

# CXL Experts' Meeting

Epi-on and epi-off applications

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Antwerp, Belgium

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No financial interest



## Transepithelial or epi-on CXL

*Addresses the limitations and safety issues of epi-off CXL:*

- No wound related complications



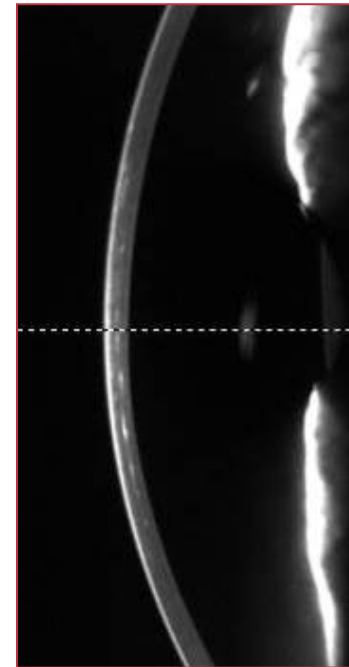
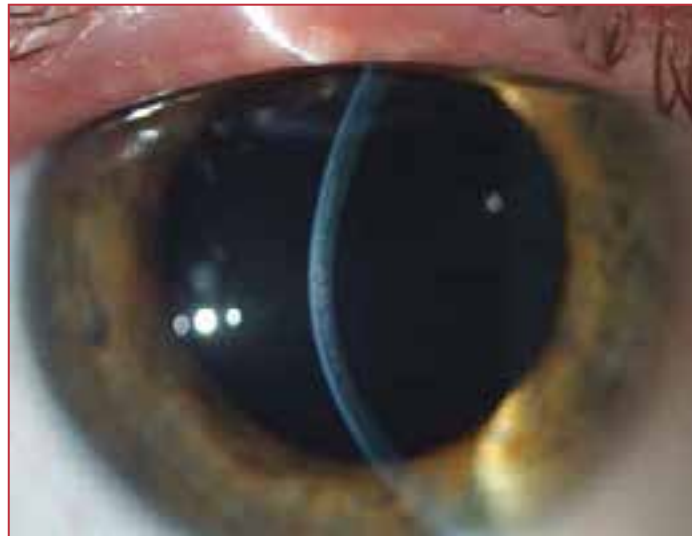
*Koppen C, Vryghem J et al. Keratitis and corneal scarring after UVA/riboflavin cross-linking for keratoconus. J Refract Surg. 2009;25:S819-823.*

*Koppen C et al. Riboflavin/UVA cross-linking for keratoconus in Down syndrome. J Refract Surg. 2010;26:623-624.*

## Transepithelial or epi-on CXL

*Addresses the limitations and safety issues of epi-off CXL:*

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- Less deep effect (demarcation line at  $\pm 100$  versus  $300 \mu\text{m}$ )
  - *Less toxicity for the stroma and keratocytes (haze)*



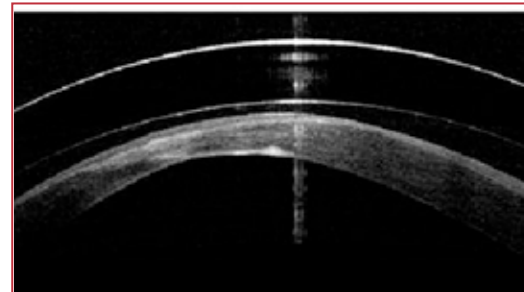
Greenstein SA, et al. Natural history of corneal haze after collagen crosslinking for keratoconus and corneal ectasia: Scheimpflug and biomicroscopic analysis. *J Cataract Refract Surg* 2010;36:2105-14.

Raiskup et al. Permanent corneal haze after riboflavin-UVA-induced cross-linking in keratoconus. *J Refract Surg*. 2009;25:S824-8.

