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

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ABSTRACT.

Purpose: **To evaluate the cost-effectiveness of ultrathin Descemet stripping automated endothelial keratoplasty (UT-DSAEK) versus standard DSAEK.**

Methods: **A cost-effectiveness analysis using data from a multicentre randomized clinical trial was performed. The time horizon was 12 months postoperatively. Sixty-four eyes of 64 patients with Fuchs' endothelial dystrophy were included and randomized to UT-DSAEK (n = 33) or DSAEK (n = 31). 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 questionnaire. The main outcome was the incremental cost-effectiveness ratio (ICER; incremental societal costs per QALY).**

Results: **Societal costs were €9431 (US$11 586) for UT-DSAEK and €9110 (US $11 192) for DSAEK. Quality-adjusted life years (QALYs) were 0.74 in both groups. The ICER indicated inferiority of UT-DSAEK. The cost-effectiveness probability ranged from 37% to 42%, assuming the maximum acceptable ICER ranged from €2500–€80 000 (US $3071–US$98 280) per QALY. Additional analyses were performed omitting one UT-DSAEK patient who required a regraft [ICER €9057 (US$11 127) per QALY, cost-effectiveness probability: 44–62%] and correcting QALYs for an imbalance in baseline utilities [ICER €23 827 (US$29 271) per QALY, cost-effectiveness probability: 36–59%]. Furthermore, the ICER was €2101 (US$2581) per patient with clinical improvement in best spectacle-corrected visual acuity (≥0.2 logMAR) and €3274 (US$4022) per patient with clinical improvement in National Eye Institute Visual Functioning Questionnaire-25 composite score (≥10 points).**

Conclusion: **The base case analysis favoured DSAEK, since costs of UT-DSAEK were higher while QALYs were comparable. However, additional analyses revealed no preference for UT-DSAEK or DSAEK. Further cost-effectiveness studies are required to reduce uncertainty.**

Key words: corneal transplantation – cost-effectiveness – costs – Descemet stripping automated endothelial keratoplasty – Fuchs' endothelial dystrophy – quality-adjusted life years – ultrathin Descemet stripping automated endothelial keratoplasty

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Introduction

Fuchs' endothelial dystrophy (FED) is the most common indication for corneal transplantation. (Park et al. 2015). Without treatment, many patients with FED would become visually impaired and accrue substantial costs to society (The Lewin Group 2013).

Endothelial keratoplasty (EK), involving selective transplantation of posterior corneal layers, accounts for over 90% of keratoplasties in FED patients (Eye Bank Association of America (EBAA) 2016; Dickman et al. 2016b). Descemet stripping automated endothelial keratoplasty (DSAEK) is the most frequently performed subtype of EK (Park et al. 2015). Previous cost-effectiveness analyses demonstrated that DSAEK and other (less advanced) EK techniques were cost-effective compared to traditional full-thickness penetrating keratoplasty (Beauchemin et al. 2010; van den Biggelaar et al. 2012; Bose et al. 2013; Prabhu et al. 2013). In recent years, innovative EK techniques using thinner corneal grafts have emerged aiming to further improve visual outcomes (Neff et al. 2011). These include Descemet membrane endothelial keratoplasty (DMEK) and ultrathin DSAEK (UT-DSAEK). While DMEK is technically challenging and considered unsuitable

for eyes with difficult anatomy, UT-DSAEK may provide results superior to DSAEK using grafts that are easier to prepare and manipulate than DMEK grafts (Busin et al. 2012, 2013). A recent cost-effectiveness study demonstrated that DMEK was cost-effective compared to DSAEK from a societal perspective (Gibbons et al. 2019).

