Prevention of graft rejection

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Declaration

- Consultant for Allergan, Alcon, Bayer, Gene Signal, LuxBioscience, Pfizer

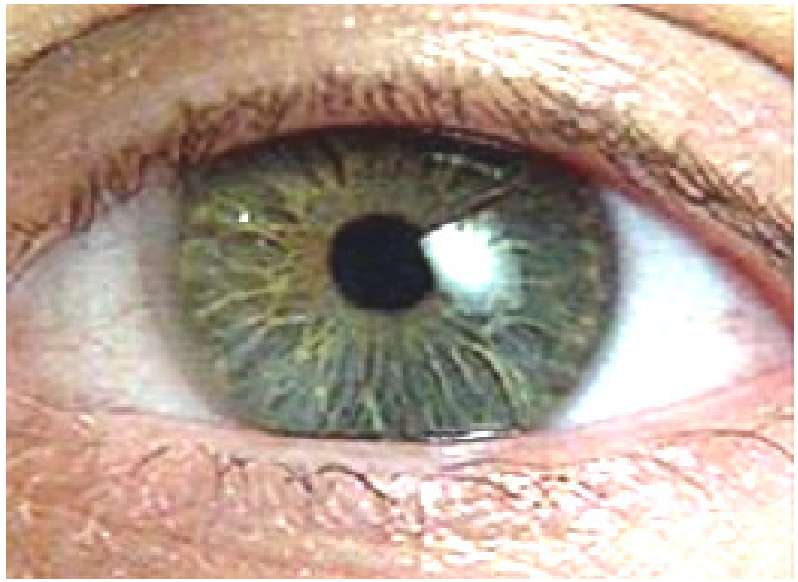
Presentation Outline

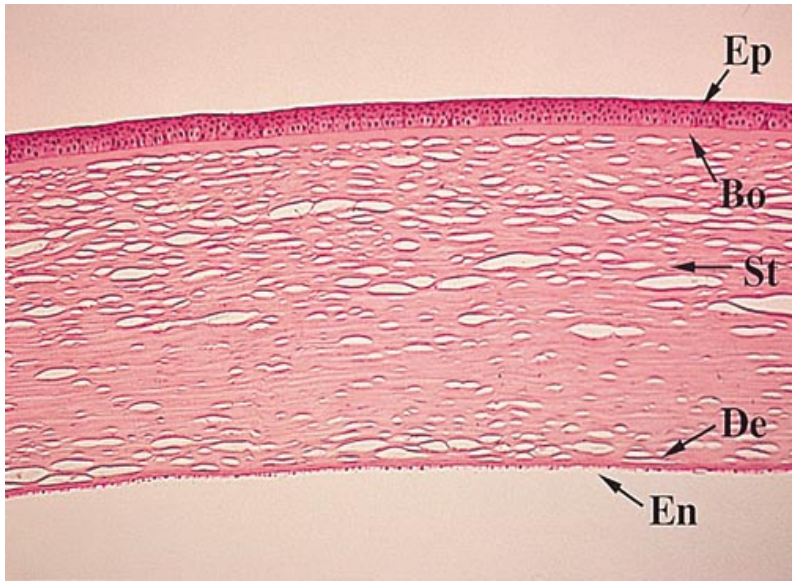
- **Introduction: Corneal neovascularisation: causes, molecular pathways and clinical consequences**

- **Corneal neovascularisation and graft survival:**
  - **Relationship**
  - **Unmet medical needs**

- **Treatment of Corneal Neovascularisation:**
  - **Clinical study inclusion criteria**
  - **Clinical study endpoint**
  - **Quantification of corneal neovascularisation**
  - **Summary**

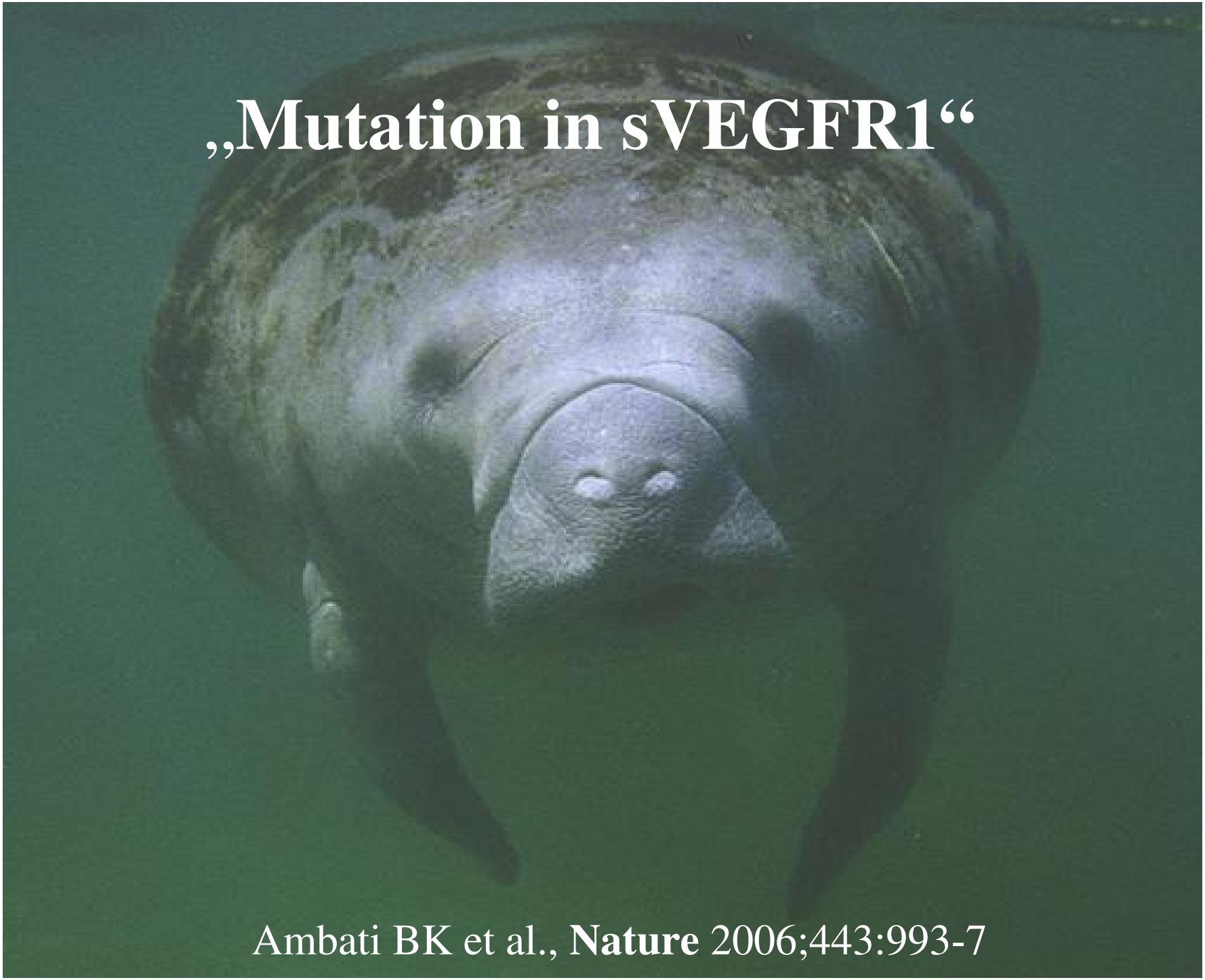
„Corneal angiogenic privilege“





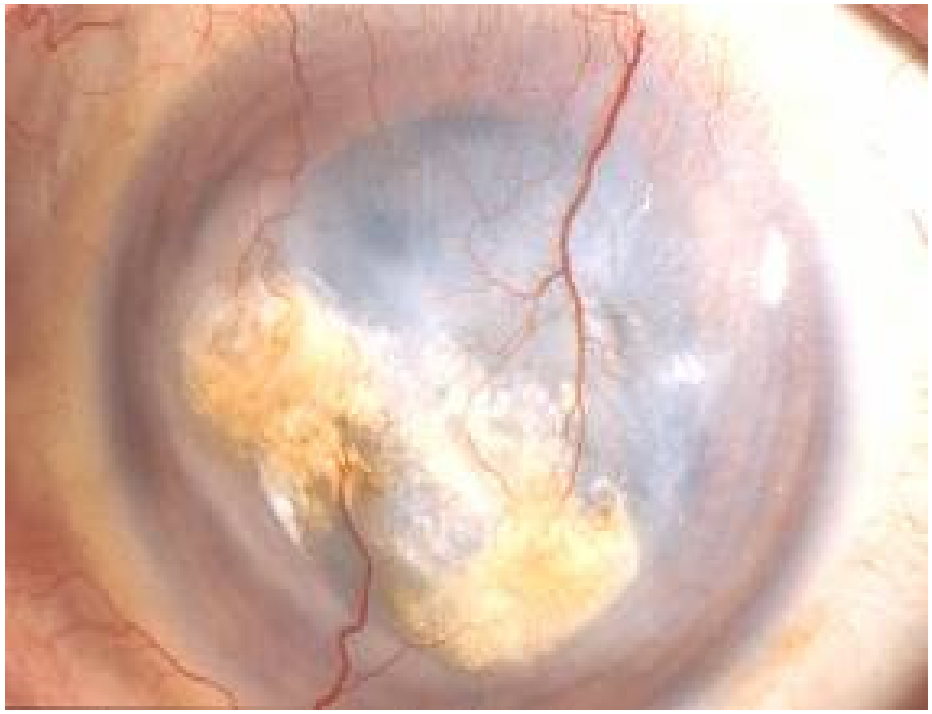
Streilein JW. **Nat. Rev. Immunol**. 2003;3:879-89