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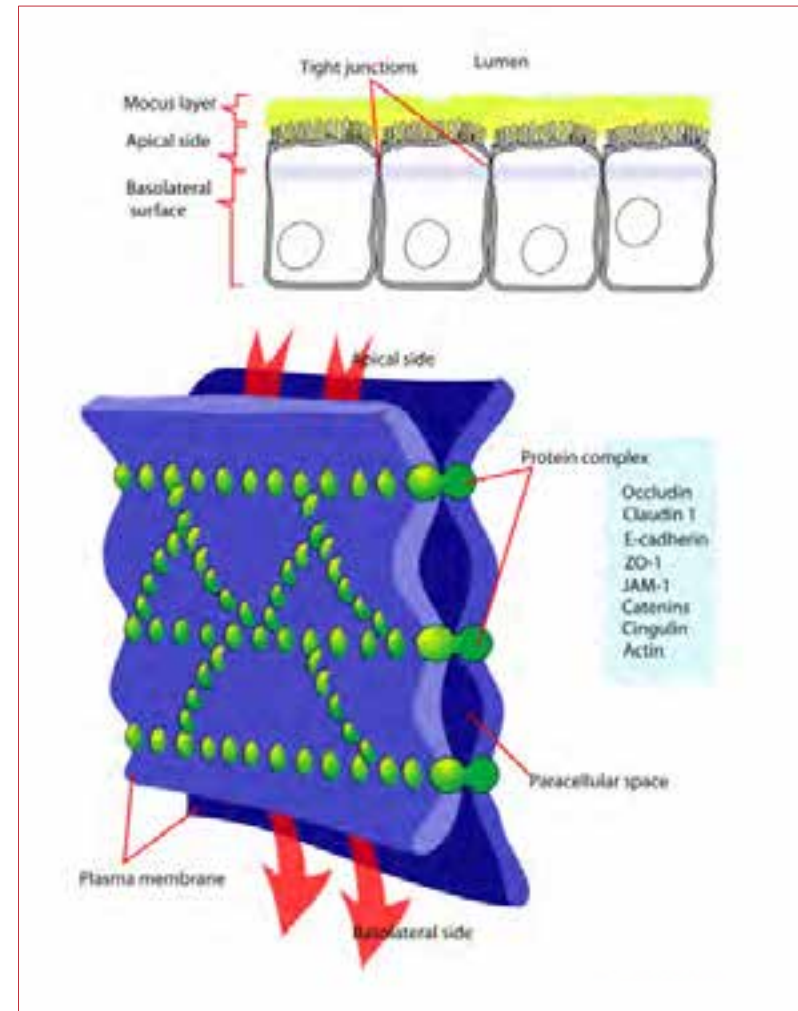
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- Shorter interruption of contact lens wear

## Transepithelial or epi-on CXL

*But what about efficacy?*

1. Riboflavin is a large hydrophylic molecule that cannot penetrate through an intact epithelium
2. Intact epithelium blocks about 20% of UV rays



## *TE CXL: Pharmacological modification of epithelial permeability*

- *Wollensak et al have studied the TE CXL treatment in rabbits using the protocol proposed by Boxer Wachler and Pinelli:*
  - Pretreatment with Proparacaine 0.5% every 5' for 30' (BAC 0.005% preserved), followed by standard instillation of riboflavin in dextran 30' and UVA 365 nm 3mW/cm<sup>2</sup> 30'
- Conclusions of this rabbit experiment:
  - *Biomechanical effect reduced by about 1/5 compared to standard CXL: increase in rigidity 62% for TE-CXL versus 320% for standard CXL*
  - *Cytotoxic damage restricted to anterior 200 μm stromal depth*

*Pinelli R. Corneal collagen crosslinking: is it necessary to remove the epithelium?  
Journal of the intraocular implant and refractive surgery society, India. 2008;4:28-34*

*Wollensak G et al. Biomechanical and histological changes after corneal crosslinking with and without epithelial debridement.  
J Cataract Refract Surg. 2009;35:540-6.*



