Descemet Membrane Endothelial Keratoplasty versus Ultrathin Descemet Stripping Automated Endothelial Keratoplasty

A Multicenter Randomized Controlled Clinical Trial

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Purpose: To compare best spectacle-corrected visual acuity (BSCVA), endothelial cell density (ECD), refractive astigmatism, and complications after Descemet membrane endothelial keratoplasty (DMEK) and ultrathin Descemet stripping automated endothelial keratoplasty (UT-DSAEK).

Design: Prospective, multicenter randomized controlled trial.

Participants: Fifty-four pseudophakic eyes of 54 patients with corneal endothelial dysfunction resulting from Fuchs endothelial corneal dystrophy were enrolled in 6 corneal centers in The Netherlands.

Methods: Participants were allocated to DMEK (n = 29) or UT-DSAEK (n = 25) using minimization randomization based on preoperative BSCVA, recipient central corneal thickness, gender, age, and institution. Donor corneas were prestripped and precut for DMEK and UT-DSAEK, respectively. Six corneal surgeons participated in this study.

Main Outcome Measures: The primary outcome measure was BSCVA at 12 months after surgery.

Results: Central graft thickness of UT-DSAEK lamellae measured 101 μm (95% confidence interval [CI], 90−112 μm). Best spectacle-corrected visual acuity did not differ significantly between DMEK and UT-DSAEK groups at 3 months (0.15 logarithm of the minimum angle of resolution [logMAR] [95% CI 0.08−0.22 logMAR] vs. 0.22 logMAR [95% CI 0.16−0.27 logMAR]; $P = 0.15$), 6 months (0.11 logMAR [95% CI 0.05−0.17 logMAR] vs. 0.16 logMAR [95% CI 0.12−0.21 logMAR]; $P = 0.20$), and 12 months (0.08 logMAR [95% CI 0.03−0.14 logMAR] vs. 0.15 logMAR [95% CI 0.10−0.19 logMAR]; $P = 0.06$). Twelve months after surgery, the percentage of eyes reaching 20/25 Snellen BSCVA was higher in DMEK compared with UT-DSAEK (66% vs. 33%; $P = 0.02$). Endothelial cell density did not differ significantly 12 months after DMEK and UT-DSAEK (1870 cells/mm^2 [95% CI 1670−2069 cells/mm^2] vs. 1612 cells/mm^2 [95% CI 1326−1898 cells/mm^2]; $P = 0.12$). Both techniques induced a mild hyperopic shift (12 months: +0.22 diopter [D; 95% CI −0.23 to 0.68 D] for DMEK vs. +0.58 D [95% CI 0.13−1.03 D] for UT-DSAEK; $P = 0.34$).

Conclusions: Descemet membrane endothelial keratoplasty and UT-DSAEK did not differ significantly in mean BSCVA, but the percentage of eyes achieving 20/25 Snellen vision was significantly higher with DMEK. Endothelial cell loss did not differ significantly between the treatment groups, and both techniques induced a minimal hyperopic shift. *Ophthalmology 2020;127:1152-1159 © 2020 by the American Academy of Ophthalmology*

Descemet membrane endothelial keratoplasty (DMEK) is the latest iteration in endothelial keratoplasty. The primary advantage of DMEK over previous techniques has been suggested to be superior visual recovery.[1] Consequently, corneal surgeons are increasingly adopting DMEK for the treatment of corneal endothelial dysfunction.[2] Currently, a lack of consensus exists regarding the definition of Descemet stripping automated endothelial keratoplasty (DSAEK) at various thicknesses. In line with our previous randomized controlled trial (RCT) comparing ultrathin DSAEK (UT-DSAEK) and DSAEK and a large prospective series of UT-DSAEK by Busin et al,[3] we defined ultrathin as DSAEK grafts with intended central graft thickness of 100 μm.[4]

In 4 meta-analyses, DMEK showed superior best spectacle-corrected visual acuity (BSCVA) compared with DSAEK,[5−8] but studies comparing DMEK with UT-DSAEK are scarce. A single RCT reported superior BSCVA

after DMEK compared with UT-DSAEK.[9] However, in that RCT, 70% of corneal transplantations were combined with cataract extraction and intraocular lens placement (triple procedure), which hinders attributing visual recovery to corneal transplantation only. Both eyes of 12 patients were enrolled in the study, leading to a dependency between eyes, and the visual recovery in the UT-DSAEK arm was reduced in the first 6 postoperative months compared with previous studies assessing UT-DSAEK.[3,4,10] The purpose of the current RCT was to compare BSCVA, endothelial cell density (ECD), refraction, and complications of DMEK versus UT-DSAEK in pseudophakic eyes with Fuchs endothelial corneal dystrophy in a multicenter setting.

