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Rebubbling and graft failure in Descemet membrane endothelial keratoplasty: a prospective Dutch registry study

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ABSTRACT

Aims To identify risk factors for rebubbling, and early graft failure after Descemet membrane endothelial keratoplasty (DMEK).

Methods In this prospective registry study, all consecutive DMEK procedures registered in the Netherlands Organ Transplant Registry were assessed (n=752). Univariable and multivariable analysis was performed using logistic regression. The effect of rebubbling on endothelial cell density was analysed using a linear mixed model.

Results 144 of 752 (19%) eyes underwent rebubbling. Rebubbling was successful in 101 eyes (70%). In eyes that underwent rebubbling, the graft failure rate was significantly higher than eyes that did not undergo rebubbling (30% vs 9%, respectively; OR: 4.28, 95% CI 2.72 to 6.73, p<0.001). In multivariable analysis, independent risk factors for rebubbling were surgical complication (OR: 2.28, 95% CI 1.20 to 4.33, p=0.012) and older recipient age (OR: 1.04 (per increase of 1 year), 95% CI 1.01 to 1.07, p=0.003). Risk factors for developing graft failure within 3 months were transplant before 2016 (OR: 3.32, 95% CI 1.87 to 5.90, p<0.001), and surgical complication (OR: 2.93, 95% CI 1.42 to 6.04, p=0.004). Throughout the study period, rebubbling and early graft failure were inversely related. Eyes that underwent rebubbling showed significantly lower endothelial cell densities at 3, 6 and 12 months compared with eyes that did not undergo rebubbling (all p<0.001).

Conclusions This Dutch registry study identified independent risk factors for DMEK graft detachment leading to rebubbling, namely recipient age and surgical complication, and early graft failure, namely transplantation before 2016 and surgical complication. Rebubbling was associated with significantly higher endothelial cell loss in the first year after surgery.

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INTRODUCTION

In the last decade, Descemet membrane endothelial keratoplasty (DMEK) gradually gained popularity as the technique of choice for treating corneal endothelial disease.[1 2] While DMEK provides excellent visual and refractive outcomes, early postoperative graft detachment requiring intracameral gas reinjection (rebubbling), and graft failure remain the Achilles heel of this procedure.

The incidence of graft detachment and graft failure in the literature ranges considerably after DMEK. According to the American Academy of Ophthalmology Ophthalmic Technology Assessment the incidence of graft detachment ranges between 2% and 82% (averaging 28%), and the incidence of primary graft failure ranges between 0% and 12.5%.[3] Previous studies identified risk factors for graft detachment related to donor,[4 5] recipient[6–8] and surgery.[5 6 8–20] These mostly originate from single-centre retrospective studies. Registries capture prospective data from multiple centres and are therefore poised to assess incidence and risk factors for complications.

In the current study, we analyse prospectively collected data from the Netherlands Organ Transplant Registry (NOTR) to identify donor, recipient and surgery-related risk factors for graft detachment leading to rebubbling, and graft failure after DMEK.

METHODS

Graft registry and data collection

This prospective multicentre registry study obtained data from the NOTR, a Dutch national database founded by the Netherlands Transplantation Foundation (Nederlandse Transplantatie Stichting (NTS), https://www.transplantatiestichting.nl/over-de-nts). In the Netherlands, donor corneas are centrally allocated by the NTS. Using NOTR, the NTS prospectively captures data on donor, recipient, eye bank processing and surgical procedure of all corneal transplantations in the Netherlands except for one clinic. Using a standardised electronic data capture system, corneal surgeons complete relevant follow-up data at predefined time points. Data collection continues until graft failure or loss to follow-up. Except for a few cases, DMEK grafts were prepeeled by the eye bank. All donor corneas were stored in organ culture, and transplantation took place within 3 days after graft preparation.

Early graft failure was defined as any graft failure occurring within 3 months after surgery. In the Netherlands, information on repeated transplantation is complete, since donor corneas are allocated centrally by NTS. The date of repeated transplantation served as a surrogate for graft failure date unless otherwise indicated in the registry.

Population

The first DMEK surgery registered in NOTR was performed on 5 October 2011. The study cohort included all consecutive DMEK procedures until 31 May 2018.

Outcome measures

The cohort was categorised into eyes that underwent rebubbling versus eyes that did not undergo rebubbling, and eyes developed early graft failure versus eyes that did not develop early graft failure. Parameters related to the recipient, donor and surgery were analysed and outcomes compared.