# Refractive and topographic results of BAC-assisted TE CXL

Prospective study<sup>1</sup> on 53 eyes of 38 patients stage I – III  
Statistical analysis for a follow up of 18 months

- *Efficacy? Statistically significant changes?*
  - DCVA improved
  - majority of parameters including K max on EyeSys remained stable
  - K max on Pentacam and I-S value on Placido based topography deteriorated
- *Failures: 7/53 eyes (13%) versus*
  - standard CXL (own results): 2/27 eyes (7%)
  - epi-off CXL in the literature: 7.6%<sup>2</sup>
- Haze: none, *complications: none*

<sup>1</sup>Koppen et al. Refractive and topographic results of benzalkonium chloride-assisted transepithelial crosslinking. J Cataract Refract Surg. 2012;38:1000-5.

<sup>2</sup>Koller et al. Complication and failure rates after corneal crosslinking. J Cataract Refract Surg. 2009;35:1358-62.

## TE CXL with Ricrolin TE (Riboflavin 0.1%, trometamol and EDTA)

### *Efficacy?*

- TE CXL appeared to halt progression, with a statistically significant improvement in visual and topographic parameters

...

- Functional results after TE CXL showed keratoconus instability, in particular in pediatric patients 18 y old and younger – 50% of pediatric patients were retreated with epi-off CXL after 12 months of follow-up
- This technique does not effectively halt keratoconus progression in children compared to standard CXL

... basic research is lacking

*Filippello et al. Transepithelial corneal collagen crosslinking: bilateral study.*

*J Cataract Refract Surg. 2012;38:283-91.*

*Caporossi et al. Transepithelial corneal collagen crosslinking for progressive keratoconus: 24-month clinical results.*

*J Cataract Refract Surg. 2013;39:1157-63.*

*Buzzonetti et al. Transepithelial crosslinking in pediatric patients: early results.*

*J Refract Surg. 2013;28:763-7.*

## Other methods of TE CXL

### Epithelial disruptor



### Intrastromal pocket (femtolaser)



Rechichi et al. Epithelial-disruption collagen crosslinking for keratoconus: one-year results.  
*J Cataract Refract Surg.* 2013;39:1171-8.

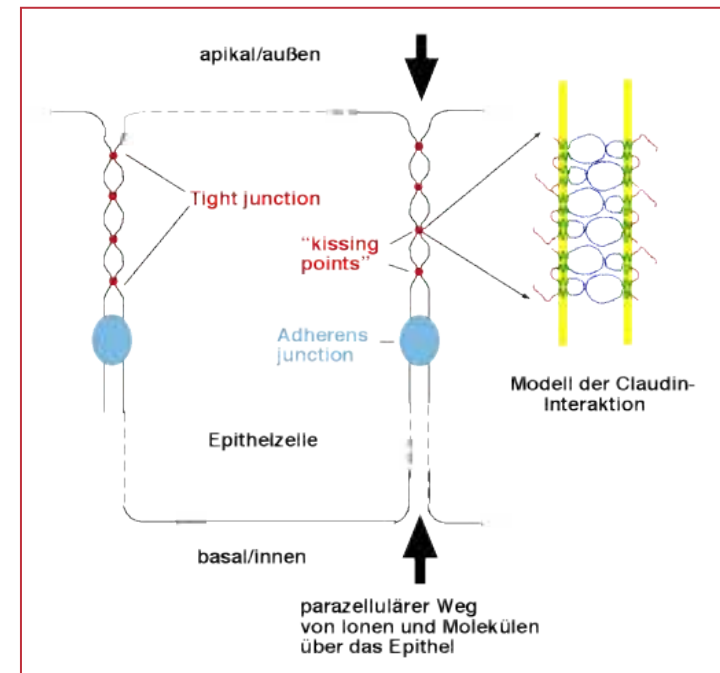
Wollensak et al. Biomechanical efficacy of collagen crosslinking in porcine cornea using a femtosecond laser pocket.  
*Cornea.* 2014;33:300-5.

