Transplantation Publish Ahead of Print

DOI: 10.1097/TP.0000000000003735

Secondary Endothelial Keratoplasty – A Narrative Review of the Outcomes of Secondary Corneal Endothelial Allografts

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Disclosure: The authors declare no conflicts of interest.

Funding: No funding was received for this work.

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Abbreviations:

AC: anterior chamber

CCTS: Collaborative Corneal Transplantation Study

CEC: corneal endothelial cell

CDS: Cornea Donor Study

CDVA: corrected distance visual acuity

CMV: cytomegalovirus

CPTS: Cornea Preservation Time Study

DLEK: deep lamellar endothelial keratoplasty

DM: Descemet's membrane

DMEK: Descemet membrane endothelial keratoplasty

DNA: deoxyribonucleic acid

DSAEK: Descemet stripping automated endothelial keratoplasty

DSEK: Descemet stripping endothelial keratoplasty

EDM complex: Endothelial cell layer and Descemet's membrane complex

EK: Endothelial keratoplasty

FECD: Fuchs' endothelial corneal dystrophy

GD: Graft detachment

HSV: herpes simplex virus

IOL: intraocular lens

IOP: intraocular pressure

LEGF: Late endothelial graft failure

PCR: polymerase chain reaction

PGF: Primary graft failure

PKP: Penetrating keratoplasty

SF6: Sulfur hexafluoride

SGF: Secondary graft failure

USA: United States of America

UT-DSAEK: Ultra-thin Descemet stripping automated endothelial keratoplasty

%ECL: Endothelial cell loss rate

GLOSSARY OF TERMS

Descemet lamellar endothelial keratoplasty (DLEK): Technique of posterior lamellar keratoplasty in which a posterior lamellar disc is manually dissected from the recipient cornea through a 9 mm sclerocorneal incision and replaced by an equally sized donor disc, placed against the recipient posterior cornea with an air bubble.

This technique has fallen into disuse, given the surgical complexity of the manual resection of the posterior lamellar disc.

Descemet membrane endothelial keratoplasty (DMEK): Technique of corneal endothelial transplantation in which only the donor's EDM is transplanted.

Descemet stripping (automated) endothelial keratoplasty (DSEK/DSAEK): Technique of endothelial keratoplasty in which the donor's EDM complex is "stripped" from the stroma either manually (DSEK) or with a microkeratome (automated – DSAEK). This method of stripping results in the donor graft having variable levels of stromal tissue.

Descemetorhexis: Removal of the recipient's EDM complex.

Endothelial cell loss rate: In endothelial keratoplasty, the diseased corneal endothelial cell layer is replaced with a donor lenticule of Descemet's membrane and corneal endothelial cell layer. Corneal endothelial cells are highly susceptible to injury and death upon surgical manipulation of the donor graft, and during the surgery there is an average 30% endothelial cell loss. Factors influencing increased iatrogenic endothelial cell loss include surgeon experience, excessive manipulation of the donor lenticule, and history of glaucoma. Afterwards, the endothelial cell loss is continuous and linear in the long term, which may eventually lead to late endothelial graft failure.

Endothelial keratoplasty: Allogeneic corneal transplantation techniques indicated in eyes with diseases of the corneal endothelial layer leading to corneal decompensation (corneal oedema and decreased visual function). In these techniques, only the patient's (recipient) endothelial layer and Descemet's membrane (endothelial-Descemet complex, EDM complex) are removed, leaving the remaining corneal layers (epithelium, Bowman layer, and stroma). Following removal of the diseased corneal layer, the donor's EDM (with or without some corneal stroma), called lenticule, is inserted into the anterior chamber of the eye and apposed to the recipient's stromal bed using either air or sulfur hexachloride 6 (SF6), which ensure the graft adhesion.

Graft detachment: The EK grafts are apposed to the recipient's stromal bed using air or sulfur hexafluoride 20%, placing them at risk of detachment. The detachment may be partial or complete, producing a loose graft in the anterior chamber. Detachment of EK grafts is related with increased endothelial cell loss and with increased risk of graft failure.

Posterior lamellar keratoplasty: Forms of corneal allograft transplantation in which only the posterior layers of the donor cornea (endothelial layer, Descemet's membrane, with or without posterior corneal stroma) are transplanted into the host. This technique is indicated in cases of primary or secondary corneal endothelial cell failure, such as Fuchs' endothelial corneal dystrophy, postoperative bullous keratopathy, or viral endotheliitis. These techniques differ from penetrating keratoplasty, in which the full-thickness cornea of the patient is replaced with a full-thickness corneal allograft.

Rebubbling: Injection of an air bubble in the anterior chamber in the setting of partial or complete graft detachment after endothelial keratoplasty, to increase the chance of graft adherence to the recipient's corneal stromal bed and to reduce the risk of primary graft failure.

Ultrathin DSAEK (UT-DSAEK): In UT-DSAEK, the donor graft has a thickness < 100 µm, minimizing the stromal thickness of the lenticule. This technique emerged following the notion that the graft lenticule thickness influenced visual acuity and optical quality after DSEK/DSAEK, with thinner grafts correlating with better visual outcomes.

Upside-down graft: Both DMEK and DSEK grafts are inserted into the anterior chamber during surgery using graft injectors. The correct position of the graft is with the Descemet's membrane facing "up" towards the recipient's corneal stromal bed. These grafts may be inadvertently positioned "upside-down", with the endothelial cell layer facing the host stromal bed. These grafts evolve to primary graft failure.

ABSTRACT

Background: We review the literature on the efficacy and safety outcomes of secondary Descemet stripping endothelial keratoplasty (DSEK) and Descemet membrane endothelial keratoplasty (DMEK).

Methods: Literature search of English-written publications up to 27th September 2020 in PubMed database, using the terms "endothelial keratoplasty" in combination with keywords "secondary" or "repeat". In addition, we manually searched the references of the primary articles.

Results: 27 studies (n = 651 eyes) were retained and reviewed, including 10 studies on repeat DSEK, 8 studies on repeat DMEK, 6 studies of DMEK following DSEK, and 3 studies of DSEK after failed DMEK. All studies reported significant improvement in visual acuity after secondary EK. Twelve studies compared visual outcomes between primary and secondary EK, reporting conflicting findings. Sixteen studies reported endothelial cell loss rates (%ECL) after secondary EK, and only one study reported significantly increased %ECL compared with primary EK. Allograft rejection episodes occurred in 1.8% of eyes (range 0-50%). Six studies compared complication rates between primary and secondary EK eyes, and only one study found a higher median number of complications. However, two studies reported higher regraft failure rates compared with primary EK eyes.

Conclusions: Secondary EK is surgically feasible and renders significant visual improvement after failed primary EK, although it is not clear whether visual outcomes and allograft survival are comparable with primary EK, raising the question of whether secondary EK eyes are "low-risk" as primary EK eyes. Further larger, prospective studies are encouraged to obtain additional quality data on secondary corneal endothelial allotransplantation.

Online Supplemental Appendix; http://links.lww.com/TP/C177

INTRODUCTION

Posterior lamellar keratoplasty, including Descemet stripping membrane endothelial keratoplasty (DSEK) and Descemet membrane endothelial keratoplasty (DMEK) has significantly progressed in the last decade, and endothelial keratoplasty (EK) techniques have superseded penetrating keratoplasty (PKP) as the corneal allograft transplantation techniques of choice in the management of corneal endothelial disease (Figure 1).[1-3] Primary or secondary corneal endothelial cell failure is currently the main indication for corneal transplantation worldwide, representing 56% of all corneal transplants in the United States of America (USA);[2] of these, 90% were EK grafts and only 10% were PKP grafts.[2] PKP may still be indicated in certain cases of primary or secondary corneal endothelial disease, particularly in eyes with significant corneal subepithelial or stromal scarring, where outcomes of EK may be suboptimal.[4] Although an increasing body of evidence favors DMEK over DSEK in terms of efficacy and safety,[5] DSEK may have a lower rate of rebubbling,[5] and is still the most performed EK surgery among corneal specialists worldwide.[2,6]

Graft failure after endothelial keratoplasty

In contrast to other forms of allogeneic transplantation, primary corneal allografts are regarded has having high long-term success rates. However, graft failure is a potential complication following EK, as may occur after PKP grafts. The causes of failed EK grafts have been classified as either primary graft failure (PGF) or secondary graft failure (SGF). The most common cause of SGF is late endothelial graft failure (LEGF),[7,8] followed by immune rejection and glaucoma; other causes include infection, trauma, and epithelial ingrowth. The graft survival rate decreases with time, with reported mean survival rates after DMEK ranging from 83% to 96% at 5 years,[9-11] and 79% at 10 years;[11] reported mean 5-year survival rates following DSEK range from 79.4% to 96% 5 years.[12-15]

