Received: 26 April 2022 | Accepted: 18 October 2022

DOI: 10.1111/aos.15280

Acta Ophthalmologica

ORIGINAL ARTICLE

Trial-based cost-effectiveness analysis of Descemet membrane endothelial keratoplasty (DMEK) versus ultrathin Descemet stripping automated endothelial keratoplasty (UT-DSAEK)

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Funding information
Algemene Nederlandse Vereniging ter voorkoming van Blindheid; Dr. F.P. Fischer-Stichting; Landelijke Stichting Blinden en Slechtzienden (LSBS); Oogfonds; ZonMw, Grant/Award Number: 843001603; European Society of Cataract and Refractive Surgeons

Abstract

Purpose: To evaluate the cost-effectiveness of Descemet Membrane Endothelial Keratoplasy (DMEK) versus Ultrathin Descemet Stripping Automated Endothelial Keratoplasty (UT-DSAEK).

Methods: A cost-effectiveness analysis using data from a multicenter randomized clinical trial was performed. The time horizon was 12 months postoperatively. Patients with Fuchs' endothelial dystrophy were randomized to DMEK (n = 29) or UT-DSAEK (n = 24). Relevant resources from healthcare and societal perspectives were included in the cost analysis. Quality-Adjusted Life Years (QALYs) were determined using the Health Utilities Index Mark 3 (HUI3) and the EuroQol EQ-5D-5L questionnaires. The main outcome was the incremental cost-effectiveness ratio (ICER; incremental societal costs per QALY).

Results: Societal costs averaged €8851 (US$11 406) for DMEK and €8320 (US$10 722) for UT-DSAEK. Higher costs in the DMEK group were mainly caused by higher rebubbling and regraft rates (21% and 7%, vs. 4% and 0% in the UT-DSAEK group). HUI3 QALYs were 0.70 (DMEK) and 0.79 (UT-DSAEK). EQ-5D-5L QALYs were 0.83 (DMEK) and 0.86 (UT-DSAEK). The ICER indicated DMEK was dominated by UT-DSAEK in both analyses. The cost-effectiveness probability for DMEK ranged from 21% to 5% (HUI3 QALYs) and 27%–14% (EQ-5D-5L QALYs), assuming the maximum acceptable ICER ranged from €2500 to €80.000 (US$3222–US$103 093) per QALY.

Conclusion: The base case cost-effectiveness analysis favoured UT-DSAEK over DMEK, as costs of DMEK were higher while QALYs were lower. Further studies are required to assess long-term rebubbling and regraft rates and graft survival.

KEYWORDS
corneal transplantation, cost-effectiveness, costs, DMEK, Fuchs' endothelial dystrophy, QALY, UT-DSAEK

†DMEK versus DSAEK Study Group shown in Appendix A.

1 | INTRODUCTION

Descemet Stripping Automated Endothelial Keratoplasty (DSAEK) is the commonest endothelial keratoplasty (EK) technique used for treating corneal endothelial disorders such as Fuchs' endothelial dystrophy (FED). However, since the introduction of Descemet Membrane Endothelial Keratoplasty (DMEK), the number of DSAEK procedures has been declining in favour of DMEK (Eye Bank Association of America (EBAA), 2020; Dunker et al., 2021; Dunker, Armitage, et al., 2021). DMEK has been shown to result in better visual outcomes and potentially better endothelial cell count and rejection rates compared to DSAEK (Chamberlain et al., 2019; Dunker et al., 2020; Marques et al., 2019; Stuart et al., 2018). However, DMEK has also been associated with a higher incidence of graft detachments and potentially more primary graft failures. This increases the costs of DMEK in the short term and may affect patient quality of life.

Cost-effectiveness analyses of healthcare interventions are increasingly used to support decisions on the allocation of healthcare resources. Effectiveness of healthcare interventions is preferably expressed as Quality-Adjusted Life Years (QALYs), which combine the intervention's effect on both quantity and quality of life. QALYs are calculated by measuring generic health-related quality of life (HRQL) using standardized questionnaires. Because of the generic nature of QALYs, they can be applied in all fields in healthcare to investigate and compare the cost-effectiveness of different types of healthcare interventions. Health policy-makers determine cost-effectiveness of a healthcare intervention by calculating the incremental costs per QALY and comparing it to a predefined threshold value (Drummond et al., 2015).

A previous cost-effectiveness analysis found that corneal transplantation is a cost-effective treatment because of the high medical and societal costs associated with low vision and blindness (The Lewin Group, 2013). In addition, several cost-effectiveness analyses showed that EK is cost-effective compared to traditional full-thickness penetrating keratoplasty (Beauchemin et al., 2010; Bose et al., 2013; Prabhu et al., 2013; van den Biggelaar et al., 2012). So far, one model-based study reported on the cost-effectiveness of DMEK and found that DMEK was cost-saving and generated more QALYs compared to DSAEK, making it a cost-effective treatment (Gibbons et al., 2019).

Our study group previously reported a randomized clinical trial (RCT) on the effectiveness of DMEK compared to Ultrathin-DSAEK (UT-DSAEK), a variant of DSAEK utilizing thinner grafts to achieve better visual outcomes compared to standard DSAEK. (Dunker et al.) The study was not able to demonstrate a significant difference in best spectacle-corrected visual acuity and in endothelial cell density, although more DMEK patients had visual acuity of 20/25 or higher (66% vs. 33%). In the current paper, we describe the results of a cost-effectiveness analysis of DMEK versus UT-DSAEK from a societal perspective, based on the data from that study.

