

Epi-on Iontophoresis CXL

Latest clinical data

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HUMANITAS
CENTRO OCULISTICO

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UNIVERSITY

Financial interest

Consultant

Nidek, Oculus, Schwind,

Epi Off → CONS



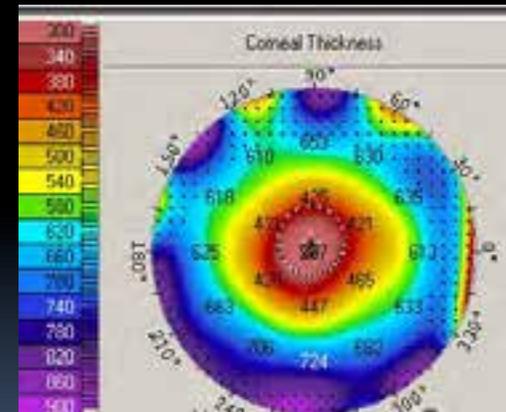
- Pain



- Slow visual acuity recovery



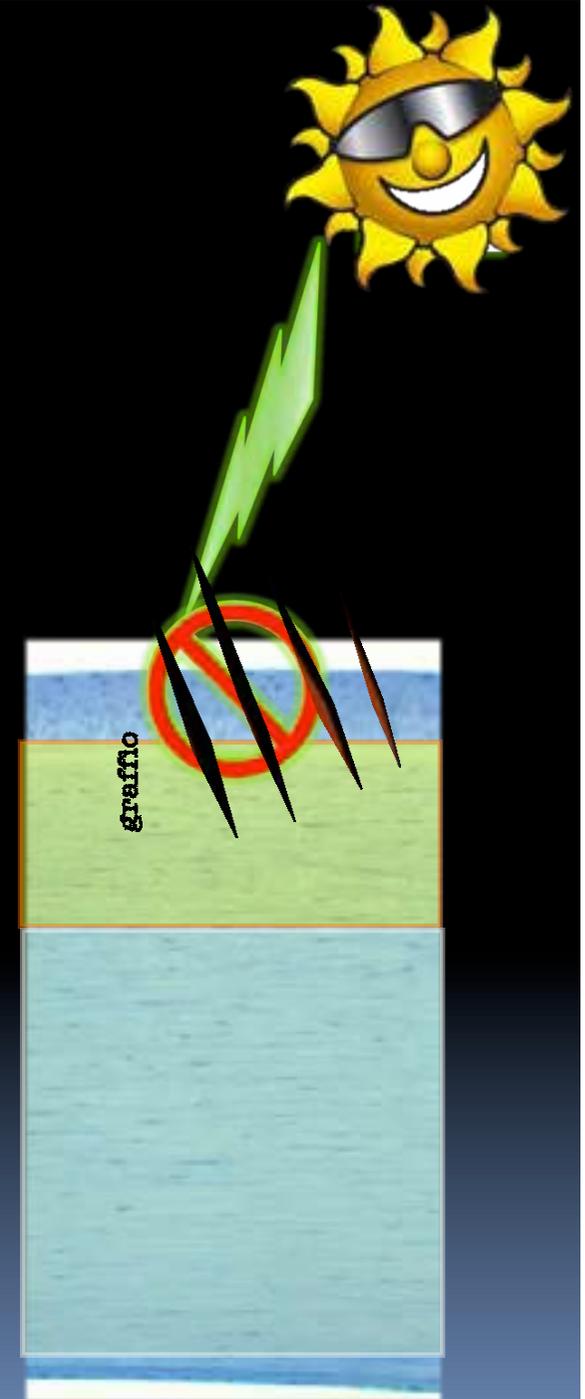
- Risk of Infections



- Problems with thin corneas (swelling solutions)

Epithelium and CXL (1)

