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► To cite this version:

Lauren Béal, Valentin Navel, Bruno Pereira, Florent Magnier, Stephanie Watson, et al.. Efficacy of Thin and Ultrathin Descemet Stripping Automated Endothelial Keratoplasty and Influence of Graft Thickness on Postoperative Outcomes: Systematic Review and Meta-analysis. American Journal of Ophthalmology, 2022, 240, pp.170-186. 10.1016/j.ajo.2022.03.022 . hal-03682152

HAL Id: hal-03682152

<https://hal.science/hal-03682152>

Submitted on 22 Jul 2024

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Efficacy of thin and ultrathin DSAEK and influence of graft thickness on post-operative outcomes: systematic review and meta-analysis

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Financial disclosures: none reported

Running title: Influence of graft thickness in UT-DSAEK

Word count for text only (not including abstract, acknowledgment, references, and citations of references within the text): 3406

Abstract

Purpose: To conduct a systematic review and meta-analysis on the efficacy of thin and ultrathin Descemet stripping automated endothelial keratoplasty (T-DSAEK and UT-DSAEK, with graft thickness <130 and <100 μm , respectively), depending on graft thickness.

Design: Systematic review and meta-analysis.

Method: PubMed, Cochrane Library, Embase, ClinicalTrials.gov and ScienceDirect databases were searched till 1st October 2021. We computed random-effect meta-analysis on post-operative outcomes of T/UT-DSAEK, stratified by graft thickness (<80 μm , 80-100 μm and 100-130 μm). The main post-operative outcome was visual acuity (LogMAR). Secondary outcomes were pachymetry (μm), endothelial cell count (cell/ mm^2), spherical equivalent (diopter), rebubbling rate (%), and rejection rate (%). Meta-regressions compared post-operative outcomes depending on graft thickness and search for putative confusion factors.

Results: We included 47 articles for a total of 2141 eyes of 2040 patients. T/UT-DSAEK globally improved visual acuity (effect size = -0.38 LogMar, 95% CI -0.46 to -0.30 LogMar), without difference depending on graft thickness. Overall, pachymetry improved (-60.6 μm , -101 to -19.7 μm), endothelial cell count decreased (-1039 cells/ mm^2 , -1209 to -868 cells/ mm^2), spherical equivalent resulted in a hyperopic shift (0.74 D, -0.50 to 1.97 D), graft rejection rate was 0.2% (-0.1 to 0.4%) and rebubbling rate was 8.7% (6.8 to 10.5%). Grafts >100 μm induced a hyperopic shift. Metaregressions did not demonstrate differences between the 3 groups (<80 μm , 80-100 μm , 100-130 μm) in any outcomes.

Conclusion: All T/UT-DSAEK thickness groups provided similar visual acuity, pachymetry, endothelial cell count, rejection and rebubbling rate regardless of graft thickness. A hyperopic shift was induced by grafts >100 μm .

Keywords: Corneal transplantation – Endothelial keratoplasty – Ultrathin DSAEK – UT-
DSAEK – Thin DSAEK – Graft thickness

Highlights

- Thin and ultra-thin DSAEK (T/UT-DSAEK) were developed to increase the visual outcomes of DSAEK, keeping their technical accessibility.
- Conducting a systematic review and meta-analysis on post-operative outcomes of T/UT-DSAEK stratified by graft thickness (<80 μm , 80-100 μm and 100-130 μm), we included 47 articles (i.e. 2141 eyes of 2040 patients).
- We showed that T/UT-DSAEK globally improved post-operative outcomes, without difference depending on graft thickness.
- Performing the first meta-analysis on T/UT-DSAEK, we showed that visual acuity, pachymetry, endothelial cell count, rejection and rebubbling rate were similar regardless of graft thickness.

Introduction

Endothelial keratoplasty (EK) is becoming the gold standard surgery for the treatment of endothelial corneal failure, replacing penetrating keratoplasty.¹ Descemet stripping automated endothelial keratoplasty (DSAEK), with corneal endothelium and Descemet membrane being grafted with a thin layer of donor stroma,^{2,3} currently remains the most performed EK in both the USA and Europe.^{4,5} Recently, interesting results highlighted that DSAEK with grafts thinner than 130 μm could involve better postoperative visual acuity, suggesting relationships between graft thickness and visual outcomes.⁶ Thereby, thin and ultra-thin DSAEK (T/UT-DSAEK) (i.e. DSAEK with graft thickness $<130 \mu\text{m}$ ⁷) were developed to increase the visual outcomes of DSAEK and to maintain their technical accessibility.^{7,8} Further studies supported these findings, while showing a similar complication rate and endothelial cell loss to DSAEK.^{9,10} However, the link between graft thickness and visual outcomes is not consistent,¹¹⁻¹³ which could therefore question the pertinence of T/UT-DSAEK. Most of the published results relate to grafts generally greater than 100 μm .^{12,14,15} Currently, no data are available for grafts $<100 \mu\text{m}$. Thus, to assess the influence of graft thickness within T/UT-DSAEK grafts, we conducted a systematic review and meta-analysis on the efficacy of T/UT-DSAEK on post-operative outcomes (ie visual acuity, pachymetry, cell count, spherical equivalent, rebubbling and rejection rate), depending on the graft thickness.

Methods

Literature search

We searched for articles in PubMed, Cochrane Library, ScienceDirect, Embase and ClinicalTrial.gov databases until 1st October 2021 with the following keywords: Descemet* OR endothelial keratoplasty OR DSAEK OR DSEK AND thickness OR thin OR ultrathin OR UT-DSAEK (details of search strategy used within each database are presented in Appendix 1). The search was not limited to specific years. No language restrictions were applied. We imposed no limitation on sample size or regional origin. To be included, articles had to report clinical outcomes (i.e. visual acuity, pachymetry, endothelial cell count, spherical equivalent, rebubbling or rejection rate) of thin or ultra-thin DSAEK, defined as DSAEK with preoperative graft thickness <130 µm and <100 µm, respectively.¹⁶ Animal studies were excluded. In addition, references of all publications meeting inclusion criteria were manually searched to identify any further studies. The search strategy is presented in Figure 1. Two authors (LB, VN) conducted literature searches, collated and separately reviewed the abstracts and, based on the selection criteria, decided the suitability of the articles for inclusion. A third author (FD) was asked to review the articles where consensus on suitability was debated. We followed the PRISMA guidelines (Appendix 2).

Data collection

The data collected included first author's name, publication year, country, study design, aims, outcomes of included articles, inclusion and exclusion criteria, sample size, number of eyes, age, percentage of males, endothelial disease, graft cutting technique, type of surgery (simple or triple EK), characteristics of donors (age, sex), measurement time, central graft thickness

(CGT), central corneal thickness (CCT), spherical equivalent (SE), best spectacle-corrected visual acuity (BSCVA), endothelial cell count (ECC), graft rejection rate and rebubbling rate.