# TE CXL: research on pharmacological modification of epithelial permeability

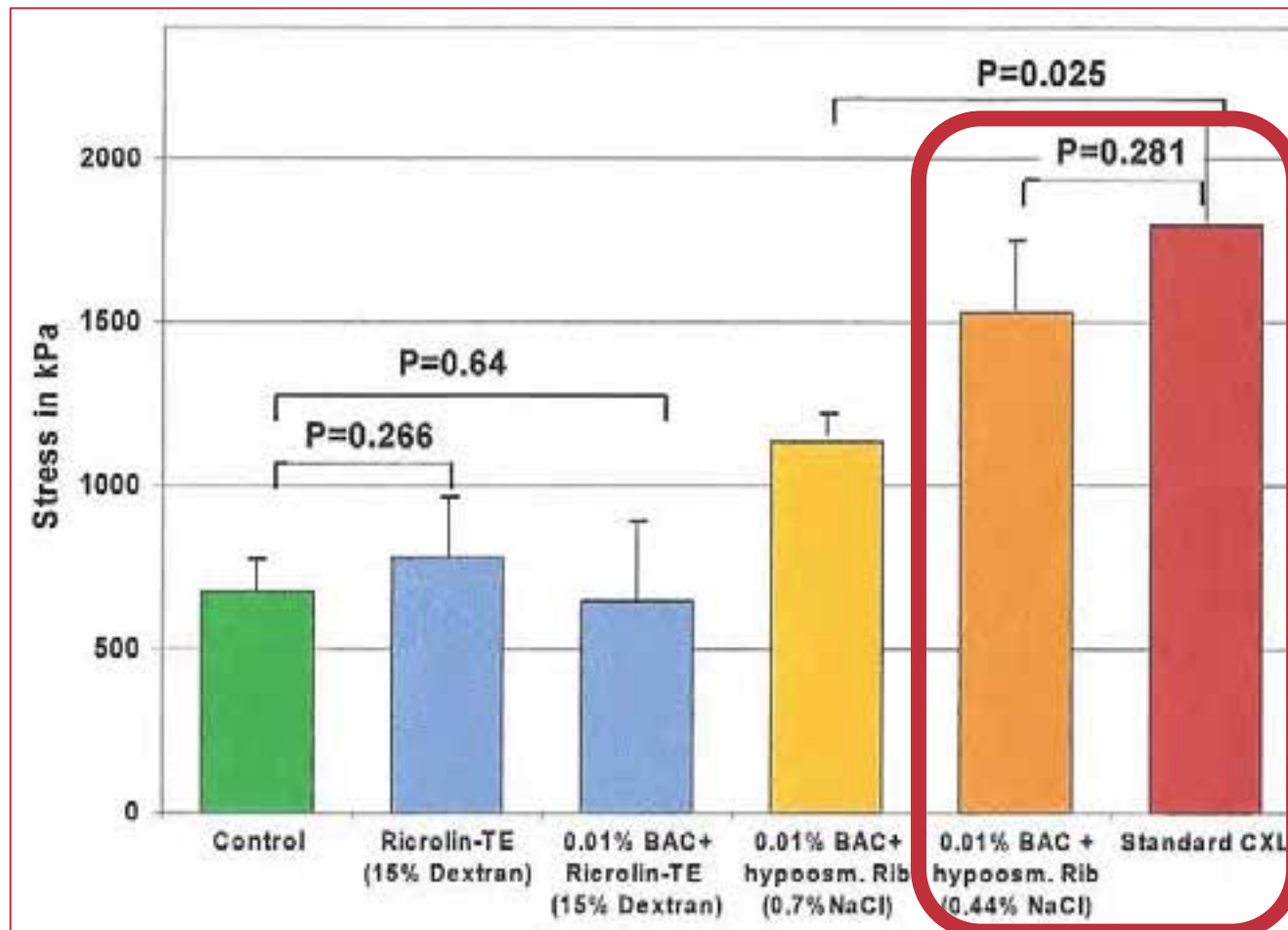
- Animal experiments by Spoerl et al: TE CXL using riboflavin 0.1% in NaCl 0.44% with BAC 0.01% results in the same biomechanical effect as standard epi-off CXL