2 | METHODS

This economic evaluation was conducted alongside a multicenter RCT at six medical centers performing corneal transplantation surgery in the Netherlands (Maastricht University Medical Center+, University Medical Center Utrecht, Radboud University Medical Center, University Medical Center Groningen, Deventer Hospital, Gelre Hospitals). The study was performed from a healthcare and societal perspective with a time horizon of 12 months, starting from the day of surgery. The methodology for the cost-effectiveness study was largely similar to an earlier study from our study group that reported the cost-effectiveness of UT-DSAEK versus DSAEK (Simons et al., 2019).

Institutional review boards of all centers approved the study before start of patient recruitment. Participants were recruited between November 2016 and November 2017 and gave written informed consent. The study was conducted in accordance with the principles of the Declaration of Helsinki and good clinical practice guidelines and was registered in a clinical trial register (ClinicalTrials.gov, identifier NCT02793310).

2.1 | Study procedures

The study population and study procedures were described previously (Dunker et al., 2020). Briefly, pseudophakic FED patients who required primary corneal transplantation due to corneal endothelial dysfunction, and who had no other vision-limiting comorbidities, were recruited. One eye per patient was included in the study. The sample size was based on corrected distance visual acuity (CDVA), the primary outcome of the study. Patients were randomized to DMEK or UT-DSAEK. Patients were blinded to treatment allocation. All donor tissues were precut by a cornea bank (ETB-BISLIFE, Leiden, the Netherlands). UT-DSAEK graft thickness was targeted at $100 \pm 20\,\mu m$. Surgery was performed by experienced cornea surgeons who, prior to the start of the study, performed hundreds of (UT)DSAEK procedures and at least 25 DMEK procedures. In cases of graft detachment, a rebubbling procedure was performed to reposition and stabilize the graft. In cases of graft failure, a regraft procedure was performed.

2.2 | Cost analysis

The economic evaluation was performed in accordance with national guidelines (Hakkaart-van Roijen et al., 2015). All relevant resources consumed from a societal and healthcare perspective were included. To determine costs, resource use volumes were multiplied with unit cost prices including sales taxes. Costs were converted to 2018 Euros (€) using the Consumer Price Index (CPI) (Centraal Bureau voor de Statistiek), and to US$ using the 2018 purchasing power parity for gross domestic product (PPP for GDP; US$1.00 = €0.776) (Organization for Economic Co-operation and Development).

Data on resource use were obtained through hospital registries and self-administered patient questionnaires. Hospital-based resources included operating room times, corneas, hospital admissions, outpatient visits, and medication use. Patient-reported resources included general practitioner visits, home care, visual aids (including spectacles), travel, informal care, and productivity loss. The patient-reported resource use questionnaire was completed 3, 6, and 12 months postoperatively.

Operating room times were valued using integral cost prices provided by Maastricht University Medical Center+, which included costs of personnel, standard materials and equipment, and overhead. Two costs drivers were applicable: general operating room costs (cost per minute spent in the operating room) and ophthalmology costs (cost per minute spent in surgery). Few patients required secondary procedures for which procedure times were unknown, and reimbursement prices, also provided by Maastricht University Medical Center+, were used instead. Prices of (precut) donor corneas were not available. Therefore, previously reported cornea prices were used (van den Biggelaar et al., 2012). Standardized prices provided by national guidelines for cost analysis were used to value hospital admissions, outpatient visits, general practitioner visits, home care, travel, informal care, and productivity loss (Hakkaart-van Roijen et al., 2015). Spectacle costs were based on average costs provided by an optometry market research report (Q&A Research & Consultancy & Terra, 2011). Prescription medication was valued using reimbursement prices (including a standard pharmacy service fee) (Zorginstituut Nederland).

2.3 | Effectiveness

Effectiveness was based on generic HRQL (main outcome), vision-related quality of life, and CDVA (secondary outcomes).

HRQL was determined using the Health Utilities Index Mark 3 questionnaire (HUI3, Health Utilities Inc., Hamilton, Canada) and the EuroQol EQ-5D-5L questionnaire (EuroQol Research Foundation, Rotterdam, The Netherlands). The HUI3 is one of few HRQL questionnaires that includes questions about visual functioning. It assesses eight dimensions of health with five to six levels per dimension. Consequently, the HUI3 is capable of distinguishing 972 000 different health states. Each health state is associated with a utility score, which ranges from −0.36 (health state worse than death) to 1.00 (perfect health) (Horsman et al., 2003). The EQ-5D-5L determines HRQL by assessing five dimensions of health with five levels per dimension: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. This allows for 5125 possible health states and all health states are associated with a specific utility score (range −0.446 to 0.953) which have been determined for the Dutch population (Versteegh et al., 2016). For both HRQL questionnaires, utility scores were used to calculate QALYs for each patient separately by determining the area under the curve of subsequent utility measurements, assuming linear changes in utilities over time (Manca et al., 2005).