Outcomes

The primary outcome was BSCVA (in logMAR). Secondary outcomes were pachymetry as CCT (in μm), ECC (in cell/ mm^2), SE (in diopter), graft rejection rate and rebubbling rate (in %).

Quality of assessment

We used the Scottish Intercollegiate Guidelines Network (SIGN) criteria to assess the methodological quality of the included articles, both for randomized clinical trials and cohort studies, with the dedicated evaluation grids. SIGN Controlled Trials and SIGN Cohort Studies checklists consisting of respectively 10 and 14 items.¹⁷ We presented an overall quality score for each included study, based on the main causes of bias evaluated in section 1 of the checklist through 4 possibilities of answers (yes, no, can't say or not applicable).

Statistical considerations

Statistical analyses were conducted using Stata software (v16, StataCorp, College Station, US).¹⁸⁻²² Characteristics of subjects and parameters evaluated were reported for each study sample as mean \pm standard-deviation (SD) and number (%) for continuous and categorical variables respectively. We computed random effect meta-analysis (DerSimonian and Laird approach) on changes between after the intervention and baseline measures, for each efficacy outcome: BSCVA in LogMAR, CCT in μm , ECC from donor in cell/ mm^2 , and SE in diopter. For graft rejection and rebubbling, meta-analysis was expressed in rates (%). When a study

presented several time measurements, the last follow-up time was retained for the main analysis. When visual acuity was evaluated with a Snellen chart or a decimal scale, it was converted to LogMAR using the formula: $\text{LogMAR visual acuity} = -\text{Log}_{10}(\text{decimal visual acuity})$. Changes were calculated using the method from Borenstein et al.²³ This approach has the advantage to express results i.e. effect sizes (ES) as natural values (LogMAR, μm , cell/ mm^2 , and diopter, respectively) but suffers from statistical issues as the number of eyes is only taken into account from SD, and by choosing an arbitrary correlation coefficient of 0.5. Therefore, to be statistically accurate, we further computed aforementioned meta-analysis using standardized mean differences (SMD), by comparing measures of efficacy after the intervention to baseline measures (before the intervention).²⁴ SMD with their 95% confidence intervals (95CI) were represented graphically on forest plots. A SMD was defined as an unitless measure of the effects of T/UT-DSA EK on outcomes. A SMD centered at 0 reflects the absence of effect, 0.2 a small effect, 0.5 a moderate effect, and 0.8 a large effect.²⁵ We stratified our meta-analyses on the thickness of corneal grafts in T/UT-DSA EK (<80 μm , 80-100 μm and 100-130 μm), according to the pre-operative thickness (or the earliest post-operative graft thickness). Lastly, we performed several sensitivity analyses to verify the strength of our results. First, we repeated meta-analyses with all measurement times. Then, as recovery from surgery is likely to be achieved in the long-term, we computed previous meta-analyses using only studies with a follow-up greater than one year. As the most common surgery is the microkeratome technique for Fuchs endothelial dystrophy, we also computed sensitivity meta-analyses on those studies. Heterogeneity in our results was evaluated by examining forest plots, 95CI and the I-squared (I^2) statistic. Heterogeneity between studies is considered low for $0 < I^2 < 25\%$, modest for $25\% < I^2 < 50\%$, and high for $50\% < I^2 < 100\%$. For rigor, funnel plots (metafunnels) of meta-analyses were used to search for publication bias, and meta-analyses were conducted excluding studies not evenly distributed around the base of

the funnel.²⁶ When possible (sufficient sample size), meta-regressions were proposed to study the relationship between clinical outcomes and clinically relevant parameters such as characteristics of subjects and donors (age, sex), pathology causing endothelial failure, time, and characteristics of surgery. Results of meta-regressions were expressed as regression coefficients and 95CI. P values less than 0.05 were considered statistically significant.

Results

An initial search produced 2926 possibly corresponding articles (Figure 1). After removal of the duplicates and applying selection criteria, we included 47 articles,^{7,9,10,27-70} published between 2009 and 2021 (Table 1). All articles were written in English, except for two in French,^{29,30} one in Russian⁶⁸ and one in German.⁵⁸

Quality of articles

Using SIGN Cohort Studies criteria, the score of the 42 observational studies^{7,27-31,33,35-41,43-70} was 81.2 ± 13.6 , ranging from 28.6%⁴³ to 100%^{7,29,30,49,70} for Yes responses; Using SIGN Controlled Trials criteria, the score of the 5 randomized clinical trials^{9,10,32,34,42} was 78.6 ± 16.7 , ranging from 50%⁹ to 88.9%^{10,32} for Yes responses (Figure 2, and Appendix 3).

Population

Sample size : We included a total of 2040 patients, ranging from 5^{43,56,68} to 250⁷ per study, and 2141 eyes were treated, ranging from 5^{43,56,68} to 285⁷ eyes per study. Among the 2141 eyes who underwent T/UT-DSAEK, 461 received a graft <80 μm , 1066 between 80 and 100 μm , and 614 between 100 and 130 μm .

Sex: The mean proportion of males was 40% (95CI 32 to 47%), varying from 0%⁶⁸ to 62%.⁵⁹ Fourteen studies did not specify sex.^{9,10,29,34,47,48,51,53,54,58,61–64}

Age: The mean age of included patients was 67.2 years (95CI 62.9 to 71.6), ranging from 8 months²⁷ to 96 years.²⁹ Nine studies did not report age.^{47,48,51,53,54,61–64}

Indication for T/UT-DSAEK was Fuchs endothelial corneal dystrophy (FECD) for 62% (95CI 49 to 75%), pseudophakic bullous keratopathy (PBK) for 15% (95CI 13 to 18%), regraft for failed or decompensated keratoplasty for 7% (95CI 4 to 10%), congenital hereditary endothelial dystrophy for 2% (95CI 1 to 3%), viral endotheliitis, posterior polymorphous dystrophy, irido-corneo endothelial syndrome, and congenital glaucoma (<1% for each of them). Indication was not reported in five studies.^{35,48,51,56,64}

Follow-up

Follow-up time ranged from 1^{62,64} to 60 months,⁶⁷ with a mean of 17.5 months. Twenty-seven studies had a follow-up duration ≥ 12 months.^{7,9,10,27–38,40,42,44,46,49,50,60,65–67,69,70}

Study designs, inclusion and exclusion criteria, surgical management, outcome assessment, and aims and outcomes of included studies are presented in Table 1 and Appendix 4.

Meta-analyses on T/UT-DSAEK outcomes

Overall, **visual acuity** improved (-0.38 logMAR, 95% CI -0.46 to -0.30 logMAR, $P < 0.001$). Stratification by graft thickness showed improvements for all groups ($P < 0.001$): $<80 \mu\text{m}$ (-0.30, -0.47 to -0.14), $80\text{-}100 \mu\text{m}$ (-0.56, -0.71 to -0.41), and $100\text{-}130 \mu\text{m}$ (-0.32, -0.47 to -0.17) (Figure 3 and Appendix 5). Results were similar using the most accurate SMD statistical approach. There was an important heterogeneity between studies, overall and for subgroups (all I^2 were $>60\%$) (Appendix 6).

