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Donor, Recipient and Operative Factors Associated with Graft Success in the Cornea Preservation Time Study

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The comprehensive list of participating CPTS 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 (CIARC), 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;135:1401-09)

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Abstract

Purpose: To associate donor, recipient, and operative factors with graft success 3 years after Descemet stripping automated endothelial keratoplasty (DSAEK) in the Cornea Preservation Time Study (CPTS).

Design: Cohort study within a multi-center, double-masked, randomized clinical trial.

Participants: 1,090 individuals (1,330 study eyes), median age 70 years, undergoing DSAEK for Fuchs endothelial corneal dystrophy (94% of eyes) or pseudophakic/aphakic corneal edema (PACE, 6% of eyes).

Methods: Eyes undergoing DSAEK were randomized to receive a donor cornea with preservation time (PT) of 0-7 days (N=675) or 8-14 days (N=655). Donor, recipient, and operative parameters were recorded prospectively. Graft failure was defined as re-graft for any reason, a graft that failed to clear by 8 weeks post-operatively, or an initially clear graft that became and remained cloudy for 90 days. Failure in the first 8 weeks was further classified as primary or early donor failure, in the absence or presence of operative complications, respectively. Proportional hazards and logistic regression models were used to estimate risk ratios (RR) and {99% confidence intervals} for graft failure.

Main Outcome Measure: Graft success at 3 years

Results: 1251/1330 grafts (94%) remained clear at 3 years and were considered successful. After adjusting for PT, tissue from donors with diabetes (RR: 2.35 {1.03, 5.33}) and operative complications (RR: 4.21 {1.42, 12.47}) were associated with increased risk for primary/early failure. Preoperative diagnosis of PACE (RR: 3.59 {1.05, 12.24}) was associated with increased risk for late failure by 3 years postoperatively compared to Fuchs dystrophy. Graft success showed little variation among other factors evaluated, including donor age (RR: 1.19 {0.91, 1.56} per decade), preoperative donor endothelial cell density (RR: 1.10 {0.74, 1.63} per 500 cells), graft diameter (RR: 1.22 {0.39, 3.76} per mm) and injector use for graft insertion (RR: 0.92 {0.40, 2.10}).

Conclusions: DSAEK success in the early and entire postoperative period is more likely when the donor did not have diabetes and without operative complications, and in the long term postoperative period in recipients with Fuchs dystrophy compared to PACE. Mechanisms whereby diabetic donors and PACE recipients reduce the rate of graft success following DSAEK warrant further study.

Précis

In the Cornea Preservation Time Study, 94% of 1330 endothelial keratoplasty grafts were successful. Diabetic donors and operative complications increased risk for primary/early failures; recipient diagnosis of pseudophakic/aphakic corneal edema increased risk for late failures.

Introduction

Since the introduction of selective endothelial replacement surgery nearly two decades ago,^{1,2} it has been accepted worldwide as the preferred treatment for endothelial dysfunction. At this time, Descemet stripping automated endothelial keratoplasty (DSAEK) remains the most common surgical method of endothelial keratoplasty (EK) in the United States.³ Large case series from single centers have advanced surgical techniques⁴⁻⁶ and provided useful outcome data for clinical practice.⁷⁻¹³ Few, randomized, prospective studies have been conducted in this field^{14,15} and these lack comprehensive examination of all the major donor, recipient, and operative factors for graft success.

The Cornea Preservation Time Study (CPTS) was the largest prospective, randomized, double-masked clinical trial of modern corneal transplantation to date. Utilizing prospectively collected data on 1,330 DSAEK surgical procedures performed by 70 experienced surgeons with different surgical techniques, the CPTS has allowed analysis of a more diverse study population than can be found in prior single site studies,^{4-9,11-16} and better describes the overall outcomes of DSAEK as practiced today in the United States. The CPTS was designed to evaluate the association of preservation time (PT) to graft success and cell loss following DSAEK.¹⁷⁻¹⁹ One of the two primary outcome papers reported that PT up to 11 days had little influence on graft success,¹⁸ while the other paper reported that endothelial cell loss up to 13 days of PT was not influenced by PT.¹⁹

In anticipation that other donor, recipient, and operative factors could also be associated with graft success and cell loss, data were prospectively gathered in an effort to provide clinicians with data regarding donor cornea suitability, recipient selection, surgical technique preferences, and expected outcomes for DSAEK. The purpose of this paper is to report the donor, recipient and operative factors associated with graft success to provide evidence-based guidelines for clinical decision making to maximize the success of DSAEK surgery and allow for more efficient utilization of donor corneal tissue.

