Long-term Outcomes of Repeated Corneal Transplantations: A Prospective Dutch Registry Study

MOR M. DICKMAN, LINDSAY S. SPEKREIJSE, SURYAN L. DUNKER, BJORN WINKENS, TOS T.J.M. BERENDSCHOT, FRANK J.H.M. VAN DEN BIGGELAAR, PIETER JAN KRUIT, AND RUDY M.M.A. NUIJTS

• PURPOSE: To compare long-term outcomes of repeated corneal transplantations (CT), based on primary indication (Fuchs endothelial dystrophy [FED] vs pseudophakic bullous keratoplasty [PBK]), surgical technique (penetrating keratoplasty [PK] vs endothelial keratoplasty [EK]), and indication for repeated grafting.

• METHODS: In this nonrandomized treatment comparison with national registry data (Netherlands Organ Transplantation Registry, NOTR), data on all consecutive repeated CT following primary PK or EK for FED and PBK between 1994 and 2015 were analyzed, with a maximal follow-up of 5 years. Regraft survival was analyzed using Kaplan-Meier survival curves and univariable and multivariable Cox regression analysis. Secondary outcomes best-corrected visual acuity, spherical equivalent, and refractive astigmatism were compared using linear mixed-model analysis.

• RESULTS: A total of 332 repeated CT were analyzed. The number of regrafts increased significantly between 2007 and 2015 (*P* = .001). Overall 5-year regraft survival was 60% and was higher for FED vs PBK (77% vs 45%, HR = 0.40, *P* = .001), and re-EK vs re-PK (81% vs 55%, HR = 0.51, *P* = .041). However, multivariable analysis showed no significant difference in survival based on primary indication, surgical technique, and indication for regrafting. Corrected for baseline, secondary outcomes also did not differ between groups.

• CONCLUSIONS: We found a significant increase in repeated CT, coinciding with the introduction of EK in the Netherlands. While univariable analysis suggested better overall regraft survival for FED and (re-)EK, multivariable analysis showed no such difference. This may be owing to allocation of favorable cases to undergo (re-)EK. Similarly, secondary outcomes were determined by the primary CT technique. **(Am J Ophthalmol 2018;193: 156–165. © 2018 Elsevier Inc. All rights reserved.)**

AJO.com Supplemental Material available at AJO.com.

Accepted for publication Jun 20, 2018.

From the University Eye Clinic Maastricht, Maastricht University Medical Center+, Maastricht, Netherlands (M.M.D., L.S.S., S.L.D., T.T.J.M.B., F.J.H.M.B., R.M.M.A.N.); Department of Methodology and Statistics, Faculty of Health, Medicine and Life Sciences (FHML), Care and Public Health Research Institute (CAPHRI), Maastricht University, Maastricht, Netherlands (B.W.); and ETB-BISLIFE, Leiden, Netherlands (P.J.K.).

Inquiries to Mor M. Dickman, University Eye Clinic Maastricht, Maastricht University Medical Center+, P. Debyelaan 25, 6229 HX Maastricht, the Netherlands; e-mail: mor.dickman@mumc.nl

WITH MORE THAN 180 000 CORNEAL TRANSPLANTATIONS (CT) each year, the cornea is the second most transplanted solid tissue.[1] Recent studies show an increase in primary CT in the Netherlands, as well as worldwide.[1–4] The volume of repeated CT is also expected to rise, given the increase in primary CT, the learning curve of surgeons adopting new techniques, and the aging of the population.[5–8]

Endothelial failure owing to Fuchs endothelial dystrophy (FED) and pseudophakic bullous keratopathy (PBK) is the leading indication for CT worldwide.[1,3,7] In the last decade, endothelial keratoplasty (EK) surpassed penetrating keratoplasty (PK) as the primary treatment of choice for corneal endothelial failure. In a recent Dutch registry study, we showed that the long-term survival of primary EK and PK are comparable, despite lower short-term survival for EK. Moreover, visual acuity and refractive outcomes were better and achieved more quickly after EK.[4] However, despite these advances, primary graft failure, chronic endothelial cell loss, and immunologic reactions continue to compromise short- and long-term graft survival.

The introduction of EK also expanded our armamentarium of surgical techniques for failed CT. Besides traditional repeated PK (re-PK), other combinations for repeated CT have gained interest, including repeated EK (re-EK), PK after EK, and EK after PK. However, literature comparing the outcomes of the different surgical techniques for repeated CT is scarce.[9–12] Moreover, previous studies are limited by small sample sizes and short follow-up duration, focus only on part of the surgical options, or originate from highly specialized centers, limiting generalizability.[13–22]

In the current study, we set out to report national practice patterns and compare long-term outcomes of repeated CT for FED and PBK, based on surgical technique, primary indication, and indication for repeated CT, using prospectively collected real-world data from the Netherlands Organ Transplantation Registry (NOTR).

0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2018.06.018

TABLE 1. Dutch Registry Study: Baseline Demographics of Patients Undergoing Repeated Corneal Transplantation

FED	PK-PK (N = 81)	EK-EK (N = 85)	EK-PK (N = 24)	PK-EK (N = 13)	Between Groups *P*
Number of procedures (n/%)	81/40%	85/42%	24/12%	13/6%	
Recipient age, y (mean ± SD)	75 ± 9	70 ± 9	76 ± 9	73 ± 10	.890
Recipient sex, male (n/%)	27/33%	42/49%	5/21%	5/38%	.040*
Donor age, y (mean ± SD)	62 ± 13	67 ± 11	65 ± 13	66 ± 10	.100
Follow-up, mo (median/IQR)	35/15-55	30/21-39	32/16-48	28/19-37	.140
PBK	**PK-PK (N = 96)**	**EK-EK (N = 18)**	**EK-PK (N = 10)**	**PK-EK (N = 5)**	**Between Groups *P***
Number of procedures (n/%)	96/74%	18/14%	10/8%	5/4%	
Recipient age, y (mean ± SD)	67 ± 15	70 ± 14	64 ± 14	83 ± 4	.595
Recipient sex, male (n/%)	47/49%	8/44%	4/40%	3/60%	.880
Donor age, y (mean ± SD)	61 ± 12	64 ± 11	56 ± 17	67 ± 11	.580
Follow-up, mo (median/IQR)	33/15-52	25/11-39	23/14-32	10/6-49	.032*

EK = endothelial keratoplasty; FED = Fuchs endothelial dystrophy; IQR = interquartile range; PBK = pseudophakic bullous keratopathy; PK = penetrating keratoplasty; SD = standard deviation.
Statistically significant *P* values are indicated by an asterisk (*).