Primary graft failure has been defined as the absence of corneal clearing within 2 months following EK. This may occur due to significant iatrogenic corneal endothelial cell (CEC) loss during the preparation, insertion, or manipulation of the graft; due to "upside-down" graft (particularly during the early years of the technique, or during the surgical learning curve); or due to graft detachment (GD). Reported rates of PGF ranges from 0%-12.5% after DMEK,[8] 0%-29% after DSEK,[16] and 1.4% after ultrathin DSAEK (UT-DSAEK),[17] with a lower average PGF rate in favor of DMEK.[8] In the Cornea Preservation Time Study (CPTS), a benchmark study which analyzed the outcomes following DSEK, risk factors for primary or early failure following DSEK included patient-related factors (notably preoperative diagnosis of pseudophakic or aphakic corneal edema), donor-related factors (notably diabetes mellitus), and operative factors.[18]

Graft detachment occurs more commonly with DMEK compared with DSEK,[5,8] with mean reported rebubbling rates of 28.8% versus 14% in favor of DSEK.[8] Reported factors associated with decreased risk of GD following DMEK include increased surgeon experience, a larger descemetorhexis, the use of 20% SF6 instead of air, a normal intraocular pressure (IOP) and a well-centered graft.[8,19,20] History of donor diabetes, increased pre-lamellar dissection central corneal thickness, and intraoperative complications have been identified as predictive factors for GD in the CPTS.[21] It has been suggested that GD is associated with increased EC loss following DSEK, and therefore may decrease graft survival.[20] Rebubbling following GD achieves graft adhesion in a high percentage of patients both in DSEK and in DMEK, but even in cases of successfully reattached grafts, 31%-35% of DSEK grafts still evolve to PGF.[22,23] Rebubbling for detached DMEK grafts has a definitive benefit and may allow similar visual outcomes as in uncomplicated DMEK, and should usually be performed early.[24] However, the decision and timing of rebubbling for detached

DMEK graft must be carefully considered, since prolonged air tamponade following rebubbling causes increased, IOP-independent CEC loss.[22,24,25]

Progressive CEC loss after EK is associated with reduced graft survival and LEGF. Following uncomplicated EK, reported mean 6-month endothelial cell loss rate (% ECL) ranges from 24%-37% following DMEK, DSEK or UT-DSAEK, [8-10,26,27] and the evidence of significant differences in %ECL between EK techniques is inconclusive.[25] The CEC loss after EK has a linear profile in the medium and long terms.[11,28] Mean rates of CEC loss after conventional DSEK/DSAEK range from 36-43% after 3 years,[29] 48.7-55% after 5 years [12,14,30] (comparable with UT-DSAEK [17]), and 71% after 10 years.[28] Rates of CEC loss after DMEK range from 48-59% at 5 years,[9,11,31] and one study reported a mean 68% EC loss at 10-year follow-up.[11] The cumulative probability of LEGF after DSEK was 1.3% at 3 years in the CPTS,[32] and the cumulative probability of survival at 5 years range from 79.4% to 96%.[12-15] The average rate of LEGF after DMEK (follow-up times between 6 months and 8 years) is 2.2%,[8] with one study reporting a 6% rate of LEGF at 10-year follow-up,[11] and the graft 5-year survival probability ranges from 83%-96%.[9-11] Compared with PKP grafting, the CEC loss rate following EK is higher in the first 6-12 months postoperative, mostly due to manipulation of the graft during surgery. However, the CEC loss is comparable between EK and PKP after 3 years of follow-up,[33] and over the long term the CEC loss in PKP grafts is greater than with EK grafts. In the Cornea Donor Study (CDS), a benchmark study reporting outcomes following PKP, the median CEC loss rates at 5 and 10-year follow-up after PKP were 69-75% (in contrast with 48-59% after EK) and 76-79% (versus 68-71% for EK), respectively.[34,35]

Endothelial keratoplasty is regarded as a low-risk setting for allograft rejection episodes, with significantly lower rejection rates compared with PKP.[8,16,36] Mean rejection rates are 10% (range 0-45%) following DSEK (follow-up times between 6 months and 8 years),[8] and 1.9%

(range 0-5.9%) after DMEK (follow-up times between 6 months and 10 years);[8,11] the 5-year risk of rejection after DMEK may be as much as 71% lower than for DSEK.[31] The 5-year cumulative probability of rejection episodes after UT-DSAEK was 6.9%.[17] The rejection rates following EK grafting are significantly lower compared with those of PKP, where overall 30% may experience at least one episode of immune reaction.[37] We refer the reader to a comprehensive review on the immune mechanisms after modern lamellar keratoplasty for further detail on the clinical and pathogenic mechanisms involved in corneal allograft rejection.[38]

Rejection episodes may be a predictive factor for graft failure or need of graft exchange after EK,[15,39,40] although this is not consensual.[31,41] In the setting of PKP, about one third of grafts with history of at least one episode of allograft rejection will eventually fail.[37] There is significant variation in the reported risk of graft failure after immune rejection after DSEK. In the CPTS, the cumulative probability of rejection was 3.6% 3 years after DSEK, and 27% of eyes with definite graft rejection subsequently failed.[39]

Secondary endothelial keratoplasty

Repeat keratoplasty has become an increasing indication for corneal transplantation, being the fourth most frequent indication in the USA (13% of all corneal transplant procedures performed in 2019).[2] Repeat keratoplasty has a long track record of safety and efficacy in eyes with previously failed PKP grafts (repeat PKP),[42] but secondary PKP grafts are considered high-risk cases due to increased risk of rejection and failure.. In the Collaborative Corneal Transplantation Studies (CCTS), a benchmark study in the field of corneal allogeneic transplantation, the number of previous PKP grafts was a strong risk factor for graft failure, with a 1.2-fold increased risk with each additional graft.[43] Five-year graft survival after primary PKP is 92-95%, and decreases sequentially with each regraft (79-82% after secondary graft, 54-71% after tertiary graft, and 42-56% after ≥ 4 grafts).[44,45] Allograft rejection after PKP occurs earlier with a more fulminant course in regrafts that in primary grafts, and the risk of regraft failure is especially high if previous graft failure was a result of an allograft rejection.[46] A number of factors contribute to increased risk of immunological rejection in the setting of repeat PKP allografts,[47] including previous alloimmune response (regraft-associated sensitization) and residua of the previous surgery such as corneal neovascularization and peripheral anterior synechiae.[4]

Endothelial keratoplasty is becoming increasingly indicated in retransplantation, with estimated regraft rates of 10% in the USA and 14% worldwide.[2] In the setting of failed primary PKP graft, EK has proved to be a safe and effective technique.[48-54] A recent meta-analysis found that eyes undergoing EK for failed PKP graft had a significantly lower risk of graft rejection compared with eyes undergoing repeat PKP.[55] In our cohort of eyes undergoing DMEK after failed PKP graft,[52] we found a significant improvement in visual acuity and a high rate of clear corneal grafts at 2-year follow-up; we have however recently documented one case of DMEK graft rejection failure after PKP, which ended in graft failure requiring repeat DMEK.[56]

In eyes with failed primary EK grafts or cases of "suboptimal DSEK" (DSEK eyes with poor visual outcomes), secondary EK has been proposed as a potentially safe and effective strategy. Zafar et al. have reported an overall probability of receiving a repeat EK of 6.1% at 6 months and 16.9% at 8-years.[57] In this large retrospective study, younger age, male gender, Asian or melanodermic ethnicity, glaucoma diagnosis, prior or concurrent glaucoma surgery, macular pathology, prior anterior segment surgeries, and lower surgeon volume were found to be factors associated with increased risk of repeat EK.[57] Regrafts were also at increased risk of repeat EK in their study.[57]

In this study, we provide a qualitative literature review on the techniques, efficacy, and safety of secondary EK.

MATERIALS AND METHODS

We conducted a literature search in PubMed database to assess the functional outcomes following secondary EK. We searched English-written publications up to 27th September 2020, using the following query: "Endothelial keratoplasty"[Title/Abstract] AND ("secondary"[Title/Abstract] OR "repeat"[Title/Abstract]). To reduce the chance of missing relevant articles, we searched manually the references of the primary articles. We included case reports, case-control, cross-sectional, retrospective or prospective studies, including studies where the patient groups included EK and PKP eyes, in which we analyzed the secondary EK eye group only. We excluded studies in which the aim of the study was not assessing functional outcomes (visual acuity, graft failure). We also excluded studies of secondary EK for previously failed deep lamellar endothelial keratoplasty, as this technique has been superseded by DSAEK and DMEK. After removing duplicate records, we independently screened the titles, abstract and keywords to identify relevant articles in secondary EK (DSEK/DSAEK or DMEK). Studies not related to secondary DSEK or secondary DMEK were excluded.