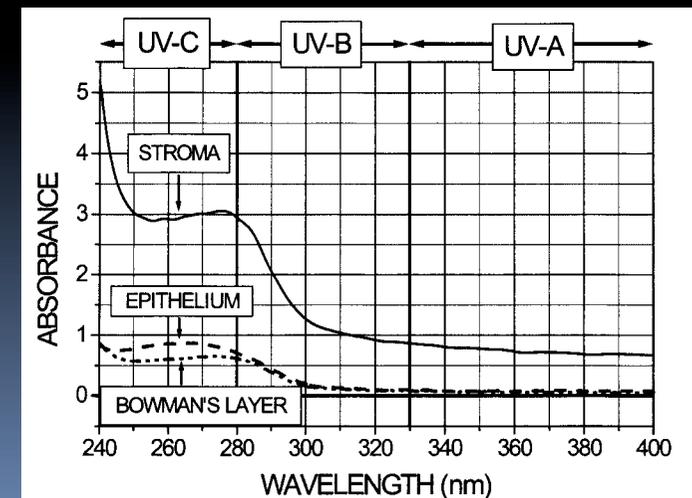
- Epithelium with riboflavin 85% UV¹
- Epi-on with scratch provides good impregnation and results²
- Reduced efficacy (1/5) if epi-on³
- Epi induces increase of Max Stress e Young's modulus of 35.9% e 15.4% more than epi-on⁴



1) Baiocchi et al. J Cataract Refract Surg (2009)
2) Alhamad et al J Cataract Refract Surg (2012)
3) Wollensak et al. J Cataract Refract Surg (2009)
4) Tao et al. Biomed Res Int (2013)

Epithelium and UV (2)

- Kolazsvari et al: Epithelium blocks only UV wavelenght < 300 nm¹ !!!
- Bottos et al: epithelium reduces CXL principally because of the reduced impregnation with riboflavin



1) Kolozsvári L et al. Invest Ophthalmol Vis Sci. 2002

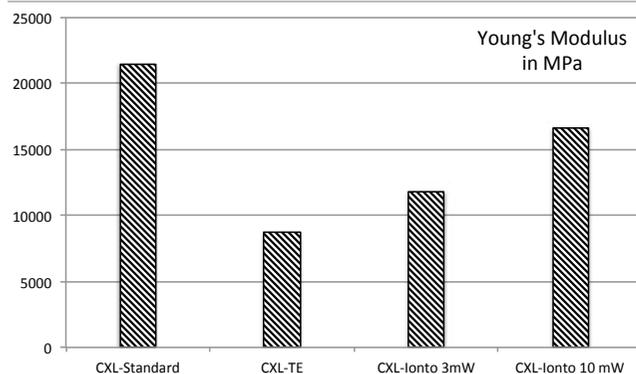
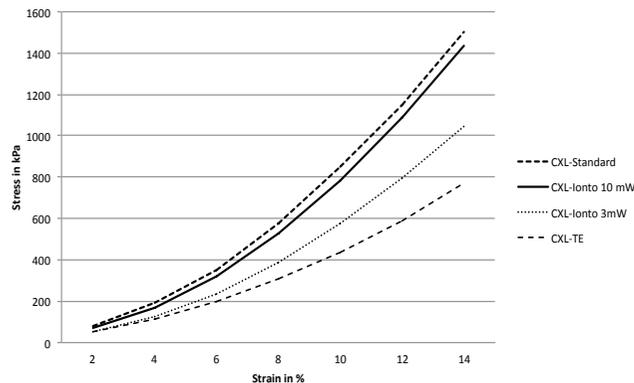
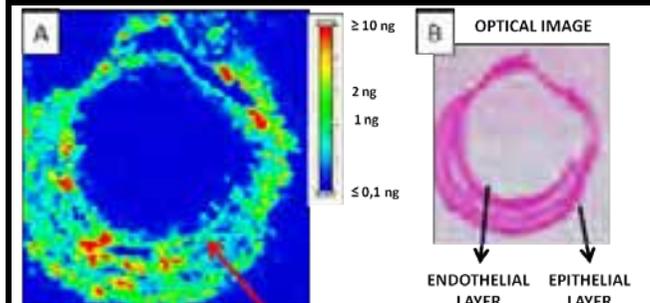
2) Bottós et al. Arq Bras Oftalmol (2011)

