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ORIGINAL ARTICLE

DMEK outcome after one year – Results from a large multicenter study in Germany

Kristina Spaniol[1] | **Martin Hellmich**[2] | **Klara Borgardts**[1] | **Christian Girbardt**[3] | **Philip Maier**[4] | **Thomas Reinhard**[4] | **Necip Torun**[5] | **Anna-Karina Maier**[5] | **Sebastian Thaler**[6] | **Karl U. Bartz-Schmidt**[6] | **Peter Wiedemann**[3] | **Berthold Seitz**[7] | **Loay Daas**[7] | **Silvia Schrittenlocher**[8] | **Claus Cursiefen**[8] | **Björn Bachmann**[8] | **Gerd Geerling**[1]

[1]Department of Ophthalmology, University Hospital Düsseldorf, Düsseldorf, Germany

[2]Institute of Medical Statistics and Computational Biology, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany

[3]Department of Ophthalmology, University Hospital Leipzig, Leipzig, Germany

[4]Eye Center, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg im Breisgau, Germany

[5]Department of Ophthalmology, Charité Universitätsmedizin – Berlin, Corporate Member of Freie Universität Berlin, Humbolt-Universität zu Berlin und Berlin Institute of Health, Berlin, Germany

[6]Department of Ophthalmology, University Hospital Tübingen, Tübingen, Germany

[7]Department of Ophthalmology, Saarland University Medical Center, Homburg/Saar, Germany

[8]Department of Ophthalmology, University Hospital Cologne, Cologne, Germany

Correspondence
Kristina Spaniol, Department of Ophthalmology, University Hospital Düsseldorf, Moorenstraße 5, 40225 Düsseldorf, Germany.
Email: kristina.spaniol@med.uni-duesseldorf.de

Abstract

Purpose: Descemet membrane endothelial keratoplasty (DMEK) accounts for >50% of all corneal transplants in Germany. So far, no data from such a large multicenter study have been published.

Methods: This retrospective study included 3200 DMEKs at seven departments performed for Fuchs endothelial corneal dystrophy (FECD) or bullous keratopathy (BK). We evaluated best corrected visual acuity (BCVA, logMAR), endothelial cell density (ECD, cells/mm^2), minimal corneal thickness (CT, µm), rebubbling-, primary transplant failure- and immune reaction-rate. Changes over time were evaluated by linear mixed models for repeated measures and correlation with case number by center by weighted linear regression.

Results: For patients without vision-limiting comorbidities (74% of all analysed eyes, $n = 2270$), mean BCVA improved from 0.6±0.4 logMAR to 0.2±0.2 logMAR 6 months ($p < 0.001$, $n = 1441$) and 0.1±0.2 logMAR 12 months ($p = 0.001$, $n = 1402$) postoperatively. BK- had a worse BCVA compared to FECD-patients (0.3±0.5 vs. 0.1±0.2 logMAR [$p < 0.001$] at 1 year). ECD declined from 2465±259 cells/mm^2 ($n = 2876$ preoperatively) to 1587±433 cells/mm^2 after 12 months ($p < 0.001$, $n = 1237$). Mean rebubbling rate was 0.4±0.7/eye. 784 eyes (25%) received at least one rebubbling. More rebubblings correlated with a lower ECD, a worse BCVA, a higher CT, and higher transplant failure and rejection rates ($p < 0.001$, $p = 0.013$ for BCVA at 12 months). A single rebubbling did not influence the BCVA ($p = 0.785$). Graft failure rate was 3% ($n = 67$), rejection rate 1.5% ($n = 48$).

Conclusion: Descemet membrane endothelial keratoplasty increases visual acuity with low transplant failure- and rejection-rates. FECD has a better outcome than BK. Since a quarter of all patients need a rebubbling, this should be included in the informed consent. Remarkably, one rebubbling has no influence on the outcome.

KEYWORDS
corneal transplant, Descemet membrane endothelial keratoplasty, rebubbling

Kristina Spaniol, Martin Hellmich, Björn Bachmann and Gerd Geerling equally contributed as first or senior authors to the study.

1 | INTRODUCTION

Since 1998, endothelial keratoplasty has become an increasingly accepted alternative to penetrating keratoplasty for the treatment of corneal endothelial dysfunctions (Price & Price, 2010). The currently most widely practiced techniques are Descemet membrane endothelial keratoplasty (DMEK), a technique for the selective transplantation of Descemet's membrane and endothelium and Descemet's stripping automated endothelial keratoplasty (DSAEK), which includes in addition parts of posterior donor stroma. Current registry studies also focus on ultrathin DSAEK in which the graft thickness is less than 100 µm (Chamberlain et al., 2019; Matsou et al., 2021).

Descemet membrane endothelial keratoplasty was introduced in 2002 by Melles et al. in the Netherlands. Today it has become a routine procedure for corneal endothelial pathologies in Germany (Melles, 2006). Regarding the Netherlands, already in 2018 slightly more DMEKs than DSAEKs were performed (Dunker et al., 2021). In the United States, the number of DMEK procedures performed per year have doubled every year since 2011 and in 2020, 45% of all endothelial keratoplasties were DMEKs while the number of DSAEKs did not further increase since 2013 (Eye Bank Association of America, 2021, Price et al., 2017). In 2016 only 4.4% of all keratoplasties performed in Germany were DSAEKs, while the number of DMEKs had reached 53% of all corneal transplantations, making it the new standard of care for endothelial corneal graft indications (Flockerzi et al., 2018).

A recent report by the American Academy of Ophthalmology reviewed 47 publications on DMEK and concluded, that DMEK was superior to DSAEK with regards to speed of visual recovery, visual outcome and rejection rate (Deng et al., 2018). The included studies showed a broad range regarding follow-up (5.7–68 month), visual acuity outcome (best corrected visual acuity (BCVA) 17%–67% of 20/20 or better), endothelial cell loss (25%–47%) and secondary air injection rate, i.e. rebubbling (0.2%–76%) at 6 months following DMEK. However, the studies analysed were all monocentric apart from one (two centers) and included a maximum of 905 eyes. Only Oellerich et al., (2017) analysed 2485 eyes from 55 centers but also only over a 6-month follow-up. In addition, Dunker et al., (2021) recently performed a registry study analysing all DMEKs performed in the Netherlands between 2011 and 2018 but analysed not more than 752 endothelial keratoplasties. A valuable randomized controlled trial was performed by Chamberlain et al., (2019) comparing DMEK to ultrathin DSAEK but due to the study design only 50 eyes of 38 patients were included. It is therefore still desirable to analyse data from large patient collectives from different DMEK centers with well-designed statistical methods over longer follow-up periods. The study presented here included 3200 eyes from seven centers throughout Germany with a minimum follow-up of 6 months after DMEK and is thus the largest multicenter study on this procedure so far.