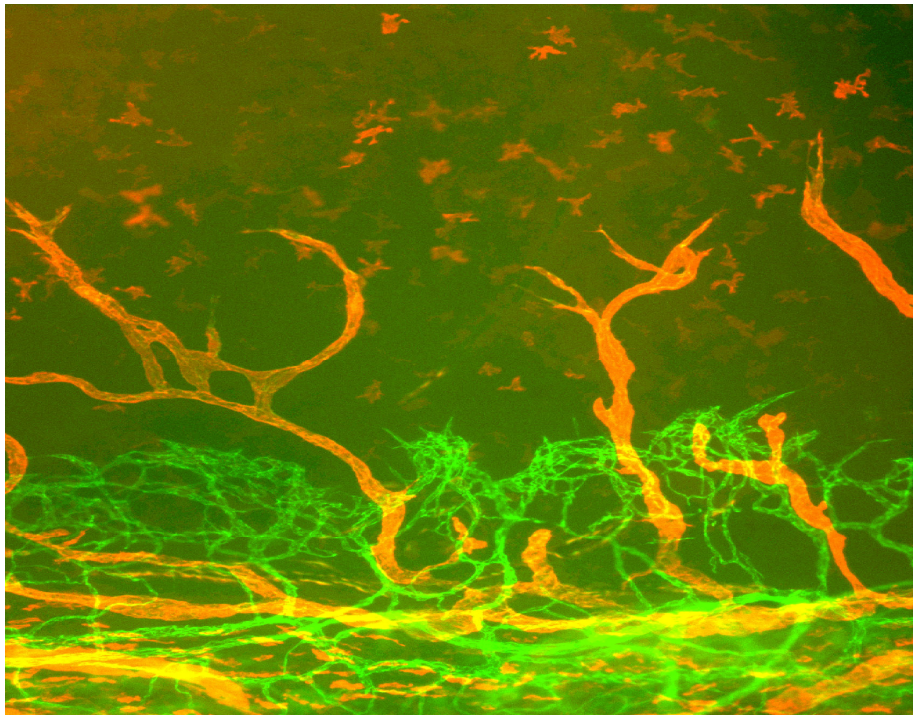
„Mutation in sVEGFR1“



Ambati BK et al., **Nature** 2006;443:993-7

Pathological corneal angiogenesis





Blood vessels:

Angiogenesis

Lymphatic vessels:

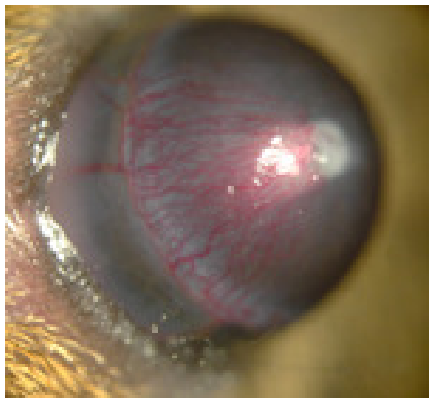
Lymphangiogenesis

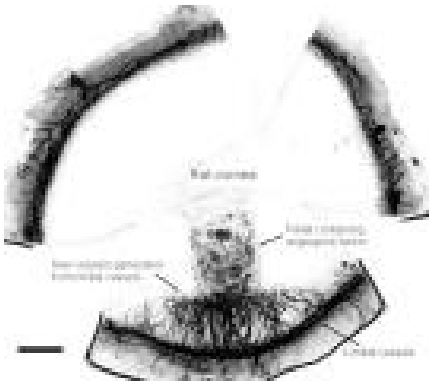
Causes and molecular pathways

- **Inflammation**
  - e.g. infectious keratitis (e.g. herpes virus)
- Hypoxia
  - e.g. caused by contact lens
- Surgery/Suture material
  - e.g. after corneal transplantation
- Limbal stem cell deficiency
  - e.g. after chemical burns

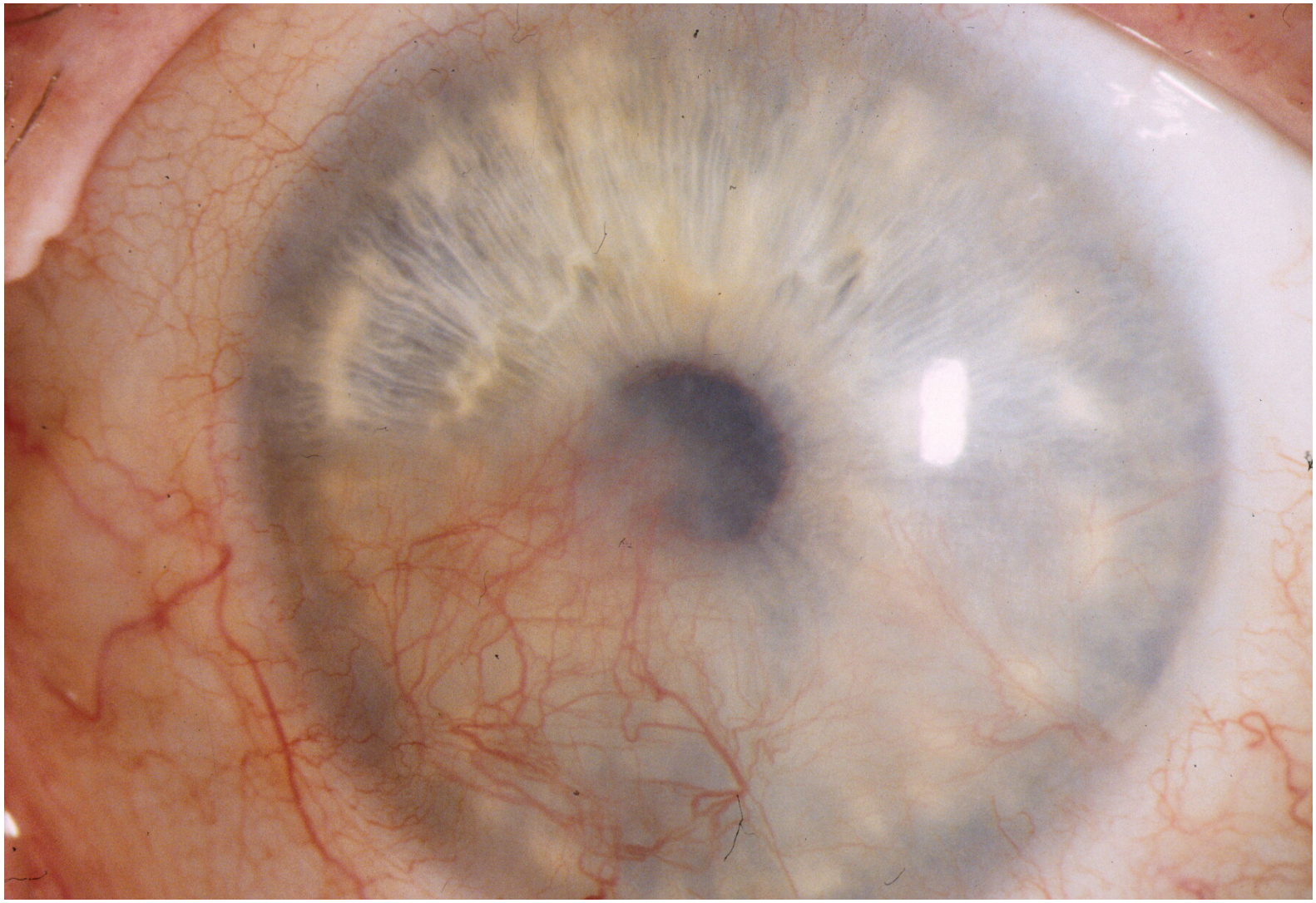
Causes and molecular pathways

- Common core molecular pathways.
- Upregulation of **VEGF** (via inflammation and hypoxia): central step independently of underlying cause.
- **IRS-1** as the up-regulatory switch necessary for pathological over-expression of VEGF and neovascular proliferation.