Statistical analysis

Statistical analyses were performed using SPSS Statistics for Windows, V.24.0 (IBM Corp). A χ^2 goodness-of-fit test was used to check whether the number of transplantations changed over time. The difference in mean time to rebubbling over years (≤2015, 2016, 2017 and 2018) was tested using a one-way analysis of variance. The percentages of eyes undergoing rebubbling, unsuccessful rebubbling and developing early graft failure were analysed using Pearson χ^2 test for categorical risk factors and using univariable logistic regression for numerical risk factors. To be included in the multivariable model, covariates were either selected based on a 0.1 significance threshold in univariable analysis or in case they were considered clinically relevant based on literature, that is, surgery indication, transplant date, recipient age, recipient and donor gender mismatch, donor age, donor graft preparation complication, surgical complication, graft diameter and peroperative lens status (pseudophakic, phakic and triple procedure). Variables with a two-sided p value ≤0.05 in multivariable analysis were considered independent risk factors. Multicollinearity, that is, intercorrelation between risk factors, was checked for the multivariable models, where a variance inflation factor (VIF) >10 indicates a (multi)collinearity problem. ORs with corresponding 95% CIs and p values were reported.

The effect of rebubbling on endothelial cell density (ECD) was assessed using linear mixed model (LMM), where rebubbling (yes/no), time (donor, 3, 6 and 12 months after surgery), the interaction rebubbling×time and potential confounders (indication, year of transplantation, lens status, surgical complication and recipient age) were included as fixed factors, and an unstructured covariance structure was used for repeated measures. Estimates means with corresponding 95% CI and p values for the difference in estimated means between rebubbling and no rebubbling were reported for each time point. Two-sided p values ≤0.05 were considered statistically significant.

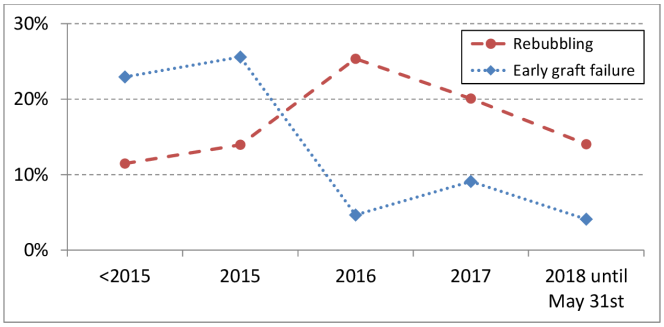

Figure 1 Rebubbling and early graft failure in Descemet membrane endothelial keratoplasty (DMEK). The percentage of eyes that underwent rebubbling (red circles) and early graft failure (blue diamonds) of all registered DMEKs in the Netherlands Organ Transplant Registry. The percentage of eyes undergoing rebubbling and developing early graft failure changed significantly over time (p=0.022 and p<0.001, respectively).

Table 1 Recipient, donor and surgery characteristics

	All consecutive performed DMEK (n=752)	
	Mean±SD or N	% or range
Recipient parameters		
Age, years	71±10	27–91
Sex, male/female	352/400	47%/53%
Baseline IOP, mm Hg	13±3	6–29
Baseline CCT, µm	647±82	456–1140
Indication, FED	678	90%
Indication, PBK	18	2.5%
Indication, graft failure	37	5%
Indication, other	18	2.5%
Lens status, PPC	579	77%
Lens status, phakic	98	13%
Lens status, PAC or other	75	10%
Ocular comorbidities, except cataract	104	14%
Donor parameters		
Age, years	72±8	45–85
Sex, male/female	478/274	63%/36%
Graft diameter, mm <8.5/8.5/>8.5	109/589/54	15%/78%/7%
Endothelial cell density, cells/mm^2	2681±173	2300–3200
Complicated graft preparation	19	2.5%
Surgery parameters		
Surgical complication	62	8%
Descemetorhexis diameter, mm <8.5/8.5/>8.5	138/280/334	18%/37%/44%
Recipient donor sex mismatch	368	49%
Surgery date after 2015	648	86%
Phakic DMEK	47	6%
Triple procedure	51	7%
Eye undergoing surgery, right/left	383/369	51%/49%

BCVA, best-corrected visual acuity; CCT, central cornea thickness; DMEK, Descemet membrane endothelial keratoplasty; ECD, Endothelial cell density; FED, Fuchs endothelial dystrophy; IOP, intraocular pressure; PAC, pseudophakic, anterior chamber; PBK, Pseudophakic bullous keratopathy; PPC, pseudophakic, posterior chamber.