2 | MATERIAL AND METHODS

This retrospective analysis included 3200 DMEK surgeries performed at the Departments of Ophthalmology of the Universities Berlin, Cologne, Duesseldorf, Freiburg, Homburg, Leipzig, Tuebingen in Germany before 08/31/2016. A local ethics committee vote was obtained if required. The research adhered to the tenets of the Declaration of Helsinki. Each center included a minimum number of 100 sequential cases, that had undergone DMEK for Fuchs endothelial corneal dystrophy (FECD) or bullous keratopathy (BK) and had a minimum follow-up of 6 months. BK was defined as an epithelial alteration with microcysts and blebs. Cases with FECD and corneal decompensation after cataract surgery were considered as BK. We did not exclude repeated keratoplasties for failed penetrating keratoplasty or previous DMEK. DMEKs with combined cataract surgery were included but phakic eyes were excluded as we wanted to eliminate the impact of lens opacities on the visual acuity outcome during follow-up (Figure 1). All procedures had to be performed by experienced DMEK surgeons, defined as a minimum of 100 previously performed DMEKs.

Data collection was performed using Excel or SPSS datasheets. The centers were pseudonymized by numbers. Surgeons were allowed to prepare the graft before

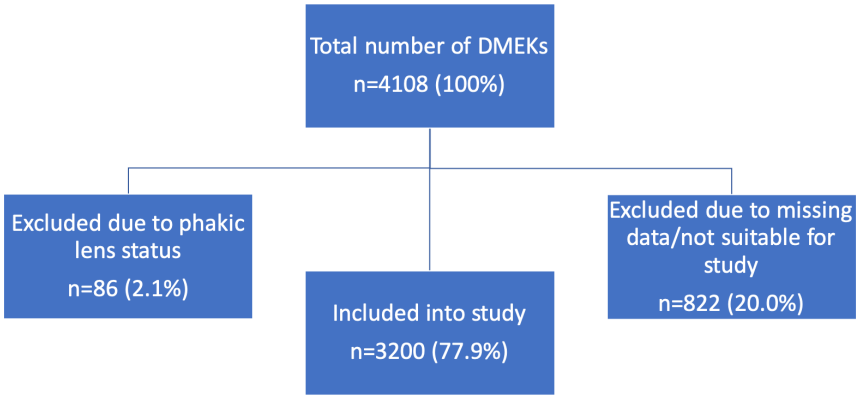

FIGURE 1 Overview of in- and excluded DMEK cases. This study included pseudophakic eyes with the diagnosis of Fuchs endothelial corneal dystrophy or bullous keratopathy. Center 3 did not report the total number of DMEKs so the number of included eyes was counted, center 3 and 6 did not report the number of phakic DMEKs. These were counted as zero. DMEK, descemet membrane endothelial keratoplasty.

or during the procedure and there were no requirements regarding specific surgical details. The study analysed best corrected visual acuity (BCVA, logMAR), endothelial cell density (ECD in cells/mm^2), minimal corneal thickness (CT in µm), rebubbling rate, primary transplant failure rate and rate of immune reactions. BCVA was tested with standard optotypes at 5-m distance. Results were noted in decimal numbers and converted to logMAR for statistical analysis. No specific definition was given for the definition of a transplant failure or an immune reaction. ECD was measured by specular endothelial microscopy and CT by Scheimpflug photography or any other method. Although the devices differed between the centers, each center always used the same method. Follow-up visits were performed six and 12 months after surgery.

2.1 | Missing data

Center five did not provide the patients' age and endothelial cell density, center six did not document the patients' gender, transplant failure and immune rejection rates, and center seven did not specify the number of patients, eyes, reoperations and pachymetry.

Some patients were lost during follow-up, so that the number of eyes analysed per time point decreased over the investigation period. Analysing all eyes including those with extracorneal comorbidities, for BCVA number per time point was $n = 3071$ preoperatively, $n = 2111$ at 6 months and at $n = 2017$ at 12 months. For endothelial cell count it was $n = 2876$ preoperatively, $n = 1384$ at 6 months and at $n = 1237$ at 12 months and for corneal thickness $n = 1405$ preoperatively, $n = 918$ at 6 months and at $n = 802$ at 12 months (Figure 2).

For BCVA, a separate analysis excluding eyes with extracorneal comorbidities was performed. Number per time point was $n = 2270$ preoperatively, $n = 1441$ at 6 months and at $n = 1402$ at 12 months.

2.2 | Statistics

Quantitative variables were summarized by mean ± SD and qualitative variables by count (percentage). Changes in quantitative outcomes over time were evaluated by linear mixed models for repeated measures with fixed effects baseline, time, site and the interaction time*site (type III SS, unstructured covariance matrix), with contrasts based on estimated marginal means. Since mixed models can be fitted to incomplete follow-up data, missing values were not imputed. A few sites failed to deliver all data items required, thus the number of obtained and valid observations is given by variable. Correlation of the number of performed surgeries by site with outcome variables was calculated by weighted linear regression. Results were not corrected for multiple testing. We did not correct our analyses for intraclass correlation (ICC). However, according to Donner et al. *p*-values may easily be corrected to account for an ICC of, say, 0.3 (upper bound) which yields a design effect of 1.3 (=(1+[cluster size-1]*ICC) = 1+(2–1)*0.3). The corresponding test statistics need to be divided by the design effect, and this will change the *p* values from 0.05 to 0.132, from 0.01 to 0.048, and from 0.001 to 0.011, for example (Donner et al., 1981). Thus, to err on the safe side, only p values below 0.01 could be considered "significant" by the cautious reader. Calculations were done with SPSS Statistics (IBM Corp., Armonk, NY, USA) and R (R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

Table 1 gives an overview of the patients' characteristics and surgical procedures performed. Mean patient age was 71 ± 10 years, while the overall male: female ratio was 1:1.31. The number of cases included per center ranged from 106 to 1035 surgeries and surgeries were performed by one to four surgeons per center. The amount of reoperations, meaning a second DMEK surgery in an eye during the study period, ranged between <1% to 4% per center. The indication for surgery was FECD in 2574 cases (83.8%) and BK in 497 cases (16.2%). Six centers used a "touch-technique", which includes touching the graft with forceps during stripping (Kruse et al., 2011; Seitz et al., 2020). Center six applied a "no-touch technique", in which any direct handling of the graft during preparation is avoided. All centers prepared the corneas on the day of the surgery, except center seven, which prepared the corneas 1–2 days prior to surgery.