METHODS

• **GRAFT REGISTRY:** Data for this multicenter registry study were obtained from the NOTR, a prospective national database founded by the Netherlands Transplantation Foundation (Nederlandse Transplantatie Stichting [NTS], https://www.transplantatiestichting.nl/over-de-nts). In the Netherlands, donor corneas are allocated centrally, and the allocation process is registered in NOTR. The NTS prospectively collects data on the recipient, donor, eye bank processing, surgical procedure, and follow-up in regular intervals using a standardized electronic data capture system (https://www.transplantatiestichting.nl/english). Data collection continues until graft failure or loss to follow-up. Institutional review board approval for data extraction and analysis was provided by the NOTR scientific council. Data were anonymized prior to analysis, and the study was performed in accordance with the tenets of the Declaration of Helsinki and Dutch legislation.

• **POPULATION AND DATA COLLECTION:** The study cohort included all consecutive repeated CT in the NOTR registry following a failed primary EK or PK for FED or PBK between January 1, 1994 and August 31, 2015 (n = 345). Only the first regraft was included, with a maximal follow-up of 5 years. For patients fulfilling inclusion criteria in both eyes (n = 13), only the first eye was included in the study. No other inclusion or exclusion criteria were applied. The term EK was used regardless of donor dissection technique, including Descemet stripping automated endothelial keratoplasty (DSAEK) using a microkeratome and Descemet stripping endothelial keratoplasty (DSEK) using manual dissection.

• **OUTCOME MEASURES:** The primary outcome measure of this study was regraft survival. Graft failure was reported either by the corneal surgeon owing to specific conditions defined in the coding guidelines of the NOTR or following a repeated CT performed in the same eye. Secondary outcomes included best-corrected visual acuity (BCVA), spherical equivalent (SE), and refractive astigmatism. BCVA was measured in Snellen acuity and converted to the logarithm of the minimal angle of resolution (logMAR) for statistical analyses. SE was defined as the sum of the spherical value and half the cylindrical value.

• **STATISTICAL METHODS:** All statistical analyses were performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp, Armonk, New York, USA). Baseline characteristics were reported as frequencies with percentages, mean ± standard deviation (SD), or median and interquartile range (IQR), where appropriate. Baseline demographics were compared using independent samples *t* test and ANOVA for numerical variables and χ^2 test (for goodness-of-fit if 1 group is considered) for categorical variables. Graft survival was assessed using Kaplan-Meier survival curves with log-rank test, and univariable and multivariable Cox regression analysis with primary indication, repeated CT technique, indication for repeated CT, recipient age, and donor-recipient sex match as explanatory factors.

Linear mixed models (LMM) were fitted to investigate the difference in longitudinal trend in BCVA and SE between groups, where group, time, and group × time were included as fixed factors. Estimated marginal means (EMM) with their corresponding standard errors of the mean (SEM) were reported and postoperative differences

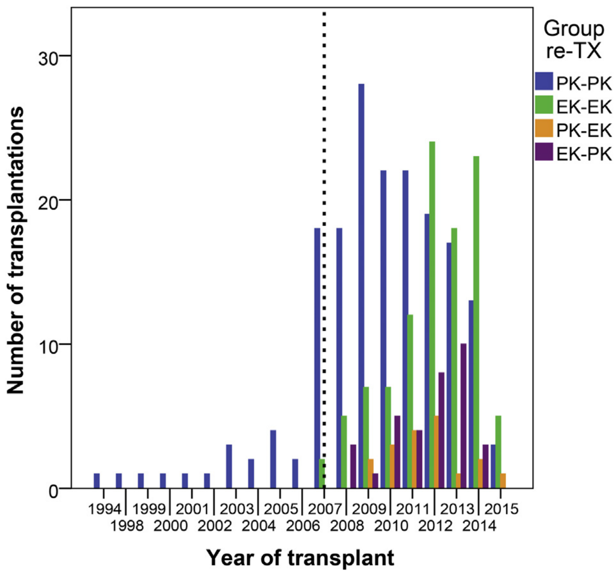

FIGURE 1. Dutch registry study: Practice pattern of repeated corneal transplantations in the Netherlands between 1994 and 2015. The total number of repeated corneal transplantations (CT) in the Netherlands remained stable between 1994 and 2006, increasing significantly between 2007 and 2014. The increase in repeated CT is attributed to a significant increase in repeat (re-) endothelial keratoplasty (EK) (green, $P < .001$), whereas the numbers of repeat penetrating keratoplasty (PK) did not change significantly (blue, $P = .432$). The dotted line indicates introduction of EK into standard clinical care in the Netherlands in 2007.

between groups were corrected for baseline differences. Vector analyses were performed using an Excel database (Office 2010, Microsoft Inc, Redmond, Washington, USA) to calculate refractive astigmatism. Although all variables were measured at baseline and at 3, 6, 12, 36, 48, and 60 months after repeated transplantation, at least until failure, secondary outcome analyses were limited to the first 24 months owing to increasing failure rate with time and recent inclusion of patients. Two-sided P values ≤ .05 were considered statistically significant for all analyses.

RESULTS

A TOTAL OF 332 EYES OF 332 PATIENTS WERE IDENTIFIED, WITH a maximum follow-up of 5 years (mean ± SD: 32 ± 18 months, range 0.23–60 months): 177 eyes underwent PK after failed PK (re-PK), 103 eyes underwent EK after failed EK (re-EK), 34 eyes underwent PK after a failed EK (EK-PK), and 18 eyes received EK after a failed PK (PK-EK).

• **DEMOGRAPHICS:** Recipient demographics per group of regraft technique are given in Table 1. Comparing FED and PBK undergoing re-PK, the proportion of female patients and mean patient age were significantly higher for FED ($P = .040$ and $P < .001$, respectively). The distribution of re-PK vs re-EK was similar for FED (40% vs 42%, respectively; $P = .756$) but significantly different for PBK (74% vs14%, for re-PK vs re-EK, respectively; $P < .001$). All other demographics were comparable between groups.