Methods

This study was conducted at 6 corneal clinics in The Netherlands. The study received approval from the medical ethics committee of the Maastricht University Medical Center, Maastricht, The Netherlands and was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all patients. Patients were recruited between November 2016 and November 2017. The trial was registered in the United States trial register as the DMEK versus DSAEK Study (Clinical-Trials.gov identifier, NCT02793310).

Inclusion criteria were pseudophakic adult patients with corneal endothelial dysfunction resulting from Fuchs endothelial corneal dystrophy. Exclusion criteria were previous corneal transplantation in the study eye, vision-limiting comorbidities, the need for a human leukocyte antigen-typed corneal transplantation, or the inability to comply with study procedures or complete the follow-up. No triple procedures were performed, and only 1 eye per patient was enrolled.

Each participant's medical history was recorded, and all eligible patients underwent a comprehensive ophthalmic examination including slit-lamp examination, manifest refraction, BSCVA using an Early Treatment Diabetic Retinopathy Study letter chart (Vector Vision, Greenville, OH), Scheimpflug tomography (Pentacam HR; Oculus Optikgeräte GmbH, Wetzlar, Germany), specular microscopy (SP-3000; Topcon, Nagoya, Japan), posterior segment OCT (Spectralis; Heidelberg Engineering GmbH, Heidelberg, Germany), and anterior segment OCT (Casia SS-1000; Tomey, Nagoya, Japan).

Donor Preparation

Descemet membrane endothelial keratoplasty and UT-DSAEK grafts were prepared by a single eye bank (ETB-BISLIFE, Leiden, The Netherlands), except for 1 DMEK graft prepared by the surgeon during surgery. The selection criteria for donor corneas were identical between DMEK and UT-DSAEK. All donor tissues were preserved in organ culture.[4] For DMEK, grafts were peeled manually by trained eye bank technicians, sparing a peripheral hinge of 10%.[11] No grafts were prestamped. For UT-DSAEK, graft dissection was performed with the Gebauer SLc microkeratome system (Gebauer Medizintechnik GmbH, Neuhausen, Germany) using a single-pass technique,[12] targeted at a central residual graft thickness of 100±20 μm. Central corneal graft thickness was assessed by anterior segment OCT (Casia SS-1000) immediately after dissection. All grafts measured 8.5 mm in diameter except for 7 UT-DSAEK grafts with a diameter of 8 mm. Corneoscleral buttons were shipped to the medical center in transport medium supplemented with 6% dextran (Sigma Aldrich, St. Louis, MO) 1 day before surgery.

Surgical Procedure

All surgical procedures were performed by experienced corneal surgeons (M.C.B., S.N., R.M.M.A.N., M.L.T., R.H.J.W., and R.P.L.W.) who completed hundreds of DSAEK and UT-DSAEK procedures and at least 25 DMEK procedures before inclusion began. The corneal surgeons were allowed to use their preferred surgical technique for DMEK and UT-DSAEK. Forty-three patients underwent neodymium:yttrium−aluminum−garnet laser iridotomy before surgery. The remaining 10 patients underwent preoperative surgical iridectomy. In DMEK and UT-DSAEK, 2.8-mm and 4.5-mm corneal incisions were made, respectively. Descemetorhexis was performed with a reversed Price-Sinskey hook (Moria, Antony, France) under air (DMEK, n = 15; UT-DSAEK, n = 15) or viscoelastic substance (Healon; Abbott Medical, Uppsala, Sweden; DMEK, n = 14; UT-DSAEK, n = 10). Descemet membrane endothelial keratoplasty grafts were stained with trypan blue (Vision Blue; Dutch Ophthalmic USA, Exeter, NH) and injected into the anterior chamber of the recipient using a Geuder shooter (n = 27) or DORC glass pipette (n = 2). External corneal tapping was used to unfold and position the graft. UT-DSAEK grafts were inserted using a Busin glide (n = 12), Tan Endo glide (n = 9), or Macaluso reusable injector (n = 4). A full anterior chamber fill was performed between 8 and 15 minutes using air in UT-DSAEK cases and either 10% to 20% sulfur hexafluoride (SF6; n = 17) or air (n = 12) in DMEK. Afterward, the size of the gas bubble was reduced to 80%. An occlusive patch was applied, and the patients were asked to remain in a supine position for the first 24 hours after surgery. After surgery, both treatment arms received topical dexamethasone 0.1% eye drops (Ratiopharm, Zaandam, The Netherlands) and topical chloramphenicol 0.5% eye drops (Ratiopharm). Anterior chamber tamponade reinjections (rebubblings) were performed in cases of corneal edema caused by large, central, or complete graft detachments.[13]