3.1 | Visual acuity

Twenty-five percent of all cases ($n = 810$) had additional, non-corneal ocular pathologies potentially limiting visual acuity outcome. The number of patients with other ocular comorbidities differed between the centers (Table 2).

Analysing all eyes without excluding vision-limiting comorbidities, for 3071 cases, preoperative data were available, a 6-month follow-up for 2111, and a 12-month follow-up for 2017 surgeries. After 6 month/1 year 21% ($n = 448$)/29% ($n = 582$) achieved a BCVA of 0.0 logMAR or better, 24% ($n = 501$)/26% ($n = 516$) reached a BCVA >0.0–0.1 logMAR, 42% ($n = 885$)/35% ($n = 699$) achieved >0.1–0.5 logMAR and 13% ($n = 277$)/11% ($n = 220$) had a BCVA worse than 0.5 logMAR 1 year after surgery (Table 4). Mean BCVA improved from 0.7 ± 0.5 logMAR before surgery to 0.3 ± 0.4 logMAR at 6 months ($p < 0.001$) and again to 0.2 ± 0.4 logMAR at 12 months ($p = 0.001$).

Excluding eyes with comorbidities (Table S1), mean BCVA improved from 0.6 ± 0.4 logMAR before surgery ($n = 2270$) to 0.2 ± 0.2 logMAR at 6 months ($p < 0.001$, $n = 1441$) and further to 0.1 ± 0.2 logMAR at 12 months ($p = 0.001$, $n = 1402$). Mean BCVA change after 12 months compared to the preoperative value was −0.5 ± 0.02 for center one, three, four and five, −0.4 ± 0.01 for center two, −0.5 ± 0.03 for center six, and −0.4 ± 0.04 for center seven (Figure 2a, Table S1). A comparison between all centers revealed a significantly lower BCVA improvement for center one and seven compared to the mean

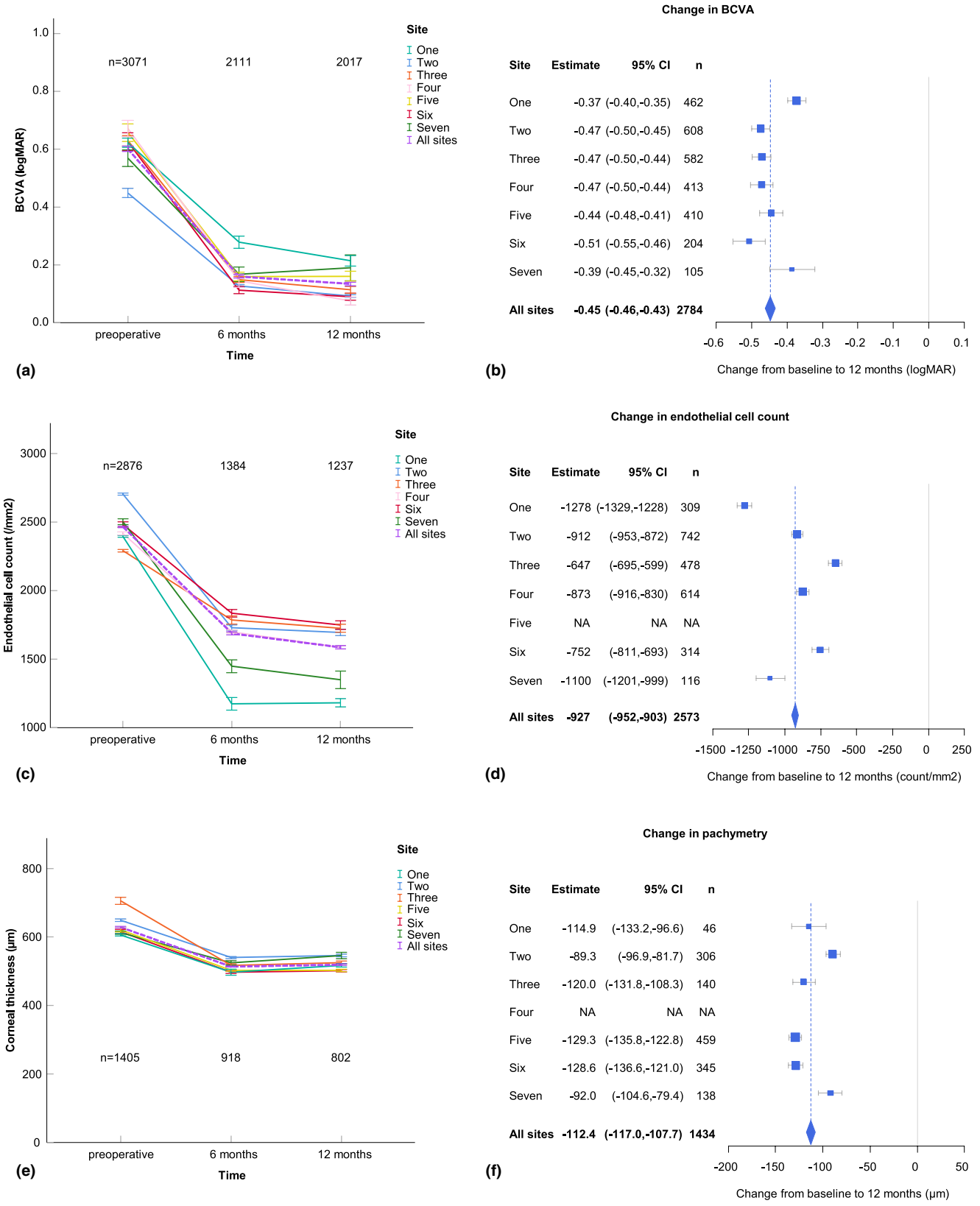

FIGURE 2 Visual acuity and endothelial cell density. Regarding all centers, the best corrected visual acuity significantly increased six and again 12 months after surgery ($p<0.001$ and $p=0.001$, A). Center three and six reported less mean BCVA improvement after 12 months compared to the other centers ($p=0.012$ and $p<0.001$, B). For all centers, the endothelial cell density significantly decreased six and again 12 months after surgery ($p<0.001$ each, C). Center three and six showed a higher mean endothelial cell loss compared to the other centers ($p<0.001$, D), which correlated with a worse BCVA outcome. The corneal thickness significantly decreased 6 months after surgery ($p>0.001$) but slightly increased after 12 months ($p=0.023$, E). Center one and three documented significantly less corneal thinning compared to the other centers ($p<0.001$ each, F).

value ($p = 0.012$ and $p<0.001$). The preoperative BCVA correlated with the BCVA 6 and 12 months after surgery ($p<0.001$, respectively). Regarding eyes without vision-limiting comorbidities, at 6 month/1 year, 29% ($n = 418$)/38% ($n = 537$) achieved 0.0 logMAR or better, 30% ($n = 439$)/31% ($n = 429$) reached a BCVA >0.0–0.1