We performed a qualitative analysis of the full-text articles assessed. We assessed 358 articles for eligibility (356 from PubMed database, and 2 articles by manual search of primary articles), and selected all the original studies (case reports, case series, and comparative studies) which reported the results following secondary EK to include in the analysis. We excluded conference abstracts, editorials and letters to the editor, irrelevant records, non-human studies and review articles. We independently extracted data into a customized database. We analyzed the outcomes of secondary EK according to type of primary and secondary EK surgeries (repeat DSEK; repeat DMEK; DMEK after failed primary DSEK; and DSEK after failed primary DMEK).The extracted information included authors of the study, publication year and journal, sample size (number of eyes), indication for secondary EK and proportion of eyes undergoing primary EK for Fuchs endothelial corneal dystrophy (FECD), time between primary and secondary grafts, preoperative corrected distance visual acuity (CDVA), postoperative follow-up time and final CDVA. When reported, we also extracted information regarding the surgical technique, %ECL, complication rates (rebubbling for GD, allograft rejection, other complications), and rate of regraft failure.

RESULTS

We found 27 studies reporting outcomes following secondary EK (n = 651 eyes). The study by Yazu et al. was excluded,[58] since visual outcomes were not reported following repeat DSEK. We excluded the studies by Dirisamer et al.[59] and by Kim et al.[60] because they reported outcomes of DSEK after failed deep lamellar endothelial keratoplasty (DLEK), an earlier technique of corneal endothelial transplantation which has fallen into disuse. Finally, we excluded the study by Agha et al.[61] because the same group had published two different comparative case series on repeat DMEK and repeat DSAEK in the same year with larger cohorts.

1. Repeat DSEK

Ten studies (n = 403 eyes) analyzed the outcomes of repeat DSEK (re-DSEK).[62-71] The two main indications for re-DSEK were failed primary DSEK graft and poor visual performance after primary DSEK. Prior aqueous shunt surgery, donor graft CEC density, and at least 1 documented postoperative rejection episode were the main factors associated with the need for DSEK graft exchange after primary DSEK in a multivariable model.[40]

Two re-DSEK studies included eyes with suboptimal primary DSEK;[64,67] the proportion of eyes which had re-DSEK for this indication was highly variable, ranging from 1.9% to 76%

(Table 1).[64,67] Even in eyes with clear primary DSEK grafts, final CDVA is variable, with a mean postoperative CDVA of 20/40 – 20/30 at 3-6 months following DSEK or UT-DSEK, and % eyes reaching CDVA ≥ 20/40 ranging from 38-100%.[16,72] In addition, the proportion of eyes reaching CDVA ≥ 20/25 following DSEK was relatively low (6-31%). Poor visual recovery after primary DSEK can occur in eyes with clear grafts due to interface abnormalities, and/or significant wrinkles and folds in the pupillary area.[64] The latter has been hypothesized to be the result of mismatch between donor and recipient corneal curvatures.[64] Proposed abnormalities contributing to poorer visual performance following DSEK include increased corneal aberrations of the posterior surface,[73,74] and increased light scattering at the host-donor interface, which may be due to host Descemet's membrane (DM) remnants, presence of interface material such as fibrocellular tissue including cytokeratin, fibronectin and vimentin,[75] or stromal contraction of the donor graft.[76] Graft thickness is likely to influence visual outcomes following DSEK, and this has been one argument favoring UT-DSEK over conventional DSEK;[27] however, this remains controversial.[77] Interestingly, DMEK has been demonstrated to result in less posterior corneal aberrations compared with conventional DSEK and UT-DSEK.[74,78]

Repeat DSEK can be performed under sub-Tenon or retrobulbar anesthesia supplemented with neuroleptic anesthesia. Repeat DSEK is performed through the same incision site as the primary DSEK procedure, by opening the original incision with a keratome. The failed DSEK donor graft can be removed using a reverse Sinskey hook to detach it from the recipient corneal stroma engaging the edge of the graft,[64,65] or alternatively using a bent 27-gauge needle inserted through the limbus at the 12-o'clock position,[67] and then removed from the anterior chamber (AC) using an intraocular forceps. It is important to make sure the graft has not adhered to the iris, as these adhesions may be quite dense with thick membranes that may lead to iris dehiscence upon graft removal.[79] The new donor graft is prepared as for standard primary DSEK or UT-DSEK, but the lenticule diameter should be the same or slightly larger than the previous failed DSEK graft. The lenticule insertion and AC filling techniques are the same as for primary DSEK procedure.[65,67] Interestingly, secondary DSAEK has anecdotally been performed without removal of the failed DSAEK graft in a recent case report, with successful improvement of pain and corneal edema in a painful red eye with bullous keratopathy and poor vision.[80] Matsumoto et al. have reported repeat DSAEK to render successful anatomical and functional results in combination with phakic intraocular lens (IOL) explantation and cataract surgery.[70]

The standard postoperative regimens following re-DSEK include topical tobramycin 0.3% eye drops for 4 weeks; proposed topical corticosteroid regimen varies between surgeons, but maintenance therapy with a topical steroid over a long period is a common aspect.[65,67] Systemic prednisolone (1.5 mg/kg body weight with tapering over 3 months) has been considered in cases of DSEK failure due to allograft rejection.[67]

Most eyes can expect clear functioning and improvement in CDVA following re-DSEK. CDVA improved in 97% of eyes that underwent re-DSEK for poor visual performance.[64] Reported visual outcomes appear to be similar to those achieved for primary DSEK surgery,[68] with mean CDVA after re-DSEK ranging from 0.50 – 0.18 logMAR (Snellen equivalent 20/30-20/63).[64,65,67,71] Besides, maximal postoperative CDVA after re-DSEK reported rates of eyes reaching CDVA ≥ 20/40 following re-DSEK range from 20% to 100%.[63-65] If studies with ≤ 2 eyes were excluded from this analysis, the proportion of eyes reaching CDVA ≥ 20/40 would be 20-82%, and no studies observed eyes reaching CDVA ≥ 20/25[63] Visual results in these eyes are negatively influenced by high-order aberrations of the posterior corneal surface,[58] and positively influenced by a higher preoperative IOP before re-DSEK.[69]

Rates of CEC loss were reported in 3 studies (n = 192 eyes), ranging from 36.7-47.3% (follow-up times ranging from 12-27 months).[65,67,68] Only one study compared %ECL between primary DSEK and re-DSEK eyes, and found not statistically significant differences.[67] However, one study suggests that their re-DSEK cohort had accelerated %ECL compared to their previously published data on primary DSEK eyes.[65]

Re-bubbling rates were reported in five studies, and ranged from 0-15%. [62,65-67.69] Immune rejection episodes were reported in four studies (n = 54 eyes),[62,65-67] and only occurred in one study (1 eye, 1.9%), which required continued topical steroid therapy for recurrent keratic precipitates.[62] Regraft failure rates were reported in eight studies (n = 245 eyes), ranging from 0-20% (follow-up times ranging from 6-27 months).[62,65-68,71] A prospective long-term analysis performed by the Netherlands Organ Transplantation Registry found that regraft survival is lower compared to primary graft survival.[68] These findings are similar to those reported in a retrospective study in which re-DSEK grafts were reported to be at increased risk of rejection and graft failure compared with primary DSEK eyes (Moura-Coelho et al., personal communication).

2. Repeat DMEK

Eight publications (n = 130 eyes) analyzed the outcomes of repeat DMEK (re-DMEK) for failed primary DMEK graft (Table 2).[56,81-87] Excluding the case report by Alió del Barrio et al.,[85] primary DMEK was performed for FECD in 78.6-100% of cases. Histopathological analysis of failed primary DMEK grafts has shown that the majority of failed primary DMEK grafts have subclinical, preoperative corneal endothelial dysfunction, and that most cases have an abnormal fibrillary posterior collagenous layer.[82,88] DMEK failure may be associated with innate immune activation and increased cytokine levels in the aqueous humor, particularly interleukins 5 and 8.[87]

Regrafting has rendered a surgically feasible approach in cases of failed primary DMEK. Compared with primary DMEK, certain particularities in the operative protocol must be considered in re-DMEK.[56,83] The previous 3.0-mm corneal tunnel incision is reopened, disinserting the failed DMEK graft from the host stroma using a reverse Sinskey hook under air, and remove the graft with a DMEK forceps.[56] At this stage, careful removal of graft remnants by scraping can be performed, while avoiding damage to the host posterior stroma;[56,83] injecting trypan blue into the AC may aid in visualizing DM remnants.[83] Donor Descemet roll preparation, insertion, positioning and tamponade into the host posterior stroma is performed as for primary DMEK surgery; 20% SF6 may be used as tamponade, leaving a relatively soft eye at the end of the surgery.[56] Particularly in cases when re-DMEK is performed to manage GD, leaving the host AC completely filled with air for 60-120 minutes can help reducing the risk of detachment occurring in the same quadrants, and then air-liquid exchange is performed to leave a 30-50% air bubble.[83] It has been reported anecdotally that a second DMEK graft without removal of the failed DMEK graft effectively restored corneal transparency and vision in a case of pseudophakic bullous keratopathy.[85] Reported postoperative medication regimens are usually the same as for primary DMEK surgery.[56,83,84] We routinely prescribe topical tobramycin 0.3% and dexamethasone 0.1% eye drops every 2 hours in the first postoperative day, then 6 times a day for the first postoperative week, then 4 times a day for 4 weeks, and then tapering the topical steroids over the following 3 months; topical dexamethasone 0.05% and chloramphenicol 1% ointment at bedtime for 12 weeks and then at bedtime three times weekly until the sixth postoperative month, with discontinuation in the absence of any inflammatory signs or symptoms of rejection; and topical ocular hypotensive medications over 3 months. In addition, we prescribe oral methylprednisolone 40 mg/day for three days, followed by tapering over the first 3 postoperative weeks.[56]