Our study group recently reported a multicentre randomized controlled clinical trial (RCT) that compared visual and refractive outcomes, endothelial cell loss and complications up to 12 months after UT-DSAEK or DSAEK in FED patients. Ultrathin Descemet stripping automated endothelial keratoplasty resulted in faster and better visual recovery, with similar hyperopic shift, endothelial cell loss and complication profile (Dickman et al. 2016a). Despite encouraging clinical outcomes, implementation of UT-DSAEK may be associated with increased costs from a healthcare perspective. Possible causes include longer surgery duration and additional surgical procedures due to graft dislocations or graft failure. A cost-effectiveness analysis is required to support health policymakers in making evidence-based decisions on allocation of scarce healthcare resources. Many countries have published guidelines on the preferred methods for conducting and reporting cost-effectiveness analyses. These guidelines advocate quality-adjusted life years (QALYs) as the primary measure of effectiveness (Drummond et al. 2015). Quality-adjusted life years (QALYs) are based on generic health-related quality of life (HRQL) measured at various points in time using designated questionnaires. They incorporate both changes in quality of life and life expectancy. Quality-adjusted life years (QALYs) are applied in all fields in health care to investigate the cost-effectiveness of different types of healthcare interventions in different populations in a standardized manner. Using the cost per QALY, health policymakers may allocate limited healthcare resources based on a predefined willingness to pay per QALY.

In this paper, we report a trial-based cost-effectiveness analysis of UT-DSAEK versus DSAEK, from a societal perspective.

Materials and Methods

This economic evaluation was conducted alongside a multicentre RCT at four tertiary medical centres in the Netherlands (Maastricht University Medical Center+, The Rotterdam Eye Hospital, University Medical Center Utrecht and University Medical Center Groningen). The study was performed from a healthcare and societal perspective with a time horizon of 12 months, starting from the day of surgery. Institutional review boards of all centres approved the study before start of patient recruitment. Participants were recruited between June 2013 and April 2014 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 (www.trialregister.nl, identifier NTR 3104).

Study procedures

The study population and study procedures were described previously (Dickman et al. 2016a). Briefly, FED patients who required corneal transplantation due to irreversible corneal endothelial dysfunction were recruited. One eye per patient was included in the study. Inclusion in the economic evaluation also depended on completion of quality-of-life questionnaires during at least one follow-up visit. The sample size was based on best spectacle-corrected visual acuity (BSCVA), the primary outcome of the study.

Patients were randomized to UT-DSAEK or DSAEK. All tissues were precut by a cornea bank (Euro Tissue Bank, Beverwijk, the Netherlands), and treatment allocation was disclosed solely to the cornea bank. Methods for selection, preservation and dissection were identical for UT-DSAEK and DSAEK corneas.

Surgery was performed by experienced cornea surgeons using identical techniques for UT-DSAEK and DSAEK. Patients were either pseudophakic or underwent combined phacoemulsification with intraocular lens implantation and corneal transplantation (triple procedure). 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.

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 2014 Euros (€) using the Consumer Price Index (Centraal Bureau voor de Statistiek 2018) and to US$ using the 2014 purchasing power parity for gross domestic product (PPP for GDP; US $1.00 = €0.814) (Organisation for Economic Co-operation and Development 2018).

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 and productivity loss. The patient-reported resource use questionnaire had a 3-month recall time period and was completed 3, 6 and 12 months postoperatively. All recurring patient-reported resource use reported at 12 months was doubled to account for the lack of data on resource use at 9 months postoperatively.

Operating room times were valued using integral cost prices provided by Maastricht University Medical Center+. While operating room cost prices may vary between different centres, cost prices of only one centre were chosen to calculate costs for all patients in order to avoid bias when using different cost prices for patients included in different centres. Cost prices 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. 2011). Standardized prices provided by national guidelines for cost analysis were used to value hospital admissions, outpatient visits, general practitioner visits, home care, travel 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). Other visual aids (loupes, television spectacles) were valued based on market prices (Worldwidevision, Oisterwijk, the Netherlands). Prescription medication was valued using reimbursement prices (including a standard pharmacy service fee) (Zorginstituut Nederland 2018), while over-the-counter medication (0.1% sodium hyaluronate eye drops in one patient) was valued using producer-recommended prices (URSAPHARM Benelux BV, Helmond, the Netherlands).