Methods

The primary outcome of the CPTS was designed to determine whether the 3-year graft success rate using corneal donor tissue preserved for 8-14 days was non-inferior to that of donor tissue preserved for 0-7 days. Enrollment occurred between April 2012 and February 2014, and follow-up ended in June 2017.¹⁷ The protocol was approved by the institutional review board responsible for oversight at each participating clinical site and eye bank, and each participant 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 study methods and primary results have been published previously.^{17,18} In brief, standard donor information was gathered and reported by the 23 eye banks participating in the study, which were all accredited by the Eye Bank Association of America (EBAA). Donor corneas met current EBAA standards for DSAEK²⁰ and included specific criteria for entry in the study: donor age 10-75 years of age; time from death to preservation 20 hours if the donor body was refrigerated, or 10 hours if not refrigerated; eye bank-determined central endothelial cell density (ECD) >2,300 cells/mm², no more than mild (slight) polymorphism/pleomorphism, absence of guttae, and no evidence of central endothelial cell damage/trauma or dystrophy. Donor corneas were either placed in Optisol GS (Bausch and Lomb) or Life 4°C (Numedis), as determined by each eye bank.

In keeping with standard eye bank practice, recorded donor data included donor age, gender, race, history of diabetes (yes/no) determined from medical records and/or next of kin as in the Cornea Donor Study (CDS)^{21,22}, cause of death, and eye (OD or OS). Procurement information included date and estimated time of death, cause of death, time to refrigeration, and time to preservation. Tissue preparation details included thickness prior to lamellar dissection by either the eye bank or surgeon, post-lamellar dissection storage solution (fresh or initial solution), observations noted during lamellar dissection, and DSAEK lenticule thickness. Central ECD was determined by the eye bank at screening and also following lamellar dissection or prior to shipment if the lamellar dissection was to be performed by the surgeon. A central reading center [Cornea Image Analysis Reading Center (CIARC)] subsequently determined ECD on these eye bank images as well as images from the clinical sites during followup.¹⁷ Results regarding the association of PT to endothelial cell loss have been previously reported.¹⁹ A companion paper reporting the association of other donor, recipient, and operative factors to endothelial cell loss has been published.²³

Inclusion criteria included those with endothelial dysfunction aged between 30 – 90 years of age who were eligible for DSAEK. Eyes at higher risk for graft failure were excluded as previously published.^{17,18} If eligible, both eyes of a participant could be enrolled. The eye undergoing surgery first was assigned randomly to a PT group and the second eye was assigned to the other PT group. Recipient data gathered on the participant included gender, race, history of corneal dystrophy, the presence of diabetes (historically determined as in the CDS^{21,22}), and smoking history. Relevant ocular history included medications, prior glaucoma surgery (i.e., trabeculectomy, laser trabeculoplasty), pre-operative recipient diagnosis [Fuchs endothelial corneal dystrophy (FECD), or pseudophakic or aphakic corneal edema (PACE)],¹⁷ and intraocular pressure.

Operative details and complications were collected prospectively in predetermined categories. All CPTS surgeons were experienced as evidenced by having performed at least 50 prior DSAEK cases with a reported primary donor failure rate of <3% and a dislocation rate requiring repositioning/rebubbling of <15% in the year prior to the study. Operative data included recipient and donor diameter, as well as incision size, location, site (cornea or scleral tunnel), and method of donor graft insertion. Use of an anterior chamber maintainer, stab incisions for venting, and peripheral host stroma scraping, as well as air fill duration, diameter of air bubble remaining at the completion of the procedure and use of viscoelastic were also collected. Any procedures performed in addition to DSAEK at the time of surgery

(e.g. cataract extraction with placement of a posterior chamber intraocular lens) as well as operative complications (**details in Table 1, footnote c**) were recorded. Finally, involvement of residents or fellows in preparation of the donor or insertion and positioning was documented.