Iontophoresis

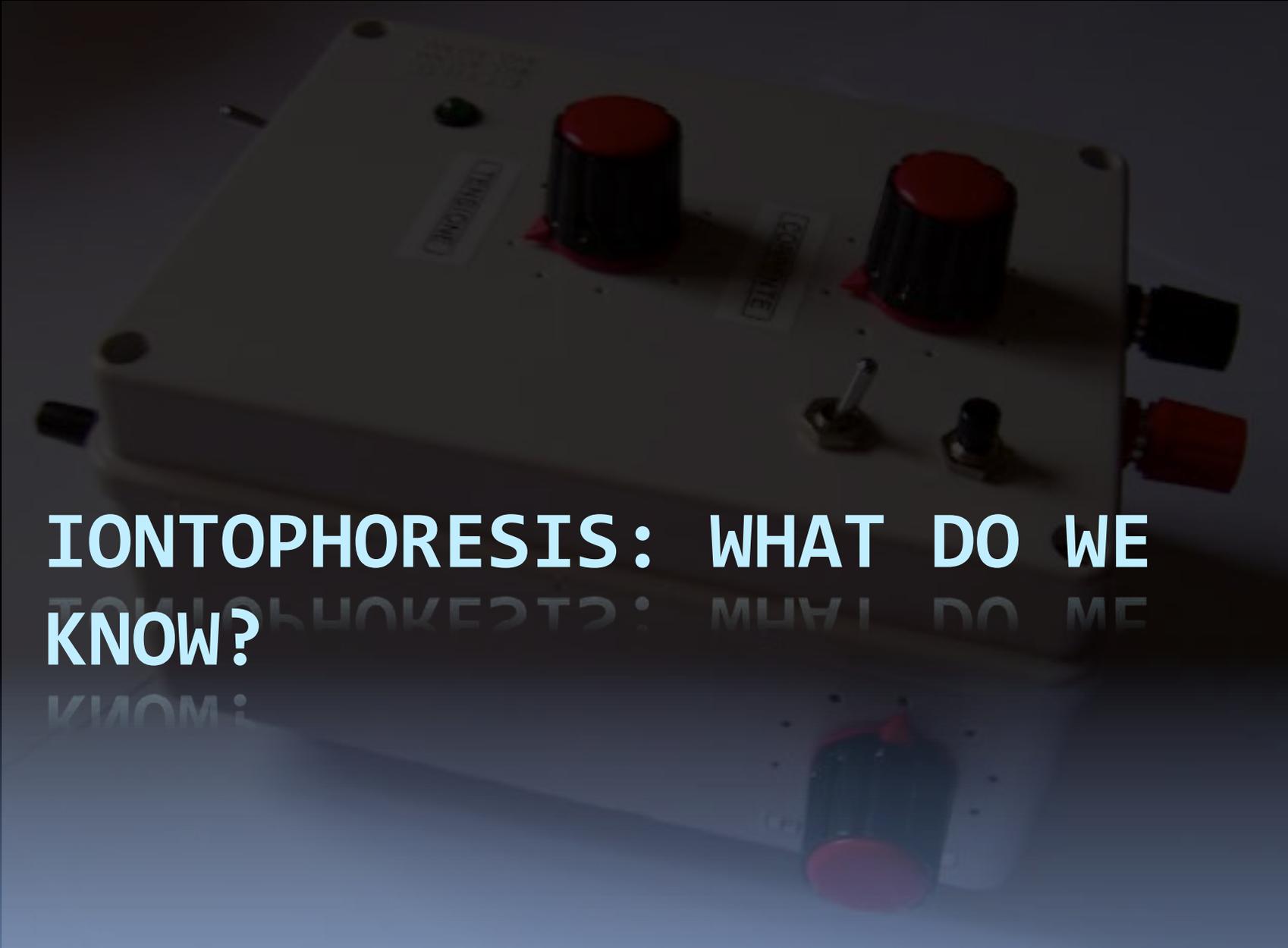
Research Article

Imaging Mass Spectrometry by Matrix-Assisted Laser Desorption/Ionization and Stress-Strain Measurements in Iontophoresis Transepithelial Corneal Collagen Cross-Linking