Effectiveness

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

Health-related quality of life (HRQL) was determined using the Health Utilities Index Mark 3 questionnaire (HUI3; Health Utilities Inc., Hamilton, ON, Canada), which is one of few HRQL questionnaires that includes questions about visual functioning. The HUI3 assesses eight dimensions of health (vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain) 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). 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 (Mangione et al. 2001). Thirteen optional questions are available to increase accuracy. Responses on the items are scored 0 to 100, and item subset scores can be averaged to obtain 12 subscales (e.g. general health, distance activities and driving). Higher scores represent better visual functioning. In addition, all subscales, excluding the general health scale, can be averaged to obtain a composite score (Mangione et al. 2001).

Best spectacle-corrected visual acuity (BSCVA) was assessed using a 100% contrast Early Treatment Diabetic Retinopathy Study chart (Vector Vision, Greenville, OH, USA) at 4 m distance and expressed in logarithm of the minimum angle of resolution (logMAR). Outcome assessors were blinded to allocated treatment at all follow-up visits.

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

Cost-effectiveness analyses

To assess cost-effectiveness, the incremental cost-effectiveness ratio (ICER) was calculated, which expresses the incremental costs of UT-DSAEK 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 2010 for Windows; Microsoft, Redmond, WA, USA). Bootstrap results were plotted on cost-effectiveness planes. Cost-effectiveness acceptability curves were constructed to estimate the probability that UT-DSAEK was cost-effective based on a range of ceiling ratios for the ICER. Ceiling ratios reflect the maximum price health policymakers 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$24 570) per QALY (Zwaap et al. 2015). No ceiling ratios for other types of (clinical or patient-reported) outcomes exist.

In the base case analysis, cost-effectiveness was based on QALYs and costs from a societal perspective over 12-month follow-up.

Secondary analyses were performed using alternative effectiveness measures and costs from a healthcare perspective. Effectiveness measures included clinical improvement in BSCVA (≥0.2 logMAR improvement) and NEI VFQ-25 composite score (≥10-point improvement) (Rosser et al. 2003; Lindblad & Clemons 2005). One UT-DSAEK patient suffered primary graft failure and required a regraft during follow-up. Graft failure is a rare and costly event that may distort the cost-effectiveness analysis results in a relatively small study population. Therefore, a post hoc secondary analysis was performed, identical to the base case analysis, excluding the patient in question.

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. In addition, to explore uncertainty in operating room costs, two-one-way sensitivity analyses were performed in which operating room costs were increased and decreased by 25%.

Statistical analysis

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 3.3.2 for Windows, The R Foundation, Vienna, Austria). The imputation regression model included the following covariates: treatment group, age, sex and study centre. Twenty imputation sets were obtained using 100 iterations per imputation. Imputation sets were analysed separately, and the results were pooled.

Differences between treatment groups were statistically tested with independent samples *t*-tests. Paired samples *t*-tests were used to test differences between preoperative and postoperative measurements (IBM SPSS Statistics Version 23.0 for Windows; IBM, Armonk, NY, USA). A p value < 0.05 was considered statistically significant.

Results

Of 187 patients assessed for eligibility for participation, 117 did not meet the inclusion criteria. Four patients

declined participation. Remaining patients were randomized to DSAEK (n = 32) and UT-DSAEK (n = 34). All patients received the allocated treatment. In the UT-DSAEK group, one patient suffered primary graft failure following intraoperative graft trauma unrelated to the intervention and this patient chose to withdraw from the study. In the DSAEK group, one patient deceased after 3-month follow-up (unrelated to the intervention). Neither patient completed postoperative quality-of-life questionnaires resulting in exclusion from the economic evaluation. Consequently, 64 eyes of 64 patients were included in the economic evaluation (DSAEK 31 patients, UT-DSAEK 33 patients). Twenty-seven DSAEK and 27 UT-DSAEK patients completed all questionnaires; the baseline questionnaire was missing in one patient in both treatment groups; one postoperative questionnaire was missing in one DSAEK and two UT-DSAEK patients; two postoperative questionnaires were missing in two DSAEK patients and three UT-DSAEK patients.