As sensitivity analyses, all logistic regression and LMM analyses were repeated on primary transplants with Fuchs endothelial dystrophy (FED) as indication.

RESULTS

The current study comprises 752 DMEK procedures performed by 15 corneal surgeons in seven corneal clinics. The number of DMEK surgeries per year are 2011, n=2; 2012, n=4; 2013, n=24; 2014, n=31; 2015, n=43; 2016, n=213; 2017, n=213; and 2018 until 31 May, n=171. The percentage of eyes that underwent a single rebubbling was 19% (144 of 752), 2% (15 of 752) received a second rebubbling, and a single eye received a third rebubbling. The percentage of eyes that underwent rebubbling changed significantly over time (p=0.022). Rebubbling rate measured 11% before 2015, 14% in 2015, 25% in 2016, 20% in 2017 and 14% 2018, figure 1. The percentage of eyes that developed early graft failure measured overall 11% and changed significantly over time (p<0.001). Early graft failure rate measured 23% before 2015, 26% in 2015, 5% in 2016, 9% in 2017 and 4% in 2018, figure 1.

Table 1 shows the recipient, donor and surgery characteristics of the entire cohort.

Table 2 Univariable analysis of recipient, donor and surgery parameters for undergoing rebubbling after DMEK surgery

	All consecutive performed DMEK (n=752)			
	Rebubbling rate (n=144) (%)	**OR**	**95% CI**	**P value**
Recipient parameters				
Age, years		1.03 (per 1 unit)	1.01 to 1.05	0.005
Sex		1.02	0.71 to 1.47	0.91
Male	19			
Female	19			
Baseline IOP, mm Hg		1.00 (per 1 unit)	0.95 to 1.06	0.97
Baseline CCT, µm		1.00 (per 1 unit)	0.99 to 1.00	0.62
Indication, FED		1.8	0.87 to 3.70	0.11
Yes	20			
No	12			
Indication, PBK		1.21	0.39 to 3.74	0.74
Yes	22			
No	19			
Indication, graft failure		0.65	0.25 to 1.70	0.34
Yes	13			
No	19			
Lens status, PPC		1.12	0.75 to 1.82	0.49
Yes	20			
No	17			
Ocular comorbidities, except cataract		0.74	0.40 to 1.3	0.29
Yes	15			
No	20			
Donor parameters				
Age, years		1.00 (per 1 unit)	0.97 to 1.02	0.76
Sex		0.88	0.60 to 1.28	0.5
Male	18			
Female	20			
Graft diameter, mm				
<8.5	17	–	–	–
8.5	19	1.16	0.67 to 2.01	0.59
>8.5	30	2.13	0.98 to 4.61	0.06
ECD, cells/mm^2		1.00 (per 1 unit)	0.99 to 1.00	0.61
Complicated graft preparation		1.53	0.54 to 4.31	0.42
Yes	26			
No	19			
Surgery parameters				
Surgical complication		2	1.13 to 3.54	0.016
Yes	31			
No	18			
Diameter descemetorhexis, mm				
<8.5	24	–	to	–
8.5	19	0.73	0.44 to 1.19	0.2
>8.5	18	0.68	0.42 to 1.11	0.12
Recipient donor sex mismatch		1.05	0.73 to 1.52	0.78
Yes	20			
No	19			
Surgery date after 2015		1.77	0.96 to 3.27	0.06
Yes	20			
No	12			
Triple procedure		0.89	0.43 to 1.89	0.78
Yes	18			
No	19			
Phakic DMEK		0.86	0.39 to 1.88	0.7
Yes	17			
No	19			

Continued

Table 2 Continued

	All consecutive performed DMEK (n=752)			
	Rebubbling rate (n=144) (%)	OR	95% CI	P value
PPC vs phakic DMEK		1.19	0.54 to 2.63	0.66
PPC vs triple DMEK		1.14	0.54 to 2.42	0.72
PPC and triple DMEK vs phakic DMEK		1.18	0.54 to 2.59	0.68
Eye undergoing surgery		0.72	0.49 to 1.03	0.07
Left	16			
Right	22			

BCVA, best-corrected visual acuity; CCT, central cornea thickness; DMEK, Descemet membrane endothelial keratoplasty; ECD, endothelial cell density; FED, Fuchs endothelial dystrophy; IOP, intraocular pressure; PBK, pseudophakic bullous keratopathy; PPC, pseudophakic, posterior chamber.

