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Descemet membrane endothelial keratoplasty compared with ultrathin Descemet stripping automated endothelial keratoplasty: a meta-analysis

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ABSTRACT

Aims This study aims to compare the clinical outcome of Descemet membrane endothelial keratoplasty (DMEK) and ultrathin Descemet stripping automated endothelial keratoplasty (UT-DSAEK) in patients with corneal endothelial dysfunction due to Fuchs' endothelial dystrophy or pseudophakic bullous keratopathy.

Methods We conducted a meta-analysis using a literature search of Embase, PubMed, Cochrane CENTRAL, ClinicalTrials.gov and WHO ICTRP databases. We included randomised controlled trials (RCTs) and cohort studies that compared DMEK and UT-DSAEK (graft<130 µm), with a follow-up of ≥12 months, published until 20 February 2022. We used the Revised Cochrane risk-of-bias tool for RCTs and the Risk of Bias in Non-Randomised Studies-of Interventions system for cohort studies.

Results Out of 144 records, 8 studies (3 RCTs, 2 fellow-eye studies and 3 cohort studies) were included, encompassing 376 eyes, (N=187 DMEK vs N=189 UT-DSAEK). The 12-month logarithm of the minimum angle of resolution best-corrected visual acuity (BCVA) was better post-DMEK (mean difference −0.06 (95% CI −0.10 to −0.02)), but with higher rebubbling risk: OR 2.76 (95% CI 1.46 to 5.22). Heterogeneity was significant I^2=57%. Findings were consistent when excluding retrospective studies, including only studies with low risk of bias or RCTs only. An analysis of studies with mean DSAEK grafts <70 µm showed no significant difference in BCVA between the procedures. Publication bias was found in the BCVA analysis (Egger's test p=0.023).

Conclusions Post-DMEK BCVA is superior to post-UT-DSAEK when using <130 µm grafts. DSAEK grafts <70 µm may not significantly differ from DMEK. The higher risk of rebubbling with DMEK necessitates an appropriate selection of patients.

PROSPERO registration number CRD42022340805.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Recent studies suggested that Descemet membrane endothelial keratoplasty (DMEK) leads to a greater improvement in visual acuity than ultrathin Descemet stripping automated endothelial keratoplasty (DSAEK) for the treatment of corneal endothelial failure, but with a higher risk of complications.

WHAT THIS STUDY ADDS

⇒ DMEK leads to a slightly improved 12-month visual acuity compared with ultrathin (UT)-DSAEK. However, DSAEK grafts of <70 µm thickness could potentially achieve visual outcomes comparable to DMEK. The number needed to harm by choosing DMEK over UT-DSAEK is 9 eyes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The selection of the surgical technique should be patient tailored. Standardised terminology for thinner DSAEK grafts should be established. Further studies to investigate the implications of rebubbling on long-term graft survival as well as the incidence of rare complications such as graft rejection, graft failure or glaucoma are warranted. Developing a validated quality-of-life questionnaire for patients requiring keratoplasty could allow better understanding of this topic in the future.

INTRODUCTION

Corneal diseases are the third-leading cause of blindness worldwide.[1] Fuchs' endothelial dystrophy (FED), pseudophakic bullous keratopathy (PBK) and failed posterior lamellar keratoplasty are the leading causes of corneal pathologies requiring corneal transplantation in Western countries.[2–6] Descemet stripping endothelial keratoplasty (DSEK),[7] or its automated cutting version Descemet stripping automated endothelial keratoplasty (DSAEK), and Descemet membrane endothelial keratoplasty (DMEK) are the leading surgical treatments for endothelial failure.[8] Compared with DSAEK, DMEK is technically more challenging, has more contraindications,[9] higher risk of intraoperative tissue loss[4] and might increase the risk of graft dislocation necessitating rebubbling for graft repositioning.[2] However, DMEK offers a faster and greater improvement in best-corrected visual acuity (BCVA) and lower rejection rates,[1 9 10] likely due to the lack of donor stroma.[9 11–13]

Thinner DSAEK grafts with less stromal tissue, including ultra-thin-DSAEK

(UT-DSAEK), micro-thin-DSAEK and nano-thin-DSAEK were developed to combine the benefits of both procedures.[14–17] Studies comparing the results of UT-DSAEK and DMEK showed contradicting results.[18–25] These studies differed significantly in methodology, including the study design, inclusion criteria, sample size and DSAEK graft thickness. Recent meta-analyses found that patients who underwent DMEK had a better 12 months BCVA compared with UT-DSAEK, although the rate of complications was higher in the former.[26–29] Evidence from meta-analyses is usually ranked at the highest level in clinical practice.[30] However, combining data from different studies entails methodological challenges necessitating careful analysis and preplanned protocols.[31–33] Among these challenges are the assessment of heterogeneity and exploring its sources, as well as minimising and evaluating publication bias.[32–34] Nevertheless, these aspects were not adequately addressed in prior meta-analyses.[26–29] Accordingly, gaps in knowledge remain particularly regarding which specific factors are most decisive for the clinical success of endothelial keratoplasty.