Mean/median follow-up periods after re-DMEK ranged from 3.3-18 months (range: 3-89 months).[56,80-84,86,87] Reported mean final CDVA following re-DMEK ranged from 0.33-0.09 logMAR [Snellen equivalent 20/25-20/43]. Five studies (n = 105 eyes) reported the proportion of eyes reaching higher CDVA at final observation[56,82-85]: 82-100% of eyes reached CDVA ≥ 20/40, and 13.3-81% of eyes reached CDVA ≥ 20/25. Three of these studies (n = 86 eyes) additionally reported that 18.2-61% of eyes reached final CDVA ≥ 20/20.[56,83,84] The changes in corneal pachymetry were reported in six studies (n = 110 eyes).[82-87] Mean central corneal thickness before re-DMEK ranged from 631-931 µm, and decreased to 512-576 µm at 6 to 12-month follow-up after re-DMEK.

All studies except the case report by Alió del Barrio et al.[85] reported comparative analyses between primary and re-DMEK eyes (n = 129 re-DMEK eyes): one study (n = 6 eyes) compared the pre- and post-operative CDVA after the first and the second DMEK grafts;[81] two studies compared re-DMEK eyes with the subgroup of patients with successful fellow-eye primary grafts (n = 38 eyes),[82,84] and four were retrospective, comparative case series (n = 50 eyes).[56,83,86,87] Five studies (n = 68 eyes) reported that visual outcomes were comparable between primary and re-DMEK eyes,[56,81,84,86]including the percentage of eyes that reached higher levels of CDVA at 1-year comparisons.[56,84] However, two studies reported inferior visual outcomes after re-DMEK compared with primary DMEK.[82,83] The time between graft failure and regrafting may influence visual outcomes, since average intervals between PGF or GD and regrafting ranged from 9 days and 2.9 months in the series reporting comparable visual outcomes,[56,81,84] contrasting with the two studies reporting inferior visual outcomes, in which average times ranged from 146 days to 16 months.[82,83] Prompt regrafting minimizes the duration of host corneal decompensation and associated stromal changes,[83,84,86] which can lead to increased backscatter.[61]

Mean %ECL following re-DMEK was reported in six studies (n = 123 eyes),[56,82-84,86,86] ranging from 29.8-49.5% at 6-month follow-up,[83,84,86,87] from 34-49.8% at 12-month follow-up,[82,84,87] and 48.2% in eyes with medium-term follow-up.[56] Six studies (n = 111 eyes) reported rebubbling rates following re-DMEK, ranging from 5.9% to 33% after excluding the case report by Alió del Barrio et al.[56,81,83,84,86,87] Eyes which had GD after primary DMEK may be at increased risk of rebubbling after re-DMEK,[56,83] which suggests that host intrinsic properties may interfere with graft adherence. Four studies (n = 104 eyes) reported rejection rates,[56,82-86] ranging from 0% to 14.3%.[56,82-84] In the studies reporting eyes with immune rejection episodes in the regraft, one eye of each cohort had undergone re-DMEK for rejection of the primary graft.[54,83] All studies reported regraft failure rates, ranging from 0% to 21.4% (with follow-up times ranging between 3-89 months). Five studies (n = 110 eyes) reported other complications after re-DMEK,[56,82-84,87] including cataract or IOL opacification (n = 4),[56,82,83,87] IOP spikes or glaucoma progression requiring additional medication or surgery (n = 16),[56,83,84,87] macular edema (n = 3),[56,87] pupillary block (n = 1),[56] and corneal ulcer (n = 1).[83]

3. Secondary DMEK for eyes with previous DSEK grafts

Six publications reported the outcomes of secondary DMEK for eyes with previous DSEK grafts (n= 79, Table 3).[75,89-93] Early re-intervention should be considered, since fibrotic processes might be anticipated in this setting.[75] DSEK grafts are carefully mobilized using a reverse Sinskey hook or blunt spatula and then explanted. In this setting, adjacent remnants of host DM have been found to be present at the donor-to-host stromal interface in as many as 50% of eyes, and in most cases in the visual axis.[90] Meticulous search for adjacent remnants of host DM and tags of stroma should thus be performed;[92] these can be removed using a reverse Sinskey hook or a corneal scraper under air after trypan blue staining.[93] Graft tamponade into the recipient's stroma can be made using air or 20% SF6. Proposed techniques to improve the visibility of the AC include the mechanical removal of the edematous corneal epithelium, application of methylcellulose on the corneal surface during surgery, and optimal illumination.[91]

The optical quality of the transplanted cornea can be fully restored by careful removal of the DSEK graft and implantation of a DMEK graft,[89,91] and therefore DMEK for eyes with poor visual performance after DSEK has gained increasing interest among corneal surgeons. Mean CDVA improved significantly following secondary EK in all studies (n = 79 eyes) over mean follow-up times ranging from 6-18 months (mean preoperative CDVA ranged from 0.50-1.72 logMAR, and mean final CDVA ranged from 0.06-0.51 logMAR). Two studies (n = 15) reported that 91.7% to 100% of eyes reached CDVA ≥ 20/40 and CDVA ≥ 20/25 at 6-month follow-up;[89,90] in these two studies, 33-42% of eyes reached final CDVA ≥ 20/20.[89,90] Only one study compared outcomes between primary DMEK and secondary DMEK after primary DSEK (n = 8),[75] and reported the inferior outcomes in the latter group. Fibrotic changes in the host cornea due to persistent corneal edema after graft failure and suboptimal status of the DM-stromal interface may account for inferior outcomes.[75]

Three studies (n = 56 eyes) reported the rate of CEC loss, with mean %ECL rangingd from 34.7% to 43.7% over 6 to 18-month follow-up periods.[91-93] This outcome is comparable to reported %ECL following primary DMEK.[8] Four studies (n = 59 eyes) reported rebubbling rates, ranging from 0% to 20%.[89,91-93] Four studies (n = 59 eyes) reported rejection rates in this setting, ranging from 0-3.8%;[88,91-93] only one study documented cases of immune rejection episode (1 eye), which ended in graft failure.[92] All six studies reported graft failure rates, ranging from 0% to 19.2% (mean follow-up times ranging from 6 to 18 months).[75,89-93]

4. Secondary DSEK for eyes with failed primary DMEK grafts

Three studies (n = 39 eyes) have analyzed the outcomes of secondary DSEK in cases of failed primary DMEK (Table 4).[94-96] Two studies (n = 18 eyes) used "conventional" DSEK grafts (one using manual preparation of the graft, and another one using DSAEK),[94,95] and one study (n = 21 eyes) used UT-DSAEK.[96] This approach may be particularly useful during the learning curve of DMEK surgery,[95,96] as well as in some cases where significant corneal edema hinders a good visualization of the AC.[94] In the secondary surgery, the 3.0-mm corneal incision fashioned for the primary DMEK is re-opened, the primary graft is stained by injecting trypan blue 0.06% into the AC, then the failed graft is disinserted from the host using a reverse Price-Sinskey hook and removed from the eye using an intraocular forceps. The host posterior stromal bed should be checked for irregularities under air, and the AC thoroughly irrigated to remove all remnant graft tissue.[94] The DSEK graft is then inserted through the corneal incision, unfolded and positioned onto the recipient posterior stroma; all three studies used air filling of the AC leaving a 50% air-filled AC at the end of the surgery.[94-96]

All three studies found an improvement in mean CDVA after secondary EK. After excluding eyes with comorbidities (6 eyes in two studies), mean final CDVA improved from 0.69-1.52 logMAR to 0.06-0.40 logMAR at 6 to 12-month follow-up analyses.[94-96] The percentages of eyes reaching CDVA ≥ 20/40, ≥ 20/25 and ≥ 20/20 ranged from 62-100%, 0-92%, and 0-31%, respectively.[94-96] The study of UT-DSAEK for failed DMEK reported better visual outcomes than those of conventional DSEK/DSAEK. In eyes undergoing conventional DSEK/DSAEK for failed DMEK, 62-87% reached CDVA ≥ 20/40, and only one case in both studies reached CDVA ≥ 20/25 (range 0-13%);[94,95] in contrast, in the study by Graffi et al. 92% of eyes undergoing UT-DSAEK for failed DMEK reached CDVA ≥ 20/25, and 30% reached CDVA ≥ 20/20.[96] These differences likely reflect the influence of graft thickness and regularity of the donor graft on visual performance following DSEK, although the role of the learning curve and experience in DMEK surgery may also play a role in these outcomes, since DSEK publications antedated that of UT-DSAEK by 5 to 8 years. One study found an increase in central corneal light scattering after secondary DSAEK performed after a failed DMEK compared with primary DSAEK eyes.[95]