Endothelial cell count decreased globally (-1039 cells/mm², -1209 to -868 cells/mm²), and for all groups: <80 μm (-1035, -1405 to -665), 80-100 μm (-984, -1222 to -745), and 100-130 μm (-1157, -1457 to -857) (P < 0.001) (Figure 3 and Appendix 5). The use of SMD showed similar results. All I² were >50% (Appendix 6).

Pachymetry showed an overall decrease (-60.6 μm, -101.4 to -19.7 μm, P = 0.004), also shown in the 100-130 μm group (-153.1, -277.8 to -28.3, P = 0.016), but only a tendency in the two thinnest groups (<80 μm: -82.5, -171.2 to 6.2, P = 0.068; 80-100 μm: -38.8, -92.7 to 15.1, P = 0.158) (Figure 3 and Appendix 5). Using the most accurate SMD statistical approach, all groups improved pachymetry: <80 μm (-1.37, -2.62 to -0.11, P = 0.032), 80-100 μm (-0.78, -1.47 to -0.09, P = 0.027), and 100-130 μm (-1.30, -1.81 to -0.80, P < 0.001). All I² were >60% (Appendix 6).

Spherical equivalent showed no significant hyperopic shift, overall (0.74 D, -0.50 to 1.97 D, P = 0.242) as well as for all groups: <80 μm (0.37, -9.85 to 10.59, P = 0.943), 80-100 μm (0.61, -3.68 to 4.90, P = 0.781), and 100-130 μm (0.76, -0.55 to 2.06, P = 0.255) (Figure 3 and Appendix 5). Using SMD, there was a significant overall hyperopic shift (SMD = 0.48, 95% CI 0.2 to 0.76, P = 0.001, I² = 24.9%), also shown in the 100-130 μm group (0.66, 0.35 to 0.97, P < 0.001, I² = 0%) without changes in the two thinnest groups (<80 μm: 0.09, -0.43 to 0.62, P = 0.733; 80-100 μm: 0.32, -0.25 to 0.89, P = 0.273) (Appendix 6).

Overall **graft rejection** rate was 0.2 % (-0.1 to 0.4%, I² = 33.5%). Results were similar in the 3 thickness groups: <80 μm (0.5%, -0.4 to 1.3%, I² = 52.3%), 80-100 μm (0.4%, -0.1 to 0.9%, I² = 34.9%), and 100-130 μm (0.1%, -0.3 to 0.5%, I² = 34.8%) (Figure 3 and Appendix 5).

Rebubbling rate was 8.7% (6.8 to 10.5%), with a prevalence of 3.4% (0.9 to 5.9%) in the <80 μm group, 9.3% (6.6 to 12%) in the 80-100 μm group and 13% (8.3 to 17.7%) in the 100-130 μm group. All I² were >50% (Figure 3, and Appendix 5).

Metaregressions and sensitivity analyses

Metaregressions did not demonstrate significant differences between the 3 groups (<80 µm, 80-100 µm, 100-130 µm) in any outcomes (Figure 4 and Appendix 7). Prevalence of rebubbling was higher in PBK (coefficient 0.23, 95% CI 0.02 to 0.44), and decreased with donor age (-1.70, -3.24 to -0.14). Other meta-regressions did not demonstrate significant results (Figure 5).

After exclusion of studies from the metafunnel results, sensitivity meta-analyses showed similar findings, as well as with all measurement times, including only studies with a follow-up ≥12 months, or only patients with FECD and graft prepared with microkeratome (Appendix 8).

Discussion

Performing the first meta-analysis on T/UT-DSAEK, we demonstrated its efficacy on the improvement of visual acuity and pachymetry, resulting in an acceptable complication rate. We did not show any relationship between visual acuity and graft thickness within grafts <130 µm. Similarly, there were no significant differences in endothelial cell count, pachymetry, rejection and rebubbling rate according to graft thickness. The thinnest grafts did not result in refractive change, as opposed to grafts >100 µm that induced a hyperopic shift.

Determinants of visual outcomes after EK

The hypothesis of the impact of graft thickness on visual acuity led to contradictory results.^{13,57,71} In 2015, Wacker et al conducted a meta-analysis attempting to decide this issue, and concluded that visual acuity was weakly correlated with graft thickness after DSAEK.⁷² Similarly, we did not demonstrate relationships between graft thickness and visual acuity for

T/UT-DSAEK grafts <130 μm . Although factors involved in visual recovery after EK had not been fully elucidated, some studies did attempt to provide some answers. Considering that Descemet Membrane Endothelial Keratoplasty (DMEK) achieved better visual acuity comparing to DSAEK,⁷³⁻⁷⁵ the stromal layer had been questioned to explain these results. In fact, light scatter and interface reflectivity between recipient and graft stroma were shown to impair visual acuity.⁷⁶⁻⁷⁹ In a similar way, it might explain why posterior corneal higher-order aberrations, correlated with visual acuity,⁸⁰ were greater in DSAEK and T/UT-DSAEK compared with DMEK.^{80,81} Other factors had been suggested, such as recipient age, pachymetry, graft regularity, or match in curvature between graft and recipient cornea.⁸² In short, visual recovery after EK is multifactorial, and it remains unclear to what extent the causal factors are involved.⁸² We showed that a hyperopic shift was induced by grafts >100 μm , unlike thinner grafts. This is consistent with previous studies, demonstrating that larger graft thickness induced greater hyperopic shift.^{83,84} On the other hand, it appeared that grafts thicker in the periphery than in the center favored hyperopic shift by reducing the radius of curvature of the posterior cornea.⁸⁴⁻⁸⁶ Thus, the shape of the graft in its entirety needs to be considered. It is interesting to note that some authors described a slight hyperopic shift following DMEK.^{87,88} However, this may be related to the decrease in corneal edema, thus not actually a real hyperopic shift but a resolution of the myopic shift caused by the edema.⁸⁹

Factors influencing post-operative complications

Identifying factors involved in endothelial cell loss is crucial, as it is a leading cause of graft failure.^{90,91} Instruments used for graft insertion, the shape of the incision, graft detachment, lens status or diabetes were suggested.^{92,93} Our findings are consistent with previous reports, as we did not highlight relationships between endothelial cell loss and recipient factors such as age, sex, or pre-operative graft thickness.^{9,10,14,57,94} However, indirectly, achieving thinner

grafts can require more traumatic tissue preparation susceptible to damaging the graft. Contradictory results claimed that the double pass microkeratome technique would be responsible for increased endothelial cell loss compared to the single pass technique.^{95,96} Although not significant, interestingly, there seemed to be a trend towards less rebubbling for thinner grafts, while previous studies showed otherwise.⁹ If graft tamponade with sulfurhexafluoride (SF6) gas demonstrated less rebubbling procedures than air in DMEK,⁹⁷ almost all T/UT-DSAEK were tamponed with air bubble. Other influencing parameters, as surgeon learning curve, recipient comorbidities, or postoperative time supine⁹⁸⁻¹⁰⁰ were various and/or not adequately reported, thus could not be included in the analyses. We reported a very low rejection rate, far below what was reported for DSAEK (6-10%).^{101,102} Consistently, reducing the stromal lamellar thickness could reduce the antigen load and then the risk of rejection.¹⁰³ Nevertheless, included studies rarely exceeded 12 months of follow-up, which provided only a limited overview and thus prevented reliable comparisons.