• **REGRAFT PRACTICE PATTERNS:** The total number of regrafts did not change significantly between 1994 and 2006 ($P = .382$) and increased significantly between 2007 and 2014 ($P = .002$), coinciding with the introduction of EK into standard clinical care in the Netherlands (Figure 1). The total increase in regrafts between 2007 and 2014 was attributable to a significant increase in re-EK ($P < .001$), whereas re-PK did not change significantly ($P = .432$).

• **INDICATIONS FOR REGRAFTING:** Indications for repeated CT were analyzed per primary CT technique (ie, failed EK and PK). Endothelial failure was the predominant indication for repeated CT (50% vs 65%, after failed EK and PK, respectively, $P = .014$). Irreversible rejection was the second and third most frequent indication for repeated CT after failed PK and EK, respectively (20% vs 17%, $P = .542$). Primary graft failure was the second most frequent indication for repeated CT after failed EK (25%). Other indications for regrafting (9% vs 15%, following failed EK and PK, respectively, $P = .152$) included trauma, infectious keratitis, interface haze, and high irregular astigmatism.

• **REGRAFT SURVIVAL:** Univariable Cox regression analysis showed higher 2-year regraft survival for FED vs PBK (93% vs 84%, hazard ratio [HR] 0.44, 95% confidence interval [CI] 0.21–0.92, $P = .024$) and comparable 2-year regraft survival for re-EK vs re-PK (91% vs 90%, HR 0.97, 95% CI 0.43–2.20, $P = .945$) (Figure 2). Multivariable Cox regression analysis showed higher 2-year regraft survival for FED vs PBK (HR 0.35, 95% CI 0.13–0.96, $P = .041$) and no significant difference in regraft survival based on surgical technique (re-EK vs re-PK, HR 1.50, 95% CI 0.55–4.07, $P = .425$), and indication for repeated CT ($P = .729$).

Furthermore, univariable Cox regression analysis showed higher 2- to 5-year regraft survival for FED vs PBK (81% vs 53%, HR 0.37, 95% CI 0.19–0.71, $P = .003$) and re-EK vs re-PK (89% vs 61%, HR 0.17, 95% CI 0.04–0.71, $P = .015$) (Figure 2). However, multivariable Cox regression analysis showed no significant differences in 2- to 5-year regraft survival based on primary indication (FED vs PBK, HR 0.76, 95% CI 0.32–1.83, $P = .538$), surgical technique (and re-EK vs re-PK, HR 0.38, 95% CI 0.08–1.76, $P = .215$), and indication for repeated CT ($P = .538$).

Overall 5-year regraft survival was 60% (95% CI 51%–68%). Univariable Cox regression analysis showed higher 5-year regraft survival for FED vs PBK (77% vs 45%, HR 0.40, 95% CI 0.25–0.65, $P < .001$) and for re-EK vs re-PK (81% vs 55%, HR 0.51, 95% CI 0.26–0.98, $P = .041$)

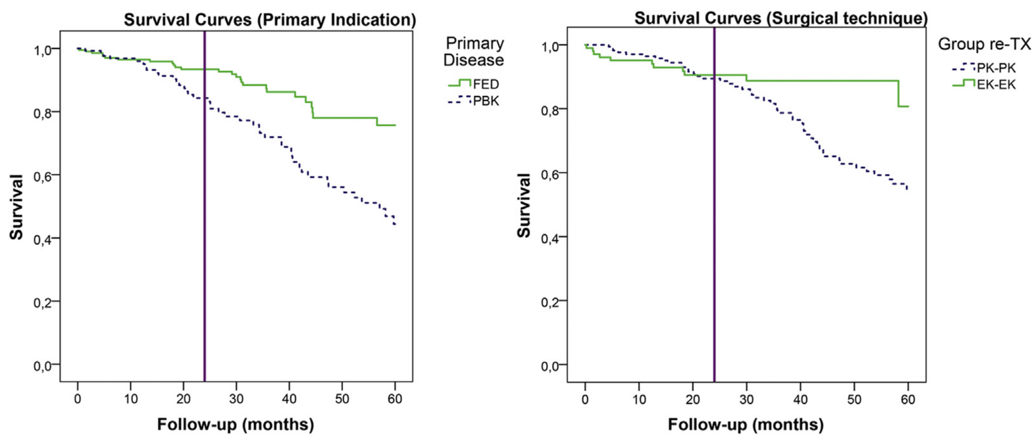

FIGURE 2. Dutch registry study: Kaplan-Meier survival curves of repeated corneal transplant survival based on primary indication (Fuchs endothelial dystrophy [FED] vs pseudophakic bullous keratopathy [PBK]) (Left) and surgical technique (repeated endothelial keratoplasty [EK-EK] vs repeated penetrating keratoplasty [PK-PK]) (Right). The purple line indicates 24 months of follow-up.

TABLE 2. Dutch Registry Study: Best-Corrected Visual Acuity[a] Before and After Repeated Corneal Transplantation

Primary Indication	FED (N = 203)		PBK (N = 129)		FED vs PBK
Follow-up	N	LogMAR ± SEM	N	LogMAR ± SEM	*P*
Preoperative	202	1.40 ± 0.08	126	1.88 ± 0.10	<.001*
3 months	171	0.54 ± 0.05	99	0.96 ± 0.07	.531
6 months	180	0.43 ± 0.05	110	0.88 ± 0.06	.783
12 months	177	0.43 ± 0.06	105	0.95 ± 0.07	.742
24 months	140	0.44 ± 0.07	84	0.93 ± 0.09	.948
Surgical Technique	**PK-PK (N = 177)**		**EK-EK (N = 103)**		**EK-EK vs PK-PK**
Follow-up	N	LogMAR ± SEM	N	LogMAR ± SEM	*P*
Preoperative	174	1.82 ± 0.09	103	1.46 ± 0.10	.005*
3 months	137	0.86 ± 0.06	89	0.64 ± 0.06	.216
6 months	152	0.71 ± 0.05	92	0.60 ± 0.06	.027[b]
12 months	149	0.76 ± 0.06	91	0.62 ± 0.07	.094
24 months	123	0.80 ± 0.08	72	0.57 ± 0.09	.389

EK = endothelial keratoplasty; FED = Fuchs endothelial dystrophy; LogMAR = logarithm of the minimum angle of resolution; PBK = pseudophakic bullous keratopathy; PK = penetrating keratoplasty; SEM = standard error of the mean.

