3]; Table 2). When graft attachment was evaluated as 4 subgroups, the 3-year cumulative probability of graft

success was 65.6% (99% CI 50.3–77.1%) for eyes with total detachment, 66.7% (99% CI 31.1–86.9%) for eyes requiring graft repositioning, 91.2% (99% CI 81.6–95.9 for eyes with partial detachment (interface fluid) in the absence of either total detachment or repositioning, and 96.8% (99% CI 95.0–98.0%) for eyes without total detachment, repositioning, or interface fluid (Table 3).

After accounting for preoperative ECD, donor diabetes, PT, recipient diagnosis, operative complications, and surgeon and recipient (random effects), graft dislocation was associated with a lower mean (\pm standard deviation) 3-year postoperative ECD of 1127 (\pm 546) cells/mm² (59% endothelial cell loss) compared with 1719 \pm 614 cells/mm² (37% endothelial cell loss) for eyes without graft dislocation ($P < .001$; Table 4). Based on a 3-subgroup analysis (graft dislocation or not; if not, interface fluid or not), the results remained similar (Table 5).

- **IOP:** Among the 1330 study eyes, 9% (n = 117) had a history of glaucoma, 6% (n = 86) were from patients who were taking glaucoma medications, 1% (n = 18) were from patients who had a history of glaucoma surgery, and 1% (n = 13) were from patients who had a history of both glaucoma surgery and medications. Twenty-three percent of eyes (n = 295) with a functioning graft 1 month after surgery experienced an abnormal IOP event ≥ 1 month after DSAEK (217 placed on new glaucoma medication without glaucoma surgery, 67 had IOP >25 mm Hg without additional glaucoma medication or surgery, and 11 underwent glaucoma surgery). The combination effect of history of glaucoma and elevated IOP >1 month after surgery did not have a significant effect on either graft outcome or endothelial cell loss ($P = .28$ for graft success; $P = .02$ for ECD; Tables 6 and 7).

Two percent of eyes (n = 24) experienced early acutely elevated IOP (>40 mm Hg) within the first week postoperatively. Of those 24 eyes, 25% (6/24) were classified as failures through 3 years. The 3-year graft success rate for those 24 eyes (75.0% [99% CI 43.8–90.5%]) was significantly lower than in eyes without early acutely elevated IOP (94.1% [99% CI 92.1–95.6%]; hazard ratio 3.42 [99% CI 1.01–11.53]; $P = .008$; Table 6).

TABLE 3. Effect of Graft Dislocation (4 Groups) on 3-Year Graft Success

Graft Dislocation	Graft Attachment Status	N = 1330, n (%)	Failures		3-Year Cumulative Graft Success, % (99% CI)	3-Year Hazard Ratio (99% CI)	P Value ^a
			Primary Donor/Early, n (%)	Late, n (%)			
Yes	≥1 occurrence of total detachment	86 (6)	24 (27.9)	5 (5.8)	65.6 (50.3–77.1)	11.0 (5.3–22.9)	<.001
	≥1 occurrence of graft repositioning (with no TD)	18 (1)	6 (33.3)	0 (0.0)	66.7 (31.1–86.9)	6.2 (1.6–23.5)	
No	≥1 occurrence of interface fluid (with no TD or GR)	152 (11)	9 (5.9)	3 (2.0)	91.2 (81.6–95.9)	3.2 (1.3–7.9)	
	None	1074 (81)	6 (0.6)	26 (2.4)	96.8 (95.0–98.0)	1.0	

CI = confidence interval; GR = graft repositioning; TD = total detachment.

^aModel adjusted for preservation time, recipient diagnosis, donor history of diabetes, operative complications, and surgeon effects.

TABLE 4. Effect of Graft Dislocation (2 Groups) on 3-Year Endothelial Cell Density Among Eyes with Successful Grafts

Graft dislocation	N = 913, ^a n (%)	Mean (SD) Cells/mm ²	P Value ^b
Yes (defined as total detachment or graft repositioning)	45 (5)	1127 (546)	<.001
No	868 (95)	1719 (614)	

SD = standard deviation.

^aOf 1330 study eyes, 913 had functioning grafts at 3 years with acceptable endothelial images.