Two studies (n = 31 eyes) reported CEC loss rates 12 months after secondary DSEK after failed primary DMEK, ranging between 38-46.4%.[94,96] The differences between manually prepared DSEK and UT-DSAEK were not statistically significant (MD = 7.2%; p = 0.531). Two studies (n = 31 eyes) reported rebubbling rates ranging from 0-30%, in favor of UT-DSAEK.[94-96] Only one study (n = 21 eyes) reported outcomes regarding allograft rejection episodes after secondary EK in this setting, and found no cases of rejection episodes in the first postoperative year.[96] None of the three studies reported cases of failed regraft. Only one study (n = 21 eyes) reported other complications after secondary EK,[96] with a 23.8% complication rate (graft wrinkling, 1 eye; and IOL opacification in 4 eyes, two of which required IOL exchange).[96]

5. Postoperative care and optimization of graft survival

As mentioned earlier, EK grafts are considered low-risk for immune rejection episodes. Typical postoperative regimens to reduce the risk of allograft rejection episodes after primary EK include topical corticosteroid therapy with tapering over 6-12 months.[31,38,41] Our immune rejection prophylaxis regimen after EK includes tobramycin 0.3% and dexamethasone 0.1% eye drops every 2 hours in the first postoperative day, then 6 times a day for the first postoperative week, then 4 times a day for 4 weeks, and then tapering the topical steroids over the following 3 months, plus dexamethasone 0.05% and chloramphenicol 1% ointment at bedtime for 12 weeks and then at bedtime three times weekly until the sixth postoperative month.[19] In addition, we also include oral methylprednisolone 40 mg daily for three days, then 20 mg daily from postoperative day 4 to day 6, then 10 mg daily during the second postoperative week, and then 10 mg every 48 hours during the third postoperative week. We also include topical timolol eye drops twice daily for three months and oral acetazolamide in the first postoperative day to prevent IOP spikes and corticoid-responsive IOP elevations. However, recent evidence suggests that continued use of a topical corticosteroid may be protective against rejection episodes after the first postoperative year following DMEK.[41,97] The reported post-operative rejection prophylaxis protocols after secondary EK are usually the same as for primary EK.[56,83,84] In contrast, repeat PKP is considered a high-risk keratoplasty scenario, and in addition to continuing topical corticosteroids indefinitely, many corneal surgeons also advocate the use of systemic immunosuppressants to reduce the risk of allograft rejection; these include systemic corticosteroids, mycophenolate mofetil, cyclosporine A, rapamycin, and tacrolimus.[47,98] However, the evidence for the effects of immunosuppressants is limited at present.[47,99]

Fourteen studies (n = 275 eyes) reported rejection rates. (excluding single-patient case reports). Five eyes had allograft rejection episodes (average rejection rate = 1.8%; range: 0-50%), which is comparable with the mean 1.9% rejection rate following primary DMEK reported by the American Academy of Ophthalmology.[8] One case of re-DMEK rejection had previous history of immune rejection of the primary DMEK graft,[83] and one case of re-DMEK rejection occurred in an eye with previously rejected DMEK graft performed for failed PKP. [56] Three of the five regrafts with rejection episodes eventually failed (two re-DMEK eyes and one DMEK for failed primary DSEK graft).[56,92] One retrospective study of repeat DSEK eyes found that these eyes may have a higher risk of allograft rejection compared with primary DSEK (Moura-Coelho et al., personal communication). These findings raise the question as to whether secondary EK eyes (as well as eyes undergoing EK for failed PKP) graft may be at a higher risk of graft rejection and rejection-related graft failure, compared with the low risk of rejection-related graft failure of primary EK eyes. An aggressive steroid regimen may be needed in the postoperative period, at least in the subset of patients undergoing repeat keratoplasty for graft rejection.[55,79] In these cases a longer duration or indefinite period of topical corticosteroid prophylaxis could be considered, with careful attention to IOP rises and/or development or progression of glaucoma.[38] Interestingly, Alió del Barrio et al. have suggested adding oral steroids for one month plus topical tacrolimus 0.03% and systemic tacrolimus 1 mg every twelve hours in a case of repeat DMEK for primary DMEK failure due to allograft rejection, and the regraft did not experience rejection episodes.[85]

A potential cause of increased %ECL and graft failure after DSEK and DMEK is viral infection caused by herpes simplex virus (HSV) or cytomegalovirus (CMV). When considering retransplantation in a failed corneal graft, the clinician should maintain a high index of suspicion for CMV and HSV infection as potential causes of graft failure.[100] HSV-1 antigen immunoreactivity has been detected in 2%-14% of failed DSEK grafts, [7,101] and HSV endotheliitis should be kept in mind in the early postoperative period after DMEK.[102] CMV endotheliitis after corneal transplantation is an increasingly recognized complication, and may be at least as common as graft rejection in Asia,[100] although this has not been confirmed in a study conducted in the United Kingdom.[103] Viral endotheliitis post-EK can closely resemble EK graft rejection with keratic precipitates and mild anterior uveitis, and it is important to differentiate endotheliitis from rejection, since the immunosuppressive treatment for rejection episodes can exacerbate the infection. This diagnosis should be suspected in eyes with presumed episodes of allograft rejection unresponsive to steroids, in eyes with hypertensive anterior uveitis, and in eyes with unexplained EC loss in relatively quiet eyes.[104] Viral endotheliitis tends to occur earlier postoperatively usually within the first postoperative year compared with immune rejection episodes.[105] Clinical findings for eyes with AC inflammation after keratoplasty may be indicative of the etiology of the inflammation, and IOP elevation may mirror the activity of the endotheliitis in cases of HSV and CMV endotheliitis.[106] A relatively low threshold for aqueous paracentesis and CMV-DNA and HSV-DNA PCR analysis has been proposed by some authors,[100] who perform aqueous PCR to exclude viral endotheliitis before treating for immune rejection.[105]

With expanding indications for EK in recent years, there is a growing experience with EK for the indication of corneal decompensation secondary to HSV or CMV endotheliitis. In eyes with HSV-related corneal endothelial failure, DMEK leads to improvement in CDVA, although visual recovery is limited compared with DMEK for other etiologies.[107]

Importantly, these eyes have a higher rate of postoperative complications, including PGF and recurrence of endotheliitis in 12% and in 29% of eyes, respectively.[107] One study has found promising outcomes of DMEK in this setting; the disease should be quiescent for ≥ 6 months before surgery, that PCR for HSV be performed and negative 10 days before surgery, and that intensive, perioperative prophylactic oral antiviral and topical antiviral therapy should be continued for at least one year to prevent recurrence.[108] Some corneal surgeons suggest keeping topical antivirals indefinitely to reduce the risk of recurrence and subsequent graft failure in eyes undergoing EK for HSV-related endotheliitis.[109]

In the setting of EK for CMV-related corneal endothelial failure, the management of post-EK recurrent endotheliitis is challenging for corneal specialists. In one study, all the patients with detectable CMV-DNA in the aqueous at the time of keratoplasty developed CMV endotheliitis post-keratoplasty and experienced graft failure.[110] Moreover, one study found that patients diagnosed with CMV-endotheliitis prior to EK are more likely to have recurrent endotheliitis within the first postkeratoplasty year, even when preoperative anti-CMV treatment and confirmed eradication of CMV and ocular inflammation before keratoplasty was performed.[105] Early recognition and effective treatment is therefore indicated to optimize graft survival following EK in this setting.[111] Optimizing IOP and ensuring quiescence of intraocular inflammation prior to transplantation is advocated. Preoperative aqueous polymerase chain reaction (PCR) analysis for CMV-DNA has been recommended prior to corneal transplantation by some authors.[111] In their center, CMV-positive patients should undergo a systemic and topical antiviral treatment and only after repeat PCR becomes negative is EK performed; postoperatively, the patient is kept on prophylactic systemic oral antiviral therapy for 3 weeks and on long-term topical ganciclovir therapy, and a repeat aqueous CMV-DNA PCR analysis is performed to ensure no recurrence of infection.[111] Long-term topical ganciclovir may prevent recurrence of CMV-associated graft failure after EK.[112] Notably, no optimal treatment regime for CMV corneal endotheliitis has been established to date. Intravenous ganciclovir and oral valganciclovir have shown comparable efficacy for CMV disease in solid organ recipients,[113] and this has been extrapolated for keratoplasty by corneal surgeons. Cessation of treatment of CMV endotheliitis has been based on clinical response, with a conservative goal of maintaining 3 months of antiviral therapy after clinical resolution coupled with a negative aqueous CMV-DNA analysis.[100]

DISCUSSION

Our study provides good evidence that secondary EK renders surgical feasibility and significant improvement in visual acuity, and has a good safety profile. Table 5 summarizes the main functional and anatomical outcomes for each scenario in secondary corneal endothelial transplantation. While both secondary DSEK and secondary DMEK produce significant functional improvement with comparable safety profiles, the findings in this review suggest that eyes undergoing secondary DMEK or secondary UT-DSAEK *may be* more likely to reach higher levels of visual acuity compared with eyes undergoing secondary DSEK (Table 5). However, the quality of this evidence is low, as few publications have reported the proportions of eyes with higher levels of visual acuity. We consider that reporting the proportion of eyes reaching CDVA ≥ 20/40, ≥ 20/25 and ≥ 20/20 should be made a standard of quality in future studies of endothelial keratoplasty (both primary and subsequent grafts), and that further studies are needed to ascertain whether visual outcomes after secondary DSEK are comparable with those of secondary DMEK.