The main objective of this meta-analysis was to compare the 12-month logarithm of the minimum angle of resolution (logMAR) BCVA of UT-DSAEK and DMEK for patients with corneal endothelial dysfunction due to FED or PBK. We also explored the differences between the two procedures in the occurrence of complications including graft rejection, graft failure, graft dislocation, rebubbling and glaucoma, and the vision-related quality of life (QOL). We assumed that other recipient or graft characteristics may play a role, such as baseline BCVA, specific UT-DSAEK graft thickness and indication for transplantation, thus conducted subgroup analyses, including a comparison of the outcomes between DSAEK grafts <70 µm and DMEK. Finally, we reviewed all prior meta-analyses compared with our study to synthesise comprehensive evidence on the outcomes of UT-DSAEK and DMEK.

METHODS

A systematic literature review and meta-analysis was undertaken following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[35] The study protocol was registered in PROSPERO.[36]

Eligibility criteria

The inclusion criteria were randomised controlled trials (RCTs) and cohort (prospective and retrospective) studies comparing the results of UT-DSAEK (<130 µm graft) and DMEK for patients with corneal endothelial dysfunction due to FED or PBK, with a mean follow-up of ≥12 months. Studies with <10 eyes or patients with a history of eye diseases or surgeries that could impair vision recovery were excluded. For duplicate records, only one record was kept.

Search methods

We searched the Embase, PubMed, Cochrane CENTRAL, ClinicalTrials.gov and WHO ICTRP databases using the terms thin, ultrathin, microthin or nanothin Descemet stripping endothelial keratoplasty and Descemet membrane endothelial keratoplasty until 20 February 2022. The search strategy is presented in online supplemental file 1. Additionally, a manual search of the references list was performed. We contacted researchers if their trial had been registered but results were not published to uncover unpublished data.

Study selection

The title and abstract of all records were screened, and full-text articles that met the inclusion criteria were reviewed. Study selection, data extraction and risk of bias assessment were performed by two investigators (TCS, MI) independently, and disagreements between them were solved via discussions.

Data abstraction and risk of bias assessment

Data were extracted from each study into an Excel file (Microsoft, Washington, USA). The main independent variable was the type of surgery, UT-DSAEK or DMEK. The main outcome variable was logMAR BCVA 12-month postsurgery. Secondary outcomes included logMAR BCVA 6-month post-transplantation, endothelial cell density (ECD) at 6 and 12 months, rates of rejection, graft failure (primary failure or failure due to severe detachment requiring repeat transplantation), graft dislocation, rebubbling and glaucoma, all at 12-month postsurgery and vision-related QOL. We collected data on potential sources of heterogeneity for the sensitivity analysis, including study type (RCT, fellow-eye, prospective/retrospective cohort study), patients' characteristics and the performed surgery (sex, age, indication for the surgery, baseline BCVA, follow-up duration and DSAEK graft thickness). Data on study methodology (randomisation, allocation concealment and blinding where relevant, statistical analysis, lost to follow-up, intention-to-treat (ITT) or per-protocol analysis) were collected for quality assessment. In cases of missing data, we contacted the authors. The risk of bias was evaluated using the Revised Cochrane risk-of-bias tool for randomised trials (RoB 2)[37] for RCTs and the Risk Of Bias In Non-Randomised Studies of Interventions (ROBINS-I)[38] system for cohort studies.

Data analysis

Heterogeneity across the studies was assessed using the χ^2 test for heterogeneity and the I^2 index. A meta-analysis was performed using the random-effect or fixed-effect models, based on the results of the heterogeneity tests. For the meta-analysis of continuous outcomes, logMAR BCVA and ECD (cells/mm^2), the mean difference was calculated. Complication rate was compared between groups using risk difference, and where relevant (number of events >0 in more than one study) OR was calculated. Forest plots were generated. The main analysis was performed combining data from all eligible studies and repeated while including only data from RCTs