Follow-up examinations were performed at 1 day, 1 week, and 1, 6, 12, 24, and 36 months postoperatively. Participants consenting to extension of follow-up in the study had visits scheduled at 48 and 60 months postoperatively. Postoperative care was provided according to each investigator's standard practice. Graft failure was defined as the occurrence of one of the following: 1) re-grafting for any reason; 2) a cloudy or equivocally cloudy cornea on the first postoperative day that did not clear within 8 weeks; or 3) a cornea that was initially clear postoperatively but became and remained cloudy for 90 days (late failures).¹⁷ Grafts that failed during the first 8 postoperative weeks were further classified as primary failures or early donor failures, depending on whether failure occurred in the absence or presence of operative complications, respectively.

Statistical Analysis

Each baseline donor, recipient and operative factor was assessed for association with all types of graft failures occurring through 3 years. Additionally, we assessed the association of these factors with primary and/or early graft failure, and late graft failures separately. The analysis for all failures as well as only primary and early donor failures included all study eyes in the CPTS (N=1330), while late failures (N=1285) were analyzed excluding the primary and early donor failures.

Cumulative probabilities of graft success at 3 years along with 99% CIs were calculated using the Kaplan-Meier method. Cox proportional hazards regression models were used to assess the association of risk factors with all failures and late failures, while logistic regression models were used to assess the association between risk factors and primary and early donor failures. A continuous time-scale was used; time to failure or censor was calculated as the number of days between surgery and declaration of failure or censor. A base model for evaluating candidate predictive factors included PT, because of its influence on graft success in the CPTS,¹⁸ and the recipient diagnosis, because of the influence on graft outcome identified in the CDS.^{22,24} All models included surgeon as a random effect to accommodate the potential correlation in graft success among DSAEKs performed by the same surgeon ("surgeon effect"). All candidate factors that were considered are listed in Table 1 and e-Table 1. Each factor was first evaluated by adding the factor to the base model. Candidate factors were selected for inclusion in a final multivariable model in two stages. In stage 1, baseline recipient and donor factors associated with $p < 0.10$ were included in a multivariable backward model selection procedure.²⁵ In stage 2, all factors selected in stage 1 were retained and operative factors associated with $p < 0.10$ were included in another multivariable backward model selection procedure to yield a final model. To adjust for multiple comparisons, only factors with $p < 0.01$ were considered statistically significant and retained in the final models. To provide additional information, hazard ratios adjusted for the factors in the final model were provided for each factor discarded during variable selection.

The proportional hazards assumption was tested using time-dependent variables. No significant deviations from the proportional hazards assumptions were detected.

Missing data were treated as a separate category for discrete factors, and a missing indicator was created for continuous factors. Continuous covariates were included in all models in continuous form but were categorized for display and ease of interpretation in the tables. All reported p-values were 2-sided. Statistical analyses were conducted using SAS, version 9.4 (SAS Inc).²⁶

Results

The overall 3-year graft success rate for DSAEK was 94.1% (1251/1330) in the CPTS. Among 79 graft failures occurring through 3 years, 45 (57%) were classified as primary or early donor failures and 34 (43%) were late failures.

All Failures

The Kaplan-Meier estimates of 3-year graft success are shown in Table 1 and eTable 1. Predictors found to have a corresponding p-value of <0.10 in the base model were included in a subsequent multivariable model selection and are listed in Table 1. Diabetic donors (HR: 2.04, 99% CI {1.12, 3.71}), and operative complications (HR: 3.56, 99% CI {1.62, 7.85}) were independently associated with increased risk for graft failure after accounting for PT and recipient diagnosis in the final multivariable model. The 3-year cumulative probability of graft success was 95.0% (99% CI {92.8%, 96.6%}) for study eyes receiving corneas from non-diabetic donors and 90.3% (99% CI {85.3%, 93.6%}) for study eyes receiving corneas from diabetic donors. The 3-year probability of graft success was 94.6% (99% CI {92.6%, 96.1%}) for study eyes without operative complications and 79.5% (99% CI {62.4%, 89.4%}) for those with complications. Eyes that had undergone surgery for glaucoma had a lower 3-year graft success rate in the CPTS (80.1% versus 94.1% for eyes without glaucoma surgery). However, after adjustment for the factors included in final model, the p-value (0.05) was greater than the value of 0.01 required for inclusion in the final model. The subgroups with prior glaucoma surgery alone, those with prior surgery and medication, and medication alone were too small to conduct analyses on any differential influence of these conditions on subsequent graft success. Donor age, pre-lamellar dissection thickness, and incision site were also included in the model selection procedure but were not included in the final model (Table 1). Results of analyses including data on the 444 eyes followed beyond the 3-year visit to 4 years paralleled the 3-year analyses, with similar hazard ratios and confidence intervals associated with PACE, donor history of diabetes and operative complications (eTable 2)