The visual outcomes following primary and secondary EK in the setting of corneal endothelial failure have been consistently superior to those of repeat PKP. Although repeat PKP produces significant visual improvement, visual outcomes are decreased in eyes undergoing multiple regrafts, with a lower proportion of eyes achieving higher levels of visual acuity.[42,46,47,114,115] Importantly, PKP may also be considered in some cases of failed EK when there is significant opacification of the anterior cornea. Particular considerations in the operative protocol compared to primary EK surgery are to be taken into consideration in secondary EK. Identification and correction of potential factors influencing graft failure (for example glaucoma, IOL, infection) should be addressed preoperatively and at the time of the surgery.

Our review has several limitations, and it highlights several knowledge gaps which warrant further research efforts concerning secondary EK. Firstly, most available studies to date are retrospective with short follow-up times, and there is a lack of prospective studies. In addition, most studies represent relatively small case series, although this is expected given that DMEK and DSEK are recent techniques. Visual outcomes are likely comparable to those of virgin primary EK eyes, although this is not definite. A shorter interval between graft failure and regrafting likely influences positively the visual outcomes of secondary EK, before fibrotic changes induced by corneal edema ensue. Complication rates following secondary EK, including the CEC loss rate, rebubbling rate, and allograft rejection rate may also comparable with those of primary EK, and the complication rates following secondary DSEK and secondary DMEK appear to be comparable (Table 5). However, a careful preparation and manipulation of the graft is warranted in secondary EK, in order to minimize EC loss. Likewise, meticulous removal of potential graft remnants under air must be performed to optimize the adherence of grafts, particularly in eyes in which GD occurred in the primary graft, as these eyes may be at a higher risk of detached regraft. Immune rejection protocols in secondary EK may require longer term steroid therapy or even indefinite steroid therapy, particularly in cases of immune rejection of the primary graft.

Finally, secondary EK grafts may be at a higher risk of failure compared to primary grafts, raising the question as to whether these should be regarded as a slightly higher-risk group compared to primary EK eyes. In a large analysis of EK procedures performed in Medicare beneficiaries, 11.6% of eyes underwent repeat keratoplasty, and approximately 17% of eyes received more than 1 repeat graft.[57] This is in line with the notion that repeat PKP grafts are high-risk corneal transplants, and in these cases rejection episodes occur in 30-60% of grafts and up to 70% will fail within 10 years despite local or systemic immunossupression.[47] It must be emphasized, however, that suboptimal surgical technique in the primary EK procedure may also contribute to increased risk of poor adherence of the secondary EK grafts. Prospective, multicenter, comparative studies are encouraged to determine whether medium- and long-term rates of EC loss and graft failure after secondary EK are comparable to primary EK. In these eyes, promoters of EC proliferation and migration, such as Rho kinase inhibitors, may have a particularly relevant role in improving graft transparency and survival.[47,116,117]

In conclusion, with the growing experience and expanding indications for corneal endothelial transplantation, surgeons dealing with EK surgery will find an increasing number of patients with failing DSEK and DMEK grafts. In these cases, secondary EK grafts provide significant visual improvement. Importantly, our literature review raises relevant questions in secondary EK surgery for which additional studies are strongly encouraged. These include 1) understanding if secondary DMEK or secondary UT-DSAEK are associated with better visual outcomes compared with the "conventional" DSEK/DSAEK techniques, and in which clinical scenarios secondary DSEK or PKP should be considered over secondary DMEK; 2) ascertaining whether the visual outcomes of EK regrafts are comparable to those of primary EK eyes; 3) understanding whether secondary EK eyes are in fact a higher-risk subgroup in corneal transplantation compared with primary EK eyes; and 4) ascertaining whether middle and long term endothelial cell loss and regraft failure rates are comparable with those of primary EK.

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FIGURE LEGEND

Figure 1 – Schematic representation of the corneal allograft transplant procedures, including penetrating keratoplasty (PKP) and posterior lamellar keratoplasty (PLK) techniques.

In PKP (top left), the full-thickness of the recipient cornea composed of epithelium and Bowman's membrane (light green), corneal stroma (blue) and endothelial layer and Descemet's membrane (dark green) is trephined and replaced by a full-thickness donor corneal allograft. In deep lamellar endothelial keratoplasty (DLEK, top middle), an early PLK technique no longer in use, a posterior lamellar disc composed of endothelium, Descemet's membrane and posterior stroma is manually dissected from the recipient cornea through a 9 mm sclerocorneal incision and replaced by an equally sized donor disc, placed against the recipient posterior cornea with an air bubble. In Descemet stripping endothelial keratoplasty (DSEK, top right), the endothelial-Descemet's complex (EDM) is stripped from the recipient cornea, and is replaced with a donor allograft composed of EDM, plus posterior stroma of variable thickness using a manual dissection or automatic dissection with a microkeratome (DSAEK). In ultra-thin DSAEK (bottom left), the donor lenticule thickness is < 100 µm owing to decreased stromal thickness, which may improve visual outcomes compared to the "conventional" DSEK techniques. In Descemet membrane endothelial keratoplasty (DMEK, bottom middle), the recipient's EDM complex is replaced only by donor Descemet's and endothelium. Donor lenticule grafts in DSEK and DMEK are positioned against the recipient's posterior stroma with air or with 20% sulfur hexachloride, and may be at risk of graft detachment (bottom right).

TABLES LEGEND:

Table 1: Outcomes of repeat Descemet stripping endothelial keratoplasty (DSEK) reported in the literature.

Author	**Journal (month/year)**	**Eyes (n)**	**Patient age (years)**	**Fuchs indication for primary EK (%)**	**Cause of re-DSAEK**	**Ocular comorbidities (%)**	**Time between primary DSAEK and re-DSAEK (months)**	**Follow-up time after repeat DSAEK (months)**	**CDVA before re-DSAEK**	**Mean preoperative CCT (µm)**	**CDVA after re-DSAEK**	**% Eyes reaching CDVA ≥ 20/40**	**%ECL**	**Mean final CCT (µm)**	**Re-bubbling rate (%)**	**Rejection rate (%)**	**Graft failure rate (%)**	**Comments**
Gorovoy et al.[61]	Cornea (Feb/2008)	2	59.5 ± 9.5	100%	Rej (50%) / Late endothelial failure (50%)	50%	20 ± 7	6	0.80 ± 0.20 logMAR	Patient 2 = 875 µm	0.20 ± 0.10 logMAR	100%	N/R	Patient 2 = 625 µm	0%	50%	0%	No signs of interface scarring after failed graft removal

Lee JA et al.[62]	Cornea (Jun/2009)	5	68.4 ± 6.6	40%	Dislocated graft (40%) / Iatrogenic PGF (60%)	60%	3.2 ± 2.7	7.6 ± 3.7	N/R	N/R	0.85 ± 0.62 logMAR	20%	N/R	638.5 ± 31.4 µm	0%	0%	20%	One patient experienced primary graft failure
Letko et al.[63]	Ophthalmology (Feb/2011)	37	69.0 ± 12.0	86%	Unsatisfactory visual outcome (76%) / Endothelial decompensation (24%)	24.3%	11 / 13	N/R	Snellen 20/60 / counting fingers	809/787	Snellen 20/30 / Snellen 20/60	82%	N/R	678/666	N/R	N/R	N/R	Improved visual acuity in 97% of eyes
Kim et al.[64]	Cornea (Oct/2012)	20	69.9 ± 11.9	55%	PGF (40%) / Rejection (20%) / endothelial failure (40%)	15%	13.1 ± 10.3	27.0 ± 13.4	1.76 ± 0.62 logMAR	N/R	0.50 ± 0.41 logMAR	59%	47.3% (final F-U)	N/R	5%	0%	0%	IOP change non-significant; in eyes without comorbidities, mean CDVA improved to 0.37 logMAR
Ghosh et al.[65]	Clin Ophthalmol. (May/2013)	1	77	100%	Epithelial ingrowth	Dry AMD	22	18	1.0 logMAR	N/R	0.10 logMAR	100%	N/R	N/R	0%	0%	0%	Careful stripping and cleaning of the interface to remove any epithelial cells in cases of epithelial

																		ingrowth after DSEK in warranted
Nahum et al.[66]	Cornea (May/2016)	51	69.6 ± 13.1	39.1%	Rejection (29.4%) / EC exhaustion (68.6%) / Interface abnormalities (1.9%)	31.3%	26.4 ± 22.8	21.2 ± 17.4	1.38 ± 0.60 logMAR	N/R	0.34 ± 0.49 logMAR	N/R	44 ± 21 % (2-year F-U)	N/R	0%	0%	9.8%	Visual outcomes between re-DSAEK and primary DSAEK were similar
Dickman et al.[67]	Am J Ophthalmol. (Sep/2018)	103	70 ± 9	42%	PGF (25%) / Endothelial failure (50%) / Rej (17%) / others (9%)	N/R	N/R	24	1.46 ± 0.10 logMAR	N/R	0.57 ± 0.09 logMAR	N/R	N/R	N/R	N/R	N/R	9% at 2 years	81% cumulative probability of 5-year regraft survival