Why is there interest in thinner grafts?

Since the introduction of T/UT-DSAEK, producing ever-thinner grafts seems to be an objective to achieve, in order to improve the post-operative outcomes.¹⁰¹ Recently, Cheung et al proposed the term “nanothin DSAEK” to describe grafts <50 µm thick, and reported a technique to achieve this threshold.¹⁰⁴ However, the dissection of ultrathin grafts is not without risk. A higher complication rate during lamellar dissection, including perforations, has been shown with double pass microkeratome techniques, all occurring during the second pass.^{7,101} Thus, various techniques had subsequently been developed to reduce complications during the preparation of T/UT-DSAEK grafts. They included reduction of donor cornea thickness prior to dissection by evaporation,^{33,42,49} drying in polyvinyl alcohol⁵¹ or using THIN-C medium,¹⁰⁵ presoaking in balanced saline solution,⁶² and/or using nomograms to

select appropriate microkeratome head.^{47,104} On the other hand, the thinner the grafts, the more difficult they are to handle. Thus, the only benefit of using ultrathin grafts is that they induce minimal, if any hyperopic shift. This is of particular interest in pseudophakic eyes, so as not to entail refractive change. Hyperopic shift is less challenging in T/UT-DSAEK triple surgery, as it can be anticipated when deciding the intraocular lens power. Except this specific case, there is no clear advantage to aim for thinner T/UT-DSAEK grafts. In the light of these results, we might question whether reducing the thickness of DSAEK grafts in general is valuable, challenging the rationale of T/UT-DSAEK. To date, only two randomized controlled trials comparing UT-DSAEK with conventional DSAEK are available, both favoring UT-DSAEK on visual outcomes, with a similar complication rate.^{9,10} The main benefit of T/UT-DSAEK over DMEK is also easier graft preparation and surgical procedure, allowing its indication even in eyes with complicated anatomy. Further studies are required to balance the medical and economic issues of the different techniques of EK (DMEK, thin and UT-DSAEK, DSAEK).

Limitations

Our systematic review and meta-analysis had several limitations, including the inherent limitations of the 47 individual included studies. Studies were not similar in their design. Despite included studies having overall good quality scores, some had a low level of evidence, especially case series with few patients (retrospective non randomized data), and may have led to heterogeneous effect sizes limiting the quality of the meta-analysis.¹⁰⁶ Furthermore, inclusion and exclusion criteria were not identical across included studies. Some did not exclude eyes with comorbidities impairing vision, which could have disrupted the analysis of visual acuity. Studies contained a variable proportion of T/UT-DSAEK combined with cataract surgery, and indications for T/UT-DSAEK were diverse. However, meta-

regressions did not show significant effects of these two parameters on visual acuity. Heterogeneity between studies may preclude robust conclusions. Severity of pathology, which could also have influenced our primary outcome, was mentioned in only one study,³¹ precluding further analyses. To limit the influence of extreme results, we reperformed analyses after exclusion of results that were not evenly distributed around the funnel plots. Also, studies with several arms mostly did not report whether surgery were performed by the same surgeon, which may add a reproducibility bias. The meta-analyses were only conducted on published articles, so there was the potential for publication bias.¹⁰⁷ Most studies were conducted in Europe, which can also preclude generalizability of our results. Another limitation was the variable length of follow-up (from 1^{62,64} to 60 months⁶⁷). Most of the studies did not report data after one year of follow-up, precluding long-term visibility. The method for measuring graft thickness may be a source of variability (e.g. technician, OCT unit), however no study detailed this putative issue. The definition of ultra-thin DSAEK grafts is also not consistent, varying from threshold under 100^{10,36} to 130^{7,49} μm of central graft thickness. In addition, studies referred either to the postoperative graft thickness,^{108,109} or thickness immediately after cutting.^{7,9,29} In this meta-analysis, we considered thin DSAEK as DSAEK grafts <130 μm thick and ultra-thin DSAEK grafts <100 μm thick,¹⁶ based on their pre-operative thickness to provide predictable results. We failed to show significant differences between the thickness groups of T/UT-DSAEK on the studied outcomes. However, highlighting very small differences may not have an impact on routine clinical practice. Moreover, some studies were excluded because of missing data. Further prospective studies should overcome these shortcomings. As no study has ever compared the influence of several grafts thickness <130 μm , there is a strong need for randomized controlled trials depending on graft thickness using only the T/UT-DSAEK technique.

Conclusion

Performing the first meta-analysis on T/UT-DSAEK, we showed that visual acuity, pachymetry, endothelial cell count, rejection and rebubbling rate were similar regardless of the graft thickness. A hyperopic shift was induced by grafts >100 microns. It seems that there is no clear benefit in reducing the thickness of T/UT-DSAEK grafts and to aim for a lower threshold. However, our conclusions were based on heterogeneous studies involving many variables, which may have affected the results. Further randomized clinical trials on the same pathology and using the same graft preparation technique would be worthwhile to support our findings.

Acknowledgements

We thank Nathalie Piñol-Domenech, librarian of the Clermont Auvergne University, and the librarians of University Health Sciences Library in Paris for their support in the elaboration of database search strategies and the collection of the full-text articles.

Competing interests

The authors declare that they have no competing interests in relation with this article.

Contributors

LB, VN, and FD were responsible for the design and conception of the study. LB and VN searched and collected studies and data. LB, VN, FC, FD and BP analysed and interpreted data. LB, VN, FD and BP oversaw statistical analyses. LB, VN, FD, FC and JSB wrote the manuscript. All authors made critical revisions to the article. All authors gave their final approval of the article.

Funding

None

Data sharing statement

No additional data are available.

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Figures Legend

Figure 1. Search strategy

Figure 2. Summary of methodological quality of included articles using SIGN model

We used the Scottish Intercollegiate Guidelines Network (SIGN) criteria to assess the methodological quality of the included articles, both for randomized clinical trials (10 items) and cohort studies (14 items), with the dedicated evaluation grids. We presented an overall quality score based on the main causes of bias through 4 possibilities of answers (yes, no, can't say or not applicable).

Figure 3. Summary of all meta-analysis on efficacy of T/UT-DSAEK stratified by graft thickness, using natural values

Each overall summary of a meta-analysis is represented in the graph by a losange on a horizontal line and each stratification by a dot. The losange / dots represent the overall pooled-effect estimate of individual meta-analyses (pooled effect size - ES), and the length of each horizontal line around the dots represent their 95% confidence interval (95CI). Shorter lines represent a narrower 95CI thus higher precision around pooled-ES. Conversely, longer lines represent a wider 95CI and less precision around pooled-ES. The black solid vertical line represents the null estimate (with a value of 0 for pooled-ES). Horizontal lines that cross the null vertical line represent a non-significant overall summary of the meta-analysis, for each efficacy outcome.