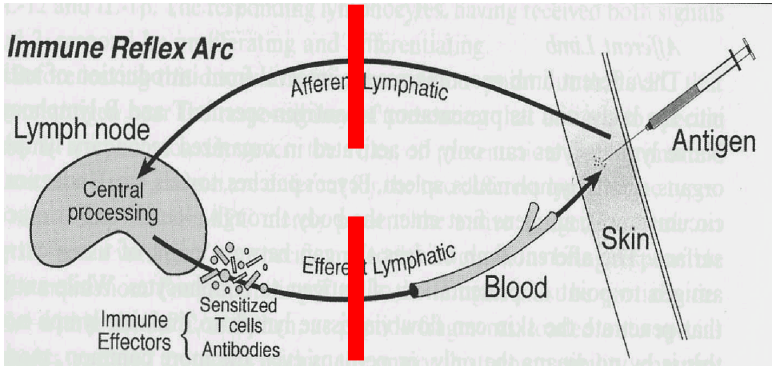




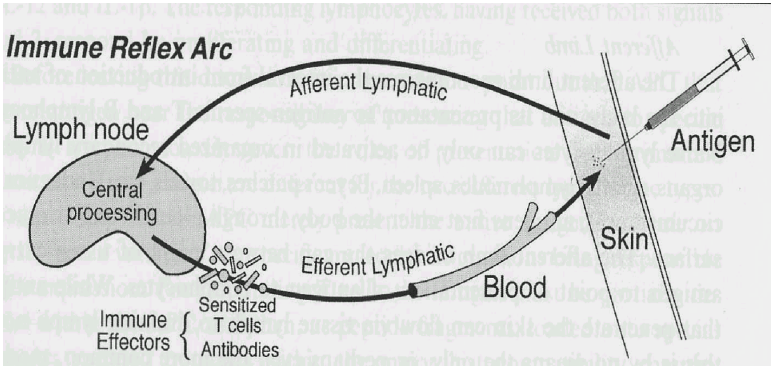
Consequence for patient: blindness



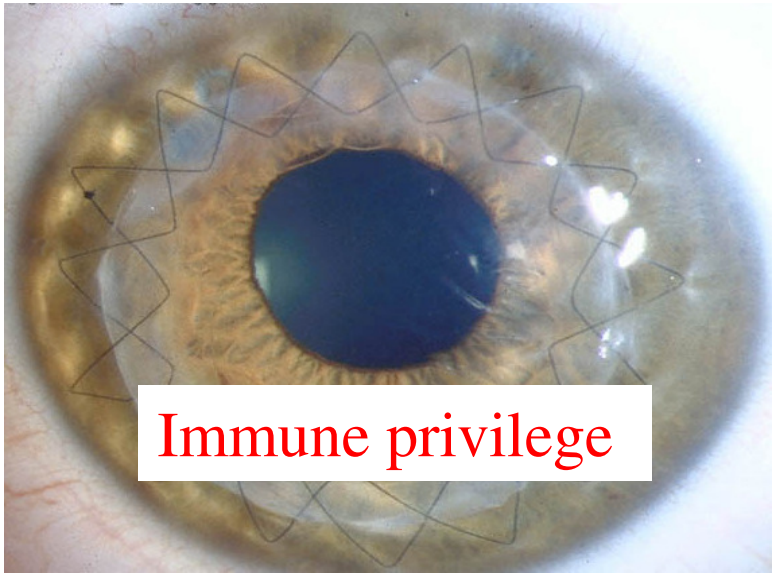
Consequence for patient: graft rejection

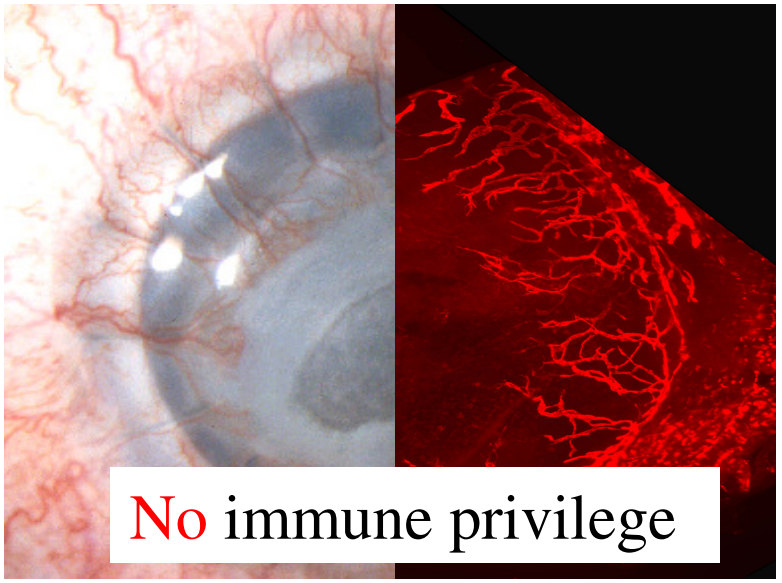


Normal-risk



High-risk

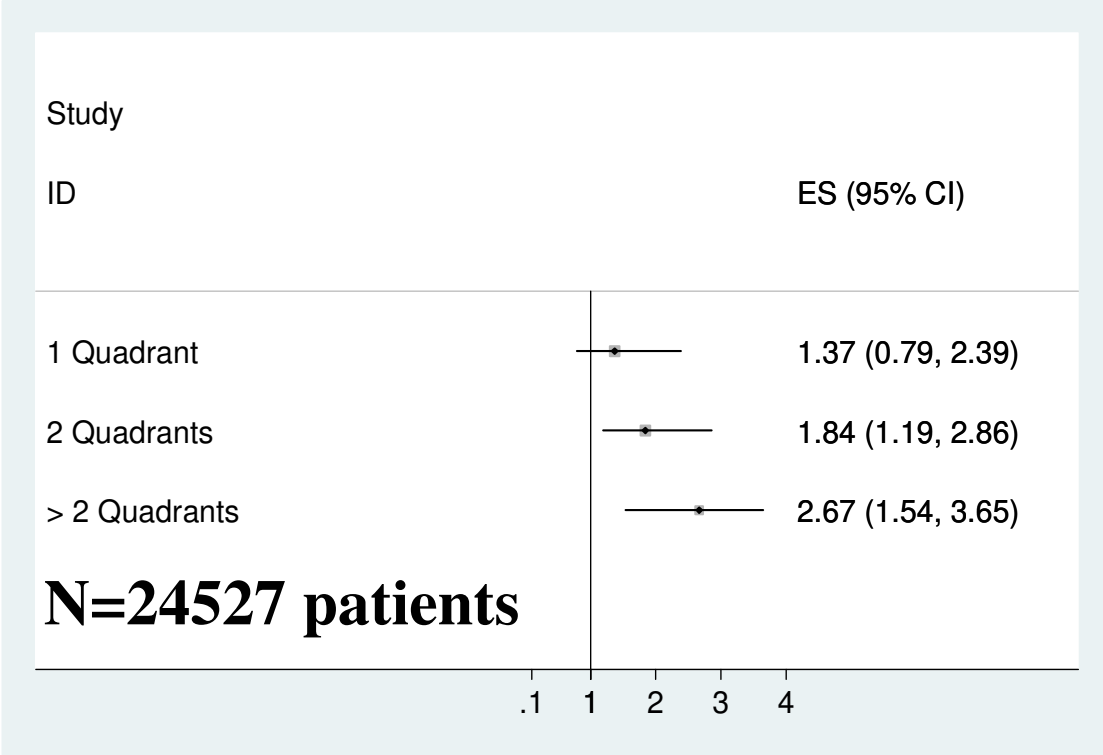




10-year-survival: > **90%**

0 - **50%**

Neovascularization and graft survival: evidence-based meta-analysis



➔ **Graft failure & graft rejection risk increased with number of corneal quandrants affected by neovascularisation before keratoplasty**

Bachmann, Taylor, Cursiefen **Ophthalmology** 2010;117:1300-5

Social and economic consequences

- Regrafting: expensive
- Individual health burden of patient: unemployment and absence from work
- Costs for surgery and transplants
- Waiting list
- Side-effects of systemic immunosuppresants

Presentation Outline

- **Introduction: corneal neovascularisation: causes, molecular pathways and clinical consequences**

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  - **Relationship**
  - **Unmet medical needs**

- **Treatment of Corneal Neovascularisation:**
  - **Clinical study inclusion criteria**
  - **Clinical study endpoints**
  - **New treatment approach**
  - **Summary**

Unmet medical needs in corneal neovascularisation management

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BJO Online First, published on June 28, 2011 as 10.1136/bjo.2011.204701

Review

Consensus statement on indications for anti-angiogenic therapy in the management of corneal diseases associated with neovascularisation: outcome of an expert roundtable

Claus Cursiefen,[1] Joseph Colin,[2] Reza Dana,[3] Manuel Diaz-Llopis,[4,5,6] Lana A Faraj,[7] Salvador Garcia-Delpech,[4,5,6] Gerd Geerling,[8] Francis W Price,[9] Lies Remeijer,[10] Barry T Rouse,[11] Berthold Seitz,[12] Patricia Udaondo,[4,6] Daniel Meller,[13] Harminder Dua[7]

Unmet medical needs in corneal neovascularisation management

CN context	Available therapeutic options	Therapeutic options limitations	Unmet need
Infectious keratitis	Main objective: pathogen control	When recurrence (when applicable), resistance to treatment, (re)-activation of NV	
Herpetic viruses	Antiviral agents Inflammation and CN: steroids* CN: surgery†	Recurrence or resistant viruses → no control of viral load Drawbacks of long-term steroid use	Presence of large stromal feeder new vessels causing lipid keratopathy or endangering graft survival after keratoplasty; active stromal new vessels after virus control endangering VA
Fungal	Antifungal agents Inflammation and CN: steroids* CN: surgery†	None known	Progressing, uncontrolled or chronic infection after first-line treatment failure CN endangering central vision Preparation for PK
Bacterial	Antibacterial agents Inflammation and CN: steroids* CN: surgery†	First-line treatment failure eading to chronic bacterial keratitis	
Parasitic	Antiparasitic treatments Inflammation (persisting): steroids* CN: rare CN: surgery†	Organism's ability to encyst Epithelial toxicity of long-term anti-amoebic (biguanide, diamidine) use	
Keratoplasty	Main objective: corneal reconstruction or repair	Uncontrolled immunological and NV processes	
Pre-keratoplasty	Inflammation: steroids* CN: steroids* and surgery†	Uncontrolled CN → high risk of CGR	Stromal vessels in graft intended area
Post-keratoplasty	Inflammation: steroids* CN: steroids* and surgery†	Uncontrolled CN → high risk of CGR	Post-PK prophylaxis, when stromal new vessels in graft area at pre-PK stage Development of active stromal new vessels Active rejection and high-risk corneal grafts

&

Cursiefen et al., **Br J Ophthalmol** (in press)

Unmet medical needs in corneal neovascularisation management

Current situation:

•40.000 corneal transplants/year in Europe

•10% high-risk: 50-100% rejection rate despite local and systemic immunosuppressants

•No effective therapy so that often surgery is not performed at all

Current management options are insufficient:

•Steroids (partly effective, major side-effects)

•Anti VEGF strategies (off-label, stability issues, side-effects)