Of eyes that underwent rebubbling, 30% (43 of 144) developed graft failure. Rebubbling was successful in 101 eyes (70%). In eyes that did not undergo rebubbling, graft failure rate was significantly lower (9%, 55 of 608; OR: 4.28, 95% CI 2.72 to 6.73, p<0.001).

In patients that received a DMEK in one eye and a subsequent DMEK in the fellow eye, the percentage of eyes that underwent rebubbling was 13% (14 of 111) in the first eye and 18% (20 of 111) in the fellow eye. Eyes that underwent rebubbling in one eye did not have significantly higher risk of undergoing rebubbling in the fellow eye compared with eyes that did not undergo rebubbling in the first eye. The time to rebubbling averaged 15 days (95% CI 13 to 17), and did not differ significantly over the study period (≤2015: 19 days, 95% CI 10 to 27; 2016: 16 days, 95% CI 11 to 20; 2017: 15 days, 95% CI 12 to 18 and 2018: 11 days, 95% CI 8 to 14; p=0.27). There was no statistically significant relationship between the timing of rebubbling (ie, within 1 week or longer) and incidence of graft failure.

Rebubbling

In univariable analysis, significant risk factors for undergoing rebubbling were recipient age, and surgical complication, table 2. The most frequently registered complications were related to graft insertion (10%), unfolding (16%) or centration (8%), intraocular haemorrhage (10%) and graft folds (10%). In 37% of complications, no specific details were recorded. No donor demographics were significantly related to rebubbling, table 2. In multivariable analysis, significant risk factors for undergoing rebubbling were surgical complication (OR: 2.28, 95% CI 1.20 to 4.33, p=0.012), and recipient age (OR: 1.04 (per increase in 1 year), 95% CI 1.01 to 1.07, p=0.003). There were no (multi) collinearity issues (all VIFs≤1.05).

Unsuccessful rebubbling

In univariable analysis, significant risk factors for unsuccessful rebubbling were recipient age (OR: 1.051, 95% CI 1.001 to 1.102, p=0.045) and grafts smaller than 8.5 mm (OR: 2.9, 95% CI 1.02 to 8.06, p=0.046). Grafts bigger than 8.5 mm showed a higher OR but did not reach statistical significance (OR: 2.15, 95% CI 0.71 to 6.52, p=0.18). In multivariable analysis, no parameter reached statistical significance (all p≥0.27).

Early graft failure

In univariable analysis, significant risk factors for developing early graft failure were older recipient age, graft diameter smaller or larger than standard, surgical complication and transplant date before 2016, table 3. One hundred and twenty-four grafts (16%) were larger and 334 grafts (44%) were smaller than the rhexis diameter. Neither were significant risk factors for early graft failure (all p≥0.1). In multivariable analysis, significant risk factors were transplant date before 2016 (OR: 3.32, 95% CI 1.87 to 5.90, p<0.001), and surgical complication (OR: 2.93, 95% CI 1.42 to 6.04, p=0.004). There were no (multi) collinearity issues (all VIFs≤1.05).

Preoperative donor ECD of grafts that underwent rebubbling did not differ significantly compared with grafts in eyes that did not undergo rebubbling (estimated mean=2738 cells/mm^2, 95% CI 2565 to 2911, n=607 vs 2722 cells/mm^2, 95% CI 2559 to 2884, n=144; p=0.62). After surgery, eyes that underwent rebubbling showed statistically significant lower ECD compared with eyes that did not undergo rebubbling at 3 months (1564 cells/mm^2, 95% CI 1360 to 1769, n=209 vs 1851 cells/mm^2, 95% CI 1680 to 2022, n=38; p<0.001), 6 months (1433 cells/mm^2, 95% CI 1232 to 1635, n=190 vs 1827 cells/mm^2, 95% CI 1656 to 1998, n=44; p<0.001) and 12 months (1295 cells/mm^2, 95% CI 1080 to 1510, n=152 vs 1764 cells/mm^2, 95% CI 1590 to 1937, n=29; p<0.001).

Sensitivity analyses (only primary transplants with FED as indication) showed similar results.