LogMAR: Logarithm of the Minimum Angle of Resolution; D: Diopter

Figure 4. Comparison of efficacy of T/UT-DSAEK depending on graft thickness

The blue square represents the coefficient of the metaregression comparing the groups of different thickness, two by two, on each efficacy outcome. The length of each line around the dots represent their 95% confidence interval (95CI). The black solid vertical line represents the null estimate (with a value of 0). Horizontal lines that

cross the null vertical line represent non-significant variables on the outcome. For each efficacy outcome, a blue square closer to a group is significantly in favor of this group when its 95CI does not cross the null estimate.

Figure 5. Summary of meta-regressions i.e. influencing variables on outcomes

The effect of each variable on the outcome is represented in the forest-plot by a dot on a horizontal line. The dots represent the coefficient for each variable, and the length of each line around the dots represent their 95% confidence interval (95CI). The black solid vertical line represents the null estimate (with a value of 0). Horizontal lines that cross the null vertical line represent non-significant variables on the outcome.

Tables Legend

Table 1. Characteristics of included studies.

Appendix

Appendix 1. Details for the search strategy used within each database

Appendix 2. PRISMA checklist (2020)

Appendix 3. Methodological quality of included articles using the SIGN model. (Yes: “+”, No: “-“, Can’t say: “?”, Not applicable: “NA”)

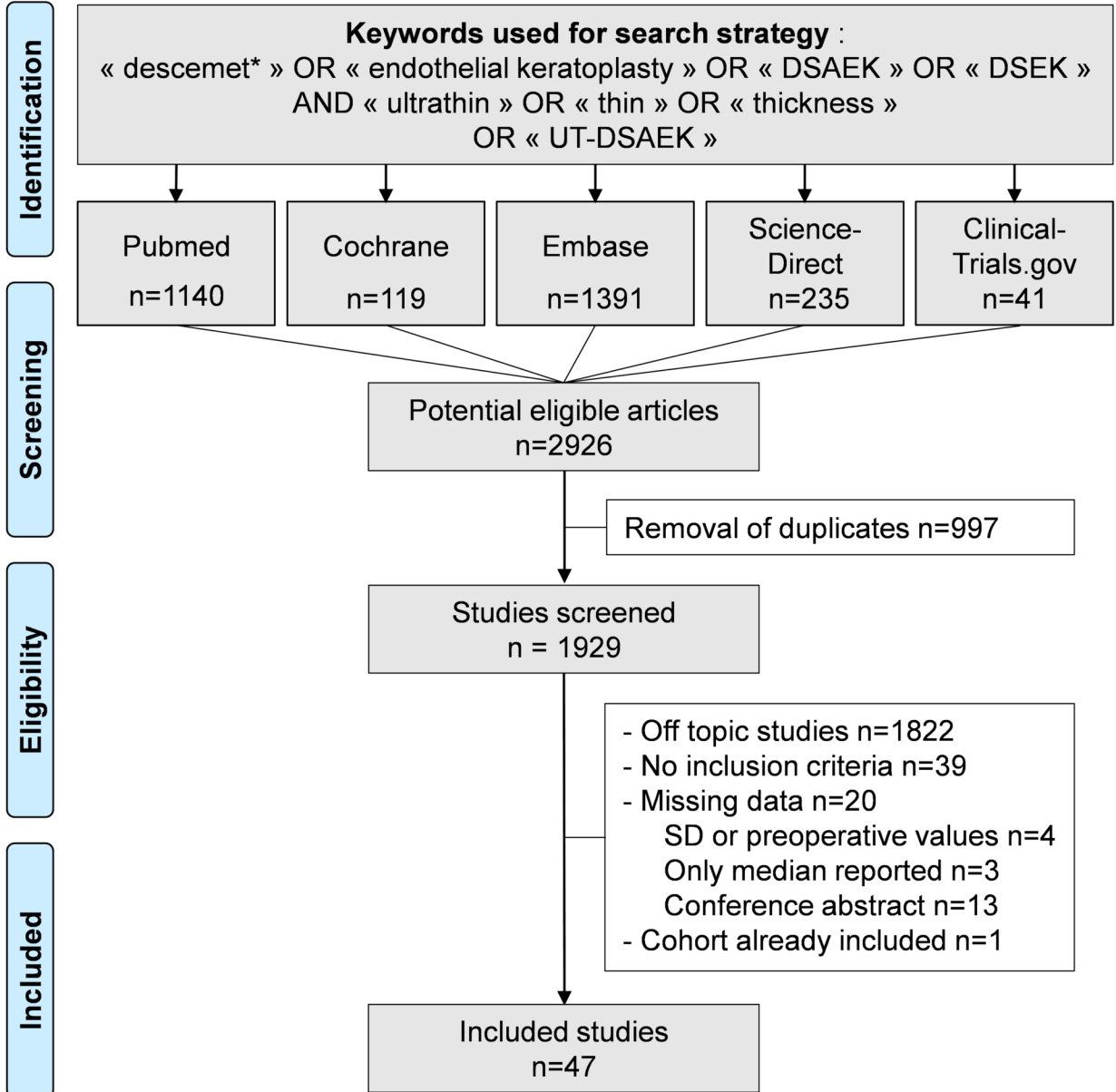
Appendix 4. Details on study designs, inclusion and exclusion criteria, surgical management, outcome assessment, aims and outcomes of included studies.

Appendix 5. Individual meta-analysis on visual acuity, endothelial cell count, pachymetry, spherical equivalent, graft rejection, and rebubbling after T/UT-DSAEK, using natural values

Appendix 6. Summary and individual meta-analysis on visual acuity, endothelial cell count, pachymetry, spherical equivalent, graft rejection, and rebubbling after T/UT-DSAEK, using standardized mean differences (SMD)

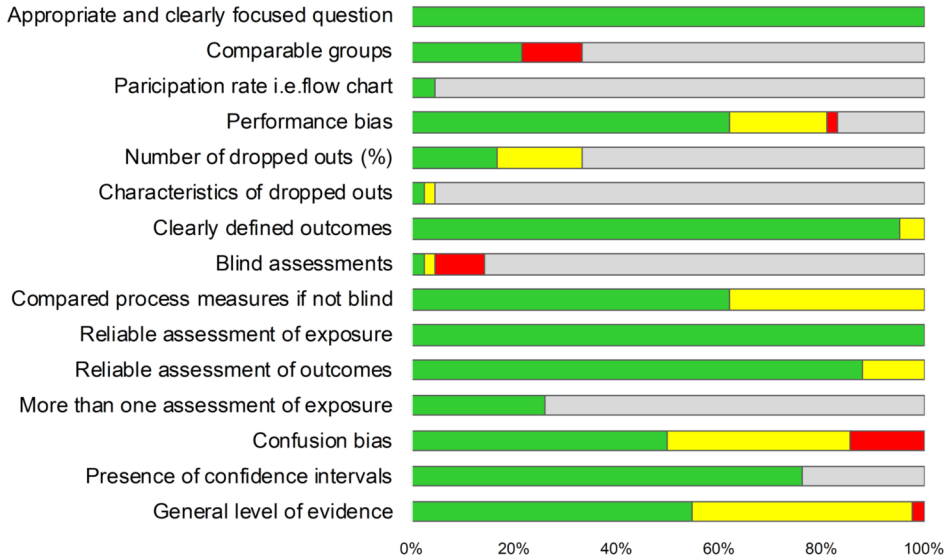
Appendix 7. Detailed comparison of efficacy of T/UT-DSAEK depending on graft thickness

Appendix 8. Sensitivity analyses: summary of all meta-analysis on efficacy of T/UT-DSAEK stratified by graft thickness for studies with a follow-up ≥ 12 months, for patients with FECD and graft prepared with microkeratome, and for all follow-up times.