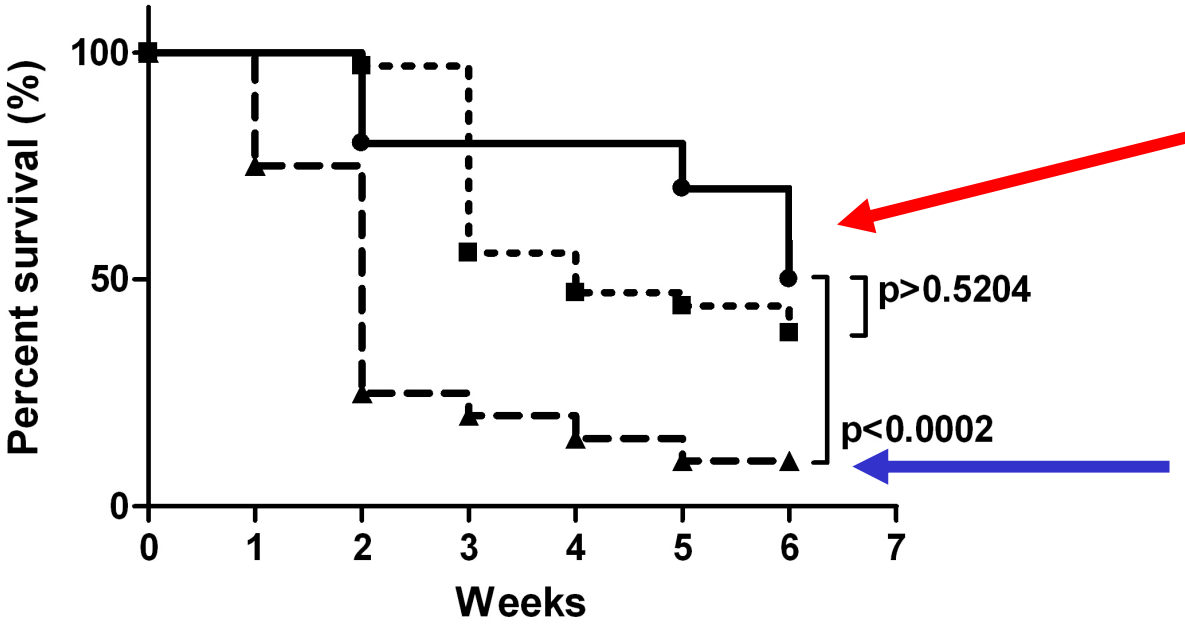
Need new treatment approaches are needed:

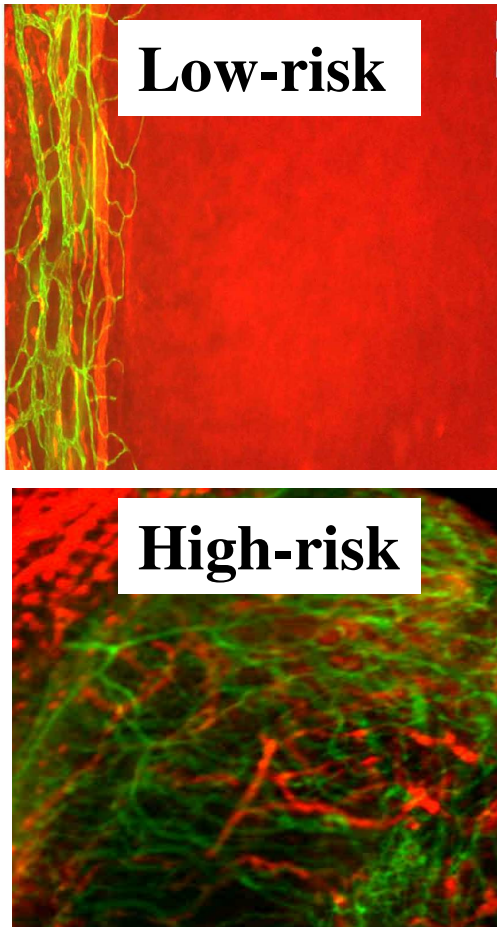
•Anti IRS-1/VEGF strategies currently in clinical trials

Regenfuss et al. ***Lymphat Res Biol****. 2008;6:191-201*

Strong preclinical evidence suggesting that antiangiogenic therapy promotes graft survival

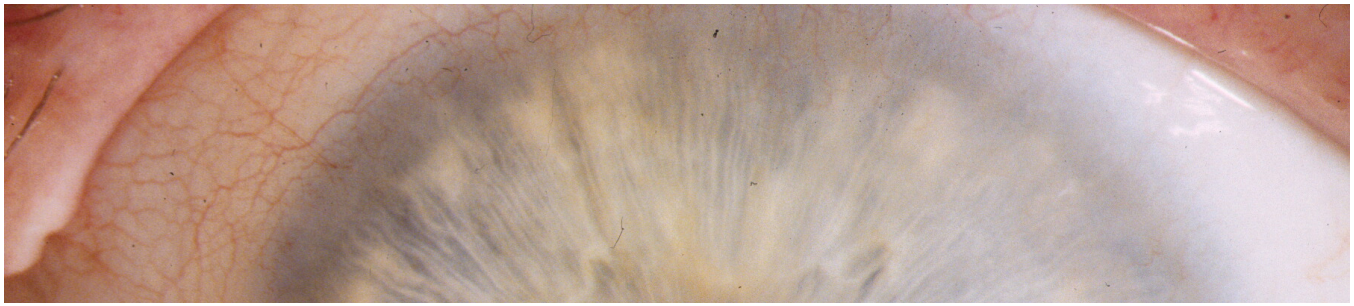
Primary prevention promotes graft survival





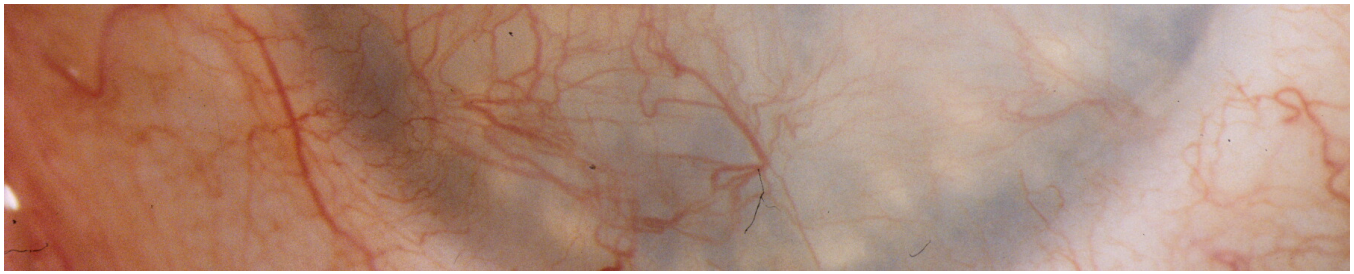
Dietrich et al., **J Immunol** 2010;184:535-9

Antiangiogenic therapy prior to keratoplasty



PRECONDITIONING

„Primary prevention“



Inhibition of angiogenesis e.g. during keratitis

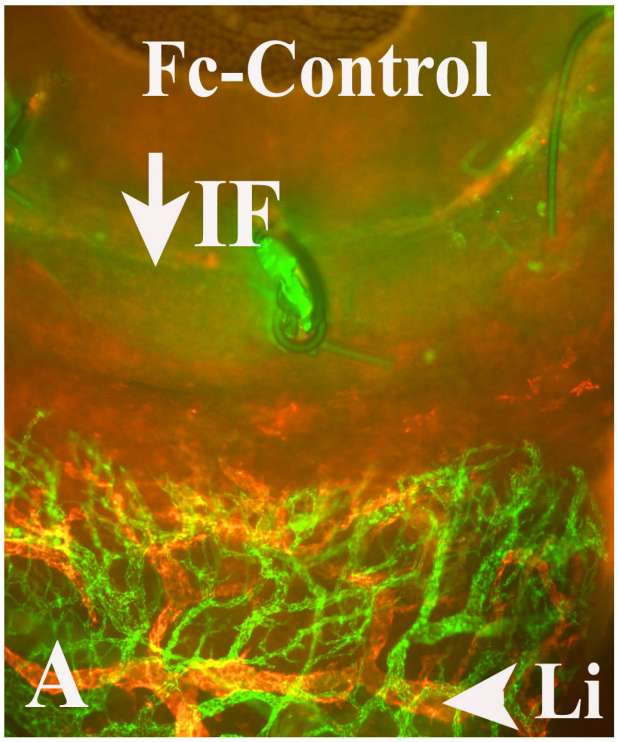
Antiangiogenic therapy prior to keratoplasty