Vision-related quality of life was measured with the National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25, National Eye Institute, Bethesda, MD, USA). The NEI VFQ-25 is a 26-item questionnaire (25 vision items and 1 general health item) evaluating the impact of visual impairment on quality of life. Thirteen optional questions are available to increase accuracy. Responses on the items are scored 0–100, and item subset scores can be averaged to obtain 12 subscales (e.g., general health, distance activities, driving). Higher scores represent better visual functioning. In addition, all subscales, excluding the general health scale, were averaged to obtain a composite score (Mangione et al., 2001).

CDVA was assessed using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart at 4 m distance and expressed in logarithm of the minimum angle of resolution (logMAR).

All data were collected during the preoperative visit, and 3, 6, and 12 months after surgery.

2.4 | Cost-effectiveness analyses

Analyses were performed according to the intention-to-treat principle. Incomplete cost and effectiveness data were assumed missing at random and imputed using multiple imputation with predictive mean matching (mice package; R version 4.0.0 for Windows, The R Foundation, Vienna, Austria). The imputation regression model included the following covariates: treatment group, age, sex, study center, and whether the patient underwent corneal transplantation or cataract surgery in the fellow eye during follow-up. Twenty imputation sets were obtained using 100 iterations per imputation. Imputation sets were analysed separately and the results were pooled. Differences in effectiveness outcomes were tested for statistical significance using the independent samples T test for continuous variables and the Chi-squared test for discrete variables. Because Chi-squared p values could not be pooled, the range of p values for the 20 imputation data sets was reported instead.

To assess cost-effectiveness, the incremental cost-effectiveness ratio (ICER) of DMEK versus UT-DSAEK was calculated, which expresses the incremental costs of DMEK for each additional unit of the health effect. Uncertainty in incremental costs and effects was assessed using non-parametric bootstrapping with 1000 replications (Microsoft Excel 2016 for Windows, Microsoft, Redmond, WA, USA). All imputation sets were entered into the bootstrap analysis, and the size of each resample was equal to the original sample size. Bootstrap results were plotted on cost-effectiveness planes. Cost-effectiveness acceptability curves were constructed to estimate the probability that DMEK was cost-effective based on a range of ceiling ratios for the ICER. Ceiling ratios reflect the maximum price health policy-makers are willing to pay for an additional QALY. In the Netherlands, the ceiling ratio for conditions with limited burden of disease is €20 000 (US$25 773) per QALY (Vijgen et al., 2018). No ceiling ratios for other types of outcomes (e.g., clinical or patient-reported outcomes) exist.

In the base case analysis, cost-effectiveness was based on HUI3 QALYs and costs from a societal perspective over 12 months follow-up. EQ-5D-5L QALYs were used in a similar secondary analysis. Additional secondary analyses were performed using alternative effectiveness measures and costs from a healthcare perspective. These effectiveness measures included clinical improvement in CDVA (≥0.2 logMAR improvement) and NEI VFQ-25 composite score (≥10 points improvement) (Lindblad & Clemons, 2005; Rosser et al., 2003).

In a sensitivity analysis, the base case analysis was repeated with a correction for baseline utility differences by adding the mean difference in baseline utility between treatment groups to all utility measurements in the treatment group with the lower mean baseline utility, resulting in equal baseline values. This sensitivity analysis was performed once for HUI3 QALYs and once for EQ-5D-5L QALYs. In addition, to explore the impact of the higher rate of rebubbling and regraft procedures in the DMEK group on cost-effectiveness, a subgroup analysis was performed that excluded patients who underwent these secondary procedures. Another subgroup analysis was performed with exclusion of patients that underwent cataract or corneal transplantation surgery in the fellow eye during study follow-up.

3 | RESULTS

Patients were randomized to DMEK (n = 29) and UT-DSAEK (n = 25). One patient randomized to UT-DSAEK postponed the transplantation surgery and was withdrawn from the analysis. The remaining patients received the allocated treatment and none were lost-to-follow-up.

Mean patient age was 72.0 years (standard deviation [SD] 6.6) and 71.0 years (SD 7.2) in the DMEK and UT-DSAEK group, respectively. The proportion of male patients was 48% (n = 14) in the DMEK group compared to 38% (n = 9) in the UT-DSAEK group. Corneal transplantation and/or cataract surgery of the fellow eye during the 12-month follow-up was performed in 38% (n = 11) and 38% (n = 9) of patients in the DMEK and UT-DSAEK group, respectively. Costs directly related to second-eye surgery were not included in the cost analysis.

The following percentages of data were missing and imputed for the DMEK and UT-DSAEK group, respectively: HUI3 3.7% and 3.0%, EQ-5D-5L 5.2% and 5.2%, CDVA 0.0% and 1.0%, VFQ-25 5.4% and 6.9%, cost data 2.6% and 1.8%.

3.1 | Costs

In Table 1, mean resource use and costs are reported. Total costs from a societal perspective averaged €8851 (US$11 406; standard error of the mean [SE] €710) in the DMEK group and €8320 (US$10 722; SE €732) in the UT-DSAEK group, i.e., DMEK was €531 (US$684) more expensive. From a healthcare perspective, average costs were €7982 (US$10 286; SE €581) and €7255 (US$9349; SE €127) for DMEK and UT-DSAEK, respectively (difference €727 [US$937]). The higher costs of DMEK were mainly caused by the larger number of rebubbling and regraft procedures. In the DMEK group, three regraft procedures (2 patients [7%]) were performed, while there were none in the UT-DSAEK group (p = 0.19). Furthermore, there were seven rebubbling procedures (six patients [21%]) in the DMEK group, and one (4%) in the UT-DSAEK group (p = 0.08). Additional differences in costs included visual aids postoperatively (DMEK €439 [US$566]; UT-DSAEK €125 [US$161]) and costs for lost productivity (DMEK €272 [US$351]; UT-DSAEK €826 [US$1064]). In the DMEK group only one patient reported lost productivity (8 days absent) while in the UT-DSAEK group two patients reported lost productivity (one patient 10 days absent, one patient 90 days absent).