DISCUSSION

Graft detachment and graft failure are two of the most common adverse events after DMEK.[3] In the literature, numerous risk factors for graft detachment have been identified, but agreement across reports is weak. These include donor characteristics, such as donor age,[4] low ECD and poor morphology[5 19]; recipient factors, such as primary disease,[6] recipient age[7] and lens status[6 20]; and surgical parameters, such as descemetorhexis diameter,[8] use of viscoelastic,[9] graft folding and orientation,[19] use of plastic instruments,[19] synechiae,[19] irregularity of the main incision,[19] graft decentration,[5 10 11] anterior chamber tamponade agent and dimensions,[6 12 13 19] Descemet remnants,[14 15] postoperative intraocular pressure[13 16] and surgeon experience.[17 18]

This prospective multicentre registry study captured all DMEK procedures in the Netherlands from the first procedure registered in October 2011 until mid-2018. While most reports on risk factors originate from single-centre retrospective studies, data of the current study were prospectively collected in multiple corneal clinics. In our cohort, independent risk factors for rebubbling after DMEK were surgical complications and older recipient age. With regard to early graft failure, independent risk factors were surgical complication, and transplant date before 2016.

The risk of rebubbling increased with recipient age (OR 1.04 per year). Maier *et al* postulated that older patients may be unable to maintain a supine position postoperatively, leading to inadequate air bubble support for the graft.[7] This hypothesis is supported by the fact that graft detachments develop most

Table 3 Univariable analysis of recipient, donor and surgery parameters for developing early graft failure after DMEK surgery

	All consecutive performed DMEK (n=752)			
	Early graft failure (n=85) (%)	**OR**	**95% CI**	**P value**
Recipient parameters				
Age, years		1.03 (per 1 unit)	1.00 to 1.06	0.037
Sex		1.55	0.98 to 2.44	0.06
Male	14			
Female	9			
Baseline IOP, mm Hg		1.03 (per 1 unit)	0.96 to 1.10	0.43
Baseline CCT, µm		1.00 (per 1 unit)	1.00 to 1.01	0.43
Indication, FED		0.8	0.39 to 1.62	0.53
Yes	11			
No	14			
Indication, PBK		1.59	0.45 to 5.61	0.47
Yes	16			
No	11			
Indication, graft failure		1.24	0.47 to 3.27	0.66
Yes	14			
No	11			
Lens status, PPC		1.59	0.87 to 2.89	0.13
Yes	12			
No	8			
Ocular comorbidities, except cataract		0.81	0.41 to 1.63	0.56
Yes	10			
No	12			
Donor parameters				
Age, years		0.98 (per 1 unit)	0.95 to 1.01	0.15
Sex		1.12	0.70 to 1.80	0.64
Male	12			
Female	11			
Graft diameter, mm				
<8.5	20	–	–	–
8.5	8	0.37	0.21 to 0.64	<0.001
>8.5	24	1.25	0.58 to 2.74	0.57
ECD, cells/mm^2		1.00 (per 1 unit)	1.00 to 1.00	0.65
Complicated graft preparation		2.15	0.70 to 6.62	0.17
Yes	21			
No	11			
Surgery parameters				
Surgical complication		2.83	1.50 to 5.32	0.001
Yes	24			
No	10			
Diameter descemetorhexis, mm				
<8.5	11	–	–	–
8.5	8	0.67	0.33 to 1.33	0.25
>8.5	15	1.41	0.76 to 2.61	0.27
Recipient donor sex mismatch		1.02	0.65 to 1.61	0.93
Yes	11			
No	11			
Surgery date after 2015		0.32	0.19 to 0.54	<0.001
Yes	9			
No	24			
Triple procedure		0.84	0.33 to 2.19	0.73
Yes	10			
No	11			
Phakic DMEK		0.33	0.08 to 1.40	0.08
Yes	4			
No	12			

Continued

Table 3 Continued

	All consecutive performed DMEK (n=752)			
	Early graft failure (n=85) (%)	OR	95% CI	P value
PPC vs phakic DMEK		3.15	0.75 to 13.35	0.1
PPC vs triple		1.29	0.49 to 3.34	0.61
PPC and triple vs phakic DMEK		3.09	0.73 to 12.98	0.11
Eye undergoing surgery		0.78	0.49 to 1.23	0.28
Left	10			
Right	13			

CCT, central cornea thickness; DMEK, Descemet membrane endothelial keratoplasty; ECD, endothelial cell density; FED, Fuchs endothelial dystrophy; IOP, intraocular pressure; PBK, pseudophakic bullous keratopathy; PPC, pseudophakic, posterior chamber.

often inferiorly, coinciding with the least air bubble support in an upright head position.