Thompson et al.[68]	Cornea (Feb/2019)	121	70 ± 12	33%	PGF (30.6%) / Rej (5.6%) / Late endothelial failure (58%) / others (5.8%)	Glaucoma (36%)	23.2 ± 22.3	12	1.54± 0.79 logMAR	673 ± 117	0.65 ± 0.62 logMAR	N/R	36.7% (6-month F-U)	N/R	15%	N/R	N/R	Higher preoperative IOP was predictive of greater improvement in CDVA after re-DSEK; glaucoma and previous PKP were not predictive of visual outcomes
Matsumoto et al.[69]	JCRS Online Case Reports (Oct/2019)	1	55	0%	Late endothelial failure (100%)	Phakic IOL (100%)	24	6	2.0 logMAR	N/R	0.0 logMAR	100%	N/R	614 µm	0%	0%	0%	Repeat DSAEK was performed in combination with phakic IOL explantation and cataract surgery

Kaur et al.[70]	Indian J Ophthalmol (Oct/2019)	62	52.6 ± 17.1	29%	PGF (55%) / Rejection (16%) / Endothelial failure (29%)	25.8%	8 (range 0.15-19)	12	N/R	732.8 ± 82.5	0.44 ± 0.25 logMAR	N/R	N/R	688.3 ± 110.9	N/R	N/R	13%	87% of eyes with clear grafts at postoperative year 1

Legend: EK – endothelial keratoplasty; re-DSEK – repeat Descemet stripping endothelial keratoplasty; CDVA – corrected distance visual acuity; CCT – corneal central thickness; %ECL –f endothelial cell loss rate; PGF – primary graft failure; Rej – rejection; AMD – age-related macular degeneration; EC – endothelial cell; IOP – intraocular pressure; F-U – follow-up time; N/R – not reported; IOP – intraocular pressure; PKP – penetrating keratoplasty.

Table 2: Outcomes of repeat Descemet membrane endothelial keratoplasty.

Author	Journal (month/year)	Eyes (n)	Patient age (years)	Fuchs indication for primary EK (%)	Cause of re-DMEK	Ocular comorbidities (%)	Time between primary DMEK and re-DMEK (months)	Follow-up time after re-DMEK (months)	CDVA before re-DMEK	Mean preoperative CCT (µm)	CDVA after re-DMEK	% Eyes reaching CDVA ≥ 20/40	%ECL	Mean final CCT (µm)	Re-bubbling rate (%)	Rejection rate (%)	Graft failure rate (%)	Comments
Yoeruek et al.[80]	Cornea (Nov/2013)	6	66.8 +/- 5.6	100%	Failed primary DMEK (unspecified)	0%	2.9 ± 1.5	3.3 ± 1.7	1.50 ± 0.28 logMAR	N/R	0.13 ± 0.05 logMAR	N/R	N/R	N/R	33.3%	N/R	0%	Visual outcomes and types of complications and their incidence were

																		comparable with the first surgery
Cirkovic et al.[81]	Cornea (Jan/2015)	18	69.0 ± 7.0	83.3%	Failed primary DMEK (78%) / graft detachment not resolved by rebubbling (22%)	17%	4,9	12	1.90 logMAR	807 ± 160	0.3 logMAR	86.7%	45 ± 11 % (12-month F-U)	576 ± 178	0.5 ± 0.9 rebubbling procedures	0%	5.6%	Telephone interviews indicative of a very strong recommendation for repeat DMEK
Baydoun et al.[82]	Ophthalmology (Jan/2015)	17	69 ± 14	88.2%	Graft detachment (82%) / EC exhaustion (12%) / Rej (6%)	0%	16 ± 9	12	N/R	703 ± 26	86% CDVA ≥ 20/40, and 57% CDVA ≥ 20/25	86%	49.8% (12-month F-U)	515 ± 39	5.9%	5.9%	17.6%	Increased %ECL and lower % eyes with CDVA ≥ 20/25 compared to primary DMEK eyes
Price et al.[83]	Ophthalmology (Aug/2015)	55	69 (range 42-89)	93%	Surgical complications (38%) / PGF	11%	21 days in surgical complication	18 (range = 3-61)	N/R	631 ± 81	20/25 Snellen	100%	31 ± 14% (12-	512 ± 40	13%	0%	2%	Re-DMEK eyes had similar %ECL and visual

					(40%) / EC exhaustion (9%) / other causes (13%)		s / 32 days in PGF / 27 months in EC exhaustion						month F-U)					outcomes compared to fellow primary DMEK eyes
Alió del Barrio et al.[84]	Cornea (Jun/2018)	1	72	0%	Rej (100%)	100%	18	6	0.70 logMAR	691 µm	0.25 logMAR	100%	N/R	529 µm	0%	0%	0%	Repeat DMEK was successful without primary DMEK graft removal (DMEK under failed DMEK)
Agha et al.[85]	Clin Ophthalmol (Mar/2019)	13	73.2 ± 7.6	84.6%	Failed primary DMEK (unspecified)	23.1%	12.5 ± 6.0	6	1.96 ± 0.99 logMAR	929 ± 217	0.33 ± 0.20 logMAR	N/R	30.1% (6-month F-U)	519 ± 43	23.1%	0%	0%	Functional and anatomical outcomes were similar between re-DMEK and primary DMEK eyes
Luznik et al.[86]	Ophthalmology (Oct/2019)	6	72 ±11	83.3%	Failed primary	N/R	18.5	12	1.50 (range:	931 ± 245 µm	0.3 (range:	N/R	49.0 ± 8.8%	524 µm	16.7%	0%	16.7% (PGF)	Increased complication

					DMEK (unspecified)				0.4-2.0) logMAR		-0.2 to 0.8) logMAR		(12-month F-U)					rates and levels of cytokines in the aqueous humor compared with primary DMEK eyes,
Moura-Coelho et al.[55]	Am J Ophthalmol. (Mar/2020)	14	68.4 ± 9.0	78.6%	PGF (57%) / EC exhaustion (29%) / Rej (14%)	35.7%	Eyes with PGF within 30 days; eyes with late graft failure 30.8 ± 20.4 months	14.5 (range 6-89)	1.30 ± 0.65 logMAR	N/R	0.09 ± 0.26 logMAR	81.8%	48.2 ± 15.1% (final F-U)	N/R	28.6%	14.3%	21.4%	Re-DMEK eyes had similar visual outcomes, %ECL and rejection rate compared with successful primary DMEK eyes, but high % graft failure after re-DMEK

Legend: EK – endothelial keratoplasty; re-DMEK – repeat DMEK; CDVA – corrected distance visual acuity; CCT – central corneal thickness; %ECL – endothelial cell loss rate; PGF – primary graft failure; EC – endothelial cell; Rej – rejection; F-U – follow-up time; N/R – not reported.

Table 3: Outcomes of secondary Descemet membrane endothelial keratoplasty (DMEK) following primary Descemet stripping endothelial keratoplasty (DSEK).