Mean patient age was 70.2 years [standard deviation (SD): 10.0] and 70.7 years (SD: 10.1) in the UT-DSAEK and DSAEK group, respectively. There were more males in the DSAEK group (58%) than in the UT-DSAEK group (42%). The frequency of triple procedures was comparable [UT-DSAEK 9 (27%), DSAEK 10 (32%)]. In the UT-DSAEK group, five patients (15%) underwent corneal transplantation of the non-study eye during follow-up, in three patients (9%) combined with cataract surgery. In the DSAEK group, six patients (19%) underwent second-eye corneal transplantation during follow-up, combined with cataract surgery in four patients (13%). One DSAEK patient (3%) underwent second-eye cataract surgery without a corneal transplantation. Costs directly related to second-eye surgery were not included in the cost analysis. In both treatment groups, seven patients (DSAEK 23%, UT-DSAEK 21%) had paid employment.

The following percentages of data were missing and imputed for DSAEK and UT-DSAEK, respectively: HUI3 5.4% and 7.9%, BSCVA 3.2% and 3.8%, VFQ-25 7.0% and 9.8%, and cost data 5.3% and 8.2%.

Costs

Mean resource use and costs are reported in Table 1. Societal costs averaged €9431 (US$11 586) in the UT-DSAEK group and €9110 (US $11 192) in the DSAEK group, that is a €321 (US$394) difference. From a healthcare perspective, costs averaged €7881 (US$9682) and €7565 (US$9294) for UT-DSAEK and DSAEK, respectively (difference €316 [US$388]). Notably, one patient in the UT-DSAEK group suffered graft failure shortly after surgery and required a regraft procedure.

Effectiveness

Effectiveness outcomes are shown in Table 2 and Figure 1.

Mean utility increased significantly after UT-DSAEK [0.14 increase, standard error of the mean (SE): 0.04, $p < 0.001$, paired t-test] and DSAEK (0.11 increase, SE: 0.04, $p = 0.003$,

Table 1. Mean resource use and costs from a healthcare and societal perspective (in 2014 €) of DSAEK and UT-DSAEK

		Resource use, mean (SE)		Costs, mean (SE), €	
	Cost per unit (€)	DSAEK (n = 31)	UT-DSAEK (n = 33)	DSAEK (n = 31)	UT-DSAEK (n = 33)
Healthcare sector					
Corneal transplantation OR time					
General operating room costs	12.14/min	97 (4.1)	99 (4.1)	1183 (50.0)	1202 (49.8)
Ophthalmology costs	3.61/min	71 (3.6)	73 (3.5)	258 (12.9)	262 (12.5)
Secondary procedures[†]	Variable	Variable		161 (61.6)	189 (79.9)
Cornea	4067/cornea	1.00	1.03	4067	4190
Hospital admission					
Day care	276/day	0.90 (0.1)	0.94 (0.1)	249 (29.6)	259 (26.7)
Inpatient days	642/day	0.48 (0.2)	0.67 (0.2)	311 (106.8)	428 (133.0)
Outpatient visits					
Ophthalmologist	163/visit	7.1 (0.3)	7.2 (0.2)	1152 (51.8)	1181 (38.9)
Other specialists	163/visit	0.10 (0.1)	0 (0)	16 (11.7)	0 (2.7)
Medication	Variable	Variable		151 (17.5)	126 (6.6)
General practitioner visits	Variable	Variable		10 (6.8)	23 (12.4)
Home care	50/hr	0.15 (0.1)	0.42 (0.2)	7 (7.3)	21 (11.6)
Subtotal				7565 (182)	7881 (293)
Patient and family costs					
Visual aids	Variable	Variable		329 (59.3)	199 (49.7)
Travel costs	Variable	Variable		28 (11.5)	13 (4.1)
Subtotal				357 (61)	211 (50)
Other sectors					
Productivity costs (paid work)	34.75/hr	34.2 (18.5)	38.5 (20.0)	1188 (643.4)	1338 (696.3)
Subtotal				1188 (643)	1338 (696)
Total costs from societal perspective				9110 (710)	9431 (736)

DSAEK = Descemet stripping automated endothelial keratoplasty, UT-DSAEK = ultrathin Descemet stripping automated endothelial keratoplasty, OR = operating room, SE = standard error of the mean.
[†]Includes rebubblings, corneal regrafts and other related (non-surgical) procedures.