Outcome Measures

The primary outcome measure was high-contrast BSCVA. Secondary outcome measures were ECD, refraction, and complications. A certified optometrist determined manifest refraction using a cross-cylinder technique for cylinder refinement. The BSCVA was recorded using the Early Treatment Diabetic Retinopathy Study letter chart at 4 m under mesopic ambient lighting conditions. The letter score was converted to the logarithm of the minimum angle of resolution (logMAR) units as follows: the log score of the last row where the patient identified all letters correctly was recorded, and 0.02 log units were subtracted for every letter that was identified correctly beyond the last row. Refractive shift was defined as the difference in postoperative spherical equivalent compared with baseline values. Donor ECD was determined at the eye bank by manual cell count using a light microscope after trypan blue staining to improve mosaic visualization. Postoperative ECD was assessed by specular microscopy. Using the corner method,[14] technicians at each site defined manually, if possible, a minimum of 50 endothelial cells of the central cornea. To reduce sampling error, the ECDs of 3 photographs were averaged.

Sample Size

The power calculation was based on the expected difference of 0.2 logMAR with a standard deviation of 0.2 logMAR between DMEK and UT-DSAEK. Assuming an α of 0.05 (2-sided), a power of 90%, and 15% loss to follow-up, at least 25 patients were required per treatment arm. Four to 5 patients were allocated per

treatment arm per center. The number of inclusions per center was not limited, and inclusion was closed when the target was reached.

Randomization and Blinding

Minimization randomization was performed centrally by an investigator from the coordinating center using a random sequence generator (Trans European Network for Clinical Trials Services; www.tenalea.net). Minimization was based on preoperative Early Treatment Diabetic Retinopathy Study BSCVA, recipient central corneal thickness, gender, age, and recruitment center. The randomization result was sent to the eye bank and the operating surgeon. Patients were blinded to treatment throughout the study period. Outcome assessors were unblinded to treatment because eyes that underwent DMEK and UT-DSAEK are distinguishable during postoperative assessment.

Statistical Analysis

An intention-to-treat analysis was performed for all outcomes measures. Statistical analysis was performed using SPSS for Windows version 24.0 (SPSS, Inc., Chicago, IL). Data were described as mean $\pm$ standard deviation (95% confidence interval [CI]) for continuous variables and as individual counts and percentages for categorical variables. Continuous data were analyzed using the Student t test for differences between treatment arms. For sensitivity analysis of the primary outcome measure, a linear mixed model with BSCVA as the dependent variable, study group and time as factors, and an unstructured covariance matrix was used. In a post hoc analysis, total adverse events and the percentage of eyes reaching 20/20 or better and 20/25 or better Snellen BSCVA at 12 months were tested using the Fisher exact test or Pearson chi-square test as appropriate. Correction for multiple comparisons was performed using the Bonferroni correction. A 2-sided P value of less than 0.05 was considered statistically significant.

Results

Participant Flow

Participant flow based on the Consolidated Standards of Reporting Trials (CONSORT) guidelines is displayed in Figure 1.[15] Fifty-four eyes of 54 patients were randomized to DMEK (n = 29) or UT-DSAEK (n = 25). A minimum of 6 patients was included per site, and every surgeon performed between 2 and 6 UT-DSAEK surgeries and between 2 and 8 DMEK surgeries. Before surgery, 1 patient in the UT-DSAEK arm chose to postpone treatment for an indefinite period. All remaining patients in both groups received the allocated treatment. Two patients in the DMEK arm underwent re-transplantation because of graft detachment. No patients were lost to follow-up.

Baseline Patient and Donor Characteristics

Baseline patient and donor characteristics are displayed in Table 1. Following the 2012 CONSORT guidelines, baseline characteristics were not tested for statistical differences.[15] Central graft thickness of UT-DSAEK lamellae measured 101 ± 25 μm (range, 90−112 μm).