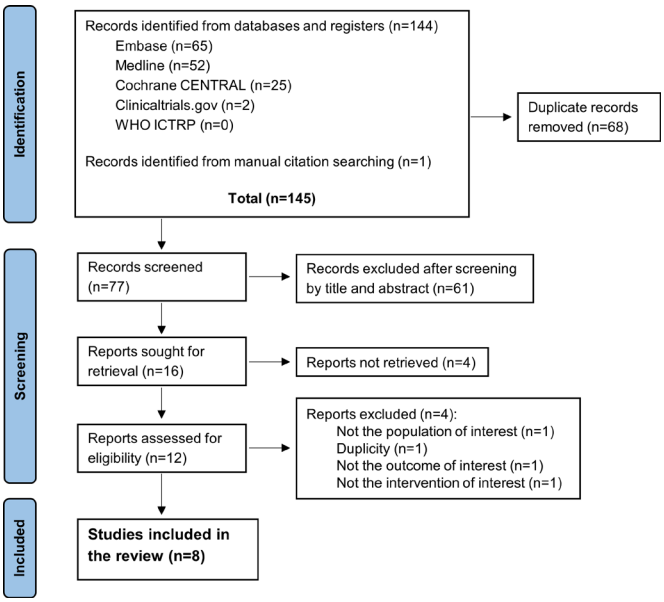

Figure 1 PRISMA 2020 flow diagram of study selection.[35] PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

and prospective cohort studies (ie, prospective data). Sensitivity analyses were conducted according to study design (RCTs or cohort studies) and limiting the analysis to studies with lower risk of bias. We also performed subgroup analyses according to the mean DSAEK graft thickness, excluding studies that contributed to heterogeneity and excluding one study with different patients' characteristics. Funnel plots and Egger's test assessed publication bias. Data were analysed using Review Manager (RevMan) V.5.4 (The Cochrane Collaboration, 2020) and Comprehensive Meta-Analysis V.4 (Biostat, Englewood, New Jersey, USA, 2022).

Review of prior meta-analyses

We reviewed all four recently published meta-analyses which compared UT-DSAEK and DMEK outcomes.[26–29] From each meta-analysis, we extracted data on the number of studies included and distribution of study design, number of included eyes, assessed outcomes, evaluation of publication bias and exploration of heterogeneity sources.

RESULTS

The systematic literature search yielded 144 records (online supplemental file 2), of those 8 studies met the inclusion criteria (figure 1), totalling 376 eyes, 189 and 187 in the UT-DSAEK and DMEK groups, respectively. This included three RCTs,[19–21] two fellow-eye studies[22 23] and three cohort studies.[24 25 39] In both fellow-eye studies, UT-DSAEK was performed before DMEK. Four studies were prospective (the three RCTs and one cohort study)[19–21 24] (table 1).

Methodological issues which might introduce bias were raised during quality assessment (online supplemental file 3). All three RCTs were registered, and study protocols were available for the quality assessment and risk of bias evaluation.[40–45] The risk of bias was low in two RCTs,[19 21] and in one RCT, there were some concerns regarding the patients selection and the reported result,[20] which differed from former publications from this trial[43 46] (figure 2A). The risk of bias was serious in one cohort study,[22] and critical in four cohort study,[23–25 39] mainly due to confounding. Other issues included the lack of assessors blinding and concerns regarding the reported result (figure 2B).

Meta-analysis

LogMAR BCVA

The baseline BCVA did not differ significantly between the UT-DSAEK and DMEK groups (combined mean difference −0.01 (95% CI −0.06 to 0.03).[19–22 24 25]

The 12-month logMAR BCVA was not available in two studies.[23 39] Combining data from 6 studies (308 eyes), using the random-effect model, DMEK showed a significantly better BCVA than UT-DSAEK 12-month postsurgery, with a mean difference −0.06 (95% CI −0.10 to −0.02) (figure 3A). Heterogeneity across studies was significant (χ^2=11.65, p=0.04) and moderate (I^2=57%). Limiting the analysis to prospective data yielded a similar result (mean difference −0.06 (95% CI −0.11 to −0.01) (figure 3B). A sensitivity analysis that included 112 eyes from 2 studies[21 24] comparing DMEK only with very thin DSAEK grafts (mean thickness <70 µm) showed no significant difference in 12-month BCVA. The results of BCBA at 6-month postsurgery were consistent with those of the 12 months (online supplemental file 4).

ECD

Data regarding 12 months ECD were available from 4 studies (196 eyes). No significant difference was found in ECD between DMEK and UT-DSAEK (mean difference 18.48 $_{cells/mm2}$ (95% CI −195.99 to 232.95)). Heterogeneity was significant (χ^2=14.79, p=0.002) and high (I^2=80%). Results were similar when limiting the analysis to prospective data (mean difference −55.18 $_{cells/mm2}$ (95% CI −342.39 to 232.04)), and consistent for the 6-month postsurgery analysis (online supplemental file 5).

Complications

Data regarding graft rejection 12-month post-transplantation were available for 300 eyes (6 studies).[19–22 24 39] Graft rejection was reported in one eye in the UT-DSAEK group.[21] The combined risk difference was −0.01 (95% CI −0.04 to 0.03).