Primary or Early Failures

The proportions of eyes with primary or early failure are displayed in Table 2 and eTable 3 for each candidate predictive factor. Factors with a corresponding p-value of <0.10 when included in the base model are listed in Table 2. Diabetic donors (HR: 2.35, 99% CI {1.03, 5.33}), and operative complications (HR: 4.21, 99% CI {1.42, 12.47}) were independently associated with increased risk of failure after accounting for PT and pre-operative recipient

diagnosis in the final multivariable model. Donor gender, prior surgery for glaucoma in the recipient, donor age, and eye bank screening ECD were included in the model selection procedure but were not included in the final model (Table 2).

Late Failures

The Kaplan-Meier estimates of 3-year graft success as conditional on not having a primary or early failure are displayed in Table 3 and eTable 4 for each candidate predictive factor. Factors with a corresponding p-value of <0.10 when included in the base model are listed in Table 3. No factors other than those in the base model were found to be influential in the multivariable model. That is, the only significant influential factor (adjusted for PT and surgeon effect) associated with increased risk for late failure was the pre-operative recipient diagnosis of PACE (HR: 3.59 {1.05, 12.24}) compared with Fuchs dystrophy (Table 3). Recipient history of diabetes, recipient age, recipient gender, donor pre-lamellar dissection thickness, donor lenticule thickness, operative complications, stab incisions for venting, and peripheral host stroma scraping were included in the model selection procedure but were not included in the final model. Analyses for late failure including data on the 444 eyes followed through 4 years are shown in eTable 5. The higher risk associated with the recipient eye having PACE was maintained (HR: 3.77 {1.11, 12.83}), and operative complications were associated with higher risk of late failure (HR: 3.91 {1.19, 12.90}).

Discussion

The CPTS was a double-masked randomized, prospective, multicenter clinical trial evaluating storage time of donor tissue for DSAEK surgery.¹⁷⁻¹⁹ Besides the findings regarding the lack of influence of PT out to at least 11 days for DSAEK graft success^{17,18}, we now report significant donor, recipient, and operative factors that impact graft success.

Donor Factors

Diabetes.—In this pre-specified secondary analysis from CPTS, we found a greater risk of graft failure with donors with a history of diabetes, and notably a rate of primary/early graft failure more than twice as high as that associated with donors without a history of diabetes ($p=0.008$; Table 2). Our finding with the CPTS data was not surprising, given animal and human literature reporting that the corneal endothelium is adversely affected biochemically,²⁷⁻²⁹ morphologically,³⁰⁻³² functionally^{30,31,33-35}, and with tissue damage with Descemet membrane endothelial keratoplasty (DMEK) membrane peeling³⁶⁻³⁸ in diabetes. More recently, human corneal endothelial mitochondria³⁹ and Descemet membrane strength⁴⁰ have also been reported to be altered in diabetes.

Despite this evidence, clinical studies of graft success after penetrating keratoplasty,^{21,22} DSAEK,⁴¹ and DMEK⁴² have not previously shown a deleterious effect of donor diabetes, and only one study of penetrating keratoplasty (PK) showed an effect of diabetes in the recipient.⁴³ The CPTS is the first large study to show that a history of diabetes in the donor can increase the risk of graft failure following DSAEK, in particular primary and early failures. However, CPTS did not collect more detailed information like duration of diabetes, insulin dependence, or ocular (e.g., retinopathy) or systemic (e.g., amputation, neuropathy,

nephropathy, peripheral vascular disease) co-morbidities. Further studies are needed to validate this finding, ideally in a randomized clinical trial. The trial should examine the impact of the severity and duration of diabetes and the systemic sequelae of diabetes on long-term graft success and endothelial cell loss³⁸ as well as include postmortem HbA1c testing to further characterize diabetes control and detect undiagnosed donors with diabetes⁴⁴. Further delineating diabetes severity may not only assist in deciding which donors with diabetes are at greatest risk for graft failure; it may also address concerns on which of these donors are suitable for DMEK lenticule preparation without damaging the tissue.³⁶⁻³⁸ In the absence of additional data at present, it is notable that in the CPTS 90% of corneas from donors with diabetes were utilized with successful outcomes.