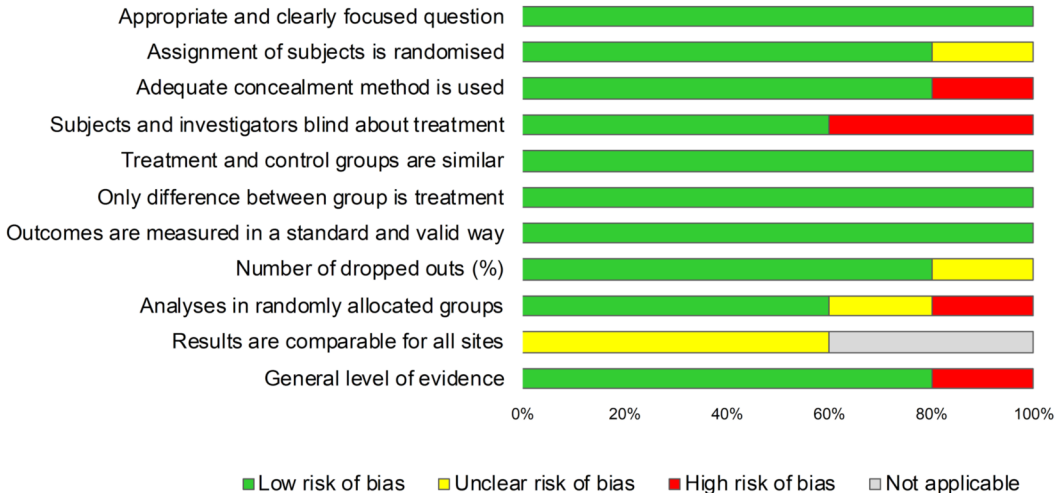


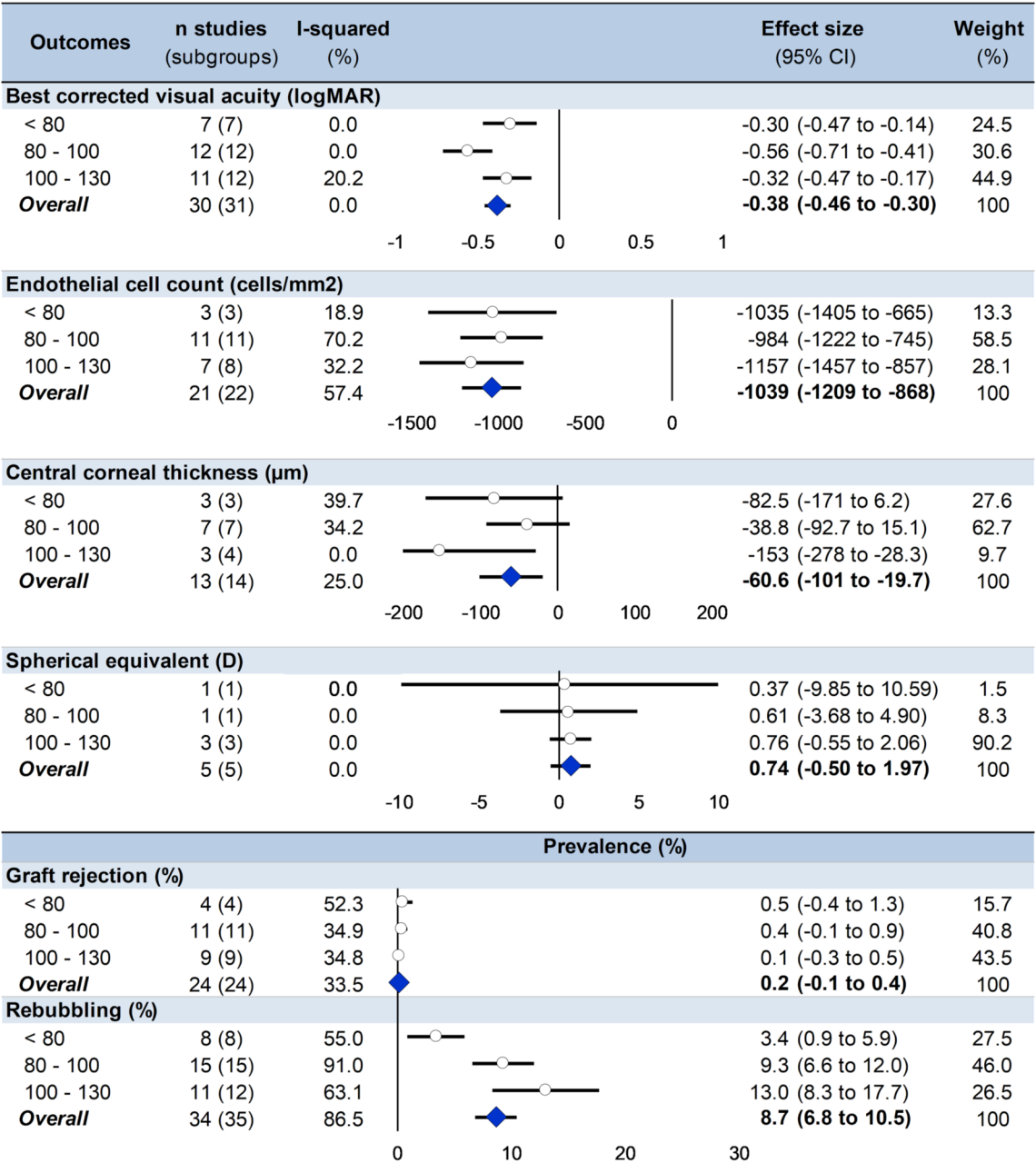
Risk of bias summary

Cohort Studies (n = 42)



Controlled trials (n = 5)