Structure of tight junctions is modified -> changes in paracellular transport lead to increased permeability for riboflavin

- Dextran ↓ ribo transport
- NaCl 0.44% ↑ ribo transport



## TE CXL: research on pharmacological modification of epithelial permeability

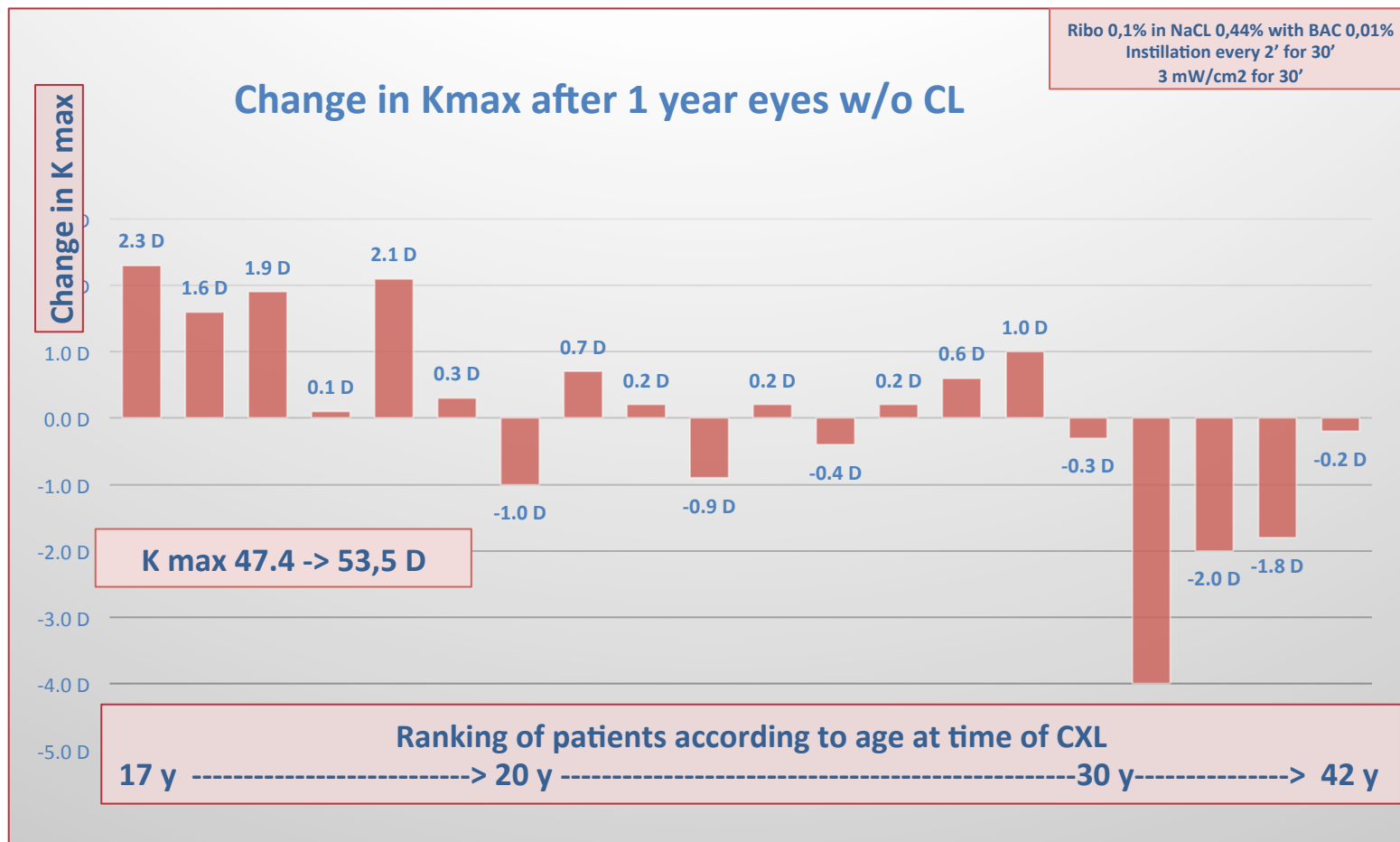


Kissner et al. Pharmacological modification of the epithelial permeability by benzalkonium chloride in UVA/riboflavin corneal collagen cross-linking. *Curr Eye Res.* 2010;35:715-21.