Paolo Vinciguerra,¹ Rita Mencucci,² Vito Romano,³ Eberhard Spoerl,⁴ Fabrizio I Camesasca,¹ Eleonora Favuzza,² Claudio Azzolini,⁵ Rodolfo Mastropasqua,⁶ and Riccardo Vinciguerra^{1,5}



- Increase in stress strain and Young's modulus
- Lower than epi-off
- Good Riboflavin concentration (lower than epi-off)



**IONTOPHORESIS: WHAT DO WE
KNOW?**



CLINICAL STUDY

Istituto Clinico Humanitas

Transepithelial Iontophoresis Corneal Collagen Cross-linking for Progressive Keratoconus: Initial Clinical Outcomes

Paolo Vinciguerra, MD; J. Bradley Randleman, MD; Vito Romano, MD; Emanuela F. Legrottaglie, MD; Pietro Rosetta, MD; Fabrizio I. Camesasca, MD; Raffaele Piscopo, MD; Claudio Azzolini, MD; Riccardo Vinciguerra, MD

ABSTRACT

PURPOSE: To report initial clinical results of transepithelial corneal collagen cross-linking with iontophoresis (I-CXL).

METHODS: Twenty eyes of 20 patients diagnosed as having progressive keratoconus who underwent I-CXL were included in this prospective non-randomized clinical study. Corrected distance visual acuity (CDVA), spherical equivalent and cylinder refraction, various corneal topography and Scheimpflug tomography parameters, aberrometry, anterior segment optical coherence tomography, and endothelial cell count were assessed at baseline and at 1, 3, 6, and 12 months postoperatively.

RESULTS: CDVA improved significantly at 3, 6, and 12 months postoperatively (logMAR difference of -0.07 ± 0.01 , -0.09 ± 0.03 , and -0.12 ± 0.06 , respectively; $P < .05$). Aberrometry remained stable during follow-up and a trend toward improvement was noted. All topographic parameters (including maximum keratometry) were stable during the follow-up, but exhibited a positive non-significant trend toward improvement. Minimum corneal thickness values were stable for up to 12 months postoperatively. None of the patients showed a progression of keratoconus. Endothelial cell counts did not change significantly ($P > .05$).

CONCLUSIONS: Preliminary results up to 1 year postoperatively indicate the efficacy of I-CXL in stabilizing the progression of this degenerative disease combined with significant improvement of CDVA. I-CXL, which spares the corneal epithelium, has the potential to become a valid alternative for halting the progression of keratoconus while reducing postoperative patient pain, risk of infection, and treatment time in select patients; however, the relative efficacy of this technique compared to standard epithelium-off techniques remains to be determined.

[*J Refract Surg.* 2014;30(11):746-753.]

Corneal collagen cross-linking (CXL) is able to change the biomechanical properties of corneas and is currently the only treatment that can potentially slow or block the progression of ectatic disease.^{1,2} Long-term follow-up studies on CXL mostly refer to the standard technique, which entails epithelial debridement to allow riboflavin penetration in the corneal stroma.^{1,3} Epithelial removal causes pain⁴ and a higher risk of corneal infection,⁵ as well as visual loss for the first few months after treatment.^{2,3} To avoid these drawbacks, transepithelial corneal collagen cross-linking (TE-CXL) was developed. The transepithelial protocol currently used employs a specially formulated riboflavin solution (Ricola TE; SOOFT, Montegiorgio, Italy) in which two enhancers (ie, trometamol and sodium ethylenediaminetetraacetic acid) are added to help riboflavin penetration in the corneal stroma.⁶ However, results of TE-CXL are limited and have not achieved the same efficacy as standard CXL, frequently due to inadequate riboflavin penetration.⁷⁻¹⁰

The use of enhancers may not be the only way to increase riboflavin penetration through the epithelium. In other specialties (ie, dermatology), iontophoresis has been adopted for a long time. It is a non-invasive technique in which a small electric current is applied to enhance an ionized drug's penetration.

Preclinical results have shown that CXL with iontophoresis (I-CXL) is able to increase the concentration of riboflavin in the corneal stroma when compared to TE-CXL¹¹⁻¹³ with

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Dr. Paolo Vinciguerra is a consultant for Nidek, Inc. and Oculus Optikgeräte GmbH. The remaining authors have no financial or proprietary interest in the materials presented herein.