Statistically significant *P* values are indicated by an asterisk (*).

[a]Corrected for best-corrected visual acuity at baseline (linear mixed-model estimated marginal means).

[b]Not significant after correction for multiple testing.

(Figure 2). However, multivariable analysis showed no significant differences based on primary indication (FED vs PBK; HR 0.56, 95% CI 0.29–1.08, *P* = .083), surgical technique (re-EK vs re-PK; HR 0.85, 95% CI 0.39–1.85, *P* = .689), and indication for repeated CT (*P* = .719).

With regard to EK after failed PK (PK-EK, n = 18) and PK after failed EK (EK-PK, n = 34), Kaplan-Meier curves showed no significant difference in survival between all 4 regraft surgical techniques during the first 2 years (*P* = .979) (data not shown). Between 2 and 5 years, PK-EK and EK-PK both followed the curve for re-PK (log-rank: re-PK vs PK-EK, *P* = .959; re-PK vs EK-PK, *P* = .961) and showed lower survival compared to re-EK (log-rank: re-EK vs PK-EK, *P* = .067; re-EK vs EK-PK, *P* = .012). Five-year survival for PK-EK and EK-PK was 73% and 63%, respectively. Multivariable analyses were not performed for PK-EK and EK-PK owing to the limited sample sizes of these groups.

• **BEST-CORRECTED VISUAL ACUITY:** The results from linear mixed-model analysis for BCVA are given in Table 2. A significant difference in baseline BCVA was

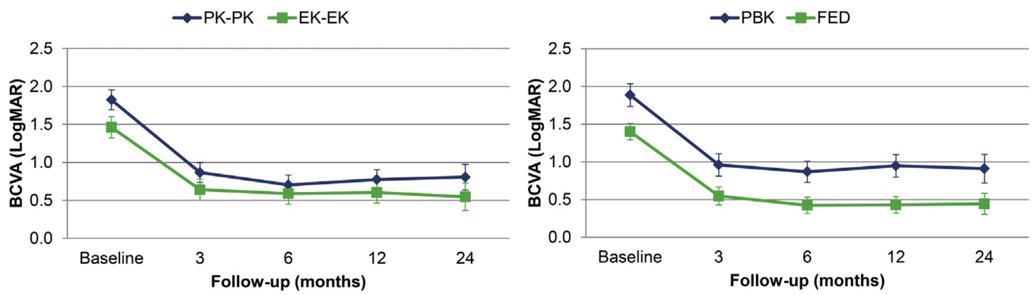

FIGURE 3. Dutch registry study: Best-corrected visual acuity before and after repeated endothelial keratoplasty (EK-EK) and repeated penetrating keratoplasty (PK-PK) (Left) for Fuchs endothelial dystrophy (FED) and pseudophakic bullous keratopathy (PBK) (Right). (Linear mixed model estimated marginal means.)

TABLE 3. Dutch Registry Study: Spherical Equivalent[a] Before and After Repeated Corneal Transplantation

Surgical Technique	PK-PK (N = 177)		EK-EK (N = 103)		EK-EK vs PK-PK
Follow-up	N	SE (D) ± SEM	N	SE (D) ± SEM	P
Preoperative	64	4.27 ± 0.33	56	1.59 ± 0.37	<.001
3 months	96	4.37 ± 0.30	79	1.41 ± 0.34	.536
6 months	122	4.44 ± 0.28	84	1.60 ± 0.34	.712
12 months	112	4.48 ± 0.29	79	1.32 ± 0.34	.282
24 months	71	4.46 ± 0.32	54	1.34 ± 0.37	.361

D = diopter; EK = endothelial keratoplasty; PK = penetrating keratoplasty; SE = spherical equivalent; SEM = standard error of the mean.
[a]Corrected for SE at baseline (linear mixed-model estimated marginal means).

observed between surgical techniques (re-EK vs re-PK; 1.46 ± 0.99 vs 1.82 ± 1.2 logMAR, respectively, $P = .005$) and primary indications (FED vs PBK; 1.40 ± 1.12 vs 1.88 ± 1.16 logMAR, respectively, $P < .001$). Corrected for baseline, BCVA was comparable for FED vs PBK ($P = .929$) and re-EK vs re-PK ($P = .133$) at all time points. As for longitudinal changes in BCVA in all patients, BCVA improved significantly at 3 months compared to baseline ($P < .001$) and from 3 to 6 months of follow-up ($P = .003$). After 6 months, no significant changes in BCVA were observed (Figure 3). Indication for repeated CT was not significantly related to baseline differences in BCVA.

• **REFRACTIVE OUTCOMES:** The linear mixed-model analysis results for absolute SE are given in Table 3. We found a significant baseline difference in SE between surgical techniques (re-PK vs re-EK; 4.27 diopter [D] vs 1.59 D, $P < .001$) (Figure 4). Corrected for baseline, SE was comparable at all postoperative time points between groups ($P = .807$). There was no significant change in SE between preoperative and postoperative time points for re-PK and re-EK. Refractive astigmatism values per group of surgical technique (re-EK and re-PK) are presented in Table 4. Achieved refractive astigmatism did not differ significantly

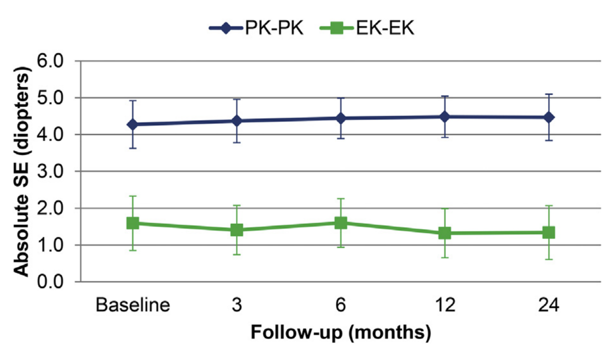

FIGURE 4. Dutch registry study: Spherical equivalent before and after repeated endothelial keratoplasty (EK-EK) and repeated penetrating keratoplasty (PK-PK). (Linear mixed model estimated marginal means.)