Visual Outcomes

Visual outcomes are shown in Figure 2. Recently published visual outcomes of the Descemet Endothelial Thickness Comparison Trial (DETECT) are shown for comparison.[9] Baseline BSCVA

measured 0.37 ± 0.18 logMAR (95% CI 0.30−0.44 logMAR; n = 29) in the DMEK arm and 0.31 ± 0.13 logMAR (95% CI 0.26−0.37 logMAR; n = 25) in the UT-DSAEK arm. After surgery, BSCVA improved in both treatment arms to a similar extent. Postoperative BSCVA did not differ significantly between DMEK and UT-DSAEK at 3 months (0.15 ± 0.18 logMAR [95% CI, 0.08−0.22 logMAR; n = 29] vs. 0.22 ± 0.13 logMAR [95% CI, 0.16−0.27 logMAR; n = 24; P = 0.15]), 6 months (0.11 ± 0.16 logMAR [95% CI, 0.05−0.17 logMAR; n = 29] vs. 0.16 ± 0.10 logMAR [95% CI, 0.12−0.21 logMAR; n = 24]; P = 0.20), and 12 months (0.08 ± 0.14 logMAR [95% CI, 0.03−0.14 logMAR; n = 29] vs. 0.15 ± 0.11 logMAR [95% CI, 0.10−0.19 logMAR; n = 24]; P = 0.06). Linear mixed model sensitivity analysis showed better visual acuity in DMEK patients, but this was not statistically significant after adjusting for multiple testing (3 months: −0.09 logMAR [95% CI, −0.17 to −0.01 logMAR; adjusted P = 0.08]; 6 months: −0.07 logMAR [95% CI, −0.14 to 0.00 logMAR; adjusted P = 0.16]; and 12 months: −0.08 logMAR [95% CI, −0.15 to −0.014 logMAR; adjusted P = 0.05]). Figure 3 shows the percentage of eyes seeing 20/32 or better, 20/25 or better, and 20/20 or better Snellen after surgery. The percentage of eyes seeing 20/25 or better Snellen BSCVA was higher in DMEK compared with UT-DSAEK patients (19/29 [66%] vs. 8/24 [33%]; P = 0.02). No statistically significant difference was observed in eyes seeing 20/20 or better Snellen BSCVA (DMEK: 7/29 [24%] vs. UT-DSAEK: 1/24 [4%]; P = 0.06).

Endothelial Cell Density and Refractive Outcomes

Endothelial cell density and refractive outcomes are shown in Table 2. After adjusting for multiple comparisons, ECD did not differ significantly between DMEK and UT-DSAEK patients at all postoperative follow-up visits. Neither inserter, type of tamponade, nor graft size of UT-DSAEK significantly influenced ECD. The spherical equivalent did not differ significantly between DMEK and UT-DSAEK patients at all postoperative time points. Both techniques induced a comparable hyperopic shift of approximately 0.5 diopter (D).