TABLE 1 Summary of patients' characteristics and surgeries

Center	1	2	3	4	5	6	7	Total
N surgeries	1035	666	462	446	284	201	106	**3200**
N patients	774	586	411	#	206	175	87	#
N eyes	1019	661	459	#	272	200	99	#
N reops (%)	16 (2)	5 (<1)	3 (<1)	#	12 (4)	1 (<1)	7 (7)	#
N surgeons	4	2	1	2	1	3	3	**16**
Age, years (mean ± SD, *n*)	71 ± 10, 1035	70 ± 10, 664	71 ± 11, 461	72 ± 10, 446	73 ± 8, 284	71 ± 8, 201	69 ± 8, 106	**71 ± 10, 3197, $p < 0.001$**
M:F	#	258:406	188:274	197:264	97:187	79:122	47:59	**934:1226, $p = 0.239$**
BCVA, logMAR (mean ± SD, *n*)	0.62 ± 0.48, 918	0.62 ± 0.53, 655	0.73 ± 0.42, 462	0.95 ± 0.70, 446	0.76 ± 0.50, 284	0.68 ± 0.37, 201	0.65 ± 0.40, 105	**0.70 ± 0.52, 3071, $p < 0.001$**
ECD (mean ± SD, *n*)	2396 ± 201, 1026	2705 ± 230, 666	2292 ± 193, 440	2418 ± 230, 446	#	2483 ± 277, 192	2503 ± 224, 106	**2465 ± 259, 2876, $p < 0.00$**
Pachy (mean ± SD, *n*)	606 ± 64, 377	649 ± 66, 366	706 ± 102, 98	#	621 ± 97, 262	616 ± 89, 196	613 ± 49, 106	**629 ± 82, 1405, $p < 0.001$**

p-values describe significance of difference between the centers (Pearson Chi ^{2} test).

Abbreviations: BCVA, preoperative best corrected visual acuity; ECD, donor endothelial cell density; reops, reoperations; M, male; f, female; pachy, pachymetry; #, data not available.

logMAR, 36% (n = 523)/28% (n = 385) of >0.1–0.5 logMAR and only 4% (n = 61)/4% (n = 51) had a BCVA worse than 0.5 logMAR (Table 4).

When analysing eyes without vision limiting comorbidities against all eyes, patients in both groups, gained in BCVA 6 months and 1 year after surgery ($p < 0.001$, respectively). In both groups the preoperative BCVA correlated with postoperative BCVA at 6 and 12 months ($p < 0.001$ all). However, there was no distinct preoperative visual acuity cut off-value, below which the patients did not gain visual acuity postoperatively.

Correlation of age with BCVA was positive at all time points, i.e. Spearman's rho = 0.260 (preoperatively), 0.280 (after 6 months), 0.303 (after 12 months).

Patients with BK had a worse BCVA compared to FECD patients at all time points. Preoperative BCVA was 0.6 ± 0.4 logMAR for FECD versus 1.4 ± 0.8 logMAR for BK patients ($p < 0.001$); 0.2 ± 0.3 logMAR versus 0.56 ± 0.03 logMAR after 6 months ($p < 0.001$) and 0.2 ± 0.3 logMAR versus 0.6 ± 0.7 logMAR after 1 year ($p < 0.001$). Excluding eyes with vision-limiting comorbidities, preoperative BCVA was 0.5 ± 0.3 logMAR for FECD versus 1.0 ± 0.6 logMAR for BK patients ($p < 0.001$); 0.1 ± 0.2 logMAR versus 0.3 ± 0.3 logMAR after 6 months ($p < 0.001$) and 0.1 ± 0.2 logMAR versus 0.3 ± 0.5 logMAR after 1 year ($p < 0.001$).

3.2 | Endothelial cell density

Endothelial cell density declined from 2465 ± 259 cells/mm^2 (n = 2876) to 1688 ± 419 cells/mm^2 after 6 months ($p < 0.001$, n = 1384) and to 1587 ± 433 cells/mm^2 after 12 months ($p < 0.001$, n = 1237) (Figure 2c, Table S1). Mean (estimated margin, ±SE) endothelial cell loss after 12 months was −1278 ± 26 cells/mm^2 (i.e. −53.3%) for center one, −912 ± 21 cells/mm^2 (−33.7%) for center two, −647 ± 24 cells/mm^2 (−28.2%) for center three, −873 ± 22 cells/mm^2 (−36.1%) for center four, −752 ± 30 cells/mm^2 (−30.3%) for center six, and −1100 ± 52 cells/mm^2 (−43.9%) for center seven (Figure 2d, Table S1). The range of endothelial cell loss from baseline was −547.5 to −1084.5 after 6 months and −600.0 to −1189.0 after 12 months. Mean endothelial cell density decrease was 31.8 ± 16.8% after 6 and 35.3 ± 17.1% after 12 months. A comparison showed differences between the centers, as center one and seven documented a higher cell loss ($p < 0.001$). For all centers, a higher endothelial cell density correlated with a better BCVA-outcome after 6 and 12 months ($p < 0.001$).

3.3 | Thinnest corneal thickness

Overall, CT declined from 629 ± 82 µm (n = 1405) preoperatively to 513 ± 52 µm after 6 months ($p < 0.001$, n = 918) and then slightly but significantly increased by 6 µm to 519 ± 53 µm after 12 months ($p = 0.023$, n = 802) (Figure 2e, Table S1). The mean CT decrease was 115 ± 9 µm for center one, 89 ± 4 µm for center two, 120 ± 6 µm for center three, 129 ± 3 µm for center five, 129 ± 4 µm for center six, 92 ± 6 µm for center seven (Figure 2f, Table S1). A

TABLE 2 Transplant failure, graft rejection and extracorneal visual limitations

Center	Primary transplant failure, count (%)	Immune rejection, count (%)	Extracorneal visual impairment, count (%)	*n*
1	#	#	52 (5.0)	1035
2	4 (0.6)	28 (4.2)	287 (43.1)	666
3	14 (3.0)	4 (0.9)	107 (23.2)	462
4	27 (6.1)	7 (1.6)	190 (42.7)	446
5	2 (0.7)	3 (1.1)	68 (24.0)	284
6	3 (1.5)	0 (0)	86 (42.8)	201
7	17 (16.0)	6 (5.7)	20 (18.9)	106
Total; *p* value[a]	67 (3.1); <0.001	48 (1.5); <0.001	810 (25.3); <0.001	

[a]For differences in proportions between centers (Pearson chi-squared test).