Dr. Randleman did not participate in the editorial review of this manuscript.

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Materials and Methods

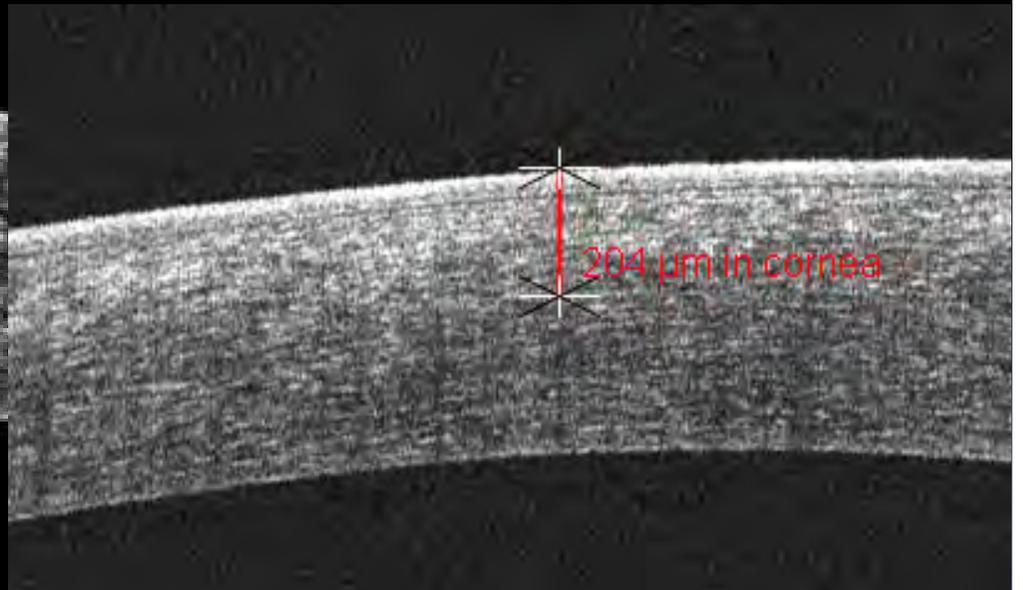
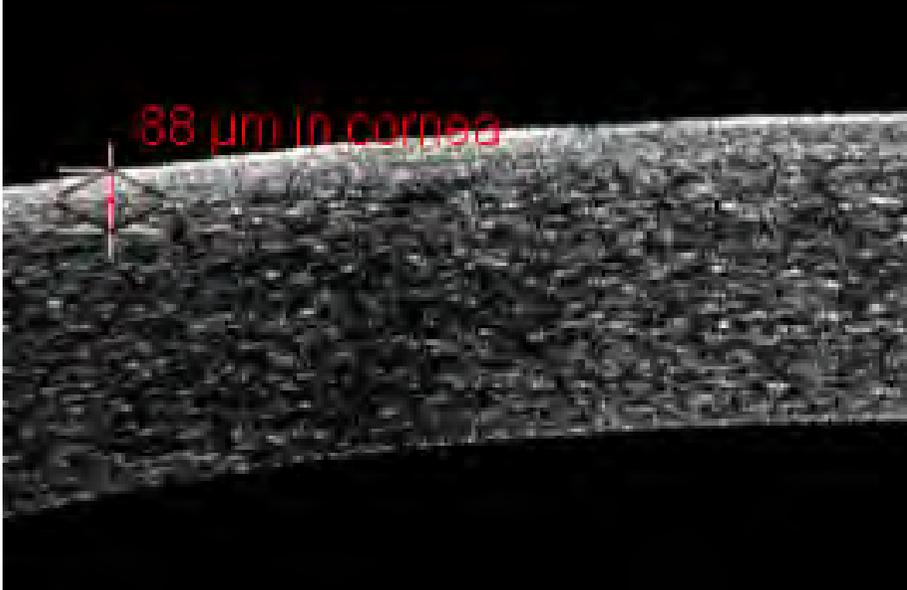
- 20 eyes of 20 patients with progressive keratoconus
- Progression proved with differential maps
- Age >18 years
- Follow up 12 months