Age.—Despite the finding of the CDS that donor age does not have a significant impact on the success of PKP in the United States,²² many surgeons still request younger tissue from their eye banks.⁴⁵ The CPTS results confirm the CDS findings, as it did not find a significant impact of donor age in its multivariable model. Although the relatively small group of grafts from donors 30 years or younger (5% of donors) had a 3-year success rate of 98.3%, there was little variation (94.6% to 93.0%) in the rate between age 31 and 75 years in the CPTS (Table 1). This observation was similarly noted in the CDS with little variation in graft success between 34 to 71 years²². The use of older donors has been particularly of recent interest for the other principal endothelial keratoplasty procedure, DMEK, to facilitate donor lenticule positioning with less elastic tissue.^{46,47} Although not the same procedure as DMEK and employing varying posterior stromal tissue, the CPTS finding regarding DSAEK graft success and donor age most likely will apply to DMEK graft success.

Preoperative ECD and lenticule diameter.—Other common surgeon preferences include higher donor preoperative ECD and a larger grafted lenticule under the assumption that more endothelial cells transplanted increases the likelihood of graft success. Prior single-site studies of DSAEK have not shown a relationship between preoperative donor ECD or increasing diameter of lenticules and graft success.^{9,12,48} The CPTS did not distribute tissue with central ECD less than 2,300 cells/mm² preoperatively (at eye bank screening). Lenticule size was decided upon by the individual surgeon with no upper limit on size. Within these parameters, there was no effect of preoperative ECD on graft success (eTable 1). The CPTS also did not find that larger grafts (> 8.5 mm) were more likely to survive than smaller ones (<8.5 mm) (eTable 1).

Other non-significant donor factors.—Other donor factors that did not have a strong influence on graft success included: gender, race/ethnicity, cause of death, death to PT, time from dissection to surgery, and donor lenticule thickness (eTables 1, 3, 4). Prior large, single center studies had also reported that these donor factors were not important for EK graft success^{7,9,11-13,16,48}. The CPTS, although not powered to assess these factors, also did not show a trend or detect significant differences in graft success due to these factors. Notably no effect of gender mismatch on graft success was noted in the CPTS that included only DSAEK cases with 94% preoperatively having Fuchs dystrophy¹⁷ (eTables 1, 3, 4, unlike a previous registry study that performed both PK (63%) and EK (37%) for their Fuchs dystrophy cases⁴⁹).

Recipient Factors

Diagnosis.—Eyes with PACE had an 83.7% rate of success at 3 years compared to a 94.3% rate of success in patients with Fuchs ($p=0.03$), with most of the difference attributable to late failures. Although the likelihood of primary/early graft failure was greater for eyes with PACE than eyes with Fuchs dystrophy, the difference was not significant. This might be explained by the fact that eyes with Fuchs dystrophy have a greater peripheral endothelial cell reserve than eyes with PACE.⁵⁰ While the absence of peripheral endothelial cell reserve would not influence the rate of early graft failure, it may make a difference in late graft survival as healthy peripheral endothelium may have the ability to populate areas of endothelial damage in the donor graft. This ability is supported by the success in some cases of descemetorhexis alone in Fuchs dystrophy.⁵¹ Numerous studies have shown the more favorable long-term graft survival with DSAEK for recipient eyes with Fuchs dystrophy vs. eyes with other causes for endothelial dysfunction.^{7,12,16,52} The CPTS has now confirmed this with strong statistical evidence.