TABLE 3 Rebubbling

		Rebubblings (*n*)					
		0	1	2	3	4	
Center		Absolute number (*n*) and percentage amount (%) of rebubblings at each center					Eyes (*n*)
1	*n*	769	212	38	14	2	1035
	%	74.3	20.5	3.7	1.4	0.2	
2	*n*	358	260	38	10	0	666
	%	53.8	39.0	5.7	1.5	0	
3	*n*	300	118	33	9	2	462
	%	64.9	25.5	7.1	1.9	0.4	
4	*n*	303	78	16	5	0	402
	%	75.4	19.4	4.0	1.2%	0	
5	*n*	241	39	1	3	0	284
	%	84.9	13.7	0.4	1.1	0	
6	*n*	159	32	8	1	0	200
	%	74.3	20.5	3.7	1.4	0.2	
7	*n*	43	45	13	4	0	105
	%	41.0	42.9	12.4	3.8	0	
Absolute number (*n*) and percentage amount (%) of rebubblings in total	*n*	2173	784	147	46	4	3154
	%	68.9	24.9	4.7	1.5	0.1	

Note: Differences in the number of eyes compared to table one attribute to missing data.
Data in the bottom row (rebubblings in total) describe crude rates.
Abbreviation: SD, standard deviation.

comparison between all centers revealed less corneal thinning for center two and seven compared to the others ($p<0.001$, both). Regarding all centers, a higher CT correlated negatively with a worse BCVA-outcome after 6 months ($p<0.001$) but not after 12 months ($p = 0.654$) (Figure S1). There was no correlation between preoperative CT and postoperative BCVA.

3.4 | Complications (rebubbling, transplant failure, graft rejection), extracorneal visual limitations

After excluding eyes with vision-limiting comorbidities, mean visual acuity increased from 0.6 ± 0.4 logMAR before surgery to 0.1 ± 0.2 logMAR at 1 year. Stratifying the patients into groups according to their postoperative visual acuity showed that 69% achieved 0.1 logMAR or better at 12 month. This reflects results from Dunker et al., (2021) who recently analysed all DMEKs registered in the Netherlands between 2011 and 2018 ($n = 752$) and found that 67% of the eyes achieved 0.1 logMAR or better 1 year after surgery. Peraza-Nieves et al., (2017) who investigated 500 eyes without ocular comorbidities after DMEK over a 2 year follow-up found that 81% of all eyes reached a visual acuity of 0.1 logMAR and better, which is superior to our results from 3200 DMEK surgeries. This may also be due to the fact that monocentric studies often achieve better results than those including multiple different centers. Accordingly, a review by the American Academy of Ophthalmology found that the number of eyes gaining a BCVA between 0.2 and 0 logMAR ranges between 37.6% to 85% including patients with a follow-up from 5.6 to 68 months (Deng et al., 2018). Compared to these data our cohort shows an above-average visual acuity

outcome. Only 4% of the eyes in this study had a BCVA worse than 0.5 logMAR after a 12-month follow-up. Therefore, our results from a large cohort support that DMEK reliably and substantially increases visual acuity.

Overall, 67.9% of all eyes (n = 2173) did not require a rebubbling. Seven hundred eighty-four eyes (24.9%) received one, 147 eyes (4.6%) two, 46 eyes (1.4%) three and four eyes (0.1%) four rebubblings (Table 3). The number of rebubblings correlated with a lower ECD, a worse BCVA and a higher CT, at 6 and 12 months and higher transplant failure and rejection rate (p each <0.001, p = 0.013 for BVCA at 12 months). A post hoc analysis revealed a significantly worse visual acuity outcome when two or more rebubblings were performed (p<0.001) compared to eyes without rebubbling. One rebubbling did not influence the postoperative BCVA (p = 0.785). For CT and ECD no post hoc testing was performed due to too few cases in these groups as not all centers documented these parameters. Also, the overall number of transplant failures (3%, n = 67) and rejections (1.5%, n = 48) was too low to perform a post hoc testing. There was no statistically significant relationship between the preoperative donor endothelial cell density and the frequency of rebubbling (R = 0.034, p = 0.070). Further, there was no relevant difference in the number of rebubblings in DMEKs with and without complications other than transplant failure and immune rejection, e.g. 72.5% with rebubbling vs. 71.9% of DMEKs without rebubbling (p = 0.910).

A primary graft failure occurred in 3% of the eyes (n = 67), while 2096 eyes (97%) did not show a graft failure (Table 2). The failure rates ranged between 0.6% and 3%, while center four and seven documented higher failure rates of 16% and 6%, respectively.

We found an overall immune rejection-rate of 1.5% (n = 48). Center two and seven documented slightly higher rejection rates of 4.2% and 5% while the rates ranged between 0% and 1.6% for the other centers (Table 2).The number of patients with extracorneal vision-limiting comorbidities ranged between 5% (center one) to 43% (center two, six and four; Table 2). At center three, five and seven between 19% to 25% of the patients had extracorneal pathologies.

Overall, the center differences remained statistically significant for change in BCVA, endothelial cell count, and mean corneal thickness (p<0.001 for each of the three outcomes), when the baseline value, extracorneal vision limiting co-morbidities and age were considered as possible confounders.

4 | DISCUSSION

4.1 | Visual acuity

After excluding eyes with vision-limiting comorbidities, mean visual acuity increased from 0.6±0.4 logMAR before surgery to 0.1±0.2 logMAR at 1 year. Stratifying the patients into groups according to their postoperative visual acuity showed that 69% achieved 0.1 logMAR or better at 12 month. This reflects results from Dunker et al., (2021) who recently analysed all DMEKs registered in the Netherlands between 2011 and 2018 (n = 752) and found that 67% of the eyes achieved 0.1 logMAR or better 1 year after surgery. Peraza-Nieves et al., (2017) who investigated 500 eyes without ocular comorbidities after DMEK over a 2 year follow-up found that 81% of all eyes reached a visual acuity of 0.1 logMAR and better, which is superior to our results from 3200 DMEK surgeries. This may also be due to the fact that monocentric studies often achieve better results than those including multiple different centers. Accordingly, a review by the American Academy of Ophthalmology found that the number of eyes gaining a BCVA between 0.2 and 0 logMAR ranges between 37.6% to 85% including patients with a follow-up from 5.6 to 68 months (Deng et al., 2018). Compared to these data our cohort shows an above-average visual acuity outcome. Only 4% of the eyes in this study had a BCVA worse than 0.5 logMAR after a 12-month follow-up. Therefore, our results from a large cohort support that DMEK reliably and substantially increases visual acuity.