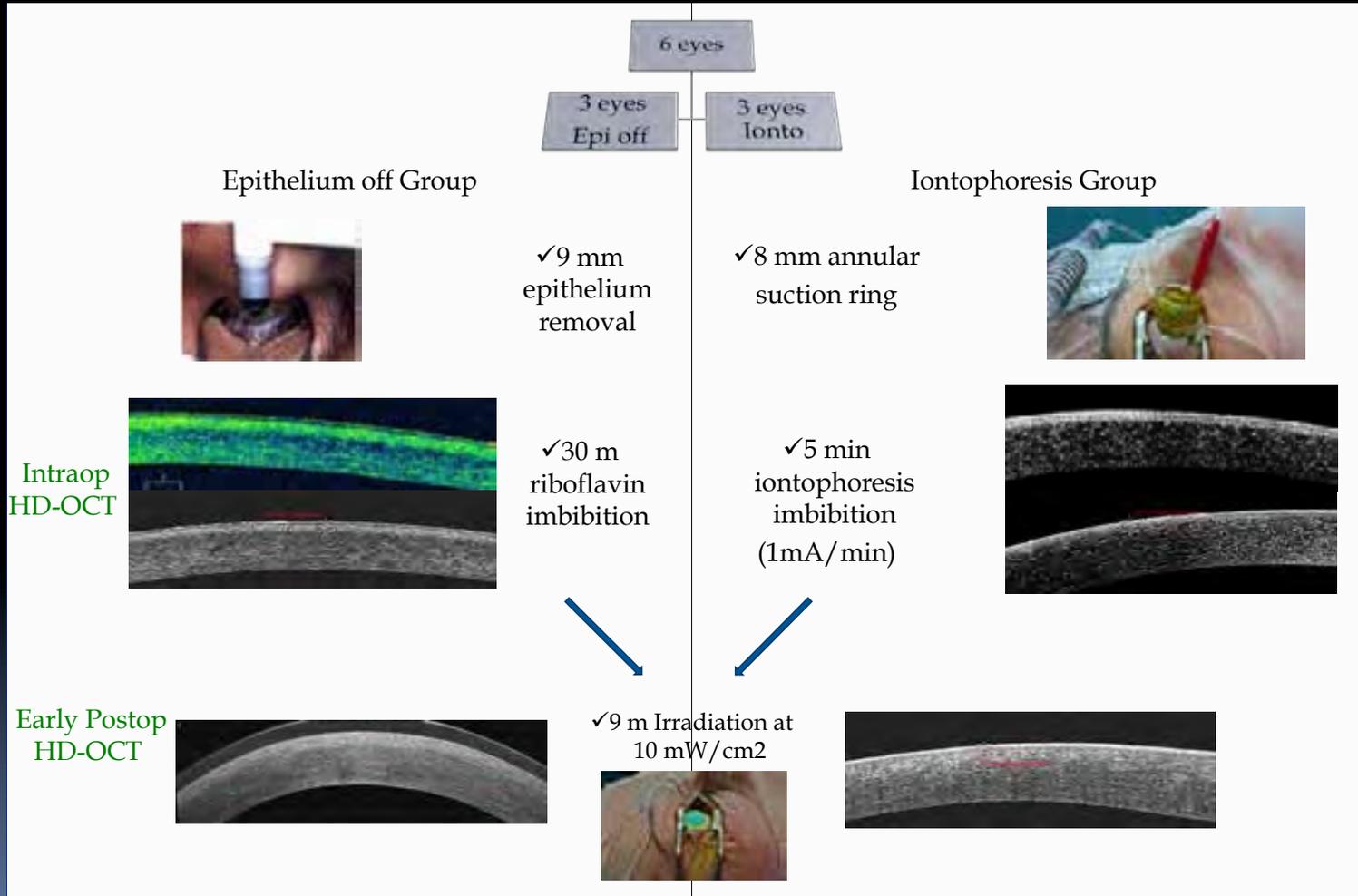
-HD-OCT after impregnation



-HD-OCT after irradiation



IntraOp OCT

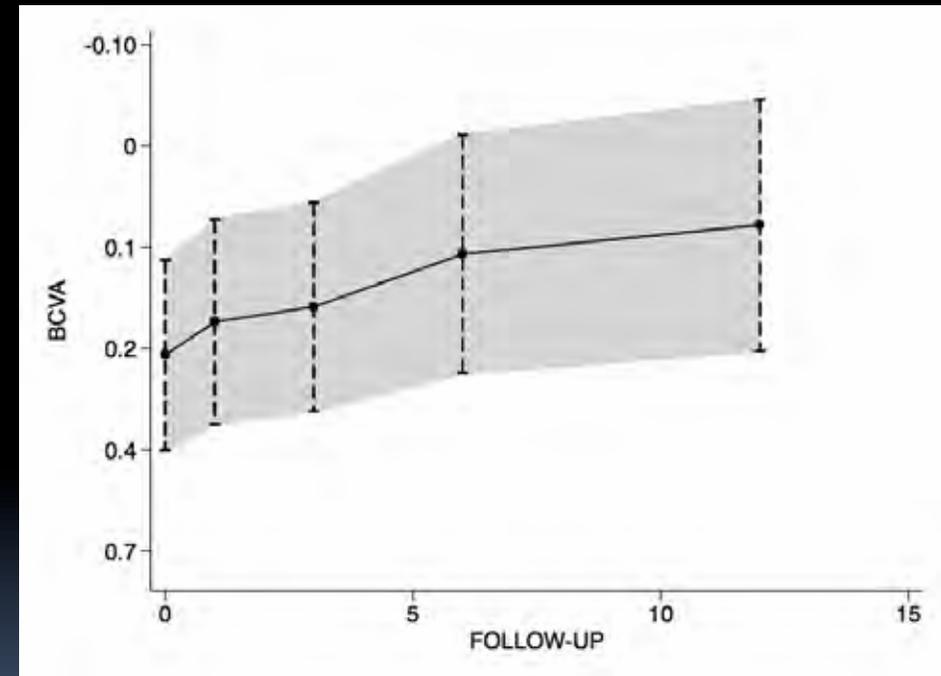


Parameters!!

	Baseline	1 month	3 months	6 months
CDVA	0.6(0.22)	0.61(0.22)	0.67(0.23) *	0.77(0.24) *
Sphere error	-2.1(2.03)	-1.95(2.13)	-2.1(2.6)	-1.8(3.3)
Cylinder	-3.07(1.44)	-3.3(1.46)	-3.32(1.58)	-3.5(1.77)
AK	58.5 (4.26)	59.03(3.4)	58.8(3.10)	58.1(4.1)
SAI	6.5(3.3) *	6.9(3.4)	6.77(3.10)	6.1(3.3)
SI	8.9(5.4)	9.02(5.4)	9.88(4.77)	9.6(5.4)
ECD. cell/mm ²	2436(132.32)	2497(224.8)	2549(172.1)	2401 (209.3)
ISV	100.3(33.1)	103.2(30.2)	99(29.4)	103.3(32.2)
IVA	1.02(0.38)	1.059(0.36)	1.02(0.35)	1.06(0.38)
KI	1.27(0.11)	14.7(42.6)	1.27(0.11)	1.29(0.13)
CKI	1.08(0.04)	1.08(0.04)	1.08(0.04)	1.08(0.04)
IHA	24.6(14.03)	26.6(29.8)	19.6(11.7)	22.5(16.6)
IHD	0.09(0.05)	0.1(0.04)	0.1(0.1)	0.1(0.04)
Rmin	5.8(0.63)	5.8(0.5)	5.8(0.6)	5.9(0.72)
Pachmin	444(42.1)	444(40.0)	447(45.3)	452(40.1)
HOA	1.07(0.53)	1.1(0.49)	1.1(0.45)	0.9(0.39)
Coma	2.2(1.11)	2.33(1.01)	2.35(0.81)	1.91(0.88)
Absph	0.349(0.448)	0.40(0.54)	0.41(0.43)	0.34(0.48)