There were 2 events of graft failure in the UT-DSAEK group and 6 events (in 5 eyes) in the DMEK group, combining data on 320 eyes (7 studies), yielding a risk difference of 0.02 (95% CI −0.02 to 0.07) and pooled OR=2.32 (95% CI 0.58 to 9.36) favouring UT-DSAEK, when including data from all available studies. The result was similar when analysing only prospective data (figure 4A).

Table 1 Characteristics of the included studies

		Chamberlain *et al*[19 40–42]	Dunker *et al*[20 43]	Matsou *et al*[21 44 45]	Mencucci *et al*[22]	Torras-Sanvicens *et al*[23]	Kurji *et al*[24]	Romano *et al*[25]	Machalińska *et al*[39]
Study type		RCT	RCT	RCT	Fellow-eye study	Fellow-eye study	Prospective cohort study	Retrospective cohort study	Cohort study
Country/ies		Oregon and California USA	Netherlands	UK	Italy	Spain	Ohio, USA	UK*	Poland
No of medical centres		2	6	1	1	1	1	1	1
Funding		Yes	Yes	Yes	None	None	None	None	None
Eyes included (n)	UT-DSAEK	25	25	28	18	10	28	31	24
	DMEK	25	29	28	18	10	28	25	24
	Total eyes	50	54	56	36	20	56	56	48
DSAEK graft thickness (µm)	Mean (SD)	73 (12)	101 (25)	63 (12.9)	80.33 (20.52)	91.1 (25.24)	41 (7.5)	75.29 (15.4†)	Was not specified
	Upper limit‡	<90	<120	<130	<130	<100	≤50	Was not specified	<100
Randomisation method		Block randomisation	Minimisation randomisation	Block randomisation	§	§	§	§	§
Allocation concealment		Yes	Yes	Yes	§	§	§	§	§
Masking		Patients and refractionists	Patients	Patients, refractionists, technicians and data analysts	§	§	Was not specified¶	§	Was not specified¶
Matched observations		In some cases**	None	None	All	All	In some cases**	None	In some cases**
Triple procedures		For all phakic patients	None	For all phakic patients	None	None	For all phakic patients	In some cases	Was not specified
Analysis		ITT	ITT	Was not specified	§	§	§	§	§
Lost to follow-up at 12 months		None	None	None	None	Was not specified	Was not specified	Was not specified	Low (7%); all UT-DSAEK
Sample size/power calculations		Satisfactory	Satisfactory	Satisfactory	Was not specified	Power was calculated only for a secondary outcome	Was not specified	Power was calculated only for a secondary outcome	Satisfactory

*Grafts were prepared in Italy, and transplantation was carried out in the UK.
†It was not clearly stated whether this value represents SD or range.
‡The predefined upper limit for the DSAEK graft thickness to be considered eligible for the DSAEK group.
§Not applicable.
¶It was not specified whether the refractionists and technicians performing the follow-up examinations were masked to the intervention.
**No correction for within-person correlation was performed.
DMEK, Descemet membrane endothelial keratoplasty; ITT, intention to treat; RCT, randomised controlled trial; UT-DSAEK, ultrathin Descemet stripping automated endothelial keratoplasty.

A

	Randomisation process	Deviations from the intended intervensions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Chamberlain et al. [19]	+	+	+	+	+	+
Dunker et al. [20]	+	+	+	!	!	!
Matsou et al. [21]	+	+	+	+	+	+

+ Low risk ! Some concerns – High risk

B

	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Mencucci et al. [22]	2	0	0	0	0	2	1	2
Torras-Sanvicens et al. [23]	3	2	0	0	1	2	1	3
Kurji et al. [24]	3	0	0	0	2	2	1	3
Romano et al. [25]	3	0	0	0	0	2	1	3
Machalinska et al. [39]	3	0	0	0	0	2	1	3

Figure 2 Risk of bias assessment (A) in RCT studies using the rob two tool[37] and (B) in the cohort studies using the ROBINS-I tool.[38] ROBINS-I, Risk Of Bias In Non-Randomised Studies of Interventions; RCT, randomised controlled trial.

Information on graft dislocation was available on 300 eyes (6 studies).[19–22 24 39] There were 14 vs 9 events of graft dislocation in the DMEK group vs the UT-DSAEK group, but the difference was not significant[19–21 24] (figure 4B).

Rebubbling risk was calculated using data of 376 eyes (8 studies).[19–25 39] Overall 37 (19.79%) and 17 (8.99%) rebubbling procedures were performed in the DMEK and UT-DSAEK groups, respectively. For the risk of need for 1 rebubbling the number needed to harm by choosing DMEK over UT-DSAEK is 9 eyes. The pooled OR for post-DMEK rebubbling was 2.76 (95% CI 1.46 to 5.22), significantly favouring UT-DSAEK, with similar results when including prospective data only[19–21 24] (figure 4C).