Including eyes with vision-limiting comorbidities revealed slightly different results as only 55% of the eyes reached a BCVA of 0.1 logMAR or better and 11% achieved a visual acuity worse than 0.5 logMAR. Although the group containing patients with extracorneal vision-limiting comorbidities had a significantly worse visual acuity compared to patients without those comorbidities, patients in both groups significantly benefited from DMEK. Therefore, DMEK also seems to be beneficial for patients with extracorneal vision-limiting comorbidities, as previously already reported for patients with retinal pathologies (Spaniol et al., 2016).

4.2 | Influence of preoperative BCVA

Our results showed that the preoperative visual acuity correlated with the visual acuity six and 12 months after surgery, irrespective of investigating patients with or without extracorneal vision-limiting comorbidities. Patients without extracorneal visual limitations had a BCVA of 0.6±0.4 logMAR preoperatively and 0.1±0.2 logMAR 6 months postoperatively (p<0.001), which is similar to results by Guerra et al. (2011) and Tourtas et al. (2012). However, a retrospective study by Phillips et al., (2017) investigated eyes, which had a significantly better preoperative BCVA of 0.3 logMAR. Six months postoperatively 54% reached a BCVA ≤0 logMAR (n = 64). In our cohort, only 29% (418/1442) reached a BCVA ≤0 logMAR 6 months postoperatively. Therefore, our findings suggest that the preoperative visual acuity influences the postoperative outcome and patients who present with a reduced visual acuity should be informed that the visual acuity outcome may be limited.

Another possibility may be that surgeons do not wait to perform DMEK until the visual acuity drops but perform surgery earlier. This has also been suggested by Schrittenlocher et al., (2019), who found that patients with a preoperative BCVA below 0.7 logMAR have a significantly worse visual acuity outcome after DMEK. However, according to our data, there was no distinct

TABLE 4 Visual acuity-outcome for eyes with and without vision-limiting comorbidities

Examination	Absolute number (*n*) and percentage amount (%)	BCVA ≤0		BCVA >0 & ≤0.1		BCVA >0.1 & ≤0.5		BCVA >0.5		Total number of investigated eyes	
		a	b	a	b	a	b	a	b	a	b
pre-operative	*n*	3	2	26	21	1462	1251	1580	996	3071	2270
	%	0.1	0.1	0.8	0.9	47.6	55.1	51.4	43.9	100	100
6 months postop.	*n*	448	418	501	439	885	523	277	61	2111	1441
	%	21.2	29.0	23.7	30.4	41.9	36.3	13.1	4.2	100	100
12 months postop.	*n*	582	537	516	429	699	385	220	51	2017	1402
	%	28.9	38.3	25.6	30.6	34.7	27.5	10.9	3.6	100	100

Note: Differences in the number of eyes compared to table one attribute to missing data. a, Including eyes with vision-limiting comorbidities; b, Excluding eyes with vision-limiting comorbidities.

Abbreviation: BCVA, best corrected visual acuity in logMAR.

BCVA cut-off value indicating which preoperative BCVA DMEK was still beneficial for the patient or not.

4.3 | Indication for surgery

Most patients in our study received DMEK because of FECD (84%), while 16% were performed for BK. In a study by Ham et al. the indication for DMEK was significantly associated with the BCVA-outcome as FECD patients had a better postoperative BCVA compared to patients with BK ($p = 0.0016$). This has also been described by Heinzelmann et al. (2016) Oellerich et al. (2017). We found similar results as FECD patients had a highly significantly better BCVA preoperatively and at both postoperative time points compared to BK-patients ($p < 0.001$ at all time points). Excluding eyes with vision-limiting comorbidities, FECD patients achieved around 0.1 logMAR BCVA while BK patients only reached 0.3 logMAR 1 year after surgery. Peraza-Nieves et al. (2017) also found that the BCVA in FECD patients was on average 0.16 logMAR better than in BK patients. This can be explained by stromal corneal alterations resulting from prolonged corneal edema, which limits the visual acuity outcome after DMEK or complex ocular comorbidities associated with prior surgery (Spaniol et al., 2016). Although BK patients significantly gained visual acuity from 1.4 to 0.5 logMAR after surgery in our cohort, this would not qualify for driving a car, which in Germany requires a BCVA of at least 0.3 logMAR. This is an important quality of life impairment. Thus, BK patients should be investigated in detail for stromal scars and the visual acuity-potential assessed preoperatively.

4.4 | Endothelial cell loss

Reviewing the current literature, endothelial cell loss after DMEK ranges between 19% and 53% in a follow-up period from 6 to 68 months (Deng et al., 2018). In accordance with these data, we found a mean overall cell loss of 35% after 12 months. However, there were differences between the individual centers as center one and seven documented significantly higher cell losses than the mean. In our large cohort, we found that the endothelial cell density correlated with the visual acuity outcome after DMEK and center one and seven, which had a lower postoperative endothelial cell density, had a worse visual acuity outcome compared to the other centers. Interestingly, the preoperative cell density of these two centers did not significantly differ from the mean. Thus, intra- or postoperative parameters are most likely responsible for the above-average cell loss.

Preparation of the DMEK graft causes stress to the endothelial cells. Livny et al., (2017) compared a traditional "touch-technique", which includes stripping using forceps before and after trephination of the central DM with a technique, which avoids directly touching the graft and did not find a significantly different endothelial cell loss. In our cohort, all centers apart from center six used a touch-technique so that the preparation technique does not explain the increased cell loss of centers one and seven.

4.5 | Corneal thickness

The corneal thickness decreased significantly over 6 months in our cohort. Investigating 500 eyes after DMEK, Peraza-Nieves et al. (2017) found that patients with a high preoperative corneal thickness had a worse visual acuity outcome and that this correlation was still evident 2 years postoperatively. In our cohort, we did not find a correlation between the preoperative pachymetry results and the postoperative BCVA at 6 and 12 months. According to our data patients with a more severe preoperative corneal edema as well as those with milder pathology benefitted from DMEK.

4.6 | Rebubbling

The most common complication after DMEK is a partial graft detachment, which can resolve spontaneously or require a second air or gas injection into the anterior chamber (rebubbling). In the current literature, the rebubbling rate ranges between 0.2% and 76% with a mean of 28.8% (Deng et al., 2018). In our multicenter cohort, a single rebubbling was required in 14%–43% of cases with

a mean of 24.5% (n = 784). Rebubbling was, therefore, a common secondary surgery after DMEK so that we recommend informing each patient prior to DMEK about the potential necessity to rebubble.

In this retrospective analysis no criteria were defined indicating when to rebubble. This may explain the varying rebubbling rates of the centers. We also did not analyse the detachment sizes previous to the rebubblings. Therefore it is possible that in some centers a rebubbling was already performed for small peripheral detachments. Peripheral graft detachments of less than 1/3 of the graft are known to usually attach spontaneously within 6 months. It is likely that centers with a lower rebubbling rate probably more often used this "watch and wait"-strategy (Dirisamer et al., 2012). Also, the use of 20% sulfur hexafluoride (SF6) instead of air was shown to reduce the rebubbling rate to about 16% in a large retrospective study including 1340 eyes (Schrittenlocher et al., 2018). However, we did not analyse the impact of different tamponades here.