Raiskup et al. Riboflavin osmolar modification for transepithelial corneal cross-linking. *Curr Eye Res.* 2012;37:234-38.

# TE CXL with ribo 0,1% in NaCl 0,44% with BAC 0,01% (preliminary results)

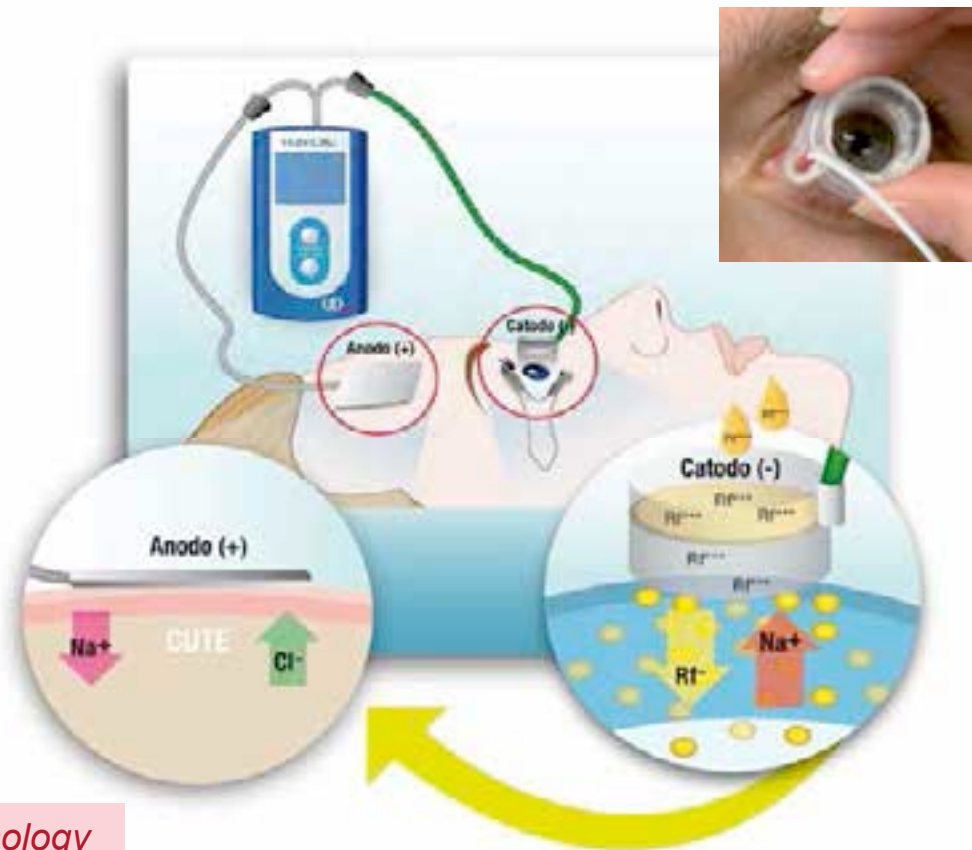
- Prospective study on 20 eyes of 15 patients stage I - III