^bModel adjusted for Cornea Image Analysis Reading Center–determined preoperative endothelial cell density, preservation time, diagnosis, donor history of diabetes, operative complications, and random surgeon and recipient effects.

Of 913 eyes that had functioning grafts at 3 years with analyzable preoperative and 3-year postoperative endothelial images, the mean (standard deviation) ECD of 1630 ± 575 cells/mm² in the 9 eyes with early acutely elevated postoperative IOP was not significantly different than the ECD of 1691 ± 625 cells/mm² in the 904 eyes without early acutely elevated postoperative IOP (difference in mean ECD was 61 cells/mm² [99% CI –479 to 601]; $P = .77$; Table 7).

DISCUSSION

POSTOPERATIVE DISLOCATION OF THE DONOR LENTICULE IS one of the most common complications of DSAEK surgery, with a reported dislocation rate of approximately 1.0% to 14.5%.^{2,13–16} Donor characteristics that have not been shown to increase the risk for graft dislocation include donor age, death to surgery time, donor lenticule thickness, and postprocessing ECD.^{14,17} In addition, recipient characteristics including preoperative corneal thickness, preoperative diagnosis, history of glaucoma or previous glaucoma surgery,¹⁰ and concurrent cataract surgery have not been associated with an increased incidence

of graft dislocation.¹⁷ However, other recipient factors, such as older age,¹⁷ aphakia,^{18,19} the presence of an anterior chamber intraocular lens,¹⁸ postoperative hypotony in eyes with previous glaucoma surgery,¹⁵ previous vitrectomy,²⁰ and concurrent IOL exchange¹⁸ have been associated with graft dislocation. To our knowledge, this is the first report to suggest that tissue from donors with diabetes and greater central donor corneal thickness before lamellar dissection are associated with an increased risk of graft dislocation.

Dislocations have been defined in various ways in the literature. Some refer to dislocation as fluid in the interface of an otherwise well-positioned graft that may include complete dislocation into the anterior chamber.^{9,10,13} Others define dislocation as those that require another injection of an air bubble to ensure adhesion (vs only requiring observation), including grafts floating freely.¹⁶ For example, Hood and associates¹⁷ defined graft dislocation as the “nonadherence of the donor graft to the recipient requiring surgical intervention with a rebubble technique either in the operating room or in an outpatient procedure room either on the same day or on a subsequent day.” Eighteen percent of their transplanted DSAEK lenticules qualified as dislocated using this definition. Finally, in an

TABLE 5. Effect of Graft Dislocation (3 Groups) on 3-Year Endothelial Cell Density Among Eyes with Successful Grafts

Graft Attachment Status		N = 913, ^a n (%)	Mean (SD) Cells/mm ²	P Value ^b
Graft dislocation				
Yes	≥1 occurrence of graft dislocation (defined as total detachment or graft repositioning)	45 (5%)	1127 (546)	<.001
No	≥1 occurrence of interface fluid (with no graft detachment)	103 (11%)	1764 (599)	
	None	765 (84%)	1713 (671)	

SD = standard deviation.

^aOf 1330 study eyes, 913 had functioning grafts at 3 years with acceptable endothelial images.

^bModel adjusted for Cornea Image Analysis Reading Center–determined preoperative endothelial cell density, preservation time, diagnosis, donor history of diabetes, operative complications, and random surgeon and recipient effects.

American Academy of Ophthalmology Ophthalmic Technology Assessment, Lee and associates¹³ broadly defined graft dislocation to include fluid in the interface of an otherwise well-positioned graft as well as complete dislocation into the anterior chamber, reporting rates of 0% to 82% with an average rate of 14.5%. We reported an 8% graft dislocation rate using a more narrow definition—that is, including only eyes that had total detachment of the graft (a complete separation of the DSAEK lenticule from the host stroma),^{9,10} or a graft that was attached but decentered and required internal or external manipulation with a surgically induced total detachment plus air injection to reposition. If we include the additional 11% of eyes in the CPTS with incomplete (partial) separation of the DSAEK lenticule from the host stroma (only 27% of which required air injection), 19% of the DSAEK procedures in the CPTS had some form of graft malattachment.