Glaucoma history.—Regarding the effect of prior history of the use of glaucoma medication and/or glaucoma surgery, no impact of prior use of glaucoma medication was noted on graft failure. Several single-site EK studies have shown that recipient eyes with prior glaucoma surgery have a higher rate of long term graft failure and cell loss than eyes without a history of glaucoma surgery.⁵²⁻⁵⁴ The CPTS study found some evidence to support this conclusion as well, with an 80% success rate at 3 years in eyes with a history of glaucoma surgery, compared to a 94% success rate in eyes without prior glaucoma surgery ($p=0.05$). However, the impact did not meet the 0.01 significance level when adjusted for multiplicity in the final model. Use of glaucoma medication among eyes with a history of glaucoma surgery was associated with a higher risk of graft failure after PK in the CDS.⁵⁵ However, with only 31 eyes in CPTS having had glaucoma surgery, the impact of glaucoma medication use in this subgroup could not be evaluated. Perhaps with longer follow up the prior glaucoma medication and/or glaucoma surgery factors may have played a greater role in DSAEK graft survival. In addition, while trabeculectomy eyes with controlled glaucoma were included in the CPTS, notably, eyes with previous tube shunts were not included. Thus, unlike other DSAEK series that identified higher graft failure in eyes with prior glaucoma surgery,⁵²⁻⁵⁴ this may have reduced the observed impact of prior glaucoma surgery in the CPTS.

Operative Factors

Technique.—As EK has evolved, the number of surgical approaches to selective endothelial replacement has become nearly as numerous as the surgeons themselves. The CPTS allowed the 70 experienced surgeons to use their own preferred technique for preparing the donor lenticule (surgeon-dissected vs eye bank “pre-cut” dissected tissue)^{8,14}, choosing the size and location of the main incision,⁵⁶ delivering the tissue using a variety of methods (with or without injectors),^{5,6,15,52,56} utilizing stab “venting” incisions⁵⁷ or not⁵, peripheral stromal scraping⁵ or not⁵⁷, and varying the size of the final supportive air bubble. We found that every combination of DSAEK surgical techniques yielded a high degree of success, with no one technique (e.g. injector or no-injector usage) showing clear dominance over another (e-Tables 5). While the use of recipient stromal scraping and avoidance of

venting incisions both showed some positive influence on graft survival at both 3 and 4 years ($p=0.04$ in the multivariable model), these factors did not reach the level of statistical significance ($p=0.01$) required for inclusion in the final model. Notably graft success was not affected by cataract surgery in conjunction with DSAEK; this was similarly found with PKP in the CDS.⁵⁵

Complications.—The only operative factor that was found to significantly impact graft success was the occurrence of complications during the surgery (Table 1, **details in footnote c**). If the surgeon encountered difficulties during the surgical procedure (e.g. inverted graft), then the likelihood of graft success at 3 years was only 79.5% compared to a 94.6% if no complications occurred at the time of surgery ($p<0.001$).

Study Strengths and Limitations

The CPTS is the largest and most rigorous study yet of DSAEK surgery, enabling the application of a comprehensive multivariable analysis of the major donor, recipient and operative factors impacting graft success. There were, however, some inherent limitations. As the indication for DSAEK surgery in over 94% of recipient eyes was Fuchs dystrophy, the 3-year high rate of graft success in the CPTS may not be generalized to include eyes with other indications for DSAEK including, e.g. more advanced glaucoma cases with tube shunts, presence of anterior chamber intraocular lenses, anterior synechiae, that were excluded in the CPTS. Additionally, with many variations in surgical technique among the CPTS surgeons, the number of eyes with any particular technique may have been too low to detect differences among techniques. Finally, the risk factors reported in this study do not include postoperative events such as graft dislocation or rejection, which could prove to be more important for graft survival and endothelial cell loss after DSAEK compared to PK; these risk factors will be reported in subsequent analyses.

Conclusions

The risk for the entire postoperative period as well as primary or early graft failure after DSAEK is increased in eyes receiving corneas from diabetic donors and in which operative complications occurred. Further studies to explore the impact of donor diabetes on the function of the donor cornea and the significance of the degree of ocular and systemic manifestations of diabetes in the donor are warranted. Late graft failure is more common in recipient eyes with PACE compared to those with Fuchs dystrophy. Donor factors such as age, preoperative ECD, and donor corneal diameter were not predictors of DSAEK graft success. Thus, the selection of donor tissue with these specific characteristics is not warranted as long as the usual range of choices within each parameter is fulfilled, as in the CPTS. Finally, the donor findings in the CPTS may apply to DMEK graft success, understanding that prospective, masked studies to establish definitively are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Association between donor, recipient and operative risk factors and 3-year graft success