Table 2. Measures of effectiveness at baseline and 3, 6 and 12 months after DSAEK or UT-DSAEK

	DSAEK (n = 31)	UT-DSAEK (n = 33)	p Value
HUI3 utility, mean (SE)			
T0	0.64 (0.04)	0.62 (0.04)	0.734
T1	0.78 (0.04)	0.74 (0.05)	0.500
T2	0.75 (0.04)	0.76 (0.04)	0.906
T3	0.74 (0.05)	0.76 (0.05)	0.802
Difference (T3–T0)	0.11 (0.04)†	0.14 (0.04)‡	0.466
Quality-adjusted life years, mean (SE)	0.74 (0.04)	0.74 (0.04)	0.912
BSCVA, mean (SE), logMAR			
T0	0.35 (0.04)	0.37 (0.03)	0.773
T1	0.28 (0.03)	0.17 (0.02)	0.001
T2	0.24 (0.02)	0.14 (0.02)	0.001
T3	0.19 (0.02)	0.13 (0.02)	0.037
Difference (T3–T0)	−0.16 (0.04)‡	−0.24 (0.03)‡	0.136
NEI VFQ-25 composite score, mean (SE)			
T0	70.2 (2.7)	69.6 (3.0)	0.885
T1	80.9 (2.6)	82.0 (2.0)	0.738
T2	82.4 (2.1)	83.5 (1.9)	0.697
T3	83.5 (2.4)	85.9 (1.7)	0.410
Difference (T3–T0)	13.3 (2.2)‡	16.3 (2.6)‡	0.383

BSCVA = best spectacle-corrected visual acuity, DSAEK = Descemet stripping automated endothelial keratoplasty, HUI3 = Health Utilities Index Mark 3, logMAR = logarithm of the minimum angle of resolution, NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire-25, SE = standard error of the mean, T0 = baseline, T1 = 3 months postoperatively, T2 = 6 months postoperatively, T3 = 12 months postoperatively, UT-DSAEK = ultrathin Descemet stripping automated endothelial keratoplasty.
†p Value = 0.003.
‡p Value < 0.001.

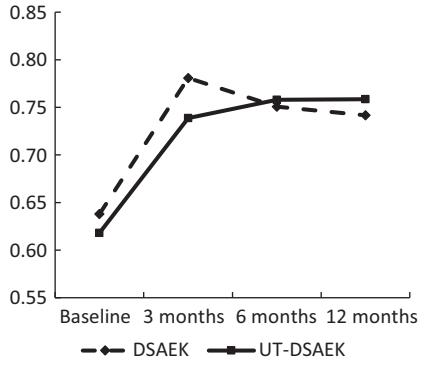

Fig. 1. Health-related quality of life (utility) at baseline and 3, 6 and 12 months after DSAEK or UT-DSAEK. DSAEK = Descemet stripping automated endothelial keratoplasty, UT-DSAEK = ultrathin Descemet stripping automated endothelial keratoplasty.

paired t-test). However, there were no significant differences in utilities between treatment groups. Mean QALYs were identical (0.74, SE: 0.04, p = 0.912, independent samples t-test). Excluding patients who underwent corneal transplantation and/or cataract surgery in the non-study eye during follow-up resulted in QALYs of 0.71 (UT-DSAEK) and 0.75 (DSAEK).

Mean BSCVA and NEI VFQ-25 composite score increased significantly in both groups. In addition, mean BSCVA was significantly better in the UT-DSAEK group at all follow-up measurements. While the mean NEI VFQ-25 composite score at 12 months postoperatively was slightly higher in the UT-DSAEK group (85.9, SE: 1.7, versus 83.5, SE: 2.4), the difference was not statistically significant (p = 0.383, independent samples t-test).

Cost-effectiveness

The results of the cost-effectiveness analyses are listed in Table 3.