For glaucoma incidence, combining data from 6 studies,[19–22 24 39] showed 4/152 and 4/148 events in the DMEK and UT-DSAEK, respectively (risk difference 0.00 (95% CI −0.04 to 0.04)).

The risk differences results for the complications are shown in online supplemental file 6.

Publication bias

A funnel plot using the 12-month BCVA, showed an asymmetry, suggesting missing studies showing an advantage for UT-DSAEK. Egger's test p=0.023. No evidence of publication bias was found for rebubbling for which information was available from all studies (Egger's test p=0.234) (online supplemental file 7).

Sensitivity analysis

A sensitivity analysis for logMAR BCVA at 12 months post-transplantation conducted while excluding the studies by Kurji *et al*[24] and Romano *et al*[25] revealed that these studies contributed markedly to the heterogeneity between the studies, and reduced the heterogeneity χ^2=4.43 (p=0.22); I^2=32%. The advantage of DMEK remained (mean difference −0.06 (95% CI −0.10 to −0.03)). Kurji *et al*[24] conducted a prospective cohort study comparing nanothin-DSAEK (≤50 µm) and DMEK. Romano *et al*[25] conducted a retrospective cohort study. All tissues were precut and preloaded by the eye bank. Baseline BCVA was notably lower compared with other studies. When limiting the analysis to RCTs only,[19–21] corresponding to excluding studies with serious or critical risk of bias, or to RCTs with the lowest risk of bias,[19 21] the result also remained stable. However, limiting the analysis to the cohort studies[22 24 25] showed no significant difference between DMEK and UT-DSAEK, neither when analysing only studies with a mean DSAEK graft <70 µm[21 24] (online supplemental file 8). The analysis for 6-month BCVA showed similar results (online supplemental file 9).

Sensitivity analysis for 12-month ECD could not attribute heterogeneity to a single study (data not shown). Limiting the analysis to RCTs did not change the results. At 6 months, excluding one study[19] reduced the heterogeneity and showed a significant advantage for DMEK over UT-DSAEK (mean difference −238.92 (95% CI −444.04

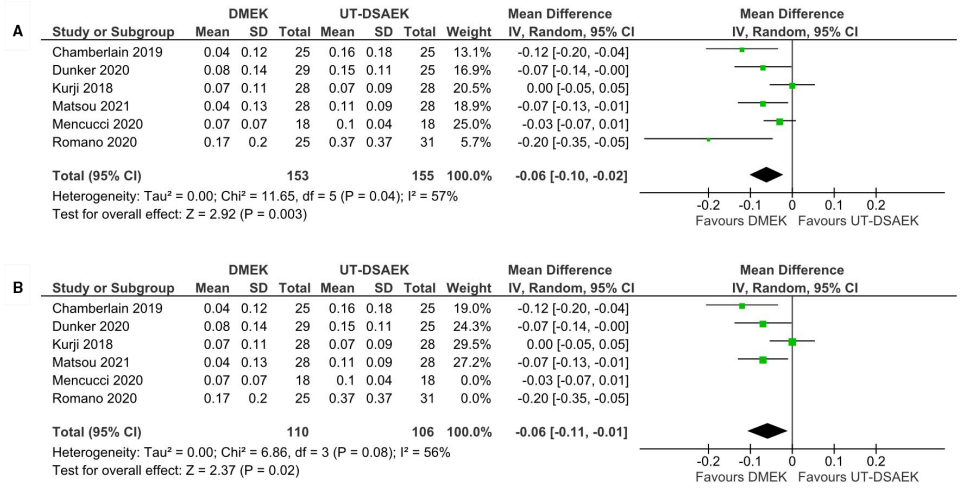

Figure 3 LogMAR BCVA at 12 months postsurgery (A) based on all included studies and (B) based only on prospective data (RCTs and prospective cohort studies). BCVA, best-corrected visual acuity; DMEK, Descemet membrane endothelial keratoplasty; IV, inverse variance; LogMAR, logarithm of the minimum angle of resolution; RCT, randomised controlled trial; UT-DSAEK, ultrathin Descemet stripping automated endothelial keratoplast.