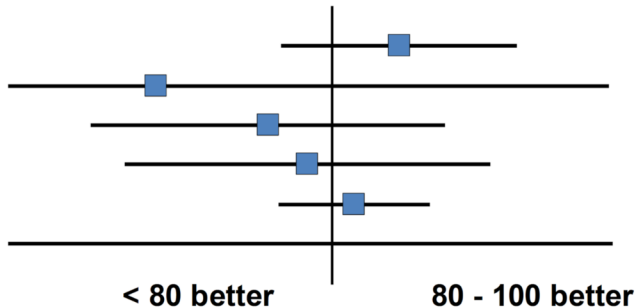




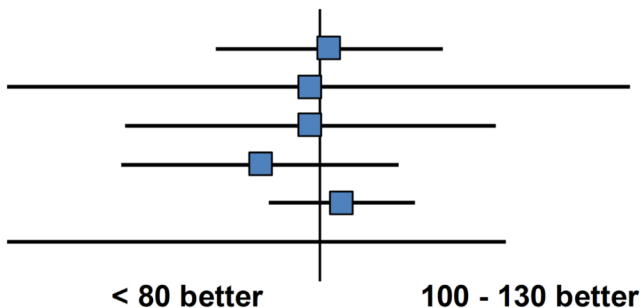
Outcomes

Standardized Mean Difference

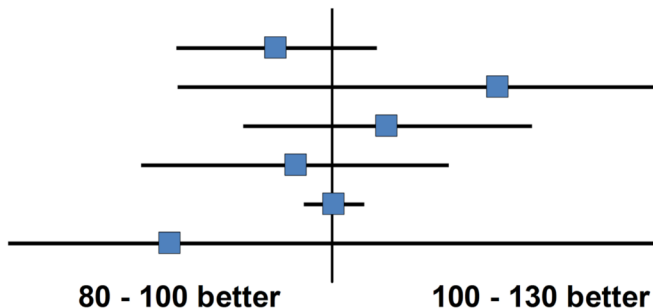
Best corrected visual acuity
 Endothelial cell count
 Central corneal thickness
 Spherical equivalent
 Graft rejection
 Rebutbling



Best corrected visual acuity
 Endothelial cell count
 Central corneal thickness
 Spherical equivalent
 Graft rejection
 Rebutbling



Best corrected visual acuity
 Endothelial cell count
 Central corneal thickness
 Spherical equivalent
 Graft rejection
 Rebutbling



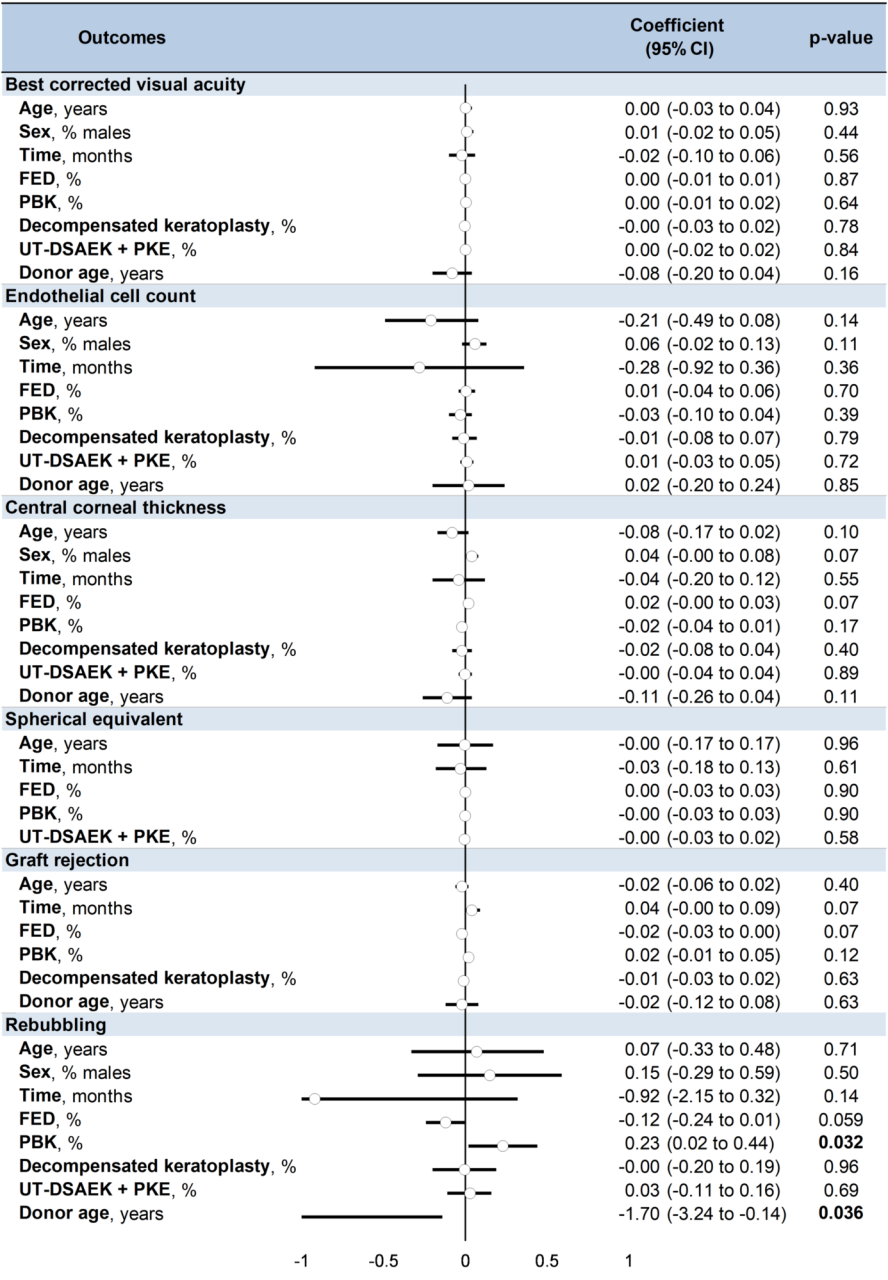


Table 1. Characteristics of included studies.