In the base case analysis from a societal perspective, costs of UT-DSAEK were €321 (US$394) higher while QALYs were comparable. Based on the ICER point estimate, UT-DSAEK was inferior to DSAEK. The data were bootstrapped, and the results were plotted in a cost-effectiveness plane (Figure 2) and cost-effectiveness acceptability curve (Figure 3). The probability that UT-DSAEK was cost-effective compared to DSAEK ranged from 37% to 42% assuming the ICER ceiling ratio ranged from €2500 (US$3071) to €80 000 (US $98 280) per QALY. Assuming health policymakers in the Netherlands are willing to pay €20 000 (US$24 570) per QALY, the cost-effectiveness probability was 37% (Zwaap et al. 2015).

Secondary analyses revealed that the ICER was €2101 (US$2581) per patient with clinical improvement in BSCVA and €3274 (US$4022) per patient with clinical improvement in NEI VFQ-25 composite score.

A post hoc secondary analysis excluding an UT-DSAEK patient who required a regraft showed that societal costs were €146 (US$179) higher and QALYs were 0.02 higher in the UT-DSAEK group. The ICER was €9057 (US$11 127) per QALY, and the cost-effectiveness probability was 54%.

A sensitivity analysis showed that QALYs were 0.02 higher in the UT-DSAEK group after correcting for baseline utility differences. The ICER was €23 827 (US$29 271) per QALY. The cost-effectiveness probability was 49%. Finally, two sensitivity analyses that explored the effects of increasing or decreasing operating room costs by 25% revealed no important differences in the cost-effectiveness probability of UT-DSAEK.

Discussion

This trial-based cost-effectiveness analysis evaluated the cost-effectiveness of UT-DSAEK versus DSAEK. In the base case analysis from a societal perspective, UT-DSAEK was slightly more costly than DSAEK and comparably effective. Uncertainty analysis revealed a 37% probability that UT-DSAEK was cost-effective compared to DSAEK. Secondary analyses from a healthcare perspective using clinical outcomes resulted in seemingly favourable ICERs. However, health policymakers have not defined the willingness to pay for outcomes other than QALYs, making it difficult to interpret these ICERs (Zwaap et al. 2015). A post hoc secondary analysis was performed because one UT-DSAEK patient suffered primary graft failure and required a regraft, which affected cost-effectiveness outcomes. The reasoning was that, due to the limited sample size, the incidence of graft failure in this study likely does not reflect the true incidence of graft failure. The ICER improved to €9057 (US $11 127) per QALY with a 54% cost-effectiveness probability.

Table 3. Results of the cost-effectiveness analyses of DSAEK versus UT-DSAEK

	Mean costs (€)	Mean effects	Incremental cost-effectiveness ratio (€)	Probability cost-effective at ceiling ratio € 2500/5000/10 000/20 000/50 000/80 000 (%)
Base case analysis				
QALYs and costs from societal perspective, 12-month follow-up				
DSAEK	9110	0.74	—	—
UT-DSAEK	9431	0.74	Inferior	37/37/37/37/40/42
Secondary analyses				
Clinical improvement in BSCVA (0.2 logMAR or more) and costs from healthcare perspective, 12-month follow-up				
DSAEK	7565	0.36	—	—
UT-DSAEK	7881	0.52	2101/patient	57/74/83/87/88/88
Clinical improvement in NEI VFQ-25 composite score (≥10 points) and costs from healthcare perspective, 12-month follow-up				
DSAEK	7565	0.50	—	—
UT-DSAEK	7881	0.60	3274/patient	43/58/68/73/75/75
QALYs and costs from societal perspective excluding a patient with regraft, 12-month follow-up				
DSAEK	9110	0.74	—	—
UT-DSAEK	9256	0.76	9057/QALY	44/45/48/54/60/62
Sensitivity analyses				
QALYs, corrected for baseline utility difference, and costs from societal perspective, 12-month follow-up				
DSAEK	9110	0.74	—	—
UT-DSAEK	9431	0.76	23 827/QALY	36/39/42/49/58/59
QALYs and costs from societal perspective, 12-month follow-up, operating room costs increased by 25%				
DSAEK	9490	0.74	—	—
UT-DSAEK	9844	0.74	Inferior	35/34/35/36/41/43
QALYs and costs from societal perspective, 12-month follow-up, operating room costs decreased by 25%				
DSAEK	8730	0.74	—	—
UT-DSAEK	9018	0.74	Inferior	38/37/37/39/42/42

BSCVA = best spectacle-corrected visual acuity, DSAEK = Descemet stripping automated endothelial keratoplasty, logMAR = logarithm of the minimum angle of resolution, NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire-25, QALYs = quality-adjusted life years, UT-DSAEK = ultrathin Descemet stripping automated endothelial keratoplasty.