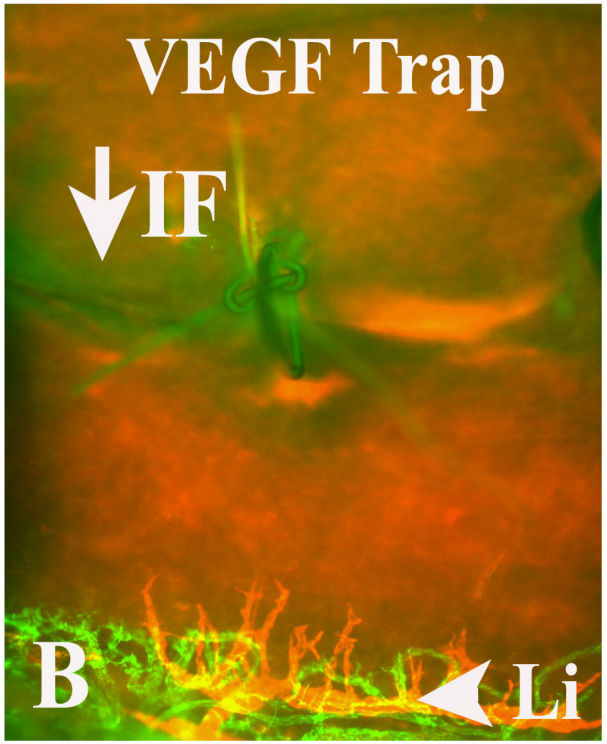
PRECONDITIONING

„Secondary prevention“

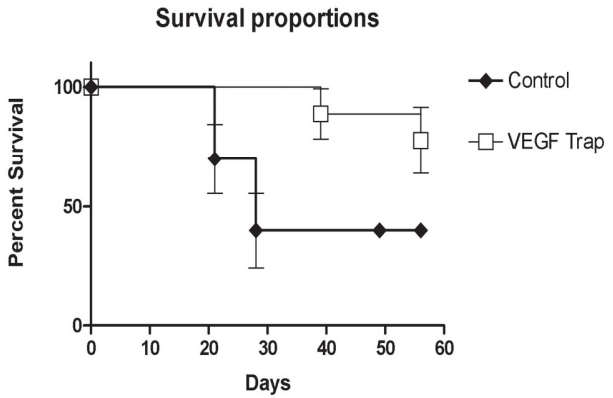
Angioregression prior to keratoplasty

Antiangiogenic therapy after keratoplasty





Low-risk keratoplasty



Anti(lymph)angiogenesis after low-risk keratoplasty promotes graft survival

Cursiefen et al., **Invest Ophthalmol Vis Sci** 2004;45:2666-73

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  - **Clinical study endpoints**
  - **Quantificatio of corneal neovascularisation**
  - **Summary**

Inclusion criteria

CN in the context of keratoplasty

•Will depend on the setting of the study (*i.e.* pre-/post-keratoplasty).

- Pre-keratoplasty setting: stromal CN should be present & documented in intended graft area.
- Post-keratoplasty setting: inclusion criteria depend on whether the intervention is intended to treat or to prevent CN & CGR:
  - For treatment, post-keratoplasty patients who develop active stromal neovascularisation or with active CGR should be included.
  - For prevention, recipients at HR of CGR should be included in initial studies. Subsequently, a broader population (mixed risk for CGR) may be chosen for inclusion in clinical studies. Inflammation should be controlled with steroids as appropriate.

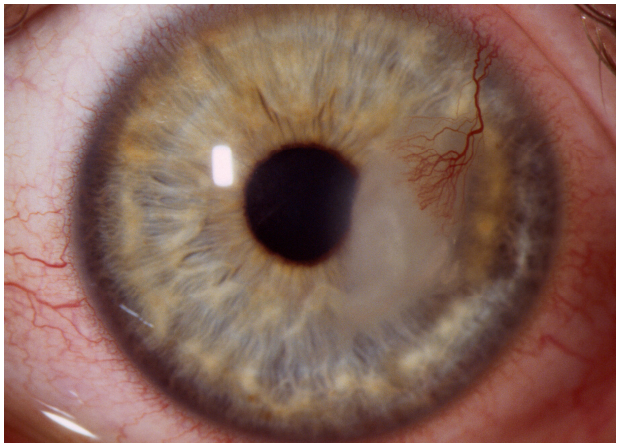
Endpoints

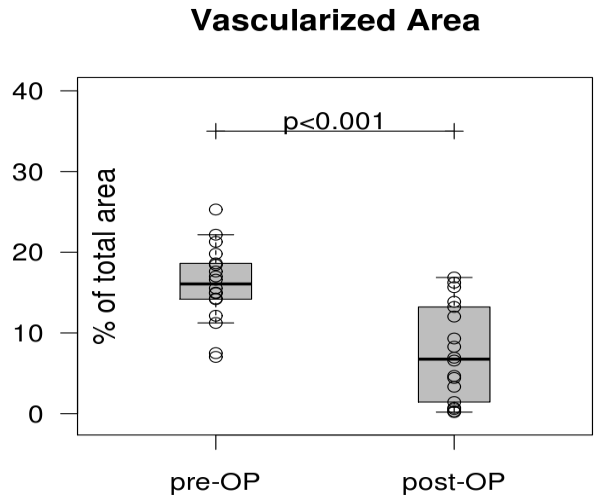
Antiangiogenic therapy to promote graft survival: Endpoints

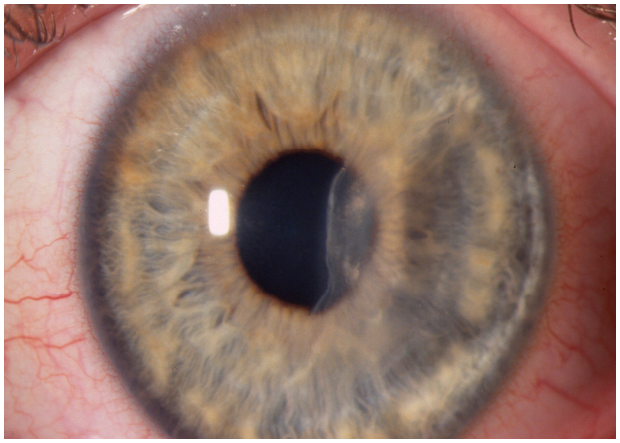
- **Visual acuity (VA)**:
  + Standard endpoint in ophthalmology
  - But: No correlation between antiangiogenic therapy and visual acuity
  - Large variability of factors affecting visual acuity after transplantation
  - ➔ Visual acuity not the most appropriate endpoint for products treating angiogenesis leading into indications pre- or post-grafting.

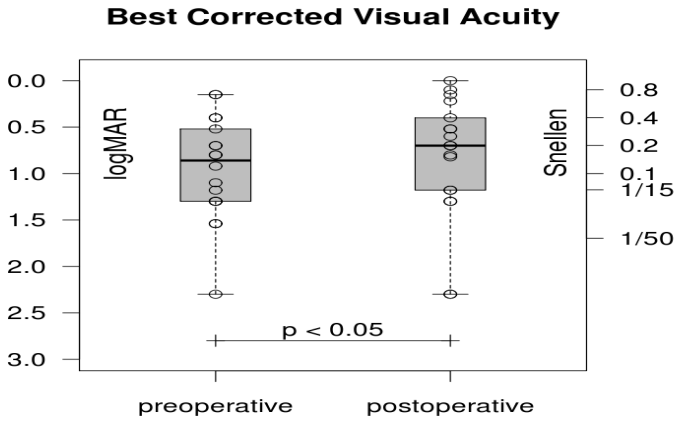
Koenig Y et al., **Cornea** 2011 (in press)

Antiangiogenesis and visual acuity









N=30

Koenig Y et al., **Cornea** 2011 (in press)

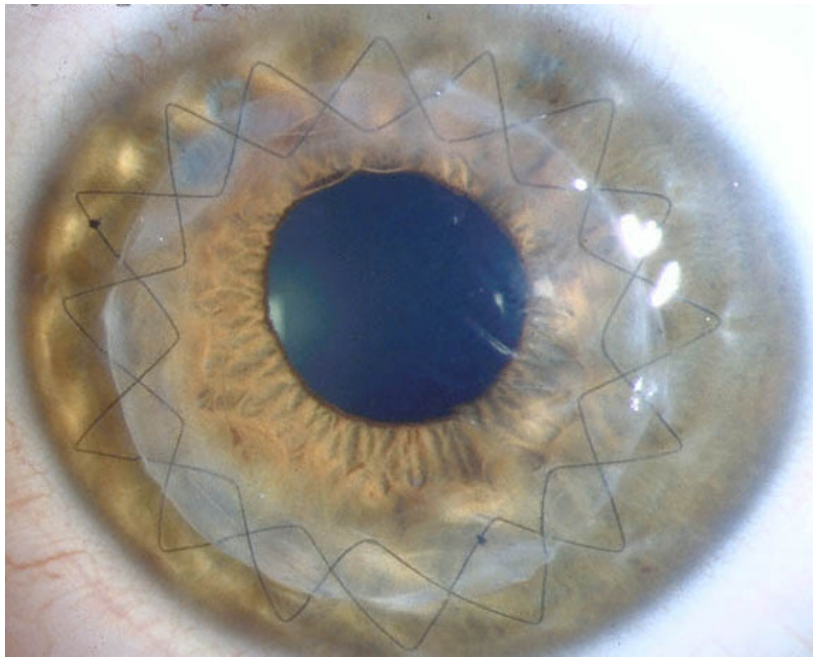
No correlation between antiangiogenic therapy and visual acuity

→Metaanalysis showed no significant effect of antiangiogenic therapy on visual acuity

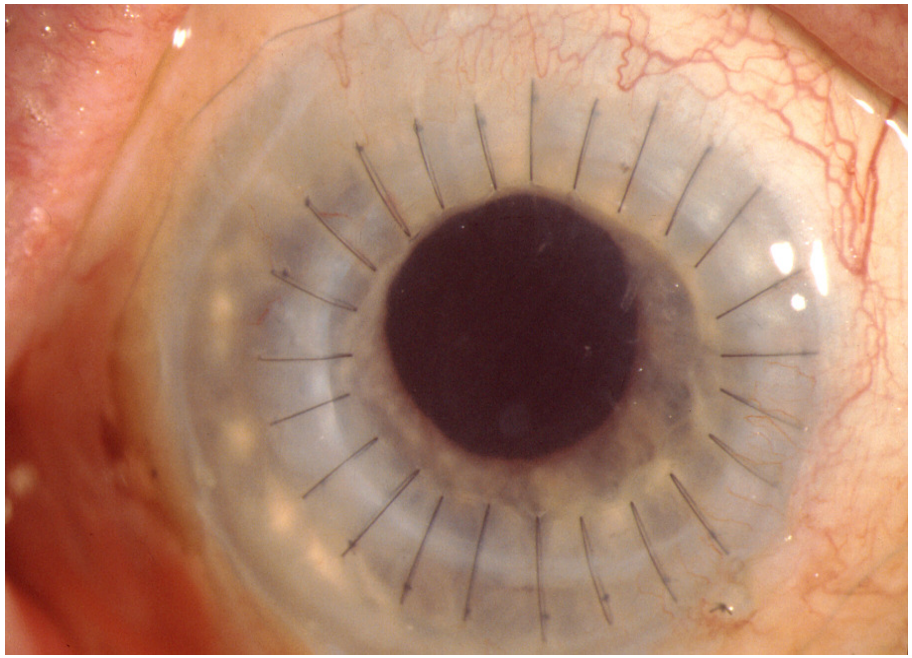
→But limited number of studies, difficult scenario