Adverse Events

Adverse events are shown in Table 2. The total number of complications during the 1-year follow-up was higher after DMEK compared with UT-DSAEK (17/29 vs. 6/24; P = 0.01). More dislocations requiring rebubbling occurred in the DMEK arm (n = 7, including 1 patient with 2 rebubblings) compared with the UT-DSAEK arm (n = 1). In the DMEK arm, 3 rebubblings were performed after primary SF6 tamponade and 4 rebubblings after primary air tamponade. Only 1 rebubbling was performed after UT-DSAEK (air tamponade). All graft detachments were partial, and rebubbling was performed only for graft detachments of more than one third of the graft surface area. Review of postoperative OCT images excluded reverse graft positioning. In the DMEK arm, 2 eyes underwent rebubbling that failed and was subsequently followed by repeated transplantation. One eye underwent a second repeat transplantation for partial graft detachment. No graft rejection occurred in either treatment arm during the first year after surgery. Four patients in the UT-DSAEK arm and 5 patients in the DMEK arm demonstrated elevated intraocular pressure (defined as >25 mmHg or an increase of $\geq$10 mmHg compared with baseline).
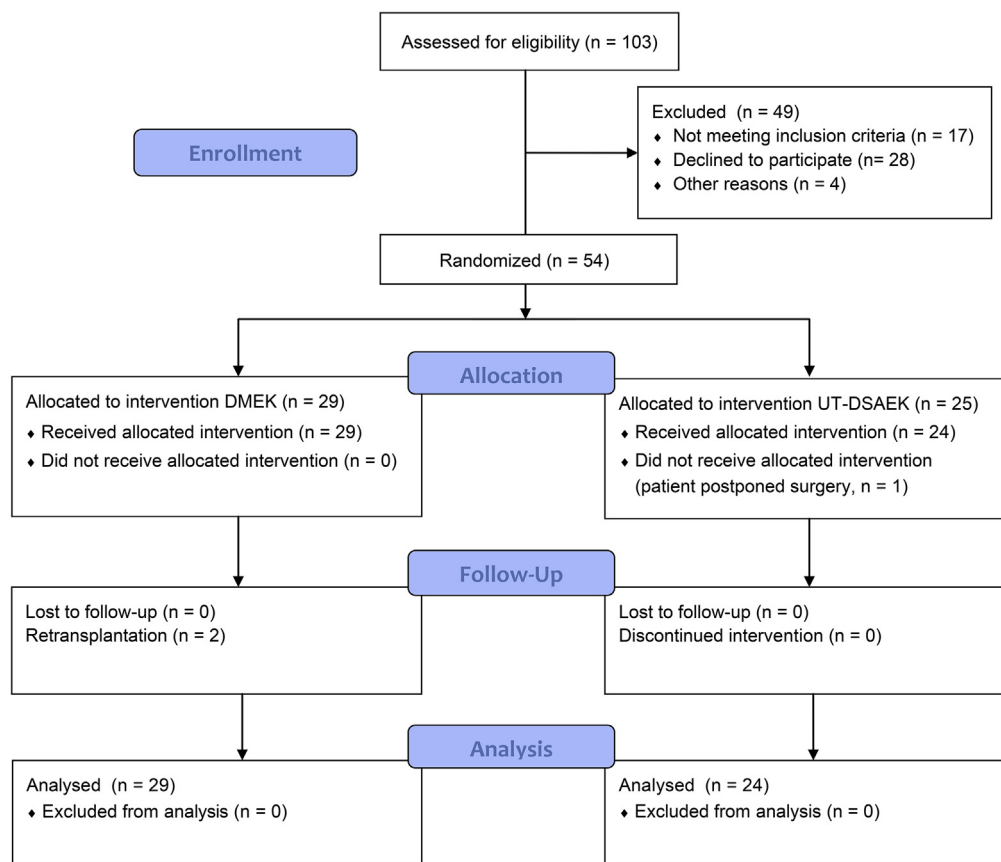
Figure 1. Participant flow chart. DMEK = Descemet membrane endothelial keratoplasty; UT-DSAEK = ultrathin Descemet stripping automated endothelial keratoplasty.

Discussion

This multicenter RCT compared BSCVA, ECD, refractive astigmatism, and complications of DMEK versus UT-DSAEK during a follow-up period of 1 year. We found neither statistically significant nor clinically relevant differences in mean BSCVA, ECD, spherical equivalent, and hyperopic shift between the treatment arms. The

Table 1. Baseline Patient and Donor Characteristics

	Ultrathin Descemet Stripping Automated Endothelial Keratoplasty (n = 25)	Descemet Membrane Endothelial Keratoplasty (n = 29)
Baseline patient characteristics		
Age (yrs)	71 ± 7 (68–74)	72 ± 7 (69–74)
ETDRS BSCVA (logMAR)	0.31 ± 0.13 (0.26–0.37)	0.37 ± 0.18 (0.30–0.44)
Spherical equivalent (D)	−0.83 ± 1.54 (−1.46 to −0.19)	−0.09 ± 1.39 (−0.63 to −0.44)
Baseline donor characteristics		
Age (yrs)	72 ± 8 (69–75)*	73 ± 5 (72–75)*
Death to enucleation (hrs)	12 ± 6 (9–14)*	12 ± 6 (9–14)*
Death to preservation (hrs)	28 ± 7 (25–31)*	24 ± 11 (20–24)*
Organ culture preservation (days)	11 ± 4 (10–13)*	14 ± 6 (12–16)*
Transport medium (days)	3.5 ± 1 (3.1–3.9)*	3.4 ± 0.8 (3.1–3.7)*
ECD (cells/mm^2)	2633 ± 158 (2567–2700)*	2679 ± 157 (2620–2739)
Central graft thickness (μm)	101 ± 25 (90–112)*	not applicable