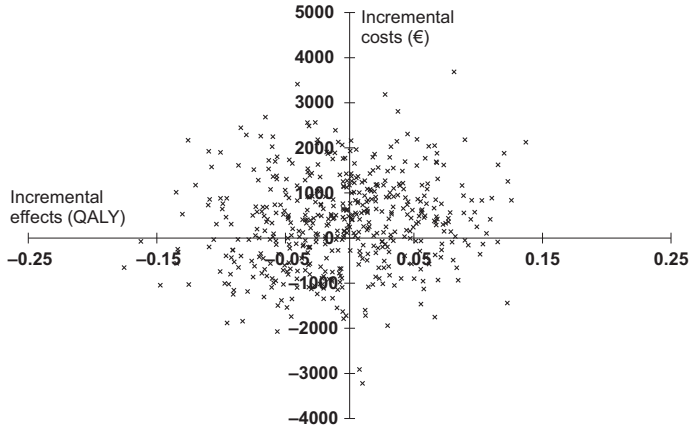

Fig. 2. Cost-effectiveness plane showing the incremental costs from a societal perspective (*y*-axis) and incremental QALYs (*x*-axis) of treatment with UT-DSAEK compared to DSAEK within a time horizon of 12 months postoperatively. Each data point represents one bootstrapped estimate of incremental costs and QALYs. DSAEK = Descemet stripping automated endothelial keratoplasty, QALY = quality-adjusted life year, UT-DSAEK = ultrathin Descemet stripping automated endothelial keratoplasty.

Utilities were measured with a well-validated generic HRQL questionnaire. A clear improvement in generic HRQL was demonstrated following either corneal transplantation technique; however, the observation that UT-DSAEK led to better visual acuity outcomes compared to DSAEK did not result in HRQL differences detectable by the HRQL questionnaire. Generic HRQL questionnaires are necessary to enable calculation of QALYs. However, because generic HRQL questionnaire aims to assess an individual's overall health status, these questionnaires do not explore the various health dimensions in as much detail as for instance a disease-specific questionnaire would. As a result, generic HRQL questionnaires are less responsive to small improvements in specific dimensions of health. Disease-specific quality-of-life questionnaires (such as the NEI VFQ-25) might be more responsive, but do not allow for calculation of QALYs (Drummond et al. 2015). It should be noted that a number of patients in the study underwent second-eye surgery during follow-up (corneal transplantation, cataract surgery or both). In the UT-DSAEK group, 15% of patients underwent second-eye surgery, compared to 22% of patients in the DSAEK group. However, a subgroup analysis of patients that did not undergo second-eye surgery during follow-up showed that this imbalance did not appear to lead to more favourable QALYs in the DSAEK group (data not shown).

This study aimed to accurately estimate incremental costs of UT-DSAEK by including all types of resource use potentially affected, for example productivity losses. Nonetheless, a number of study limitations may have affected