For early graft failure, surgery before 2016 was the most important independent risk factor. This is likely related to a learning curve on a national level, which is supported by the significant decrease in incidence of graft failures over time. This is in line with previous literature showing a relationship between surgeon experience and adverse event rate.[17 18] The large majority of graft failures (93%) occurred in the first 6 months postoperatively, indicating graft detachment and primary graft failure are the leading causes. Interestingly, rebubbling was unsuccessful in 30% of cases, and surgeons mostly opted for repeated transplantation instead of subsequent rebubbling. Univariable analysis indicated elderly patients and grafts smaller than 8.5 mm were at higher risk for failed rebubbling. However, this did not reach statistical significance in multivariable analysis. It is encouraging that only a handful of graft failures were recorded beyond 6 months after surgery.

In our cohort, rebubbling was associated with statistically significant endothelial cell loss after correcting for recipient age, indication, lens status and surgical complication. Similarly, one study found lower ECD in eyes that underwent a single rebubbling compared with eyes with complete postoperative graft attachment (1350 cells/mm^2 vs 1613 cells/mm^2, p=0.033),[21] while another study reported that two, but not one, rebubblings led to higher endothelial cell loss.[22] The adverse effect of rebubbling should be weighed against the risk of complete graft detachment. In our cohort, eyes that underwent more than one rebubbling were rare. Whether an increased cell loss is due to rebubbling, graft detachment, or donor-related factors is currently unknown.

Interestingly, we observed a concurrent decrease in graft failure rate and increased rebubbling rate over time. While correlation does not imply causation, we hypothesise that proactive rebubbling may have prevented some complete graft detachments. The indication and timing of rebubbling vary considerably in the literature. Some surgeons rebubble as early as possible to prevent graft fibrosis and corneal oedema,[6] while others await spontaneous reattachment for 1–2 weeks,[22] or even longer.[23] In our cohort, mean duration until rebubbling averaged 15 days, but decreased over time, although not significantly. Interestingly, a history of rebubbling in one eye did not increase the risk of rebubbling in the other eye. This information is of particular relevance for counselling patients. Air and SF6 gas were used in 57% and 43% of centres registering in NOTR. Few centres switched from air to SF6 after the initial 5–10 cases. Therefore, the increase in rebubbling rate in our study is not related to the type of tamponade used. In the Netherlands, grafts are prepeeled within 3 days before surgery. Subsequently, graft storage time was not a significant risk factor for rebubbling, unsuccessful rebubbling, or early graft failure.

Two studies reported that phakic DMEK was protective against graft detachment requiring rebubbling and graft failure compared with eyes that were either preoperatively pseudophakic or underwent a triple procedure.[6 20] We included this parameter in univariable and multivariable analysis, but it showed neither a statistically significant nor clinically relevant effect.

The current study also has several limitations. Being a registry study, internal validity is low due to heterogeneity in surgical technique, postoperative medication and measurement technique. On the other hand, the results are highly generalisable. The current NOTR does not capture all parameters which may be related to graft detachment, such as graft detachments that did not undergo rebubbling, location and extent of graft detachment, but also anterior chamber depth, use of intraoperative optical coherence tomography, presence of recipient Descemet remnants in the interface, and postoperative inpatient versus outpatient care. In line with institutional review board approval, data were not stratified based on individual surgeon or centre level.

In conclusion, this prospective registry study on DMEK found independent risk factors for developing graft detachment leading to rebubbling, namely recipient age and surgical complication. For developing early graft failure, independent risk factors were surgical complication and transplantation before 2016 which likely reflects a learning curve on a national level.

Based on this data, we make the following recommendations. First, we recommend close postoperative monitoring in elderly patients or in case surgical complications occur. Second, our study excludes various risk factors such as triple procedure and donor-related parameters such as donor age (within the range of 45–85 years). Therefore, triple procedures may be performed safely when indicated, and it is not necessary to select donors based on such criteria. Third, the inverse relationship between rebubbling and early graft failure rates suggests a proactive approach to graft detachment may be beneficial.

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Patient consent for publication Not required.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. The data that support the findings of this study are available from Netherlands Organ Transplant Registry but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available.

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