3.2 | Effectiveness

3.2.1 | Effectiveness outcomes are shown in Table 2

Mean HUI3 utility increased after DMEK (baseline 0.60, 12 months postoperative 0.69) and UT-DSAEK (baseline 0.66, 12 months postoperative 0.84). The HUI3 QALY was 0.70 (SE 0.04) in the DMEK group and 0.79 (SE 0.04) in the UT-DSAEK group (p = 0.10). Mean EQ-5D-5L utility also increased but the increase was much less pronounced (DMEK 0.01 increase; UT-DSAEK 0.02 increase). The EQ-5D-5L QALY was 0.83 (SE 0.02) and 0.86 (SE 0.02) in the DMEK and UT-DSAEK group, respectively (p = 0.33).

Mean NEI VFQ-25 composite score and CDVA improved in both groups. Average VFQ-25 composite score at 12 months postoperatively was comparable in both groups (DMEK group 84.2, UT-DSAEK group 83.7; p = 0.89). Clinically relevant improvement of at least 10 points compared to baseline was achieved in 64% of DMEK patients and 61% of UT-DSAEK patients (range of p values = 0.38–0.97). In addition, mean CDVA at 12 months postoperatively was higher in the DMEK group (0.08 logMAR) compared to the UT-DSAEK group (0.16 logMAR; p = 0.04). Clinically relevant improvement of at least 0.2 logMAR was achieved in 59% of DMEK patients compared to 29% of UT-DSAEK patients (range of p values = 0.03–0.03).

3.3 | Cost-effectiveness

3.3.1 | The results of the cost-effectiveness analyses are shown in Table 3

In the base case analysis, HUI3 QALYs were lower in the DMEK group, while societal costs were higher. As a result, DMEK was strongly dominated by UT-DSAEK (ICER therefore not calculated). The results of the

TABLE 1 Mean resource use and mean costs (in 2018 €) from a societal perspective.

		Resource use, mean (SE)[a]		Costs, mean (SE), €[a]	
	Cost per unit (€)	DMEK ($n = 29$)	UT-DSAEK ($n = 24$)	DMEK ($n = 29$)	UT-DSAEK ($n = 24$)
Healthcare sector					
Primary corneal transplantation surgical costs					
General operating room costs	12.63/minute	77.9 (3.9)	77.6 (4.0)	984 (50)	980 (51)
Ophthalmology costs	3.76/minute	54.1 (2.9)	55.9 (3.9)	203 (11)	210 (15)
Donor cornea	4232/cornea	1.0 (−)	1.0 (−)	4232 (−)	4232 (−)
Regraft surgical costs					
General operating room costs	12.63/minute	8.7 (6.5)	0 (−)	110 (83)	0 (−)
Ophthalmology costs	3.76/minute	6.1 (4.7)	0 (−)	23 (18)	0 (−)
Donor cornea	4232/cornea	0.1 (0.1)	0 (−)	438 (322)	0 (−)
Rebubbling surgical costs					
General operating room costs	12.63/minute	7.2 (3.0)	1.2 (1.2)	91 (37)	15 (15)
Ophthalmology costs	3.76/minute	3.3 (1.4)	0.6 (0.6)	13 (5)	2 (2)
Other procedures[b]	Variable	Variable		13 (13)	31 (22)
Hospital admission					
Day care	287.22/day	1.0 (0.2)	0.8 (0.1)	277 (44)	227 (30)
Inpatient days	668.09/day	0.3 (0.1)	0.3 (0.1)	230 (69)	195 (63)
Outpatient visits	169.62/visit	7.4 (0.5)	6.8 (0.3)	1258 (80)	1159 (46)
Medication	Variable	Variable		95 (6)	114 (10)
General practitioner visits	Variable	Variable		7 (4)	7 (4)
Home care	52.03/hour	0.1 (0.3)	1.6 (1.1)	8 (15)	82 (59)
Subtotal				*7982 (581)*	*7255 (127)*
Patient and family costs					
Visual aids	Variable	Variable		439 (71)	125 (54)
Travel costs	Variable	Variable		25 (6)	14 (5)
Informal care	14.57/hour	9.2 (6.3)	7.0 (5.3)	134 (91)	101 (77)
Subtotal				*598 (108)*	*240 (89)*
Other sectors					
Productivity costs (paid work)	36.16/hour	7.5 (11.9)	22.8 (19.6)	272 (429)	826 (710)
Subtotal				*272 (429)*	*826 (710)*
Total costs from societal perspective				8851 (710)	8320 (732)

Abbreviations: DMEK, Descemet membrane endothelial keratoplasty; SE, standard error of the mean; UT-DSAEK, ultrathin Descemet stripping automated endothelial keratoplasty.