Author	Journal (month/year)	Eyes (n)	Patient age (years)	Secondary EK	Fuchs indication for primary EK (%)	Ocular comorbidities (%)	Time between primary and secondary EK (months)	Follow-up time after secondary EK (months)	CDVA before secondary EK	Mean preoperative CCT (µm)	CDVA after secondary EK	% Eyes reaching CDVA ≥ 20/40	%ECL	Mean final CCT (µm)	Re-bubbling rate (%)	Rejection rate (%)	Graft failure rate (%)	Comments
Ham et al.[88]	Cornea (Nov/2010)	3	53.0 ± 10.7	DMEK for poor visual outcome following DSEK	100%	0%	20.0 ± 4.3	6	0.50 ± 0.31 logMAR	620.7 ± 37.5	0.07 ± 0.05 logMAR	100%	N/R	509.7 ± 18.8	0%	0%	0%	Functional results after secondary DMEK for poor visual outcome

																		of primary graft comparable to primary DMEK
Dirisamer et al.[89]	Acta Ophthalmologica (Mar/2013)	12	66 ± 13	DMEK for poor visual outcome following DSEK	91.7%	25%	32 ± 17	6	0.57 ± 0.38 logMAR	670 ± 112	0.06 ± 0.12 logMAR	91.7%	Final ECD 1709 ± 461 cells/mm2	517 ± 57	N/R	N/R	0%	Secondary DMEK allows complete visual recovery in eyes with poor visual outcomes after primary DSEK
Brockmann et al.[74]	JAMA Ophthalmol (Jul/2015)	8	79.4 ± 7.2	DMEK for graft failure following DSEK	N/R	25%	21.4 ± 17.8	12	1.13 ± 0.50 logMAR	900 ± 209	0.38 ± 0.36 logMAR	N/R	Final ECD 908 ± 143 cells/mm2	524 ± 27	N/R	N/R	0%	Functional results after secondary DMEK for graft failure inferior to primary DMEK
Weller et al.[90]	Am J Ophthalmol (Jun/2015)	15	67.3 ± 10.2	DMEK for graft failure following DSEK	93%	0%	26 ± 17	18	1.27 ± 0.34 logMAR	917 ± 184	0.14 ± 0.14 logMAR	N/R	43.7% (18-month F-U)	506 ± 66	13.3%	0%	0%	DMEK showed surgical feasibility in eyes with failed DSEK, with good adhesion of the

																		graft and good optical quality
Sorkin et al.[91]	Cornea (Jun/2018)	26	71.9 ± 12.6	DMEK after primary DSAEK (failed graft 70% or suboptimal visual outcome 30%)	57%	50%	8.5 ± 13.0	15.1 ± 10.6	0.84 ± 0.50 logMAR	N/R	0.51 ± 0.49 logMAR	N/R	39.7 ± 22.3% (6-month F-U)	N/R	11.5%	3.8%	19.2%	Search for remnant islands and tags of stroma in the host-interface area should be meticulous after removing the old DSEK graft
Agha et al.[92]	Clin Ophthalmol (Mar/2019)	15	73.6 ± 7.6	DMEK for graft failure following DSEK	80%	N/R	15 ± 8	12	1.72 ± 0.62 logMAR	869.0 ± 209.9	0.23 ± 0.24 logMAR	N/R	34.7% (12-month F-U)	511.7 ± 67.7	20%	0%	6.7%	Visual acuity and optical quality were effectively improved even in patients with longstanding corneal decompensation

Legend: EK – endothelial keratoplasty; CDVA – corrected distance visual acuity; CT – central corneal thickness; %ECL – endothelial cell loss rate; DMEK – Descemet membrane endothelial keratoplasty; DSEK – Descemet stripping endothelial keratoplasty; ECD – endothelial cell density; F-U – follow-up time; N/R – not reported.

Table 4: Secondary Descemet stripping endothelial keratoplasty (DSEK) for failed primary Descemet membrane endothelial keratoplasty (DMEK) graft.

Author	Journal (month/year)	Eyes (n)	Patient age (years)	Secondary EK	Fuchs indication for primary EK (%)	Ocular comorbidities (%)	Time between primary and secondary	Follow-up time after secondary EK (months)	CDVA before secondary EK	Mean preoperative CCT (µm)	CDVA after secondary EK	% Eyes reaching CDVA ≥ 20/40	%ECL	Mean final CCT (µm)	Re-bubbling rate (%)	Rejection rate (%)	Graft failure rate (%)	Comments

							EK (months)											
Dapena et al[93]	Br J Ophthalmol (Feb/2010)	10	67.6 ± 12.0	DSAEK for failed primary DMEK (primary graft failure)	100%	20%	0.8 ± 0.2 (2-5 weeks)	12	0.69 ± 0.41 logMAR	N/R	0.40 ± 0.23 logMAR	70% (87% after excluding eyes with comorbidities)	46.4% (12-month F-U)	N/R	30%	N/R	0%	Secondary DSEK after failed primary DMEK may yield similar clinical outcomes compared with primary DSEK.
Arnalich-Montiel et al.[94]	Graefes Arch Clin Exp Ophthalmol (Nov/2013)	8	62.1 ± 8.2	DSAEK for failed primary DMEK	100%	0%	1.7 ± 0.8	6	0.65 ± 0.22 logMAR	N/R	0.24 logMAR (range 0.13-0.52)	62%	N/R	N/R	N/R	N/R	0%	Increased corneal scattering after secondary DSAEK following primary

																		DMEK compared to primary DSAEK eyes, which has a negative impact on visual acuity
Graffi et al.[95]	Br J Ophthalmol (May/2018)	21	69.2 ± 7.2	UT-DSAEK for failed primary DMEK	85.7%	19%	3.0 ± 2.1	12	1.52 ± 0.57 logMAR	N/R	0.06 ± 0.05 logMAR (after excluding eyes with comorbidities)	100%	38.9% (12-month F-U)	N/R	0%	0%	0%	Complication rate 23.8%

Legend: EK – endothelial keratoplasty; CDVA – corrected distance visual acuity; CCT – central corneal thickness; %ECL –endothelial cell loss rate; DSAEK – Descemet stripping automated endothelial keratoplasty; DMEK – Descemet membrane endothelial keratoplasty; UT-DSAEK – ultrathin Descemet stripping automated endothelial keratoplasty; F-U – follow-up time; N/R – not reported.

Table 5: Summary of findings regarding outcomes following secondary endothelial keratoplasty.

Clinical setting	Studies (eyes, n)	F-U (months)	CDVA after secondary EK	% Eyes reaching CDVA ≥ 20/40	% Eyes reaching CDVA ≥ 20/25	%ECL	Re-bubbling rate (%)	Rejection rate (%)	Graft failure rate (%)	Comments
Repeat DSEK/DSAEK [61-70]	10 (403)	6-27	0.50 – 0.18 logMAR (Snellen 20/30 – 20/63)	20-100%*	0%** [62]	36.7-47.3% (6 to 27-month F-U)	0-15%	1/54 eyes (1.9%) Range 0-50%	0-20%	Repeat DSEK graft survival may be lower compared to primary grafts,[67] although this is not consensual.[66]
Repeat DMEK [55,80-86]	8 (130)	3.3-14.5	0.33 – 0.09 logMAR (Snellen 20/25 – 20/43)	82-100%	13.3-81%	34-49.8% (6-14.5 month F-U)	5.9-33%	3/104 eyes (2.8%) Range 0-14.3%	0-21.4%	Most, but not all, studies suggest visual outcomes are comparable between primary and secondary DMEK; 18.2-61% of eyes reached CDVA ≥ 20/20;[55,82,83] Other reported complications: cataract and IOL opacification, IOP spikes or glaucoma progression, macular edema, pupillary block, corneal ulcer.
DMEK after failed DSEK/DSAEK graft [74,88-92]	6 (79)	6-18	0.51 – 0.06 logMAR (Snellen 20/23 - 20/65)	91.7-100% (6-month F-U)	91.7-100% [89,90]	34.7-43.7% (6 to 18-month F-U)	0-20%	1/59 eyes (1.7%) Range 0-3.8%	0-19.2%	As many as 33-42% may reach final CDVA ≥ 20/20.[88,89] Visual outcomes after DMEK for failed DSEK may inferior to those of primary DMEK grafts, although this is not consensual.
DSEK/DSAEK after failed DMEK graft [93,94]	2 (18)	6-12	0.40 – 0.24 logMAR (Snellen 20/35 - 20/50)	62-87%	0-13%	46.4% (12-month F-U) [93]	30% [93]	N/R	0%	No studies reported other complications.

UT-DSAK after failed DMEK graft [95]	1 (21)	12	Mean 0.06 ± 0.05 logMAR (Snellen 20/25 ± 20/86)	100%	92%	38.9% (12-month F-U)	0%	0%	0%	31% of eyes reached CDVA ≥ 20/20 in this study.[95] Other complications reported: IOL opacification(2 eyes required IOL exchange).

DSEK – Descemet stripping endothelial keratoplasty; DSAEK – Descemet stripping automated endothelial keratoplasty; DMEK – Descemet membrane endothelial keratoplasty; UT-DSAEK – Ultrathin Descemet stripping automated endothelial keratoplasty; F-U – follow-up time; CDVA – corrected distance visual acuity; %ECL – Endothelial cell loss rate; IOL – intraocular lens; IOP – intraocular pressure; N/R – not reported.

* If reports with ≤ 2 eyes were excluded from the analysis, the proportion of eyes reaching CDVA ≥ 20/40 after repeat DSEK/DSAEK would be 20-82%.[61-65,69]

** If reports with ≤ 2 eyes were excluded from the analysis, no eyes undergoing repeat DSEK reached CDVA ≥ 20/25.[62]

Figure 1