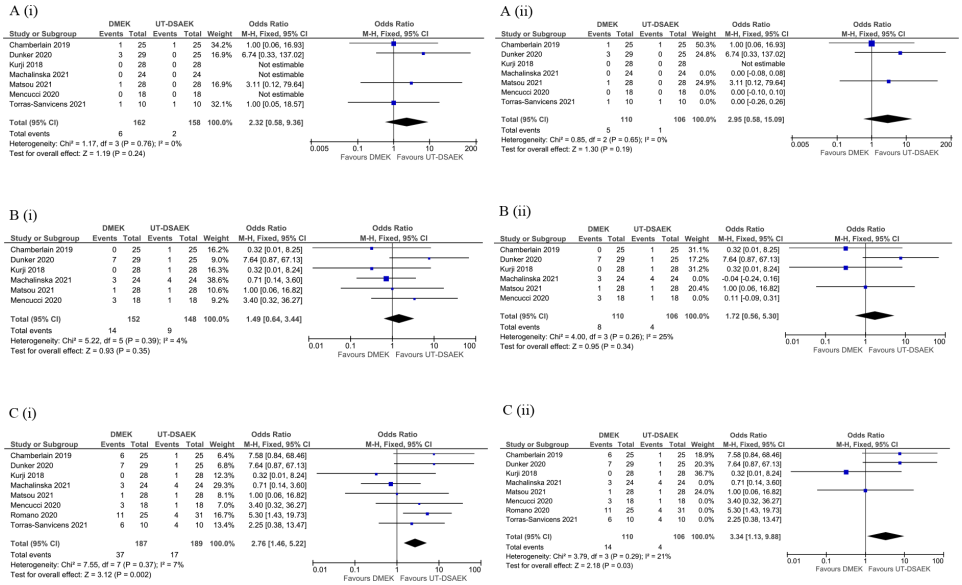

Figure 4 Differences in complications incidences at 12 months postsurgery: OR for (A) graft failure (i) based on all included studies and (ii) based on data from prospective studies only (RCTs and prospective cohort studies), (B) graft dislocation (i) based on all included studies and (ii) based on data from prospective studies only and (C) rebubbling (i) based on all included studies and (ii) based on data from prospective studies only*. *Meta-analyses were conducted using the fixed-effects model. DMEK, Descemet membrane endothelial keratoplasty; MH, Mantel-Haenszel; RCT, randomised controlled trial; UT-DSAEK, ultrathin Descemet stripping automated endothelial keratoplasty.

to −33.80) in a random-effect model. Chamberlain *et al*[19] randomised 50 eyes of 38 patients to undergo either UT-DSAEK (n=25) or DMEK (n=25). They used block randomisation, allocation concealment, masking and ITT analysis. Before surgery, there were no differences between groups in central corneal thickness, graft's ECD both preprocessing and postprocessing or in the indication for surgery. The risk of bias was low. Accordingly, no methodological issues or patients' characteristics in this study could account for the heterogeneity. Other subanalyses of RCTs only or including only studies with the lowest risk of bias[19 21] showed no significant differences in 6 months ECD between the groups (online supplemental file 10).

Quality of life

Vision-related QOL was evaluated in three of the included studies.[21–23] These studies reported different QOL parameters, thus only a qualitative analysis was performed.

Matsou *et al* evaluated the vision-related QOL using the Visual Function Questionnaire-14 and showed a significant improvement from baseline to 6 months and 12 months post-keratoplasty in both groups, with no significant differences between groups.[21] The two other studies were both fellow-eye studies[22 23] and used the same five-question questionnaire, grading the patient's satisfaction with the undergone intervention on a scale of 1–6 for each eye.[47] Mencucci *et al* reported a significantly better result for DMEK at the end of the follow-up (p=0.031).[22] The mean subjective recovery time was shorter post-DMEK (p<0.001), and most patients (66.7%) preferred DMEK over UT-DSAEK. Torras-Sanvicens *et al* found no significant difference in QOL between the groups at 6-month post-surgery.[23]

Review of prior meta-analyses

Four other meta-analyses were published on this subject in 2023.[26–29] The date of the systematic search ranged between June 2021 and September 2022. They included between 6–7 studies and 300–362 eyes, vs 8 studies and 376 eyes in our study. All meta-analyses showed better BCVA after DMEK, and no differences in ECD.[26–29] Dimtsas *et al* reported a significantly lower corneal thickness 12 months post-DMEK versus UT-DSAEK and no significant difference in the spherical equivalent.[27] Rebubbling was investigated in three meta-analyses showing significantly higher risk following DMEK.[26–28] None of the meta-analyses found significant differences in any other specific complication,[26–29] but three studies assessed total complications rate, showing significantly higher risk after DMEK.[27–29] Publication bias was evaluated in only one study, which found no publication bias.[26] Sensitivity analyses were not conducted in any of the prior meta-analyses.[26–29] Sources of heterogeneity were not explored (online supplemental file 11).