[a]Values represent pooled means and standard errors of the mean based on 20 multiple imputation data sets.

[b]Included subconjunctival injection of triamcinolone acetonide for rejection, phacoemulsification, laser capsulotomy for posterior capsular opacification, laser peripheral iridotomy for pupil block.

bootstrap analysis are plotted in a cost-effectiveness plane (Figure 1) and cost-effectiveness acceptability curve (Figure 2). The probability that DMEK was cost-effective compared to UT-DSAEK ranged from 21% to 5%, assuming the ICER ceiling ratio per QALY ranged from €2500 (US$3222) to €80 000 (US$103 093), i.e. lower probabilities at higher ceiling ratios. Assuming health policy-makers in the Netherlands are willing to pay €20 000 (US$25 773) per QALY, the cost-effectiveness probability was 7% (Vijgen et al., 2018). In a secondary analyses based on EQ-5D-5L QALYs and societal costs, the results were similar to the base case analysis, with the cost-effectiveness probability ranging from 27 to 14% (17% at ceiling ratio €20 000 [US$25 773] per QALY).

Additional secondary analyses were performed using alternative effectiveness parameters and costs from a healthcare perspective. An analysis based on patients with clinical improvement in VFQ-25 composite score revealed that the ICER was €33 628 (US$43 335) per patient, and the cost-effectiveness probability ranged from 16% to 55% assuming ceiling ratios ranged from €2500 (US$3222) to €80 000 (US$103 093). An analysis based on patients with clinical improvement in CDVA revealed that the ICER was €2469 (US$3182) per clinically improved patient, with the cost-effectiveness probability ranging from 55% to 99%.

TABLE 2 Measures of effectiveness.

	DMEK ($n = 29$)	UT-DSAEK ($n = 24$)	p Value
HUI3 Health-related utility, mean (SE)[a]			
Preoperative	0.60 (0.04)	0.66 (0.05)	0.36[b]
3 months postoperative	0.69 (0.05)	0.77 (0.05)	0.30[b]
6 months postoperative	0.73 (0.04)	0.81 (0.04)	0.21[b]
12 months postoperative	0.69 (0.04)	0.84 (0.04)	0.01[b]
Quality-adjusted life years	0.70 (0.04)	0.79 (0.04)	0.10[b]
EQ-5D-5L health-related utility, mean (SE)[a]			
Preoperative	0.82 (0.03)	0.85 (0.02)	0.46[b]
3 months postoperative	0.85 (0.02)	0.88 (0.02)	0.35[b]
6 months postoperative	0.82 (0.03)	0.86 (0.02)	0.41[b]
12 months postoperative	0.83 (0.03)	0.87 (0.02)	0.30[b]
Quality-adjusted life years	0.83 (0.02)	0.86 (0.02)	0.33[b]
VFQ-25 composite scores, mean (SE)[a]			
Preoperative	67.3 (2.6)	69.0 (2.7)	0.64[b]
12 months postoperative	84.2 (2.3)	83.7 (2.2)	0.89[b]
10 or more points improvement (%)	64%	61%	0.38–0.97[c]
CDVA (study eye), mean (SE), logMAR[a]			
Preoperative	0.37 (0.03)	0.30 (0.03)	0.14[b]
12 months postoperative	0.08 (0.03)	0.16 (0.02)	0.04[b]
0.2 logMAR or more improvement (%)	59%	29%	0.03–0.03[c]

Abbreviations: CDVA, corrected distance visual acuity; DMEK, Descemet membrane endothelial keratoplasty; EQ-5D-5L, EuroQol-5D-5L; HUI3, Health Utilities Index Mark 3; logMAR, logarithm of the minimum angle of resolution; SE, standard error of the mean; UT-DSAEK, ultrathin Descemet stripping automated endothelial keratoplasty; VFQ-25, Visual Functioning Questionnaire-25.

[a]Values represent pooled means/frequencies and standard errors of the mean based on 20 multiple imputation data sets.

[b]Independent samples T test, values represent pooled p values based on 20 multiple imputation data sets.

[c]Chi-squared test, p values cannot be pooled, range of p values is reported based on 20 multiple imputation data sets.

Sensitivity analyses were performed correcting for baseline differences in HUI3 and EQ-5D-5L utilities. Because baseline utilities were lower in the DMEK group, the QALYs in the DMEK group increased after correction for baseline differences. Nonetheless, QALYs were still lower than in the UT-DSAEK group. As a result, DMEK remained the inferior treatment. The cost-effectiveness probability at ceiling ratio €20 000 [US$25 773] per QALY was 23% in the sensitivity analysis based on HUI3 QALYs and 30% in the sensitivity analysis based on EQ-5D-5L QALYs. A subgroup analysis excluding patients that underwent regraft or rebubbling procedures showed that average costs in the DMEK group became lower than in the UT-DSAEK group. The ICER was €2132 (US$2747)/QALY (i.e., for every lost QALY, €2132 was saved). The cost-effectiveness probability was 9% at ceiling ratio €20 000 [US$25 773] per QALY. Another subgroup analysis, excluding patients who underwent procedures in the second eye, showed results similar to the base case analysis (DMEK dominated by UT-DSAEK, cost-effectiveness probability 18% at ceiling ratio €20 000 [US$25 773] per QALY).