The injection of air into the anterior chamber to promote graft adherence is a frequent treatment for graft detachment and dislocation, while repeated air injections into the anterior chamber may increase the risk of endothelial failure because prolonged air exposure has been shown to be toxic to the corneal endothelium.^{21–23} In our study, 139 eyes (10.5%) required ≥1 air injection postoperatively. We were interested in exploring the effect of repeated air injections on graft failure; however, we could not assess this variable in other relatively uncomplicated eyes (without total detachment), with only 2 eyes requiring such multiple interventions. O'Brien and associates²⁴ have reported that donor endothelial failure is more common after surgical intervention for donor dislocation. We have shown that graft dislocation influences graft success with about an 8-fold increased risk for graft failure. In fact, there appears to be a dose-response effect for degree of detachment on graft success: grafts that were totally detached conferred an 11-fold increased risk of graft failure, grafts that were attached but required repositioning conferred about a 6-fold increased risk, and partially detached grafts had an ~3-fold increased risk of

graft failure compared with donors that were not totally or partially detached, or decentered requiring additional surgical intervention. Our findings are similar to those of Hood and associates,¹⁷ who reported that DSAEK lenticule dislocation was associated with a higher rate of repeat transplantation. We also found that graft dislocation but not grafts that were partially detached with interface fluid detrimentally impacted ECD in clear grafts 3 years postsurgery. This may adversely affect graft survival at longer durations of follow-up. However, the limitation of our findings and others is that it is difficult to distinguish whether the dislocation is a marker of donor corneal endothelial dysfunction or if it is the intervention for the dislocation (ie, air injection) that increases the risk of endothelial failure. One way to distinguish is with direct measures of endothelial function (eg, mitochondrial respiration and glycolysis activity²⁵), but current eye banking practices use only the slit lamp examination and specular microscopy and do not have such measures.

Our findings are consistent with reports from the CPTS of tissue from donors with diabetes being associated with worse DSAEK outcomes than those from donors without diabetes. Notably, we reported a significant relationship between diabetes in the donor and graft failure after DSAEK, with tissue from donors with diabetes exhibiting a 2.35-fold increased risk for primary donor and early graft failures.³ In addition, diabetes in the donor was associated with lower ECD at 3 years after DSAEK in the CPTS.⁴ We are now the first to report an increased risk of dislocation of donor corneas from diabetics, which likely explains the significantly increased risk of primary donor and early graft failures. While the cause(s) of the increased dislocation risk remain(s) unknown, there is evidence to support poor outcomes resulting from detrimental effects of diabetes on the biochemical,^{26,27} morphologic^{28–31} and functional properties of the corneal endothelium,^{28,29,32,33} including abnormalities in the mitochondria²⁵ and Descemet membrane strength.³⁴ It is therefore likely that the negative effect of diabetes in the donor on DSAEK graft success that we recently reported in a separate publication³ is caused

TABLE 6. Effect of Intraocular Pressure on 3-Year Graft Success

	n	3-Year Graft Success, % (99% CI)	Hazard Ratio (99% CI)	P Value ^a
History of glaucoma ^b /postoperative abnormal IOP ^c ≥1 month after DSAEK, n = 1277				.28
No/no	927	97.9 (96.1–98.9)	1.00	
Yes/no	55	98.1 (78.2–99.9)	0.77 (0.05–11.66)	
No/yes	239	95.8 (90.2–98.2)	1.81 (0.60–5.47)	
Yes/yes	56	91.8 (73.3–97.7)	2.59 (0.50–13.41)	
Early acute IOP event, ^d N = 1330				.008
No	1306	94.1 (92.1–95.6)	1.00	
Yes	24	75.0 (43.8–90.5)	3.42 (1.01–11.53)	

CI = confidence interval; DSAEK = Descemet stripping automated endothelial keratoplasty; IOP = intraocular pressure.
^aBase model adjusted for preservation time, recipient diagnosis, donor history of diabetes, operative complications, and surgeon effects.
^bHistory of glaucoma defined as having had glaucoma surgery and/or having taken glaucoma medications.
^cPostoperative abnormal IOP defined as having had new glaucoma surgery or having been prescribed new glaucoma medications without new glaucoma surgery or having had IOP >25 mm Hg without any new glaucoma surgery or medications. (Eyes failed or censored within 1 month after DSAEK were eliminated). New glaucoma surgery performed included tube shunt only (5 eyes), trabeculectomy only (2 eyes), laser trabeculoplasty only (3 eyes), and all 3 procedures (1 eye) in 11 participants.
^dEarly acute IOP defined as any occurrence of IOP >40 mm Hg or paracentesis for pupillary block or angle closure in the first week post-operatively.