DISCUSSION

The main findings of this meta-analysis show that patients who underwent DMEK had better BCVA 6 months and 12 months after corneal transplantation than patients who had UT-DSAEK. The ECD postsurgery was comparable between the two groups, but the risk of graft dislocation warranting rebubbling was higher in the DMEK group. These results were consistent between the

analysis of all included studies and the analysis of only prospective data.

The advantage of DMEK in 12-month BCVA remained stable in most of the subanalyses, except for when we included only cohort studies, or when limiting the analysis to studies with a mean DSAEK graft thickness of <70 µm, in which there was no significant difference between the two procedures. While UT-DSAEK leads to better results than DSAEK,[11] our meta-analysis showed that it does not fully compare with the visual results of DMEK. However, the results of the analysis limited to DSAEK grafts of <70 µm thickness may suggest that thinner grafts (nanothin) could potentially fully compare with DMEK. Another meta-analysis compared the results of thin DSAEK graft with <80 µm, 80–100 µm, 100–130 µm thicknesses, showed no difference in the clinical outcome including BCVA between the groups.[48]

As for the cohort studies-only analysis, these studies have the potential for better generalisability only if they have a robust methodology, as they represent real-world data. Nonetheless, a major limitation of observational studies is the lack of random allocation and confounding. Indeed, the cohort studies included in our meta-analysis were classified as having serious or critical risk of bias,[22–25 39] thus limiting their generalisability.

We found no difference in ECD between the procedures. At 6 months, the study by Chamberlain *et al*[19] introduced heterogeneity, probably because of its result rather than its methodology.

Graft dislocation is common following both DMEK and UT-DSAEK, and often requires further intervention such as rebubbling.[49–51] Complete detachment sometimes necessitates a repeat transplantation.[50 51] We found a higher rate of graft dislocation after DMEK, but the difference from UT-DSAEK was not significant. Notably, some DMEK dislocations, including peripheral dislocations or small dislocations of <1/3 of the graft surface area, often resolve spontaneously.[50 52–54] Nevertheless, we found a significantly higher risk of post-DMEK rebubbling than after UT-DSAEK. In a study that used machine learning approaches to recognise risk factors for graft detachment based on all (n=3647) the posterior lamellar keratoplasties recorded in the Dutch Cornea Transplant Registry between 2015 and 2018, DMEK was found to be a risk factor for graft detachment.[49] In the results from the DMEK report based on the Netherlands Organ Transplant Registry, rebubbling rate was 19%,[55] similar to the 19.79% observed in our meta-analysis. It is unclear whether rebubbling decreases ECD or reduces the graft survival, as results were contradicting.[54 56–59] The increased rebubbling risk after DMEK should be considered, and close observation after surgery is needed.

In the current meta-analysis, graft rejection was rare, and graft failure was also low, possibly due to the short follow-up period (12 months), thus a longer follow-up period is needed to better understand the difference between the procedures in these outcomes. Three recent large studies using real-world data reported worse survival rates of DMEK grafts vs DSAEK (or DSEK).[6 8 55] The study using the Australian Corneal Graft Registry had the longest follow-up, and the advantage of DSAEK was consistent in all time points (1, 2, 4 and 6 years post-transplantation).[8] All these studies suggested that the ongoing learning curve could be a possible reason for the worse survival of DMEK grafts,[6 8 55] as DMEK was adopted more recently than DSAEK.[8 55] However, a retrospective cohort study comparing the 5-year survival of DMEK, DSAEK and penetrating keratoplasty, showed superior survival for DMEK over DSAEK grafts throughout the follow-up.[60] Yet, this finding was prone to confounding due to varying predominant indications for surgery: DMEK was performed mainly on FED cases, while DSAEK mostly addressed PBK cases, which showed lower survival rates. They also reported that in eyes with PBK, DMEK had better survival and survival remaind stable after the first year, unlike declining DSAEK graft survival, suggesting that failure of DMEK after the first year is rare. Yet, this finding was limited by a very small number of PBK cases in the DMEK group. A subgroup analysis showed no difference between UT-DSAEK and DMEK grafts. Price *et al* in their retrospective study reported similar 5-year graft survival rates for DSEK and DMEK, although DMEK exhibited a significantly lower rejection risk, and most rejection episodes responded well to topical corticosteroids.[61] It is possible that long-term data from larger cohorts on DMEK grafts transplanted after mastering this technique, may show an advantage over DSAEK. More evidence on long-term survival of UT-DSAEK versus DMEK are needed to better understand the potential adverse events of these procedures.

Three of the included studies reported vision-related QOL, only one of them reported a significant difference between DMEK and UT-DSAEK, with a faster subjective recovery and an overall preference for DMEK.[22] QOL was also reported separately for two other studies inculded in the current review.[62 63] Nevertheless, varying questionnaires were used,[21–23 62 63] limiting the ability to integrate the results.