4 | DISCUSSION

This trial-based cost-effectiveness analysis evaluated the cost-effectiveness of DMEK versus UT-DSAEK. Because QALYs were lower and costs were higher in the DMEK group, DMEK was not cost-effective compared to UT-DSAEK. Additional uncertainty analyses revealed that the probability of DMEK being cost-effective ranged from 21% to 5% assuming ceiling ratios ranged from €2500 (US$3222) to €80 000 (US$103 093)/QALY. DMEK is therefore unlikely to be cost-effective compared to UT-DSAEK. Further secondary and sensitivity analyses also favoured UT-DSAEK. The only exception was a secondary analysis based on clinical improvement in visual acuity (at least 0.2 logMAR) and costs from a healthcare perspective. More patients in the DMEK group showed a clinical improvement in visual acuity compared to the UT-DSAEK group (59% vs. 29%), and the ICER was €2469 (US$3182)/improved patient. However, no threshold values have been defined for effectiveness parameters other than QALYs (Vijgen et al., 2018).

The results of the current study contradict a previous model-based cost-effectiveness analysis from the United States of America, which found lower costs and higher QALYs in the DMEK group compared to the DSAEK group (Gibbons et al., 2019). Important differences between that study and the current study include: a smaller difference in the rate of graft detachments and primary graft failures between the study groups, a 15-year time horizon to account for long-term complications (higher rate of late graft failures and graft rejections in the DSAEK group), and QALYs were modelled based on visual acuity (which was assumed to be better in the DMEK group).

To accurately estimate costs of DMEK and UT-DSAEK, a comprehensive cost analysis was undertaken that included not only direct medical costs, but also costs incurred by patients and societal costs, e.g., productivity

TABLE 3 Results of the cost-effectiveness analyses.

		Mean costs (€)[a]	Mean effects[a]	Incremental cost-effectiveness ratio (€)	Probability cost-effective at ceiling ratio € **2500/5000/10 000/**20 000**/50000/80000** (%)
Base case analysis					
QALYs (HUI3) and costs from societal perspective	DMEK (n = 29)	8851	0.70	Dominated	21/16/11/**7**/6/5
	UT-DSAEK (n = 24)	8320	0.79	-	-
Secondary analyses					
QALYs (EQ-5D-5L) and costs from societal perspective	DMEK (n = 29)	8851	0.83	Dominated	27/24/20/**17**/15/14
	UT-DSAEK (n = 24)	8320	0.86	-	-
Clinical improvement in VFQ-25 composite score (≥10 points) and costs from healthcare perspective	DMEK (n = 29)	7982	0.64	33 628/improved patient	16/27/38/**47**/54/55
	UT-DSAEK (n = 24)	7255	0.61	-	-
Clinical improvement in CDVA (0.2 logMAR or more) and costs from healthcare perspective	DMEK (n = 29)	7982	0.59	2469/improved patient	55/78/93/**98**/99/99
	UT-DSAEK (n = 24)	7255	0.29	-	-
Sensitivity analyses					
QALYs (HUI3), corrected for baseline utility difference, and costs from societal perspective	DMEK (n = 29)	8851	0.75	Dominated	28/26/23/**23**/24/24
	UT-DSAEK (n = 24)	8320	0.79	-	-
QALYs (EQ-5D-5L), corrected for baseline utility difference, and costs from societal perspective	DMEK (n = 29)	8851	0.86	Dominated	28/27/27/**30**/33/36
	UT-DSAEK (n = 24)	8320	0.86	-	-
Subgroup analyses					
QALYs (HUI3) and costs from societal perspective, excluding patients who underwent rebubbling or regraft	DMEK (n = 23)	8097	0.70	2132/QALY	44/32/20/**9**/3/3
	UT-DSAEK (n = 23)	8341	0.81	-	-
QALYs (HUI3) and costs from societal perspective, excluding patients who underwent corneal transplantation or cataract surgery of the second eye	DMEK (n = 18)	9428	0.70	Dominated	26/24/21/**18**/16/17
	UT-DSAEK (n = 15)	8670	0.76	-	-

Abbreviations: CDVA, corrected distance visual acuity; DMEK, Descemet membrane endothelial keratoplasty; EQ-5D-5L, EuroQol-5D-5L; HUI3, Health Utilities Index Mark 3; logMAR, logarithm of the minimum angle of resolution; QALY, quality-adjusted life year; UT-DSAEK, ultrathin Descemet stripping automated endothelial keratoplasty; VFQ-25, Visual Functioning Questionnaire-25.

[a]Values represent pooled means based on 20 multiple imputation data sets.