TABLE 7. Effect of Intraocular Pressure on 3-Year Endothelial Cell Density Among Eyes with Successful Grafts

	n	Mean (SD), Cells/mm ²	P Value ^a
History of glaucoma ^b /postoperative abnormal IOP ^c ≥1 month after DSAEK, n = 913 ^d			.02
No/no	687	1689 (615)	
Yes/no	41	1589 (676)	
No/yes	155	1733 (638)	
Yes/yes	30	1651 (692)	
Early acute IOP event, ^e N = 1330			.48
No	904	1691 (625)	
Yes	9	1630 (575)	

DSAEK = Descemet stripping automated endothelial keratoplasty; ECD = endothelial cell density; IOP = intraocular pressure; SD = standard deviation.
^aModel adjusted for Cornea Image Analysis Reading Center–determined preoperative endothelial cell density, preservation time, recipient diagnosis, donor history of diabetes, operative complications, and random surgeon and recipient effects.
^bHistory of glaucoma defined as having had glaucoma surgery and/or having taken glaucoma medications.
^cPostoperative abnormal IOP defined as having had new glaucoma surgery or having been prescribed new glaucoma medications without new glaucoma surgery or having had IOP >25 mm Hg without any new glaucoma surgery or medications. (Eyes failed or censored within 1 month after DSAEK were eliminated.) New glaucoma surgery performed included laser trabeculoplasty (3 eyes) in 3 participants.
^dOf 1330 study eyes, 913 had functioning grafts at 3 years with acceptable endothelial images.
^eEarly acute IOP defined as any occurrence of IOP >40 mm Hg or paracentesis for pupillary block or angle closure in the first week post-operatively.

by impaired adherence and subsequent dislocation of the graft reported in this analysis. Diabetes in our corneal donors was determined from medical records and interviews of associated health care personnel and/or next of kin, if available.^{1,8} Future studies are suggested to better characterize diabetes in the donor based on duration,

severity³⁵ and HbA1c testing³⁶ to identify donors with diabetes whose corneas would be more prone to graft dislocation and failure after endothelial keratoplasty surgery.

While the thickness of the donor lenticule was not associated with the incidence of graft dislocation in this report or in another published study,³⁷ we are the first to report

that increasing donor corneal thickness before lamellar dissection is associated with graft dislocation. We note the lack of correlation between pre- and postlamellar donor lenticule thickness, which indicates that the thicker donor corneas did not result in thicker donor lenticules (ie, adjustments were made to the depth of the microkeratome dissection). Although the donor lenticule thickness was not associated with graft dislocation, the increased donor corneal thickness may have served as a marker for reduced endothelial function, which may have predisposed to donor dislocation. With the evaluation of the donor corneal endothelium performed by eye banks being limited to morphologic assessment, without any functional characterization, the cause(s) of the observed association of graft dislocation with donor corneal thickness and a history of donor diabetes remain speculative at this point. In contrast, the association between the third factor found to be associated with an increased risk of graft dislocation, operative complications, may be presumed to be secondary to direct, traumatic corneal endothelial cell loss, leading to the previously described association between operative complications and primary donor and early graft failure.³