A second rebubbling was only performed in about 5% and a third only in 1% of the eyes. Only two centers performed four rebubblings, but each center in less than 1% of the eyes (n = 2 each center). This indicates that the first rebubbling is usually sufficient to achieve adequate graft attachment or that the surgeons do not consider a second or third rebubbling to be successful. Interestingly our data also showed, that the second rebubbling was correlated with a significantly worse visual acuity after 12 months while only one rebubbling did not negatively influence the outcome.

The influence of rebubbling on the endothelial cella loss is conflicting. Most authors define rebubblings as a risk factor for an increased cell loss (Gerber-Hollbach et al., 2017) (Hayashi et al., 2020) (Agha et al., 2021). Grundlach et al. analysed 463 eyes and found a significant cell loss after only one rebubbling (157 cells/mm^2) but cell loss was more than three times higher after more than one rebubbling (504 cells/mm^2) (Gundlach et al., 2020). In contrast, Siebelmann et al. investigated 1541 DMEKs with 499 rebubblings and found no influence on the endothelial cell loss. According to our data only the fourth rebubbling, which was required in four cases (0.1%, Table 3), correlated with a significantly higher cell loss. However, these cases may also underlie a selection bias and have been more "complicated" eyes during DMEK.

Feng et al. (2014) speculated that transplants with an initially low cell count may more often require a rebubbling due to inferior quality. In our cohort, the preoperative endothelial cell count showed a borderline non-significant correlation with the postoperative rebubbling rate so that our data do not clearly support or reject this hypothesis. In addition, other authors found that the early postoperative cell count seems to be a more important risk for a transplant failure so that the perioperative cell loss should be kept as low as possible (Vasiliauskaitė et al., 2021).

As rebubbled eyes also had a higher risk for an immune rejection, one should keep the number of rebubblings low. However, we did not clearly define the clinical signs for immune rejection. Also, the number of immune rejections was too low to perform post-hoc testing, which limits the significance of this finding. Moreover, the postoperative corticosteroid therapy can impact the immune rejection rate and the therapy regimes were not analysed in this study (Schaub et al., 2019). Reasons for the higher incidence of immune rejections in rebubbled eyes are not yet known. It is possible that the repeated surgical manipulation triggered an increased immune response. In summary, our findings are important for the surgeon as well as the patient, as according to our data 95% of all patients who ever receive a rebubbling do only need one rebubbling and this rebubbling will not affect the BCVA outcome.

4.7 | Limitations

This study has certain limitations. We did not give definitions for transplant failure and immune rejection and we did not define at which detachment size a rebubbling was indicated. It is therefore possible, that detached grafts were defined as failures or the other way around (Oellerich et al., 2017). Also, there was no fix postoperative corticosteroid regimen. This might have impacted the immune rejection rate.

This is a retrospective analysis so the data assessment did not follow the same regimen at each center; e.g. we did not specify certain devices for the measurements of corneal thickness and endothelial cell count. A confounding factor that could not further be analysed but might have contributed to outcome differences between the participating centers regarding the endothelial cell count were variants in preparation techniques within the forceps-guided techniques used by six centers.

To overcome the limitations of our retrospective design we aimed to include all consecutive surgeries by study center in a defined time period. We stratified our analyses by the study center, thus reducing variability due to heterogenous outcome definitions and the use of different devices, thus increasing statistical power. Results should be interpreted in a meta-analytic type manner (i.e. based on fixed effects by study center). We applied (linear) mixed models for repeated measures, which are widely considered to yield reasonable results even in the presence of data missing at random, even with slight departures of this assumption. Further, all surgeons participating in this study were highly experienced, prohibiting meaningful analysis of surgical experience on outcome.

5 | CONCLUSIONS

In this largest retrospective multicenter study so far we found that DMEK reliably increases visual acuity with low transplant failure and rejection rates. Patients with FECD show better BCVA outcomes than those with BK. Patients with extracorneal comorbidities significantly benefit from DMEK and represent a patient group, which needs to be investigated in more detail. Twenty-five percent of all DMEK patients (n = 784) required one rebubbling, which did not affect cell density and visual

acuity during the 12 months follow-up. Repeated rebubblings may indicate a higher risk of endothelial cell loss and graft failure. The number of grafts transplanted per center was not associated with a different outcome, probably as a result of the fact that only experienced corneal surgeons were included. Based on this large multicenter study in Germany DMEK is now considered standard of care for treating corneal endothelial dysfunction.

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CONFLICT OF INTEREST

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ORCID

Kristina Spaniol https://orcid.org/0000-0003-2560-7960
Philip Maier https://orcid.org/0000-0003-4549-3585
Anna-Karina Maier https://orcid.org/0000-0002-8095-0254
Silvia Schrittenlocher https://orcid.org/0000-0001-6090-6777

REFERENCES

Agha, B., Forster, R., Kohnen, T. & Schmack, I. (2021) Influence of rebubbling on anterior segment parameters and refractive outcomes in eyes with DMEK for Fuchs endothelial dystrophy. *Graefe's Archive for Clinical and Experimental Ophthalmology*, 259, 3175–3183.

Chamberlain, W., Lin, C.C., Austin, A., Schubach, N., Clover, J., SD, M.L. et al. (2019) Descemet endothelial thickness comparison trial: A randomized trial comparing ultrathin descemet stripping automated endothelial keratoplasty with descemet membrane endothelial keratoplasty. *Ophthalmology*, 126, 19–26.

Deng, S.X., Lee, W.B., Hammersmith, K.M., Kuo, A.N., Li, J.Y., Shen, J.F. et al. (2018) Descemet membrane endothelial keratoplasty: Safety and outcomes: A report by the American Academy of Ophthalmology. *Ophthalmology*, 125, 295–310.

Dirisamer, M., van Dijk, K., Dapena, I., Ham, L., Oganes, O., Frank, L.E. et al. (2012) Prevention and management of graft detachment in descemet membrane endothelial keratoplasty. *Archives of Ophthalmology*, 130, 280–291.

Donner, A., Birkett, N. & Buck, C. (1981) Randomization by cluster. Sample size requirements and analysis. *American Journal of Epidemiology*, 114, 906–914.

Dunker, S.L., Veldman, M.H.J., Winkens, B., van den Biggelaar, F.J.H.M., Nuijts, R.M.M.A., Kruit, P.J. et al. (2021) Real-World Outcomes of DMEK: A Prospective Dutch registry study. *American Journal of Ophthalmology*, 222, 218–225.