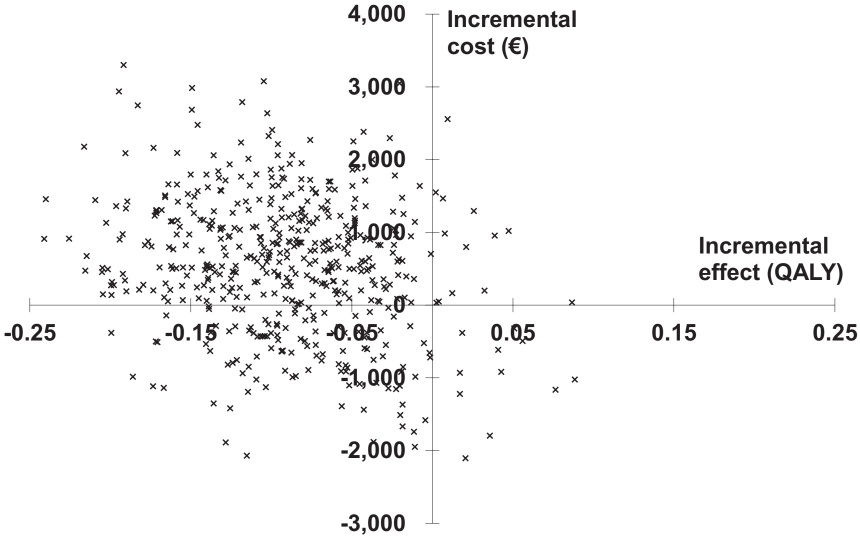

FIGURE 1 Cost-effectiveness plane showing the incremental costs from a societal perspective (y-axis) and incremental HUI3 QALYs (x-axis) of treatment with DMEK compared to UT-DSAEK within a time horizon of 12 months postoperatively. Each data point represents one bootstrapped estimate of incremental costs and QALYs. DMEK, Descemet membrane endothelial keratoplasty; HUI3, health utilities index mark 3; QALY, quality-adjusted life year; UT-DSAEK, ultrathin Descemet stripping automated endothelial keratoplasty.

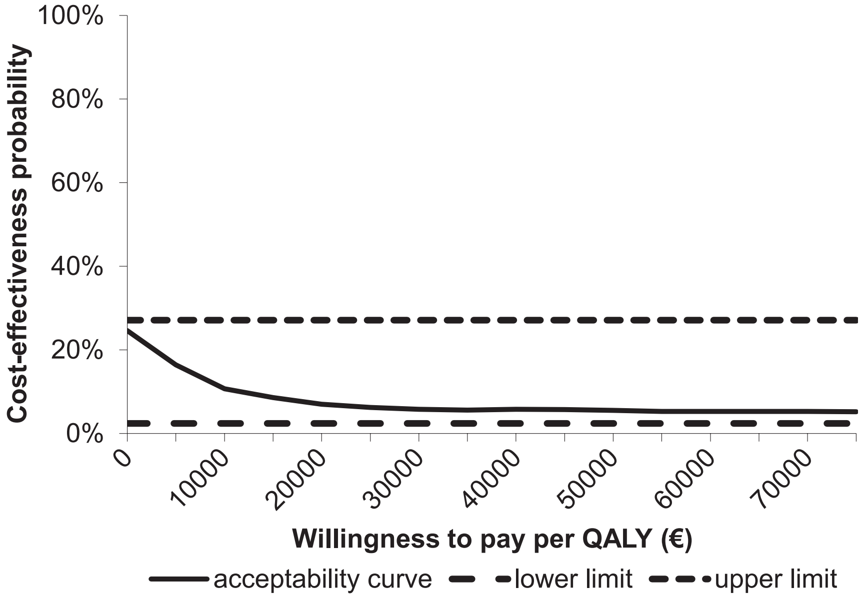

FIGURE 2 Cost-effectiveness acceptability curve for the incremental costs per HUI3 QALY gained (from a societal perspective) within a time horizon of 12 months after DMEK or UT-DSAEK. The graph shows the probabilities that DMEK and UT-DSAEK are cost-effective for a range of maximum amounts of money health policy-makers are willing to pay per QALY. The cost-effectiveness probability of DMEK equals 100% minus the cost-effectiveness probability of UT-DSAEK. DMEK, Descemet membrane endothelial keratoplasty; HUI3, health utilities index mark 3; QALY, quality-adjusted life year; UT-DSAEK, ultrathin Descemet stripping automated endothelial keratoplasty.

losses. Nonetheless, there are some study limitations that may have affected the results of the cost analysis.

First, the learning curve for DMEK may have been longer than initially anticipated for inclusion of corneal surgeons in the current study. The main cause of the higher costs in the DMEK group in the current study was the occurrence of additional rebubbling and regraft procedures. While only one rebubbling procedure (4%) occurred in the UT-DSAEK group during the 12-month follow-up, the rebubbling rate and regraft rates were 21% and 7%, respectively, in the DMEK group. A previous study using data of 752 DMEK procedures (performed between 2011 and 2018) from the Netherlands Organ Transplant Registry, reported that 19% of patients underwent a rebubbling procedure and 11% of patients developed early graft failure (Dunker et al., 2021; Dunker, Armitage, et al., 2021). However, the study reported a significant reduction in the rebubbling and graft failure rate over time to 14% and 4%, respectively, by 2018. While these rates are still higher than those for UT-DSAEK found in the current study, it suggests that the difference in costs between both treatments might be smaller with increased surgeon experience with DMEK. Surgeon experience has indeed been proposed as an important risk factor for graft detachment and graft failure (Oellerich et al., 2017; Schrittenlocher et al., 2018). Various perioperative and surgical refinements, such as methods for precutting DMEK tissues, insertion techniques, and type of gas used to fill the anterior chamber, may also affect the rebubbling and regraft rate (Parekh et al., 2018).