BSCVA = best spectacle-corrected visual acuity; D = diopter; ECD = endothelial cell density; ETDRS = Early Treatment Diabetic Retinopathy Study; logMAR = logarithm of the minimum angle of resolution.
Data are mean ± standard deviation (95% confidence interval).
*One missing value.
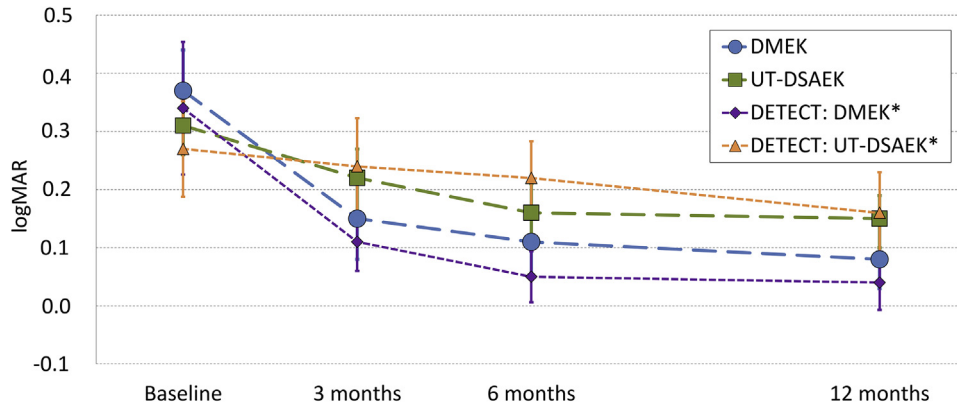
Figure 2. Graph showing best spectacle-corrected visual acuity (in logarithm of the minimum angle of resolution [logMAR] units) of Descemet membrane endothelial keratoplasty (DMEK; blue circles) and ultrathin Descemet stripping automated endothelial keratoplasty (UT-DSAEK; green squares) at baseline and 3, 6, and 12 months after surgery. DETECT = Descemet Endothelial Thickness Comparison Trial. *Best spectacle-corrected visual acuities from the DETECT study are shown for comparison (purple diamonds and orange triangles for DMEK and UT-DSAEK, respectively).[9]

percentage of eyes reaching 20/25 or better Snellen BSCVA at 12 months was significantly higher in DMEK patients compared with UT-DSAEK patients. However, significantly more adverse events occurred after DMEK.

The primary outcome measure of our study was high-contrast BSCVA. We found no statistically significant differences in mean BSCVA between both techniques 3, 6, and 12 months after surgery. In this regard, our findings differ from those of the DETECT study. Average graft thickness in the UT-DSAEK arm of the DETECT trial was thinner compared with that in our study (73 μm vs. 101 μm). However, this did not translate to better BSCVA compared with the UT-DSAEK arm in our study. Nonetheless, comparing graft thickness between trials is made difficult because of the heterogeneity in measurement timing and techniques and graft storage methods. The DMEK arm of the DETECT study showed better postoperative VA compared with our DMEK arm (Fig 2).[9] Consequently, the DETECT study reported better BSCVA after DMEK compared with UT-DSAEK. Although the primary outcome, BSCVA 1 year after surgery, did not differ significantly between UT-DSAEK and DMEK groups, we consider the significant difference in the percentage of eyes achieving 20/25 or better Snellen

vision clinically relevant and indicative of a real effect. Minor differences in design between the DETECT study and current RCT may explain the differences in mean visual acuity. Compared with the DETECT study, eligibility criteria in the current trial were limited to patients with corneal endothelial dysfunction resulting from Fuchs endothelial corneal dystrophy. No surgeries were combined with cataract extraction and intraocular lens placement, and to avoid dependency between 2 eyes, only the first eye was included in patients fulfilling the eligibility criteria for both eyes. Moreover, in the United States, donor corneas are preserved in cold storage media, whereas in Europe, preservation in organ culture medium is the standard.