# TE CXL iontophoresis: principle

## Iontophoresis

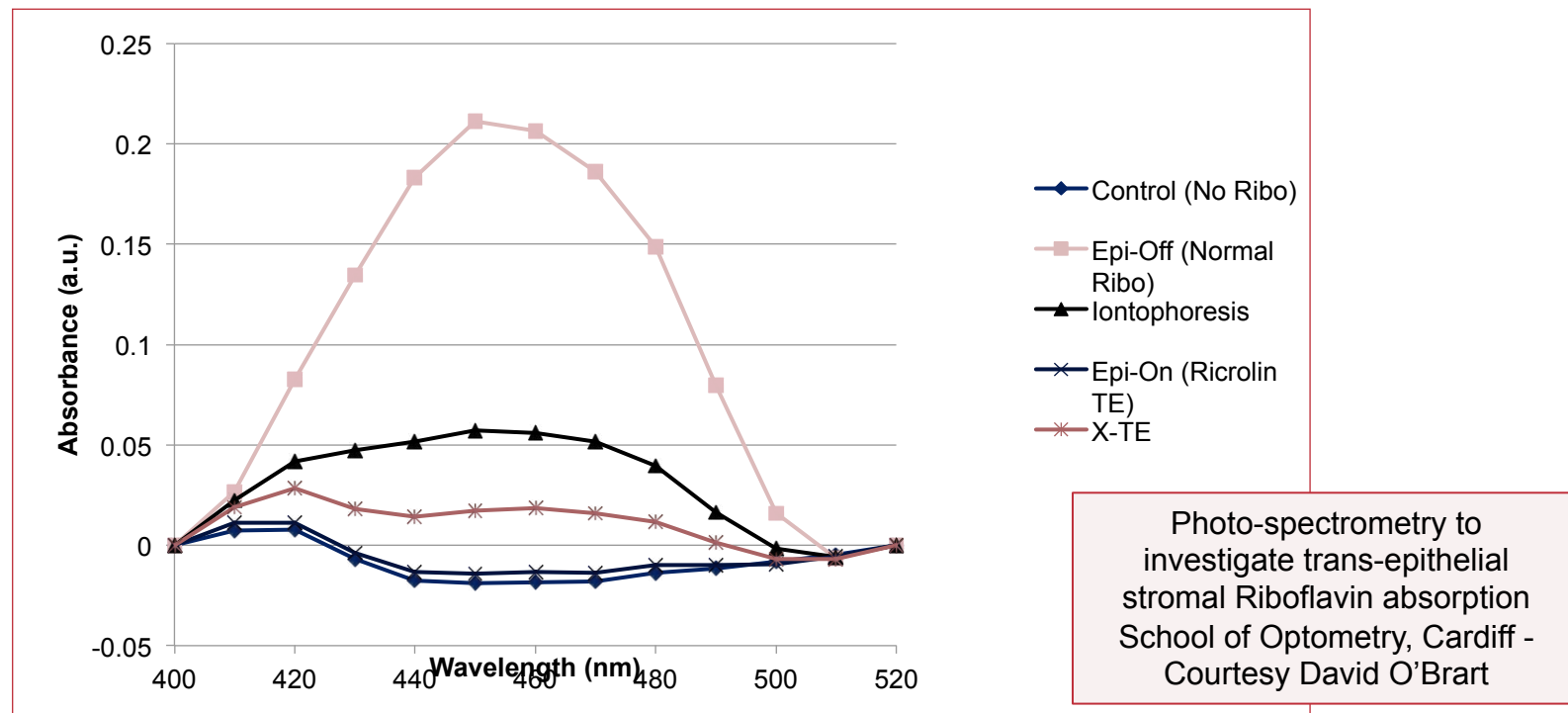
- physical process in which ions flow in a medium driven by an electric field



# TE CXL iontophoresis: stromal uptake

## Iontophoresis

- TE iontophoresis imbibition yielded greater and deeper riboflavin saturation with respect to conventional epi-on,.. but did not reach concentrations obtained with standard epi-off



Mastropasqua L et al. Corneal cross-linking: intrastromal riboflavin concentration in iontophoresis-assisted imbibition versus traditional and transepithelial techniques. *Am J Ophthalmol.* 2014;157:623-30.