Eye Bank Association of America. (2021) EBAO 2020 eye banking statistical report. Personal communication 23rd September 2021.

Feng, M.T., Price, M.O., Miller, J.M. & Price, F.W.J. (2014) Air reinjection and endothelial cell density in Descemet membrane endothelial keratoplasty: Five-year follow-up. *Journal of Cataract and Refractive Surgery*, 40, 1116–1121.

Flockerzi, E., Maier, P., Böhringer, D., Reinshagen, H., Kruse, F. & Cursiefen, C. . (2018) Trends in corneal transplantation from 2001 to 2016 in Germany: A report of the DOG-section cornea and its keratoplasty registry. *American Journal of Ophthalmology*, 188, 91–98.all GKRC

Gerber-Hollbach, N., Baydoun, L., López, E.F., Frank, L.E., Dapena, I., Liarakos, V.S. et al. (2017) Clinical outcome of rebubbling for graft detachment after descemet membrane endothelial keratoplasty. *Cornea*, 36, 771–776.

Guerra, F.P., Anshu, A., Price, M.O., Giebel, A.W. & Price, F.W. (2011) Descemet's membrane endothelial keratoplasty: prospective study of 1-year visual outcomes, graft survival, and endothelial cell loss. *Ophthalmology*, 118, 2368–2373.

Gundlach, E., Pilger, D., Dietrich-Ntoukas, T., Joussen, A.M., Torun, N. & Maier, A.B. (2020) Impact of Re-bubbling after descemet membrane endothelial keratoplasty on long-term results. *Current Eye Research*, 46, 1–5.

Hayashi, T., Schrittenlocher, S., Siebelmann, S., Le, V.N.H., Matthaei, M., Franklin, J. et al. (2020) Risk factors for endothelial cell loss after Descemet membrane endothelial keratoplasty (DMEK). *Scientific Reports*, 10, 11086.

Heinzelmann, S., Böhringer, D., Eberwein, P., Reinhard, T. & Maier, P. (2016) Outcomes of Descemet membrane endothelial keratoplasty, Descemet stripping automated endothelial keratoplasty and penetrating keratoplasty from a single centre study. *Graefe's Archive for Clinical and Experimental Ophthalmology*, 254, 515–522.

Kruse, F.E., Laaser, K., Cursiefen, C., Heindl, L.M., Schlotzer-Schrehardt, U., Riss, S. et al. (2011) A stepwise approach to donor preparation and insertion increases safety and outcome of Descemet membrane endothelial keratoplasty. *Cornea*, 30, 580–587.

Livny, E., Groeneveld-van Beek, E.A., Lie, J.T., Mangundap, K.M., Bruinsma, M., Birbal, R.S. et al. (2017) Minimizing graft preparation failure in descemet membrane endothelial keratoplasty. *Cornea*, 36, 1452–1457.

Matsou, A., Pujari, R., Sarwar, H., Rana, M., Myerscough, J., Thomson, S.M. et al. (2021) Microthin descemet stripping automated endothelial keratoplasty versus descemet membrane endothelial keratoplasty: A randomized clinical trial. *Cornea*, 40, 1117–1125.

Melles, G.R. (2006) Posterior lamellar keratoplasty: DLEK to DSEK to DMEK. *Cornea*, 25, 879–881.

Oellerich, S., Baydoun, L., Peraza-Nieves, J., Ilyas, A., Frank, L., Binder, P.S. et al. (2017) Multicenter study of 6-month clinical outcomes after descemet membrane endothelial keratoplasty. *Cornea*, 36, 1467–1476.

Peraza-Nieves, J., Baydoun, L., Dapena, I., Ilyas, A., Frank, L.E., Luceri, S. et al. (2017) Two-year clinical outcome of 500 consecutive cases undergoing descemet membrane endothelial keratoplasty. *Cornea*, 36, 655–660.

Phillips, P.M., Phillips, L.J., Muthappan, V., Maloney, C.M. & Carver, C.N. (2017) Experienced DSAEK surgeon's transition to DMEK: outcomes comparing the last 100 DSAEK surgeries with the first 100 DMEK surgeries exclusively using previously published techniques. *Cornea*, 36, 275–279.

Price, M.O., Gupta, P., Lass, J. & Price, F.W. (2017) EK (DLEK, DSEK, DMEK): New Frontier in Cornea Surgery. *Annu Rev Vis Sci*, 3, 69–90.

Price, M.O. & Price, F.W.J. (2010) Endothelial keratoplasty - a review. *Clinical & Experimental Ophthalmology*, 38, 128–140.

Schaub, F., Bachmann, B.O., Cursiefen, C. & Hos, D. (2019) Midterm follow-up of immune reactions after Descemet membrane endothelial keratoplasty (DMEK).[letter]. *Graefe's Archive for Clinical and Experimental Ophthalmology*, 257(8), 1811–1812.

Schrittenlocher, S., Bachmann, B., Tiurbe, A.M., Tuac, O., Velten, K., Schmidt, D. et al. (2019) Impact of preoperative visual acuity on descemet membrane endothelial keratoplasty (DMEK) outcome. *Graefe's Archive for Clinical and Experimental Ophthalmology*, 257, 321–329.

Schrittenlocher, S., Schaub, F., Hos, D., Siebelmann, S., Cursiefen, C. & Bachmann, B. (2018) Evolution of consecutive descemet membrane endothelial keratoplasty outcomes throughout a 5-year period performed by two experienced surgeons. *American Journal of Ophthalmology*, 190, 171–178.

Seitz, B., Daas, L., Flockerzi, E. & Suffo, S. (2020) Descemet membrane endothelial keratoplasty DMEK - Donor and recipient step by step. *Der Ophthalmologe*, 117, 811–828.

Spaniol, K., Holtmann, C., Schwinde, J.H., Deffaa, S., Guthoff, R. & Geerling, G. (2016) Descemet-membrane endothelial keratoplasty in patients with retinal comorbidity-a prospective cohort study. *International Journal of Ophthalmology*, 9, 390–394.

Tourtas, T., Laaser, K., Bachmann, B.O., Cursiefen, C. & Kruse, F.E. (2012) Descemet membrane endothelial keratoplasty versus descemet stripping automated endothelial keratoplasty. *American Journal of Ophthalmology*, 153, 1082–90.e2.

Vasiliauskaitė, I., Quilendrino, R., Baydoun, L., van Dijk, K., Melles, G.R.J. & Oellerich, S. (2021) Effect of six-month postoperative endothelial cell density on graft survival after descemet membrane endothelial keratoplasty. *Ophthalmology*, 128, 1689–1698.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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