Bachmann B et al., **Acta Ophthalmol Scand** 2011 (in press)

Large variability of corneal factors affecting visual acuity after grafting



Visual acuity = 80%



Visual acuity = 25%

Antiangiogenic therapy to promote graft survival: Endpoints

- **Graft rejection**:

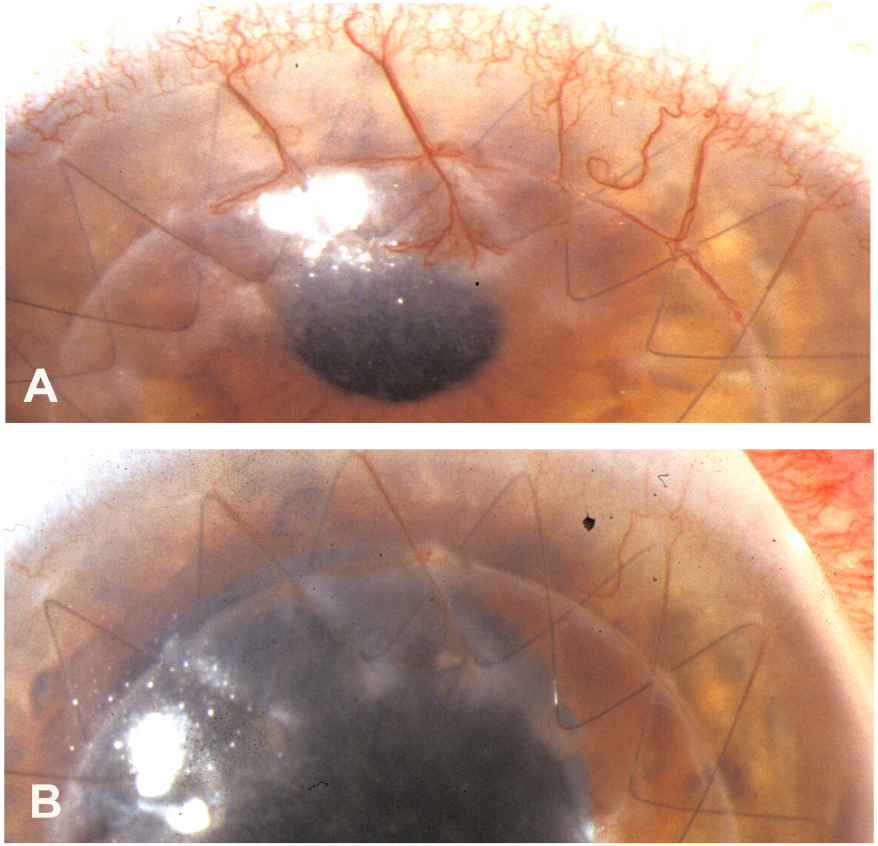
  - Not valid for primary prevention
  - Long duration of study (time of initial therapy, delay until transplantation, late occurence of graft rejections)
  - Difficult to assess in modern lamellar grafts

Nguyen, N et al., **Am J Ophthalmol**, 2007

Antiangiogenic therapy to promote graft survival: Endpoints

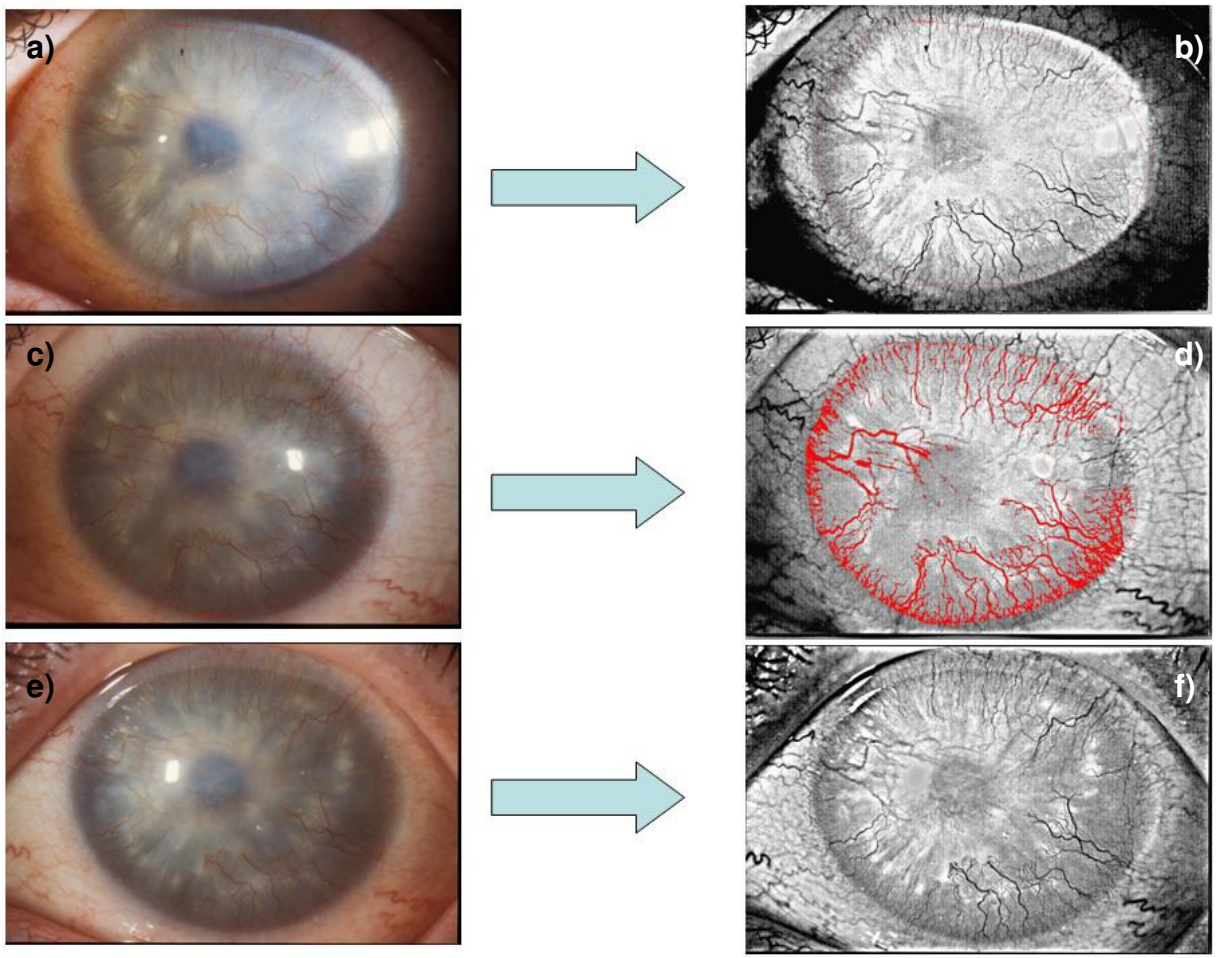
- **Antiangiogenesis**:
  - + mechanistic endpoint
  - + reliable measurement
  - + valid for both preventions

May be acceptable as a "biomarker" for a conditional approval given the strong medical need, which is then confirmed by long-term graft survival data (which then validates CNV as surrogate endpoint).