	N=1330	3-yr Graft Success (99% CI)	Base Model ^d HR (99% CI)	p-value	Multivariable Model ^b HR (99% CI)	p-value
Significant Donor/ Recipient Factors						
Donor History of Diabetes						
No	973	95.0% (92.8%, 96.6%)	1 [Ref]	0.003	1 [Ref]	0.002
Yes	357	90.3% (85.3%, 93.6%)	1.99 (1.10, 3.62)		2.04 (1.12, 3.71)	
Recipient Diagnosis						
PACE (without FECD)	75	83.7% (66.2%, 92.6%)	2.03 (0.79, 5.21)	0.05	2.15 (0.84, 5.53)	0.03
FECD	1255	94.3% (92.3%, 95.8%)	1 [Ref]		1 [Ref]	
Significant Operative Factor						
Operative Complications^c						
No	1256	94.6% (92.6%, 96.1%)	1 [Ref]	<0.001	1 [Ref]	<0.001
Yes	74	79.5% (62.4%, 89.4%)	3.46 (1.57, 7.60)		3.56 (1.62, 7.85)	
Non-significant Donor/Recipient Factors						
Donor Age (years)						
30	67	98.3% (79.6%, 99.9%)		0.09		0.15
31-50	214	94.6% (88.6%, 97.5%)				
51-60	357	93.3% (88.8%, 96.0%)	1.19 (0.91, 1.56) per decade		1.17 (0.89, 1.53) per decade	
61-70	489	93.5% (89.7%, 95.9%)				
71-75	203	93.0% (86.4%, 96.4%)				
Pre Lamellar Dissection Thickness (microns)^d						
<550	659	94.9% (92.1%, 96.8%)	1 [Ref]	0.07	1 [Ref]	0.14
>=550	628	92.5% (89.1%, 94.8%)	1.45 (0.77, 2.74)		1.37 (0.72, 2.58)	
Prior Glaucoma Surgery						
No	1299	94.1% (92.1%, 95.6%)	1 [Ref]	0.02	1 [Ref]	0.05
Yes	31	80.1% (52.9%, 92.6%)	2.95 (0.86, 10.16)		2.50 (0.74, 8.45)	

<i>Non-significant Operative Factor</i>	N=1330	3-yr Graft Success (99% CI)	Base Model ^d		Multivariable Model ^b	
			HR (99% CI)	p-value	HR (99% CI)	p-value
			Incision Site			
Cornea	978	94.7% (92.4%, 96.3%)	1 [Ref]	0.09	1 [Ref]	0.16
Scleral Tunnel	352	91.2% (86.3%, 94.4%)	1.57 (0.69, 3.56)		1.42 (0.64, 3.17)	

PACE = Pseudophakic corneal edema; FECD = Fuchs' endothelial corneal dystrophy;

^aBase models adjusted for PT, recipient diagnosis, random surgeon effect

^bMultivariable model adjusted for PT, recipient diagnosis, random surgeon effect. Donor history of diabetes, and operative complications 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

^dPre-lamellar dissection 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), non-ultrasonic method (1 eye)

Table 2.
Association between donor, recipient, and operative risk factors and primary/ early donor failure

	N=1330	Primary/ Early donor failure - n (%)	Base Model ^a		Multivariable Model ^b	
			OR (99% CI)	p-value	OR (99% CI)	p-value
Significant Donor/Recipient Factors						
Donor History of Diabetes						
No	973	24 (2)	1 [ref]	0.006	1 [ref]	0.008
Yes	357	21 (6)	2.37 (1.05, 5.34)		2.35 (1.03, 5.33)	
Recipient Diagnosis						
PACE (without FECD)	75	4 (5)	1.23 (0.27, 5.58)	0.72	1.29 (0.28, 6.02)	0.67
FECD	1255	41 (3)	1 [ref]		1 [ref]	
Significant Operative Factor						
Operative Complications^c						
No	1256	36 (3)	1 [ref]	<0.001	1 [ref]	<0.001
Yes	74	9 (12)	4.26 (1.46, 12.48)		4.21 (1.42, 12.47)	
Non-significant Donor/Recipient Factors						
Donor Gender						
Female	486	21 (4)	1.68 (0.75, 3.77)	0.10	1.54 (0.67, 3.51)	0.18
Male	844	24 (3)	1 [ref]		1 [ref]	
Donor Age (years)						
30	67	0 (0)		0.07		0.12
31-50	214	7 (3)				
51-60	357	11 (3)				
61-70	489	16 (3)				
71-75	203	11 (5)				
Screening ECD (EB Determined – cells/mm²)						
<2500	301	15 (5)		0.06		0.10
2500 to <2750	476	16 (3)				
2750 to <3000	303	11 (4)				
			0.58 (0.23, 1.26) per 500 cells		0.57 (0.24, 1.36) per 500 cells	