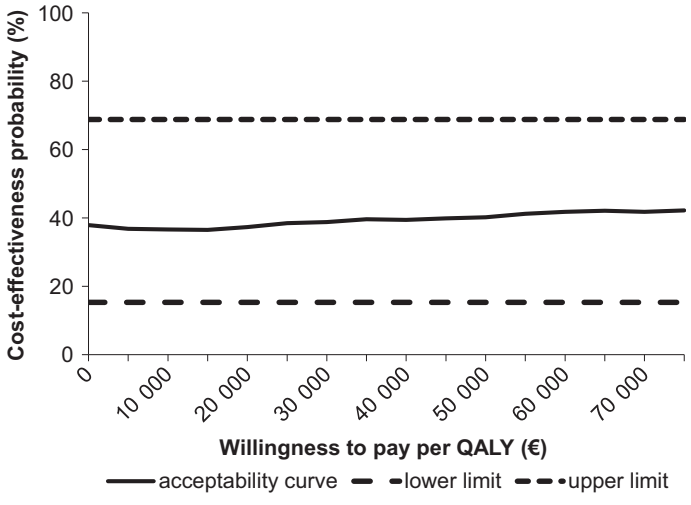

Fig. 3. Cost-effectiveness acceptability curve for the incremental costs per QALY gained (from a societal perspective) within a time horizon of 12 months after UT-DSAEK compared to DSAEK. The graph shows the probabilities that UT-DSAEK and DSAEK are cost-effective for a range of maximum amounts of money health policymakers are willing to pay per QALY. The cost-effectiveness probability of DSAEK equals 100% minus the cost-effectiveness probability of UT-DSAEK. DSAEK = Descemet stripping automated endothelial keratoplasty, QALY = quality-adjusted life year, UT-DSAEK = ultrathin Descemet stripping automated endothelial keratoplasty.

accuracy of the cost analysis. First, use of a self-administered patient questionnaire may have resulted in under-reporting of non-hospital-based resource use. In addition, patient-reported resource use was not measured at 9 months postoperatively. However, this was corrected for by doubling patient-reported resource use measured at 12 months postoperatively. As shown in Tables S1 and S2, patient-reported resource use was comparable at 6 and 12 months postoperatively. It is therefore not expected that the results have been biased by the missingness of these data. Second, the time horizon of this study was 12 months postoperatively. Little is known about possible differences in long-term graft survival between UT-DSAEK and DSAEK and its impact on cost-effectiveness. The longest follow-up after UT-DSAEK was reported in a non-comparative study by Busin et al. (2013), showing that graft survival after 2 years was 96.2%. In comparison, reported graft survival rates 2 years after DSAEK were 80.0–90.7% (Hjortdal et al. 2013; Ang et al. 2016; Heinzelmann et al. 2016). One study found a survival rate of 94% 3 years after DSAEK (Price et al. 2013). Lastly, the cost price of corneas was uncertain. In this study, all corneas were precut by a cornea bank. Methods for preparing precut UT-DSAEK and DSAEK corneas and numbers of lost donor tissues in both groups were similar (Dickman et al. 2016a). Therefore, cost differences were not expected and previously reported costs were used instead (van den Biggelaar et al. 2011).

The sample size calculation for the study was based on BSCVA as the primary outcome. Indeed, sample size calculations in clinical trial-based economic evaluations are commonly based on clinical outcomes rather than economic outcomes. However, in economic evaluations, the aim is not to test a predefined hypothesis using traditional statistical methods, but rather to support health policymakers in making reimbursement decisions. To achieve this, economic evaluations estimate average costs and effects of the comparative interventions along with indicators of uncertainty, commonly represented by bootstrap analyses and cost-effectiveness acceptability curves displaying the probability of one treatment being cost-effective compared to alternatives (Claxton 1999; O'Sullivan et al. 2005; Petrou & Gray 2011).

Although this study was performed in the Netherlands and the cost analysis was based on national cost prices, the results can be translated to other countries. To improve transferability of the results, volumes of resource use were reported separately for most resources. In addition, the PPP for GDP can convert costs to other currencies and correct for differences in price levels between countries (Organisation for Economic Co-operation and Development 2018).

Health policymakers should consider both clinical and economic outcomes when deciding on the allocation of scarce healthcare resources. While UT-DSAEK leads to improved visual acuity, the base case analysis of this economic evaluation demonstrated a slight preference for DSAEK over UT-DSAEK. Further secondary and sensitivity analyses did not show a clear preference for either treatment. Additional studies are required to reduce uncertainty in the reported outcomes.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Mean resource use and costs from a healthcare and societal perspective (in 2014 €) of DSAEK (n = 31).
Table S2. Mean resource use and costs from a healthcare and societal perspective (in 2014 €) of UT-DSAEK (n = 33).