Endothelial cell density is a major determinant for long-term graft survival.[16] The loss of endothelial cells after corneal transplantation is multifactorial and includes donor characteristics,[17,18] recipient characteristics,[19,20] and postoperative complications.[19] In our study, postoperative ECD was lower after UT-DSAEK compared with DMEK, albeit not statistically significant. In contrast to our findings, the DETECT study reported a trend of lower ECD after DMEK compared with UT-DSAEK.[9] The combined results of both RCTs may suggest that
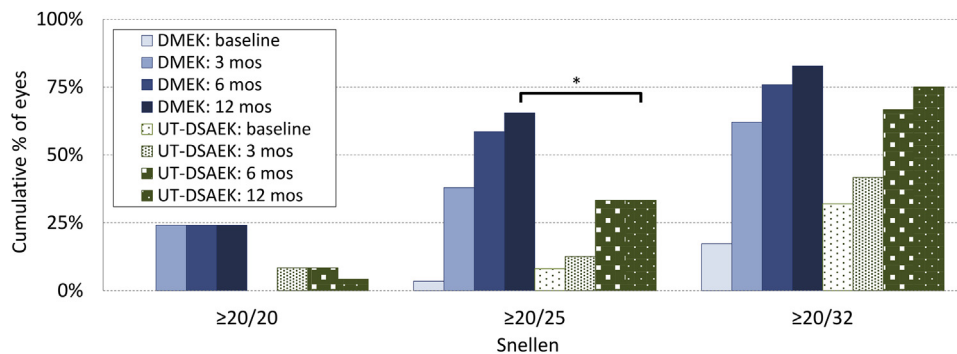
Figure 3. Bar graph showing the cumulative percentage of eyes achieving 20/32 or better, 20/25 or better, and 20/20 or better Snellen best-spectacle corrected visual acuity before surgery and 3, 6, and 12 months after Descemet membrane endothelial keratoplasty (DMEK) versus ultrathin Descemet stripping automated endothelial keratoplasty (UT-DSAEK). *P = 0.02.

Table 2. Outcomes after Ultrathin Descemet Stripping Automated Endothelial Keratoplasty and Descemet Membrane Endothelial Keratoplasty

	Ultrathin Descemet Stripping Automated Endothelial Keratoplasty (n = 24)	Descemet Membrane Endothelial Keratoplasty (n = 29)	P Value
ETDRS BSCVA (logMAR)			
3 mos	0.22 ± 0.13 (0.16–0.27)	0.15 ± 0.18 (0.08–0.22)	0.15
6 mos	0.16 ± 0.10 (0.12–0.21)	0.11 ± 0.16 (0.05–0.17)	0.20
12 mos	0.15 ± 0.11 (0.10–0.19)	0.08 ± 0.14 (0.03–0.14)	0.06
Spherical equivalent (D)			
3 mos	−0.33 ± 1.42 (−0.93 to 0.28)	0.31 ± 1.43 (−0.23 to 0.85)	0.11
6 mos	−0.08 ± 1.67 (−0.79 to 0.62)	0.07 ± 1.58 (−0.53 to 0.67)	0.74
12 mos	−0.29 ± 1.49 (−0.92 to 0.34)	0.13 ± 1.63 (−0.49 to 0.75)	0.34
Hyperopic shift (D)			
3 mos	0.53 ± 1.09 (0.07–0.99)	0.41 ± 1.25 (−0.08 to 0.88)	0.42
6 mos	0.78 ± 1.01 (0.35–1.21)	0.16 ± 1.28 (−0.32 to 0.65)	0.06
12 mos	0.58 ± 1.07 (0.13–1.03)	0.22 ± 1.19 (−0.23 to 0.68)	0.27
ECD (cells/mm^2)			
3 mos	1564 ± 726 (1257–1870)	1924 ± 446 (1754–2094)	0.04*
6 mos	1642 ± 662 (1356–1929)[†]	1944 ± 492 (1753–2135)[†]	0.07
12 mos	1612 ± 645 (1326–1898)[‡]	1870 ± 504 (1670–2069)[‡]	0.12
Adverse events			
Donor preparation failure	1	1	—
Rebubbling	1	7[§]	—
Re-transplantation	—	3[§]	—
Elevated IOP	4	5	—
Cystoid macular edema	—	1	—
Graft rejection	—	—	—
Total	6	17	0.01

BSCVA = best spectacle-corrected visual acuity; D = diopter; ECD = endothelial cell density; ETDRS = Early Treatment Diabetic Retinopathy Study; IOP = intraocular pressure; logMAR = logarithm of the minimum angle of resolution.
Data are mean ± standard deviation (95% confidence interval).
*Not significant after adjusting for multiple testing.
[†]One missing value.
[‡]Two missing values.
[§]Of which 2 in the same eye.

endothelial cell loss is comparable between DMEK and UT-DSAEK.