from preoperative values at all time points after re-EK and re-PK (Figure 5). Surgically induced astigmatism (SIA) did not differ significantly from zero for both re-EK and re-PK at all time points (Figure 6). Refractive astigmatism variability was higher for re-PK vs re-EK (Figures 5 and 6). Subgroup analysis of patients undergoing re-PK with high preoperative astigmatism (≥5 D), showed that both the difference between preoperative and achieved refractive

TABLE 4. Dutch Registry Study: Vector Analysis on Refractive Astigmatism After Repeated Corneal Transplantation

Surgical Technique	PK-PK (N = 177)	EK-EK (N = 103)	EK-EK vs PK-PK *P*
6 months			
Number of patients	50	49	
Preoperative vector mean ± SD (D @ deg)	0.71 ± 3.11 @ 86	0.38 ± 1.27 @ 92	.814
Vector mean ± SD (D @ deg)	1.84 ± 3.37 @ 90	0.37 ± 1.31 @ 90	.019[a]
SIA vector mean ± SD (D @ deg)	1.14 ± 4.20 @ 92	0.03 ± 1.48 @ 41	.266
12 months			
Number of patients	45	47	
Preoperative vector mean ± SD (D @ deg)	0.54 ± 3.05 @ 68	0.32 ± 1.33 @ 93	.615
Vector mean ± SD (D @ deg)	0.53 ± 3.22 @ 68	0.28 ± 1.44 @ 114	.488
SIA vector mean ± SD (D @ deg)	0.01 ± 4.38 @ 145	0.21 ± 1.56 @ 154	.961
24 months			
Number of patients	27	32	
Preoperative vector mean ± SD (D @ deg)	0.75 ± 3.07 @ 63	0.27 ± 1.40 @ 72	.677
Vector mean ± SD (D @ deg)	1.61 ± 3.12 @ 103	0.30 ± 1.92 @ 112	.149
SIA vector mean ± SD (D @ deg)	1.66 ± 4.35 @ 117	0.37 ± 1.96 @ 136	.267

D = diopter; Deg = degrees; EK = endothelial keratoplasty; PK = penetrating keratoplasty; SD = standard deviation; SIA = surgically induced astigmatism.

[a]Not significant after correction for multiple testing.

astigmatism and SIA did not differ significantly from zero (figures not shown).

DISCUSSION

ENDOTHELIAL KERATOPLASTY HAS LARGELY REPLACED penetrating keratoplasty as the procedure of choice in the primary treatment of corneal endothelial dysfunction. In a recent Dutch registry study, we showed that the advantages of primary EK over PK resulted in a significant increase in the volume of primary EK and a paradigm shift toward earlier surgical intervention.[4] In the current study we set out to evaluate long-term survival and outcomes of repeated corneal transplantations, based on prospectively collected Dutch registry data.

We found a significant increase in repeated CT between 2007 and 2014, coinciding with the introduction of EK into standard clinical care in the Netherlands. This was the result of an increase in re-EK, whereas the number of re-PK remained stable. Standardization of EK during the study period, and reports on lower rejection rates of EK compared to PK,[7,23–26] suggest the increase in repeated CT is related to the growing volume of primary CT. Nonetheless, it is difficult to tease out the effect of a learning curve on a national level.[5–8]

The main outcome of our study was repeated CT survival. We found a cumulative 5-year repeated graft survival of 60%. This is considerably lower compared to primary CT (95% for FED and 85% for PBK),[4] especially in so-called "low-risk" eyes.[27] Recent studies suggest sex mismatch as a risk factor for primary CT rejection and failure.[28,29] However, this was not the case in our study. While univariable Cox regression analysis indicated higher overall graft survival for FED vs PBK and re-EK vs re-PK, multivariable analysis showed no significant difference based on primary indication, surgical technique, and indication for regrafting. A larger sample size or longer follow-up may have resulted in a significant effect. However, this would only be of interest if the observed effect was clinically significant. Indeed, the corrected effect size for primary indication was considerable and almost reached significance (HR = 0.56, P = .08). However, this was not the case for surgical technique (HR = 0.85, P = .69). More importantly, this may be owing to allocation of patients with better prognosis (FED) to undergo (re-)EK, corrected for by the multivariable analysis. Indeed, a significantly higher percentage of FED patients in our study underwent (re-)EK. Likewise, secondary outcomes were significantly better at baseline after primary EK, and remained so after re-EK compared with re-PK. However, corrected for baseline, BCVA, SE, and refractive astigmatism did not differ significantly between re-EK and re-PK at all postoperative time points. This