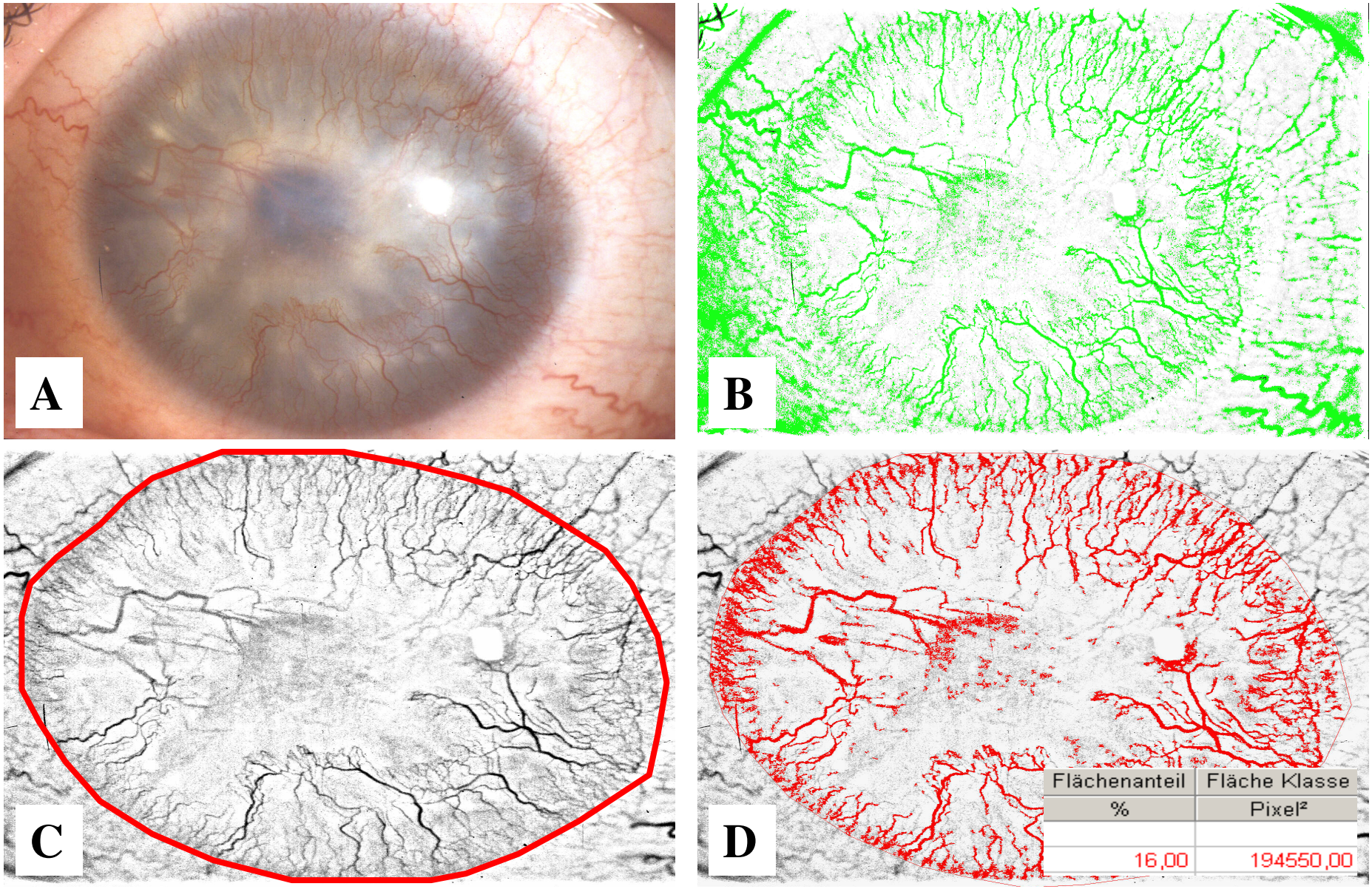
How to Measure Corneal Neovascularisation?

Standardized quantification of corneal neovascularisation



Cursiefen et al. **Ophthalmology** 2009;116:1630-7

Quantification of corneal neovascularization



Quantification of corneal neovascularization

- Semiautomatic image analysis of standardized slit-lamp pictures
- Image analysis software
- High sensitivity and specificity due to low background noise
- Reliable technique developed for and already used in phase II and III trial of topical antiangiogenesis at the cornea.

Cursiefen et al. **Ophthalmology** 2009;116:1630-7

Summary

- Unmet medical need: no specific medical treatment option for corneal neovascularisation
- Especially true for neovascularisation in the context of corneal transplantation
- Proposal: inhibition of CNV as the most relevant primary endpoint to demonstrate efficacy of anti-angiogenic agent in patients with **proliferative CNV uncontrolled under the current best available therapy**

Summary

- Given the unmet need in a developing field, thus opening the field
- Benefit for the patient in terms of either preventing the need for a corneal graft as well as improving graft survival if transplantation becomes necessary

Thanks!

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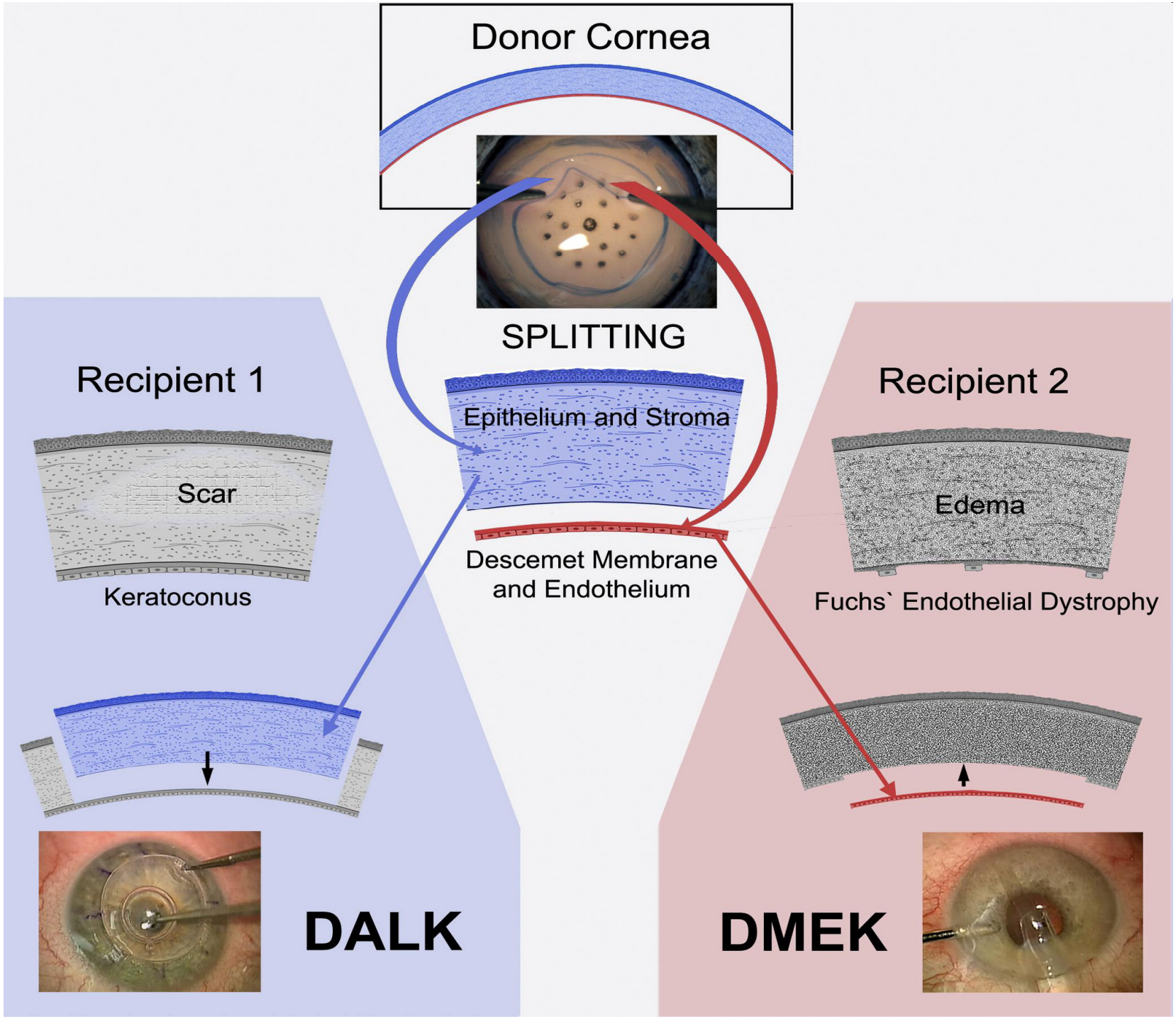
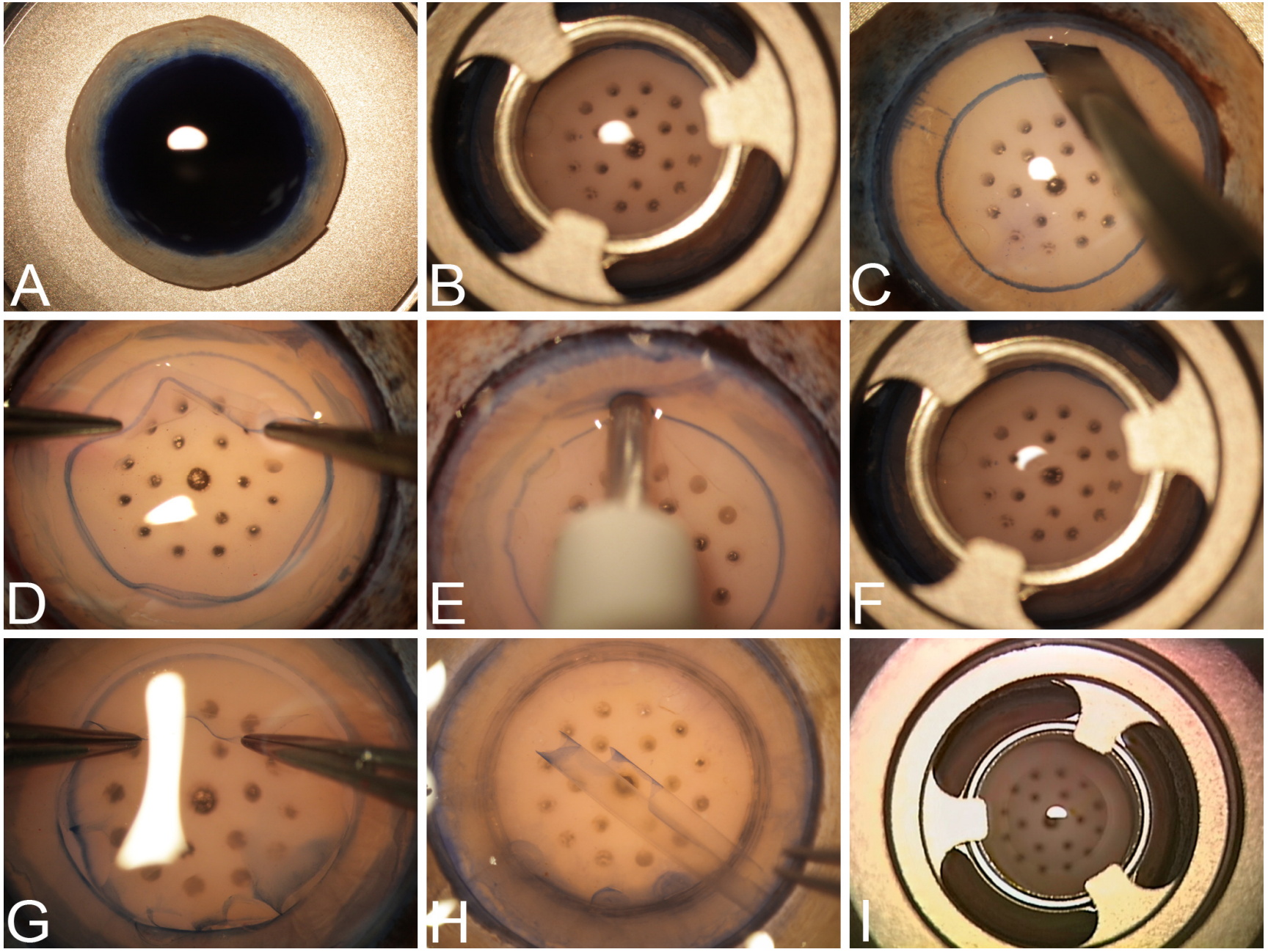
Change in corneal transplant surgery