	N=1330	Primary/Early donor failure - n (%)	Base Model ^a		Multivariable Model ^b	
			OR (99% CI)	p-value	OR (99% CI)	p-value
3000	250	3 (1)				
Prior Glaucoma Surgery						
No	1299	42 (3)	1 [ref]	0.06	1 [ref]	0.15
Yes	31	3 (10)	3.50 (0.61,20.07)		2.82 (0.44, 18.15)	

PACE = Pseudophakic/aphakic corneal edema; FECD = Fuchs' endothelial corneal dystrophy; ECD = Endothelial cell density; EB = Eye bank

^aBase models adjusted for PT, recipient diagnosis, random surgeon effect

^bMultivariate model adjusted for PT, recipient diagnosis, random surgeon effect. Donor history of diabetes, and operative complications 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

Table 3.

Association between donor, recipient, and operative risk factors and late failure up to 3 years

	N=1285 ^a	3-yr Graft Success (99% CI)	Base Model/ Multivariable Model ^a HR (99% CI)	p-value
Significant Recipient Factor				
Recipient Diagnosis				0.007
<PACE (without FECD)	71	88.5% (69.8%, 95.9%)	3.59 (1.05, 12.24)	
<FECD	1214	97.5% (95.9%, 98.4%)	1 [Ref]	
Non-significant Donor/ Recipient Factors				
Pre Lamellar Dissection Thickness (microns) ^b				0.09
<550	642	97.4% (95.0%, 98.7%)	1.01 (1.00, 1.01)	
>=550	602	96.5% (93.7%, 98.0%)	per microns	
Recipient History of Diabetes				0.02
<No	1049	97.8% (96.2%, 98.7%)	1 [ref]	
<Yes	236	93.5% (86.4%, 96.9%)	2.39 (0.91, 6.31)	
Recipient Age (years)				0.06
<42-65	357	95.8% (91.5%, 98.0%)	2.37 (0.69, 8.11)	
<66-75	541	97.4% (94.8%, 98.7%)	1.39 (0.42, 4.63)	
<76-91	387	97.7% (94.4%, 99.1%)	1 [ref]	
Recipient Gender				0.09
<Female	773	97.8% (95.8%, 98.9%)	1 [ref]	
<Male	512	95.8% (92.6%, 97.7%)	1.80 (0.73, 4.44)	
Non-significant Operative Factors				
Operative Complications ^c				0.01
<No	1220	97.4% (95.8%, 98.4%)	1 [ref]	
<Yes	65	90.5% (71.2%, 97.1%)	3.35 (0.92, 12.19)	
Venting Incisions				0.08
<No	676	97.3% (94.8%, 98.6%)	1 [ref]	
<Yes	609	96.7% (94.2%, 98.2%)	2.02 (0.59, 6.95)	
Peripheral Host Stroma Scraping				0.07
<No	459	95.1% (91.4%, 97.2%)	2.02 (0.65, 6.29)	
<Yes	826	98.1% (96.3%, 99.1%)	1 [ref]	

PACE = Pseudophakic/aphakic corneal edema; FECD = Fuchs' endothelial corneal dystrophy

^a Eyes classified as early failures or primary donor failure were eliminated from the analysis. Base models adjusted for PT, recipient diagnosis, random surgeon effect. No additional factor selected via backward selection.^b Pre-lamellar dissection thickness is missing for 41 eyes. Eye bank determined by optical coherence tomography (565 eyes), ultrasonic pachymetry (321 eyes), specular microscopy (56 eyes), optical (6 eyes). Surgeon determined by ultrasonic pachymetry (295 eyes), non-ultrasonic method (1 eye)

^c Operative 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

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