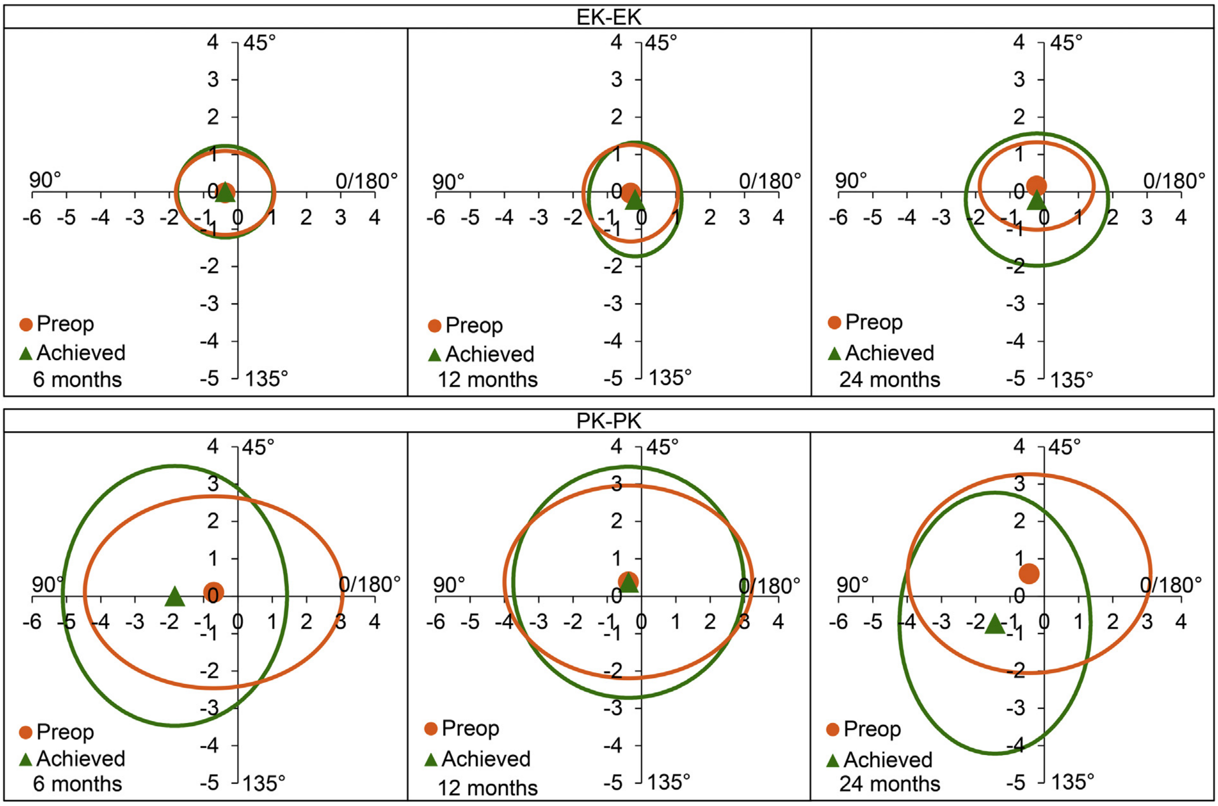

FIGURE 5. Dutch registry study: Double angle-vector diagrams of the preoperative and achieved refractive astigmatism 6, 12, and 24 months after repeated endothelial keratoplasty (EK-EK) and repeated penetrating keratoplasty (PK-PK).

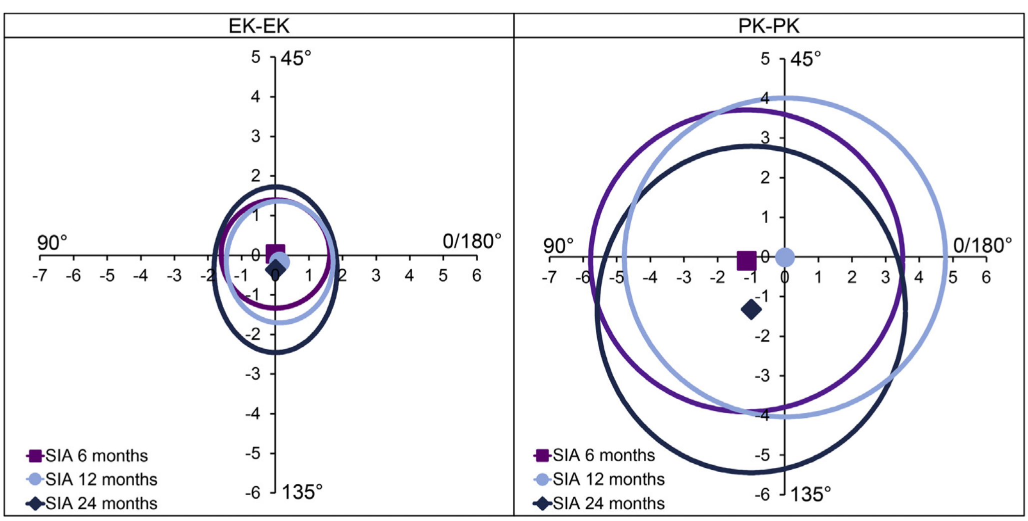

FIGURE 6. Dutch registry study: Double angle-vector diagrams of the surgically induced astigmatism (SIA) for repeated endothelial keratoplasty (EK-EK) and repeated penetrating keratoplasty (PK-PK) at 6, 12, and 24 months of follow-up.

finding suggests that repeated CT outcomes are determined by the primary CT procedure. Compared with preoperative values, BCVA improved significantly after repeated CT, whereas SE and refractive astigmatism remained stable. Interestingly, this was also the case for patients with high preoperative refractive astigmatism. This is likely owing to the high variability in refractive outcomes after re-PK compared with re-EK.

Although primary CT for endothelial dysfunction is now predominantly performed by EK, many patients treated initially by PK remain. Several studies analyzed the outcomes of re-PK for graft failure and found it is associated with lower graft survival compared to primary PK.[9–12] As an alternative, EK after failed PK has attracted increasing attention.[9–13,15,17–22] To the best of our knowledge this is the first registry study to directly compare outcomes of all 4 transplant alternatives for repeated CT. We found that EK after failed PK does not confer an advantage in graft survival compared to re-PK, in agreement with a recent systematic review and meta-analysis by Wang and associates.[30]

The leading indication for repeated CT in our study was endothelial failure, accounting for 50% and 65% of re-EK and re-PK, respectively. This finding corresponds with previous reports indicating similar long-term endothelial cell loss after EK compared to PK, despite higher early endothelial cell loss after EK.[31] Previous studies suggest that DSAEK is less likely than PK to fail as a result of immunologic graft rejection.[32] Nonetheless, irreversible rejection was the second (re-PK, 20%) and third (re-EK, 17%) most common indication for repeated CT in our study. Moreover, the clinical features of rejection in EK can be much more subtle compared to PK. Therefore, some graft failures ascribed to chronic endothelial cell loss may actually be caused by previously undetected rejection. One limitation of this registry study is lack of information on the use of topical steroids, which was not captured in detail for this cohort by the NOTR registry. Long-term low-dose topical steroids have been shown to reduce the risk of endothelial rejection in PK.[33,34] Although similar comparative prospective studies after EK are not available, it seems reasonable that repeated CT should also benefit from such treatment regardless of surgical technique.