## *TE CXL iontophoresis: CXL effect*

### *Iontophoresis*

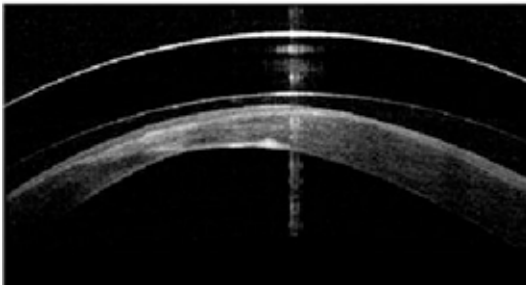
- Ex vivo biomechanical studies on rabbit and human cadaveric corneas showed an increase of the biomechanical resistance of human cornea comparable to that obtained with the standard epi-off crosslinking procedure
- Preliminary clinical results of iontophoresis assisted corneal CXL are promising: keratoconus progression is halted without significant complications

## TE CXL: conclusions

*Epi-on CXL is safer than the standard epi-off procedure*

*Efficacy, however, remains the weakness:*

Dosage UVA irradiation



Epithelial thickness profile



Combination with  
accelerated CXL

Oxygen

# EVIDENCE-BASED CXL

Epi-on, higher UV power, shorter treatment tantalise, but only epi-off is proven. *Howard Larkin reports*

**D**espite many experiments with corneal crosslinking (CXL) technologies designed to preserve the epithelium and shorten the procedure, the traditional method involving epithelium removal and 30 minutes of  $3\text{mW}/\text{cm}^2$  ultraviolet radiation remains the only proven CXL treatment for keratoconus. Frederik Raiskup MD, PhD, FEBO told the XXXII Congress of the ESCRS in London.

Dr Raiskup noted some promising tests of various epi-on, high-power radiation and iontophoresis CXL approaches. But some early studies ar long-term clinical st safety and efficacy ar



Cornea without epithelium soaked with riboflavin during CXL procedure.

Courtesy of Frederik Raiskup MD, PhD, FEBO

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## *TE CXL: enhancement of permeability versus preservation of integrity of the epithelium*

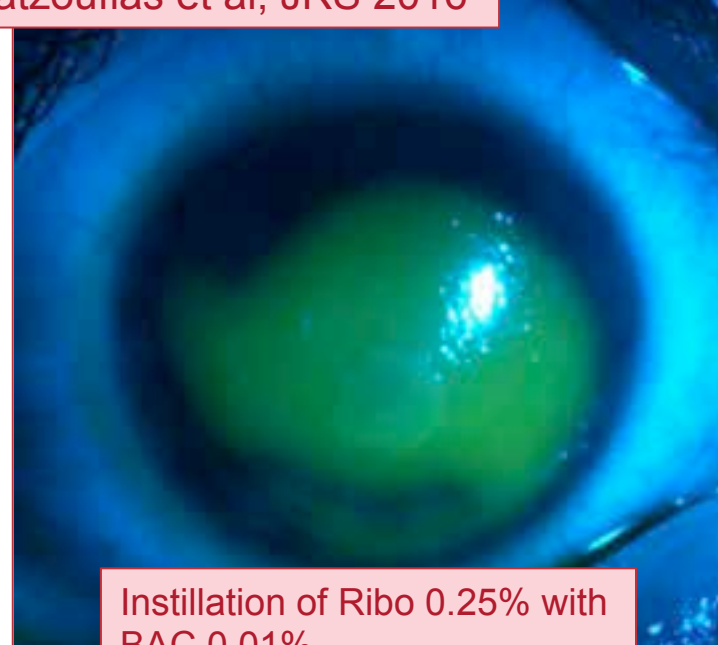
- Standardization: exact composition of drops, method of application, duration of application,...

Koppen, unpublished, 2014



Instillation of Ribo 0.1% in NaCl 0.44% with BAC 0.01%

Gatzoufias et al, JRS 2016



Instillation of Ribo 0.25% with BAC 0.01%

- There is a thin line between epi-on and epi-off