While acute, significant elevation of IOP in the first postoperative week is uncommon after DSAEK, elevated IOP ≥ 1 month after surgery is relatively common. The incidence of elevated IOP (>25 mm Hg) after DSAEK has been reported to be highest in eyes with medically controlled glaucoma (41.3%), followed by eyes with previous glaucoma surgery (23.8%) and eyes without a history of glaucoma (20.0%).¹⁰ However, the incidence of postoperative complications, including graft dislocation, was not significantly higher in eyes with a history of glaucoma surgery before DSAEK in the largest series published to date.¹⁰ Similarly, the CPTS did not find an increased incidence of graft dislocation in eyes with previous glaucoma surgery, although only 2% of eyes in the CPTS had a history of previous glaucoma surgery, and none of the eyes had previous tube shunt implantation. Even though about 25% of study

eyes experienced an abnormal postoperative IOP event ≥ 1 month after DSAEK, we did not find that a history of glaucoma meaningfully impacted overall graft success or ECD in this study. Similar to our previous findings of a lack of association between preoperative glaucoma and either graft success³ or ECD⁴ at 3 years, the lack of an association between postoperative glaucoma and either graft success or ECD could be related to the duration of follow-up. It is quite possible that longer follow-up would have demonstrated such an association. However, acutely elevated IOP in the early postoperative period did impact graft success. Overall in the CPTS, 24 of 1330 study eyes (2%) had an early acute IOP event that was associated with a >3 -fold higher risk of failure. It is well documented that sudden IOP elevation in angle closure glaucoma reduces ECD.^{38,39} However, in the surviving clear grafts at 3 years in the CPTS we did not note an impact on ECD. We suspect that acute IOP elevation leads to some endothelial damage, resulting in increased risk for graft failure; the lack of effect on ECD is likely because of the failures being selected out in the ECD analysis, as only eyes with clear grafts at 3 years were included.

The CPTS, as the largest multicenter study of DSAEK to date, continues to provide new information regarding factors associated with graft success and endothelial cell loss. Similar to our other papers describing the impact of preoperative, donor, recipient, and operative factors on graft success³ and ECD,⁴ this study also affords us the opportunity to examine the effect of these same factors on graft attachment, graft success, and endothelial cell loss. We found that corneas from donors with diabetes, those that were thicker before lamellar dissection, and intraoperative complications convey a higher risk of graft dislocation, which, along with early postoperative acute IOP events, resulted in an increased incidence of graft failure. Further studies on the use of donors with diabetes and establishing more specific criteria for maximum donor thickness before dissection to minimize graft dislocations are warranted.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST.

Financial Disclosures: The following authors have financial disclosures with companies that manufacture corneal storage solutions (considered relevant to this work): Mark Terry (Bausch & Lomb), and W. Barry Lee (Bausch & Lomb) (part of the CPTS Study Group but not an author of this article). Jonathan Lass is an Eversight and Cleveland Eye Bank Foundation Board member and medical director (Cleveland, Ohio); Maureen Maguire received payment from Genentech/Roche for service on a data monitoring committee for a clinical trial; Loretta Szczytko-Flynn is a consultant for Johnson & Johnson Vision Care, Inc. and Alcon Laboratories (consulting); Robin Chalmers is on the adjudication panel; Mark Terry has received support from Bausch and Lomb (royalties on instruments for DSAEK and unrestricted educational grant for EKG breakfast), Moria (unrestricted educational grant for EKG breakfast), and Envisia (Safety Monitoring Board for Glaucoma Study). All other authors have no financial disclosures related to this manuscript. Funding/Support: Supported by cooperative agreements with the National Eye Institute, National Institutes of Health, Department of Health and Human Services EY20797 (A.R.A.) and EY20798 (J.H.L.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Eye Institute or the National Institutes of Health. Additional support provided by: Eye Bank Association of America, The Cornea Society, Vision Share, Inc., Alabama Eye Bank, Cleveland Eye Bank Foundation, Eversight, Eye Bank for Sight Restoration, Iowa Lions Eye Bank, Lions Eye Bank of Albany, San Diego Eye Bank, and SightLife. All authors attest that they meet the current ICMJE criteria for authorship.

The Cornea Preservation Time Study Group

The comprehensive list of participating Cornea Preservation Time Study clinical sites, investigators and coordinators, eye bank investigators, members of the Operations, Executive, Eye Bank Advisory, Data and Safety Monitoring Committee, Coordinating Center, Cornea Image Analysis Reading Center, and Data Management and Analysis Center Staff and the National Eye Institute staff have been previously published (*Cornea* 2015;34:601-608; *JAMA Ophthalmology* 2017;135:1401-1409).

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