The postoperative refractive change in our study was comparable between DMEK and UT-DSAEK groups. The meniscus-shaped profile of dissected lamellae has been suggested to contribute to a hyperopic shift. Yet, a comparable hyperopic shift in DMEK and UT-DSAEK points to corneal deswelling as the potential driver for refractive change. The small hyperopic shift observed with both techniques is in line with previous studies reporting an average refractive shift of +0.3 D.[1,4] Consequently, both techniques have been used effectively in triple procedures.[21]

In our study, the most common complication was graft detachment necessitating rebubbling. Compared with 1 rebubbling in the UT-DSAEK arm (4%), 7 rebubblings occurred in the DMEK arm (24%), of which 2 were in the same eye. The rate of rebubbling in DMEK differs significantly between reports, averaging 29% but ranging from 2% to 82%.[22,23] In line with our results, the DETECT study reported rebubbling rates in DMEK and UT-DSAEK of 24% and 4%, respectively.[9] In the current study, DMEK grafts were nonstamped. Use of prestamped DMEK tissue is reported to reduce graft detachment rate.[24] Some reports suggest that an anterior chamber tamponade using SF6 gas

reduces the rate of graft detachment by facilitating cellular wound healing at the graft–host interface.[25–27] In our cohort, SF6 gas was not associated with statistically significant lower rebubbling rates compared with air, but our study was not powered to analyze these differences. Similarly, the current study is not powered to assess the relationship between complication rates and type of study center. Larger, multicenter prospective studies are needed to answer this question. We believe that graft dislocation has a multifactorial origin and cannot be attributed solely to the learning curve of an individual surgeon. This is outlined by the current multicenter study, in which the participation of 6 surgeons led to similar rebubbling rates as compared with the DETECT trial (2 participating surgeons).

Currently, no consensus exists regarding the definition of UT-DSAEK. In the current study, we aimed at a central graft thickness of 100 μm. This is in line with our previous RCT comparing UT-DSAEK and DSAEK[4] and with a large prospective study by Busin et al.[3]

The current study has a number of limitations. The assessors of the primary outcome measure, BSCVA, were not masked. Corneal surgeons were allowed to practice their own surgical technique. This heterogeneity may influence complication rates. Larger multicenter studies are needed to

address the impact of surgical variables on clinical outcomes.

All surgical procedures were performed by experienced lamellar corneal surgeons, who completed hundreds of DSAEK and UT-DSAEK procedures and at least 25 DMEK procedures before operating on study patients. The corneal surgeons completed their training in The Netherlands, where the guidelines of the Dutch Cornea Workgroup determine the qualifications required to perform lamellar keratoplasty. Multiple studies report an inverse relationship between graft detachment and surgical experience for DMEK.[28–30] However, no consensus exists regarding a cutoff point. For example, analysis of 2485 cases by Oellerich et al[30] reported a graft detachment rate of 34% for novice DMEK surgeons (<25 cases) and 22% for experienced DMEK surgeons (>100 cases). The detachment rate in our study (24%) is in line with that reported for experienced surgeons in this large multicenter study. Visual recovery and endothelial cell loss do not seem to be dependent on a surgeon's experience.[28,30]

In this study, a larger sample size might have yielded statistically significant differences. However, the observed effect size was 0.08 logMAR at 12 months, which is less than half of what can be considered a clinically relevant improvement.[31] Moreover, the loss to follow-up rate was much smaller than anticipated, which increases the power. Similar to our study, the DETECT study also included 50 eyes. Six corneal clinics participated in this study to increase generalizability. These were academic and nonacademic centers, as requested by The Netherlands Association for Health Research and Development, which provided financial support for this study.

Modern lamellar keratoplasty techniques have evolved into procedures with a predictable outcome. However, a standard for reporting outcomes is lacking. Currently, the literature on endothelial keratoplasty reports the mean visual acuity or the percentage of eyes reaching certain threshold visual acuity. This creates a set of problems when outcomes are compared across trials. It would be helpful to set standards on reporting the most important outcome measure, that is, visual acuity, as has been done in the past in refractive surgery.

In summary, DMEK and UT-DSAEK did not differ significantly in mean BSCVA, endothelial cell loss, or hyperopic shift. The percentage of eyes reaching 20/25 Snellen vision or better was higher in DMEK compared with UT-DSAEK patients, but the DMEK group also showed higher adverse event rates.

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Footnotes and Financial Disclosures

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Abbreviations and Acronyms:
BSCVA = best spectacle-corrected visual acuity; **CI** = confidence interval; **D** = diopter; **DETECT** = Descemet Endothelial Thickness Comparison Trial; **DMEK** = Descemet membrane endothelial keratoplasty; **DSAEK** = Descemet stripping automated endothelial keratoplasty; **ECD** = endothelial cell density; **logMAR** = logarithm of the minimum angle of resolution; **RCT** = randomized controlled trial; **SF6** = sulfur hexafluoride; **UT** = ultrathin.

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