Much of our knowledge on CT outcomes comes from large-scale national registries. Registries reflect prospectively collected "real-world" data from a wide range of surgeons working in various clinical settings. Although comparative interventional registry studies lack the rigor of randomization, in the current study we used multivariable models to correct for baseline values and confounders. Another limitation of registry studies is the potential for incomplete data. With regard to our main outcome measure (graft survival), missing data is not expected, since all corneal transplants in the Netherlands are centrally allocated and registered in NOTR. In addition, Kaplan-Meier and Cox regression analysis accounts for censored data. With regard to secondary outcome measures, linear mixed models use all available data and assume missingness at random instead of missingness completely at random, as is the case for list-wise deletion, used in analysis methods such as repeated measures ANOVA, which may then cause bias and reduce power.

Although Descemet membrane endothelial keratoplasty (DMEK) was introduced in the Netherlands,[35] it has only recently entered standard clinical care, and therefore falls outside the timeframe of this study. Given the rapid developments in the field of endothelial keratoplasty, it is difficult to predict future practice patterns for repeated grafting. In the short term, the learning curve associated with implementation of DMEK on a national level is likely to result in an increase in re-DMEK. However, re-DSAEK may (initially) be the preferred choice after failed DMEK. Moreover, (re-)DSAEK remains the most frequently used keratoplasty technique in the Netherlands and in the United States.[36]

In the long term, fewer repeated grafts may be needed for DMEK, given reports on lower rejection rates,[37] and following completion of the learning curve on a national level. At the same time, re-DMEK will likely become an attractive alternative following failed DSAEK and PKP, while DSAEK will likely remain a viable alternative for repeated keratoplasty, especially in highly complex eyes with inherently higher risk of graft failure. Most recently, the NOTR, together with the Swedish Corneal Transplant Register and the National Health Services Blood and Transplant Registry, established ECCTR: The European Cornea and Cell Transplantation Registry (www.ecctr.org). We expect this multinational registry to provide valuable insights into the real-world outcomes of re-DMEK and advanced cell therapies for corneal regeneration, as those become available.

In conclusion, we report a significant increase in repeated CT following the introduction of EK into routine clinical practice in the Netherlands. Overall, repeated CT survival was significantly lower compared to primary graft survival, even in so-called "low-risk" eyes. Whereas univariable analysis suggests better survival for re-EK and FED, multivariable analysis shows no significant difference. This may be owing to allocation of patients with favorable prognosis (FED) to (re-)EK. Similarly, corrected for baseline values, secondary outcomes (BCVA, SE, refractive astigmatism) were determined by the primary CT technique, reaffirming the role of (re-)EK as the preferred technique for the treatment of corneal endothelial pathology.

FUNDING/SUPPORT: NO FUNDING OR GRANT SUPPORT. FINANCIAL DISCLOSURES: RUDY M.M.A. NUIJTS: ABBOTT (STUDY grant), Alcon (Consultant, Lecture, Study grant), Asico (Consultant, Patent), Bausch & Lomb (Study grant), Carl-Zeiss (Study grant), Chiesi (Consultant, Study grant), HumanOptics (Study grant), Ophtec (Study grant), Oculentis (Study grant), Gebauer (Study grant), TheaPharma (Consultant). The following authors have no financial disclosures: Mor M. Dickman, Lindsay S. Spekreijse, Suryan L. Dunker, Bjorn Winkens, Tos T.J.M. Berendschot, Frank J.H.M. van den Biggelaar, and Pieter Jan Kruit. All authors attest that they meet the current ICMJE criteria for authorship.

Other Acknowledgments: The authors would like to thank Mrs Cynthia Konijn (MSc), Mrs Brigitte Schaefer (MSc), and Dr Martin Heemskerk (PhD) from the Dutch Transplant foundation (NTS) for their valuable statistical consultation and assistance, and the Dutch corneal surgeons for carefully registering in NOTR.