Study	Country	Study design	n eyes	Age, mean	Sex	Pathology	Triple EK	Graft dissection	CGT, μm	CGT assessment		Outcomes				Follow-up	
			(n patients)	years	% male		%		mean (range)	months	BSCVA	CCT	ECC	SE	Rejection	Rebubbling	months
Asif 2021	India	Retrospective	39	9.9	45	CHED	3	Microkeratome (single pass)	119.4	immediately after dissection	X				X		17.3
Bertino 2020	Brazil	Retrospective	15	-	53	FED, PBK, regrant	13	Manual	94.6	6					X	X	12
Bhandari 2015	India	Retrospective case series	30	55.1	60	FED	0	Microkeratome (single pass)	91.1	immediately after dissection	X	X	X		X	X	12
Bielefeld 2020	France	Retrospective	79 (75)	72	-	FED, PBK, regrant, other	-	Microkeratome	91	immediately after dissection	X	X	X		X	X	12
Bonissant 2016	France	Retrospective	70	68.1	38.6	FED, PBK, regrant, HSV, ICE	-	Manual + Excimer laser	84.1	1	X	X			X	X	12
Busin 2013	Italy	Prospective case series	285 (250)	67.9	38.4	FED, PBK, regrant, HSV, PPD, ICE, congenital glaucoma	33.7	Microkeratome (double pass)	78.3	3	X				X	X	24
Castellucci 2021	Italy	Retrospective cohort	26 (13)	67.6	46	FED	58	Microkeratome (single pass)	99.3	immediately after dissection	X					X	19.6
Chamberlain 2018	USA	RCT	25 (19)	68	36	FED, PBK	68	Microkeratome	73	immediately after dissection	X	X	X		X	X	12
Dickman 2016	Netherlands	RCT	34	73	-	FED	29	Microkeratome (single pass)	101	immediately after dissection	X		X	X	X		12
Dimitry 2017	UK	Prospective case series	12	65	16.7	FED, PBK	67	Microkeratome (single pass)	78.9	immediately after dissection						X	12
Dunker 2020	Netherlands	RCT	25	71	-	FED	0	Microkeratome (single pass)	101	immediately after dissection	X		X	X	X	X	12
El Hadad 2016	Italy	RCT	51	70.7	-	FED, PBK, regrant, PPD	49	Microkeratome (double pass)	89.3	1	X				X	X	12
Gormsen 2019	Denmark	Retrospective registry study	89	71	40	-	-	Microkeratome (single pass)	86	immediately after dissection		X	X				12
Graffi 2018	Italy	Retrospective case series	21	69.2	48	Regrant	5	Microkeratome	82	6	X		X			X	12
Guerra 2011	USA	Retrospective case series	15	67	40	FED	0	Microkeratome (single pass)	aim to 120	-					X	X	12
Jansen 2021	Sweden	Retrospective	116	75.1	38.8	FED, PBK, regrant	12	Microkeratome (single pass)	(100 – 130)	immediately after dissection	X				X	X	24
Jun 2009	USA	Retrospective case series	28	67	39.3	FED, PBK	39.3	-	106.9	immediately after dissection	X			X			4.7
Kurji 2018	USA	Prospective case series	28 (26)	67.1	39.3	FED	64.3	-	41	immediately after dissection	X				X	X	12
Lanza 2021	Italy	Retrospective	111 (96)	70.3	45.8	FED, PBK	48.6	-	90.3	immediately after dissection	X	X	X		X	X	8.5
Liarakos 2013	Netherlands	Retrospective case series	7	72.4	57.1	PBK	0	Manual	107	immediately after dissection	X		X		X	X	12
Matsou 2020	UK	RCT	28	72	50	FED	71	Microkeratome (single pass)	63	immediately after dissection	X		X	X	X	X	12
McKee 2015	Australia	Case series	5	80.2	40	FED, PBK, regrant	-	Femtosecond laser	82.8	6	X						6
Mencucci 2020	Italy	Retrospective	18	73.5	11	FED	0	Microkeratome (single pass)	80.3	immediately after dissection	X	X	X		X	X	12
Mimouni 2021	Austria	Retrospective	28	73.9	25	FED, PBK	-	-	88.5	immediately after dissection						X	-

Muijzer 2019	Netherlands	Prospective cohort	21	68	39	FED, regrant	47.6	Microkeratome (single pass) or manual	105	immediately after dissection	X	X	X	X	12
Muijzer 2019	Netherlands	Prospective cohort	53	68	39	FED, PBK, regrant	39.6	Microkeratome (single pass) or manual	106	immediately after dissection	X	X	X	X	12
Nahum 2015	Italy	Retrospective	42	-	-	FED, PBK, regrant	-	Microkeratome (single pass)	63	3				X	3
Parekh 2019	UK	Retrospective cohort	39	-	-	-	33.3	Microkeratome (single pass)	83.5	immediately after dissection			X	X	8.5
Roberts 2015	UK	Prospective cohort	130 (114)	72	50	FED, other	53	Microkeratome (single pass)	95	immediately after dissection	X		X	X	12
Romano 2017	UK	Case series	10	-	-	-	-	Microkeratome (single pass)	83.2	immediately after dissection				X	3
Romano 2020	UK	Retrospective case series	31	69.3	42.9	FED, PBK	35.5	-	75.3	immediately after dissection	X			X	12
Rosa 2013	Portugal	Prospective	25	65	32	FED, PBK	32	Microkeratome + Femtosecond laser	83.1	1	X		X	X	6
Ruzza 2015	Italy	Prospective case series	14	-	-	FED, PBK, regrant, PPD	-	Microkeratome (single pass)	102	immediately after dissection			X		6
Ruzza 2021	Italy	Retrospective case series	9	-	-	FED, PBK	22.2	-	83	8.5			X	X	8.5
Saunier 2016	France	Prospective	49	67.5	40.8	FED, PBK, other	36.7	Microkeratome (single pass)	116.5	immediately after dissection				X	6
Schaub 2016	Germany	Retrospective case series	5	60	60	-	-	Microkeratome (single pass)	64.5	immediately after dissection	X	X	X	X	3
Tereshchenko 2017	Russia		5	72	0	PBK	0	Femtosecond laser	52	6	X	X			6
Terry 2012	USA	Retrospective case series	45	64.8	31	FED	-	Microkeratome (single pass)	(80 – 124)	immediately after dissection	X				6
Thannhäuser 2014	Germany	Prospective	18	76	-	FED, PBK, other	-	Microkeratome + Excimer laser	111	immediately after dissection	X			X	6
Tomida 2015	Japan		21	70	62	FED, PBK, other	-	Femtosecond laser	aim to 120	-	X		X	X	6
Torras-Sanvicens 2021	Spain	Retrospective case series	10	75.4	40	FED	20	-	91.1	immediately after dissection			X	X	45.5
Tourkmani 2019	UK	Retrospective	29	-	-	FED, PBK, regrant, HSV	17.2	Manual	106	2				X	2
Tsatsos 2014	UK	Prospective	10	-	-	FED, PBK	0	Manual	90.7	1	X				1
Vajpayee 2013	Australia	Case series	15	-	-	FED, PBK, regrant, CHED	20	Microkeratome (single pass)	111	6	X	X			6
Villarrubia 2015	Spain	Prospective case series	60 (51)	-	-	-	-	Microkeratome (single or double pass)	99.3	1				X	1
Walter 2020	USA	Retrospective cohort	170	72	30	FED, PBK	-	-	(70 – 110)	immediately after dissection				X	48
Wang 2021	China	Prospective	85 (84)	58	52.4	FED, PBK, regrant, HSV, ICE, other	27.1	Femtosecond laser	113	3		X	X	X	24
Woo 2019	Singapore	Retrospective cohort	60	68.6	46.7	FED, PBK	-	Microkeratome	80.6	immediately after dissection				X	60

CHED: congenital hereditary endothelial dystrophy; FED: Fuchs endothelial dystrophy; HSV: herpes simplex virus; ICE: irido-corneo endothelial syndrome; PBK: pseudophakic bullous keratopathy; PPD: posterior polymorphous dystrophy.