- From perforating to lamellar
- Minimal invasive
- Lamellar surgery

- →all depend on avascular cornea


Donor Cornea
SPLITTING
Recipient 1
Scar
Keratoconus
Epithelium and Stroma
Descemet Membrane
and Endothelium
Recipient 2
Edema
Fuchs` Endothelial Dystrophy
DALK
DMEK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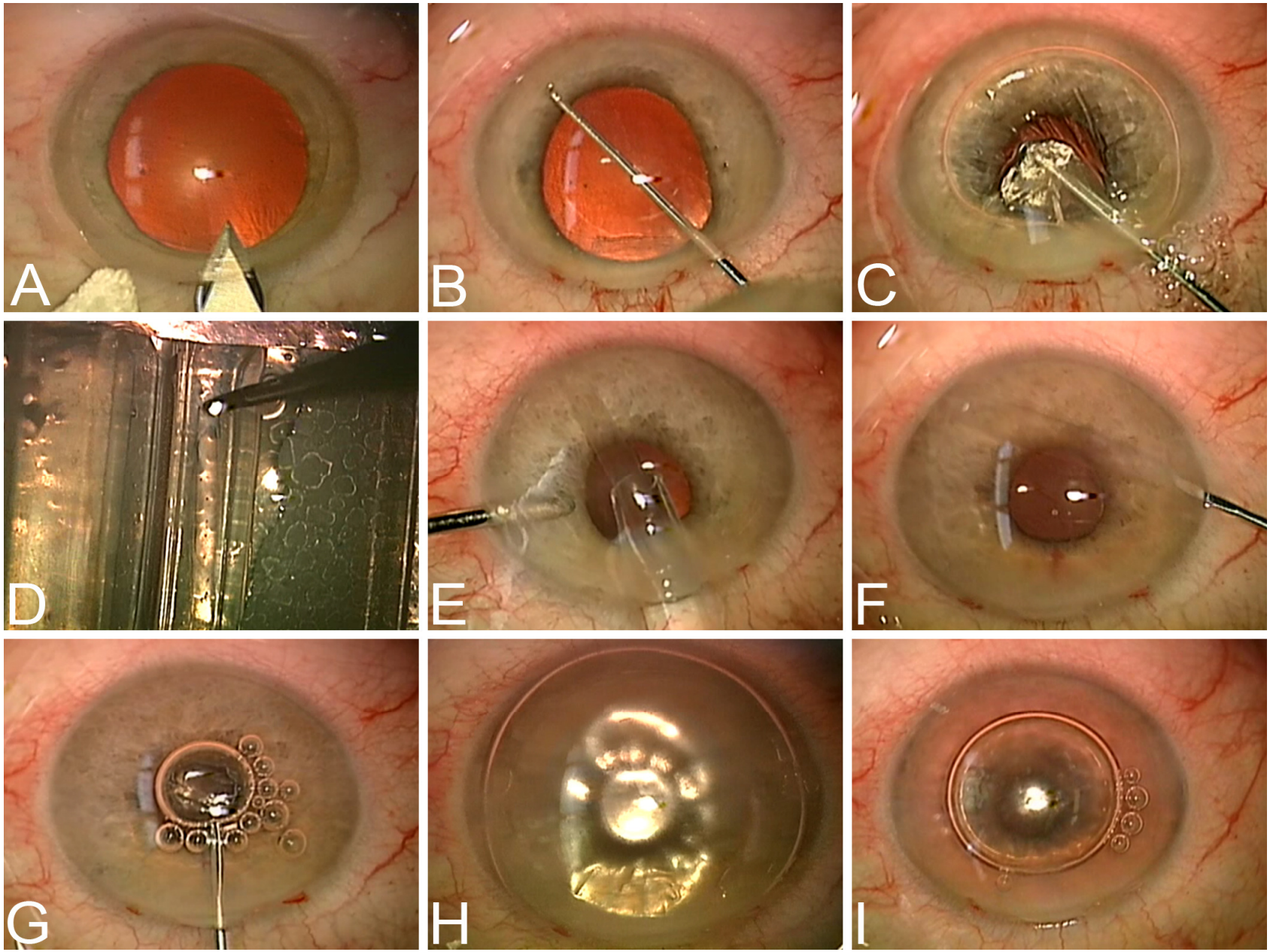
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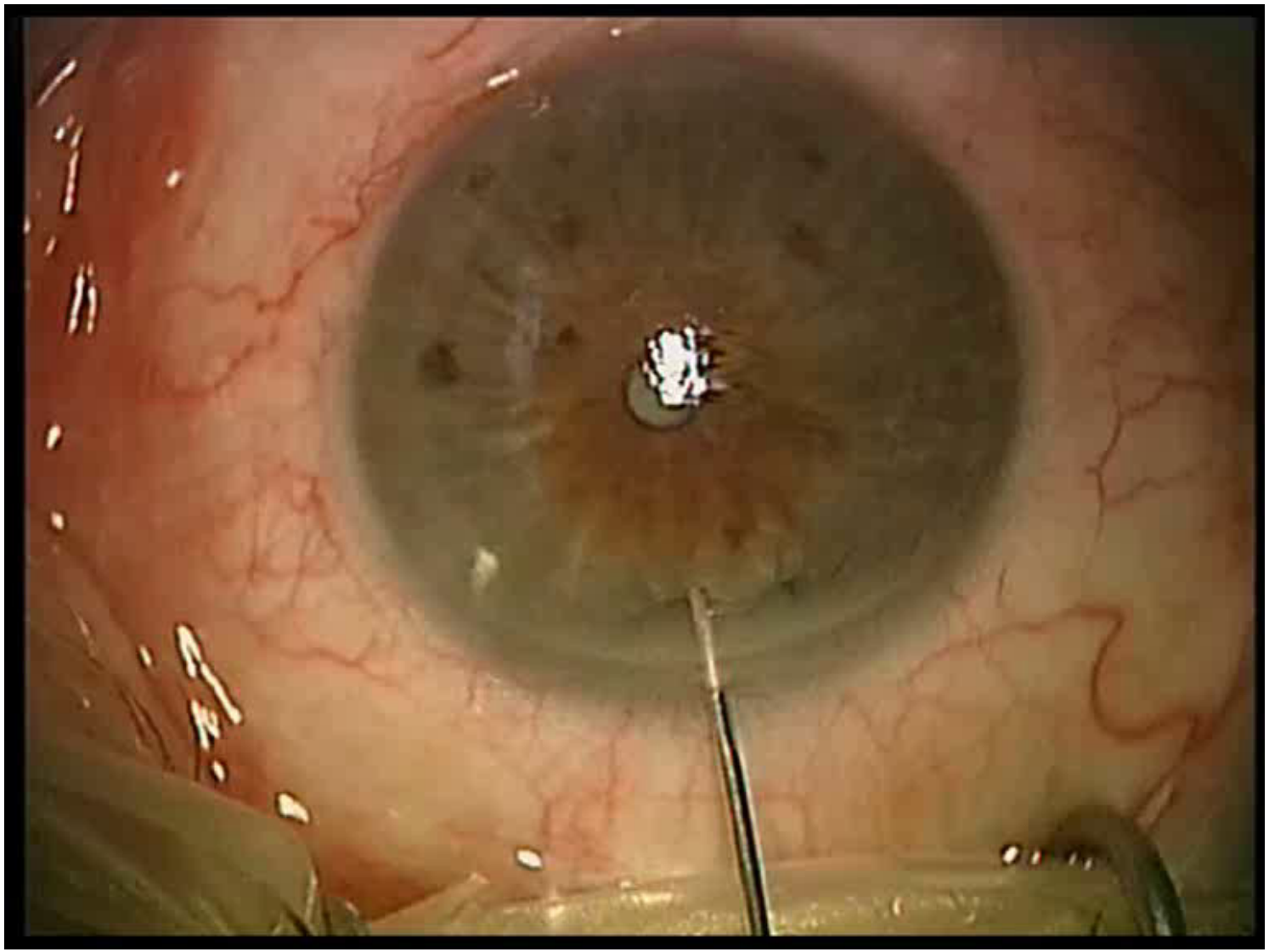

Heindl et al. **Am J Ophthalmol.** 2011;152:523-532

Vascularized cornea: no lamellar surgery possible and high rejection risk