REFERENCES

1. Gain P, Jullienne R, He Z, et al. Global survey of corneal transplantation and eye banking. *JAMA Ophthalmol* 2016;134(2):167–173.
2. Flockerzi E, Maier P, Bohringer D, et al. Trends in corneal transplantation from 2001 to 2016 in Germany: a report of the DOG-Section Cornea and its keratoplasty registry. *Am J Ophthalmol* 2018;188:91–98.
3. Kim BZ, Meyer JJ, Brookes NH, et al. New Zealand trends in corneal transplantation over the 25 years 1991-2015. *Br J Ophthalmol* 2017;101(6):834–838.
4. Dickman MM, Peeters JM, van den Biggelaar FJ, et al. Changing practice patterns and long-term outcomes of endothelial versus penetrating keratoplasty: a prospective Dutch registry study. *Am J Ophthalmol* 2016;170:133–142.
5. Keane MC, Mills RA, Coster DJ, Williams KA. Is there evidence for a surgeon learning curve for endothelial keratoplasty in Australia? *Clin Exp Ophthalmol* 2017;45(6):575–583.
6. Debellemaniere G, Guilbert E, Courtin R, et al. Impact of surgical learning curve in Descemet membrane endothelial keratoplasty on visual acuity gain. *Cornea* 2017;36(1):1–6.
7. Coster DJ, Lowe MT, Keane MC, Williams KA. A comparison of lamellar and penetrating keratoplasty outcomes: a registry study. *Ophthalmology* 2014;121(5):979–987.
8. Pillar S, Tessler G, Dreznik A, Bor E, Kaiserman I, Bahar I. First 100: learning curve for Descemet stripping automated endothelial keratoplasty. *Eur J Ophthalmol* 2013;23(6):865–869.
9. Keane MC, Galettis RA, Mills RA, Coster DJ, Williams KA. A comparison of endothelial and penetrating keratoplasty outcomes following failed penetrating keratoplasty: a registry study. *Br J Ophthalmol* 2016;100(11):1569–1575.
10. Kitzmann AS, Wandling GR, Sutphin JE, Goins KM, Wagoner MD. Comparison of outcomes of penetrating keratoplasty versus Descemet's stripping automated endothelial keratoplasty for penetrating keratoplasty graft failure due to corneal edema. *Int Ophthalmol* 2012;32(1):15–23.
11. Ang M, Ho H, Wong C, Htoon HM, Mehta JS, Tan D. Endothelial keratoplasty after failed penetrating keratoplasty: an alternative to repeat penetrating keratoplasty. *Am J Ophthalmol* 2014;158(6):1221–1227.
12. Ramamurthy S, Reddy JC, Vaddavalli PK, Ali MH, Garg P. Outcomes of repeat keratoplasty for failed therapeutic keratoplasty. *Am J Ophthalmol* 2016;162:83–88.e82.
13. Lee BS, Stark WJ, Jun AS. Descemet-stripping automated endothelial keratoplasty: a successful alternative to repeat penetrating keratoplasty. *Clin Exp Ophthalmol* 2011;39(3):195–200.
14. Letko E, Price DA, Lindoso EM, Price MO, Price FW Jr. Secondary graft failure and repeat endothelial keratoplasty after Descemet's stripping automated endothelial keratoplasty. *Ophthalmology* 2011;118(2):310–314.
15. Anshu A, Price MO, Price FW Jr. Descemet's stripping endothelial keratoplasty under failed penetrating keratoplasty: visual rehabilitation and graft survival rate. *Ophthalmology* 2011;118(11):2155–2160.
16. Kim P, Yeung SN, Lichtinger A, et al. Outcomes of repeat endothelial keratoplasty in patients with failed Descemet stripping endothelial keratoplasty. *Cornea* 2012;31(10):1154–1157.
17. Jangi AA, Ritterband DC, Wu EI, Mehta VV, Koplin RS, Seedor JA. Descemet stripping automated endothelial keratoplasty after failed penetrating keratoplasty. *Cornea* 2012;31(10):1148–1153.
18. Chaurasia S, Murthy S, Ramappa M, Mohamed A, Garg P. Outcomes of Descemet's stripping endothelial keratoplasty in eyes with failed therapeutic penetrating keratoplasty. *Acta Ophthalmol* 2014;92(2):167–170.
19. Mitry D, Bhogal M, Patel AK, et al. Descemet stripping automated endothelial keratoplasty after failed penetrating keratoplasty: survival, rejection risk, and visual outcome. *JAMA Ophthalmol* 2014;132(6):742–749.
20. Tarantino-Scherrer JN, Kaufmann C, Bochmann F, Bachmann LM, Thiel MA. Visual recovery and endothelial cell survival after Descemet stripping automated endothelial keratoplasty for failed penetrating keratoplasty grafts-a cohort study. *Cornea* 2015;34(9):1024–1029.
21. Heinzelmann S, Bohringer D, Eberwein P, Lapp T, Reinhard T, Maier P. Descemet membrane endothelial keratoplasty for graft failure following penetrating keratoplasty. *Graefes Arch Clin Exp Ophthalmol* 2017;255(5):979–985.
22. Covert DJ, Koenig SB. Descemet stripping and automated endothelial keratoplasty (DSAEK) in eyes with failed penetrating keratoplasty. *Cornea* 2007;26(6):692–696.
23. Terry MA, Ousley PJ. Deep lamellar endothelial keratoplasty in the first United States patients: early clinical results. *Cornea* 2001;20(3):239–243.
24. Lam FC, Rahman MQ, Ramaesh K. Traumatic wound dehiscence after penetrating keratoplasty-a cause for concern. *Eye (Lond)* 2007;21(9):1146–1150.
25. Price FW Jr, Feng MT, Price MO. Evolution of endothelial keratoplasty: where are we headed? *Cornea* 2015;34(Suppl 10):S41–S47.
26. Price MO, Gupta P, Lass J, Price FW Jr. EK (DLEK, DSEK, DMEK): new frontier in cornea surgery. *Annu Rev Vis Sci* 2017;15(3):69–90.
27. Maguire MG, Stark WJ, Gottsch JD, et al. Risk factors for corneal graft failure and rejection in the collaborative corneal transplantation studies. Collaborative Corneal Transplantation Studies Research Group. *Ophthalmology* 1994;101(9):1536–1547.
28. Hopkinson CL, Romano V, Kaye RA, et al. The influence of donor and recipient gender incompatibility on corneal transplant rejection and failure. *Am J Transplant* 2017;17(1):210–217.
29. Bohringer D, Spierings E, Enczmann J, et al. Matching of the minor histocompatibility antigen HLA-A1/H-Y may improve prognosis in corneal transplantation. *Transplantation* 2006;82(8):1037–1041.
30. Wang F, Zhang T, Kang YW, He JL, Li SM, Li SW. Endothelial keratoplasty versus repeat penetrating keratoplasty after failed penetrating keratoplasty: a systematic review and meta-analysis. *PLoS One* 2017;12(7):e0180468.
31. Lee WB, Jacobs DS, Musch DC, Kaufman SC, Reinhart WJ, Shtein RM. Descemet's stripping endothelial keratoplasty: safety and outcomes: a report by the American Academy of Ophthalmology. *Ophthalmology* 2009;116(9):1818–1830.

32. Price MO, Gorovoy M, Price FW Jr, Benetz BA, Menegay HJ, Lass JH. Descemet's stripping automated endothelial keratoplasty: three-year graft and endothelial cell survival compared with penetrating keratoplasty. *Ophthalmology* 2013;120(2):246–251.
33. Shimazaki J, Iseda A, Satake Y, Shimazaki-Den S. Efficacy and safety of long-term corticosteroid eye drops after penetrating keratoplasty: a prospective, randomized, clinical trial. *Ophthalmology* 2012;119(4):668–673.
34. Nguyen NX, Seitz B, Martus P, Langenbucher A, Cursiefen C. Long-term topical steroid treatment improves graft survival following normal-risk penetrating keratoplasty. *Am J Ophthalmol* 2007;144(2):318–319.
35. Melles GR, Lander F, Rietveld FJ. Transplantation of Descemet's membrane carrying viable endothelium through a small scleral incision. *Cornea* 2002;21(4):415–418.
36. 2016 Eye Banking Statistical Report.Eye Bank Association of America Washington, DC. Available at: ; 2017. http://restoresight.org/wp-content/uploads/2017/04/2016_Statistical_Report-Final-040717.pdf;. Accessed May 25, 2018.
37. Price DA, Kelley M, Price FW Jr, Price MO. Five-year graft survival of Descemet membrane endothelial keratoplasty (EK) versus Descemet stripping EK and the effect of donor sex matching. *Ophthalmology* 2018; https://doi.org/10.1016/j.ophtha.2018.03.050.