Collectively, this evidence emphasises that the decision regrading the choice of surgical method for endothelial corneal transplantation remains multifaceted. After considering the indication for keratoplasty, ocular comorbidities and surgical expirience with the different procedures, patients should be informed regarding the expected visual results and risk of complication, and understand the expected postoperative course. For example, need for frequent controls for early diagnosis of graft dislocations and need for rebubbling, or a faster expected recovery and better vision-related QOL. These factors should be carefully discussed to achieve an optimal shared decision-making and improve surgical outcomes and patient satisfaction.

Our results are in line with prior meta-analyses comparing DMEK and UT-DSAEK.[26–29] Our study has several strengths that distinguish it from the others conducted on this topic,[26–29] including the prospective

registration in PROSPERO, enabling comparison with the predesigned study protocol and enhancing internal validity, the use of the most recommended means for evaluating risk of bias (ROB 2 for RCTs and ROBINS-I for cohort studies), and a thorough sensitivity analysis which allowed us to identify sources of heterogeneity between the studies, and to validate our results. Additionally, the methodology and inclusion criteria differed across the previous meta-analyses. Maier *et al*[26] did not include the study by Machalińska *et al*,[39] due to missing data on the outcomes and baseline differences in BCVA between groups. We included this study on the complications rate. Dimtsas *et al*[27] excluded from their meta-analysis the studies by Torras-Sanvicens *et al*[23] and Kurji *et al*,[24] and reported they found the latter ineligible as they considered nanothin DSAEK as a different entity from UT-DSAEK. This approach is challenged given that the paramount question is whether thinner DSAEK grafts compare with DMEK, and even more as the definitions of UT-DSAEK, microthin-DSAEK and nanothin-DSAEK are inconsistent throughout the literature.[9 64] We therefore found the inclusion of the study by Kurji *et al*[24] of value and addressed the thickness differences in the sensitivity analysis, allowing a better understanding of the differences between these procedures. Hurley *et al*[28] did not include the studies by Machalińska *et al*[39] and Kurji *et al*[24] but included the study by Tourabaly *et al*,[65] which did not meet the inclusion criteria of 12 months results in our study. Singh *et al* conducted their literature search in June 2021,[29] prior to the publication of some of the studies included in our review.[21 39] Moreover, in the previous meta-analyses, publication bias was not adequately addressed.[26–29] The methodological issues of the previous meta-analyses,[26–29] and foremost the absence of sensitivity analysis to account for inherent risks when pooling data from heterogenous studies, challenge their findings.

Our study has limitations. Significant heterogeneity was noted across the studies in some analyses. Additionally, the study by Romano *et al*[25] was characterised by a worse mean BCVA, raising a concern regarding its effect on the results. These issues were addressed in the sensitivity analysis. Furthermore, the definition of UT-DSAEK was inconsistent between studies. For example, Dunker *et al*[20] defined UT-DSAEK as targeted central residual graft thickness of 100±20 µm, Matsou *et al*[21] declared achieving a thickness of <130 µm in 100% of grafts, and Chamberlain *et al*[19] defined UT-DSAEK as grafts that were cut to between 60 µm and 90 µm. Namely, not only the values used are inconsistent, but also whether these represent a targeted mean thickness, an upper value, or a range of thicknesses for grafts that are achieved using a specific cutting method. We believe that a standardisation of terminology is warranted for future studies, and suggest, based on our systematic review, that UT-DSAEK should refer to grafts <130 µm and the term nanothin-DSAEK to grafts <50 µm. Moreover, the duration of follow-up in most of the studies included in this review was insufficient to assess the rate of long-term complications. Currently data regarding the long-term survival UT-DSAEK and DMEK is scarce. Publication bias is a generic limitation of any meta-analysis. Since data on the main outcome of BCVA at 12 months was not available for all studies, we also assessed publication bias based on the rebubbling rate data. The significant publication bias for the 12-month BCVA results suggested potential missing studies favouring UT-DSAEK. Nevertheless, for the outcome of rebubbling no publication bias was evident. Two studies reported the rebubbling rate but not the 12-month logMAR BCVA,[23 39] one of them showed a tendency towards UT-DSAEK at 6 months.[23] This suggests minimal publication bias.

In conclusion, DMEK resulted in a better visual acuity than UT-DSAEK, but with a higher risk of rebubbling, which was required in one-fifth of the patients. This should be considered prior to surgery since DMEK patients should remain under close observation in the postoperative period. Larger studies with longer follow-up are needed to compare the long-term graft survival and the risk of rarer complications such as graft rejection, graft failure or glaucoma. Even thinner DSAEK grafts (mean thickness <70 µm) could potentially compare with DMEK. Standardisation of the nomenclature of thinner DSAEK grafts is warranted.

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