Second, the follow-up was 1 year postoperatively. Late events such as late graft failure or graft rejection may impact long-term cost-effectiveness. Price et al. (2018) investigated 5-year graft survival in FED patients that had undergone EK. While the cumulative incidence of a graft rejection episode was higher in DSAEK patients (n = 1312) than in DMEK patients (n = 705; 7.9% vs. 2.6%), graft survival was 93% in both groups. Similarly, Woo et al. (2019) demonstrated that 5-year survival of DMEK (n = 77) and DSAEK (n = 165) grafts in FED patients was 98.7% and 96.2%, respectively. Higher rates of graft rejection episodes and possibly slightly lower graft survival rates in (UT)DSAEK patients would increase costs and reduce quality of life outcomes of UT(DSAEK) as compared to DMEK in the long term. As a result, a long-term analysis using a lifetime time horizon could favour the cost-effectiveness of DMEK compared to UT-DSAEK. Such analysis would require a model-based approach (i.e., decision analytic model) using available long-term data on graft survival and other complications, and might include data from the current study on costs and QALYs.

Third, self-administered patient questionnaires were used to assess costs that could not be derived from electronic medical records. Underreporting may have occurred as a result of recall bias. However, since the study was randomized and patients were blinded to treatment allocation, it is not expected that underreporting occurred preferentially in one study group.

Fourth, the cost price of precut corneal tissues was uncertain and previously reported costs were used (van den Biggelaar et al., 2011). Both DMEK and UT-DSAEK tissues were prepared at the same eye bank using similar methods for storage and transportation. However, preparation of DMEK tissues was more labor intensive.

Utilities were measured with two well-validated generic HRQL questionnaires. Utilities measured with the EQ-5D-5L questionnaire showed only a minor improvement compared to baseline in both groups. The presumable cause is that the EQ-5D-5L questionnaire includes only five generic questions, and none pertain to visual functioning. In contrast, the HUI3 questionnaire includes two questions on visual functioning, and both groups showed a clear improvement in HUI3 utility postoperatively. There was an imbalance in baseline HUI3 utility between both groups, and a sensitivity analysis was performed to correct for this. However, after correction, the mean HUI3 QALY in the DMEK group was still less than in the UT-DSAEK group, despite slightly better CDVA and similar VFQ-25 composite scores. Possible explanations for this discrepancy include the higher incidence of postoperative complications in the DMEK group which prolonged recovery times, and the fact that utilities measured during the study period were susceptible to non-ophthalmologic health events (i.e., reduction in quality of life due to other health problems), which can affect mean QALYs, especially with smaller sample sizes. In addition, a number of patients underwent second-eye corneal transplantation or cataract surgery, which may impact quality of life. However, the proportion of patients that underwent second-eye procedures was equal, and a subgroup analysis that excluded patients who underwent second-eye procedures showed results similar to the base case analysis (DMEK 0.70 QALY; UT-DSAEK 0.76 QALY).

This study was performed in the Netherlands using Dutch cost prices, and the results are therefore applicable to the Dutch healthcare system. However, the results can be translated to other countries. Volumes of resource use were reported separately whenever possible to facilitate transferability. In addition, for those costs where volumes were not reported, the PPP for GDP as reported by the Organization for Economic Co-operation and Development can be used to convert those costs to local currencies.

In conclusion, this study found that DMEK is not cost-effective compared to UT-DSAEK within a time horizon of 12 months postoperatively. The main reason was the higher incidence of secondary procedures (rebubblings and regrafts) in the DMEK group, which increased healthcare costs. Future registry studies with long-term follow-up may help in elucidating the true incidence of secondary procedures in DMEK in the long term and in determining graft survival, which both may have an important impact on cost-effectiveness.

ACKNOWLEDGEMENTS

Presentations at meetings: European Society of Cataract and Refractive Surgeons (ESCRS) congress, Paris, France, September 2019.

FUNDING INFORMATION

This work was supported by The Netherlands Organization for Health Research and Development, The Hague, The Netherlands; Algemene Nederlandse Vereniging Ter Voorkoming Van Blindheid, Doorn, The Netherlands; Oogfonds, Utrecht, The Netherlands; Dr. F.P. Fischer-Stichting, Utrecht, The Netherlands; and Landelijke Stichting Blinden en Slechtzienden (LSBS), Ede, The Netherlands. The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Mor M. Dickman is a consultant at Chiesi Farmaceuticals. Rudy M.M.A. Nuijts is a consultant at Alcon (Fort Worth, TX, USA) and ThéaPharma (Clermont-Ferrand, France), receives financial support for research from Alcon and Ophtec (Groningen, the Netherlands), and receives lecture fees from Alcon. Robert P.L. Wisse receives financial support from Carl-Zeiss (Breda, The Netherlands) and ThéaPharma, and is equity owner of Easee (Amsterdam, The Netherlands.). Pieter J. Kruit is employee of ETB-BISLIFE (Leiden, Netherlands). All other authors report no financial disclosures.

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How to cite this article: Simons, R.W.P., Dunker, S.L., Dickman, M.M., Nuijts, R.M.M.A., van den Biggelaar, F.J.H.M., Dirksen, C.D. (2023) Trial-based cost-effectiveness analysis of Descemet membrane endothelial keratoplasty (DMEK) versus ultrathin Descemet stripping automated endothelial keratoplasty (UT-DSAEK). *Acta Ophthalmologica*, 101, 319–329. Available from: https://doi.org/10.1111/aos.15280

APPENDIX A

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