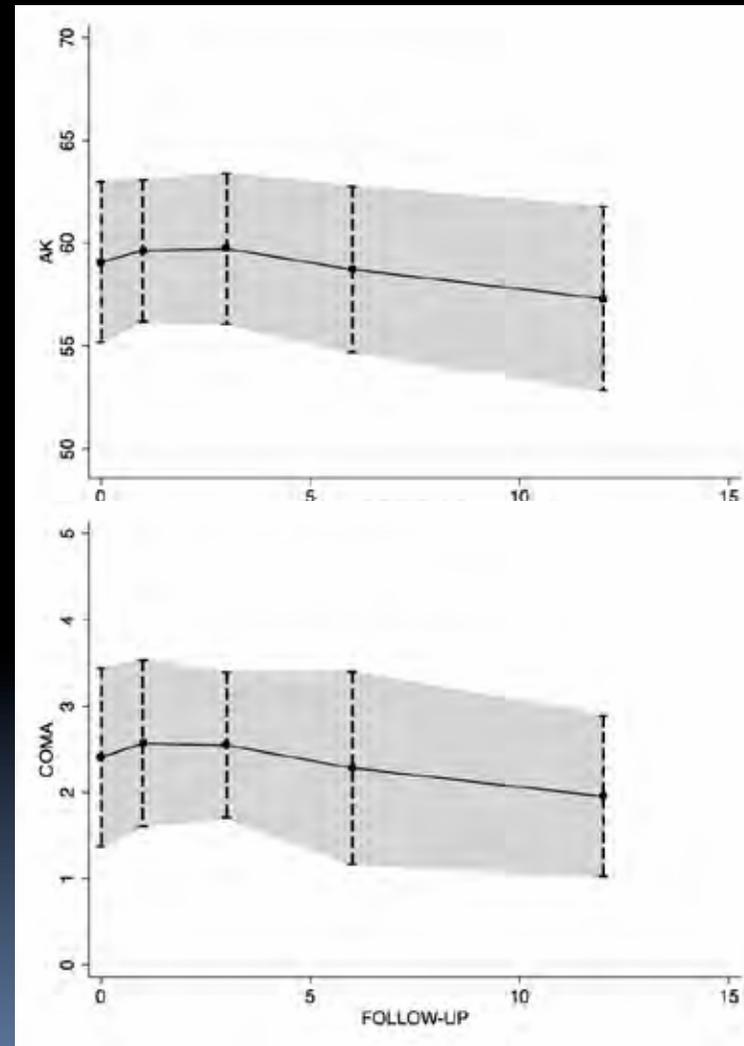
Results

- Significant improvement of BCVA at 3, 6 and 12 months of follow up
- reduction of HOA, AK.



Risultati

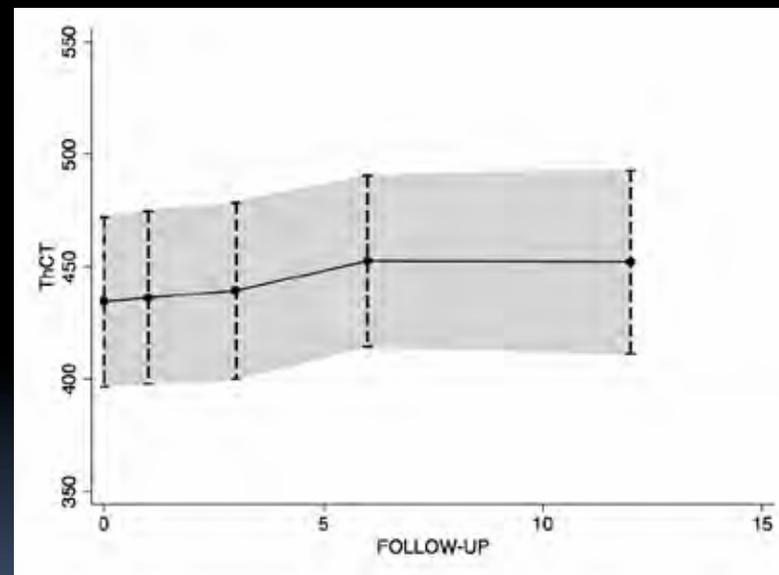
- Reduction of HOA and AK.



Numbers

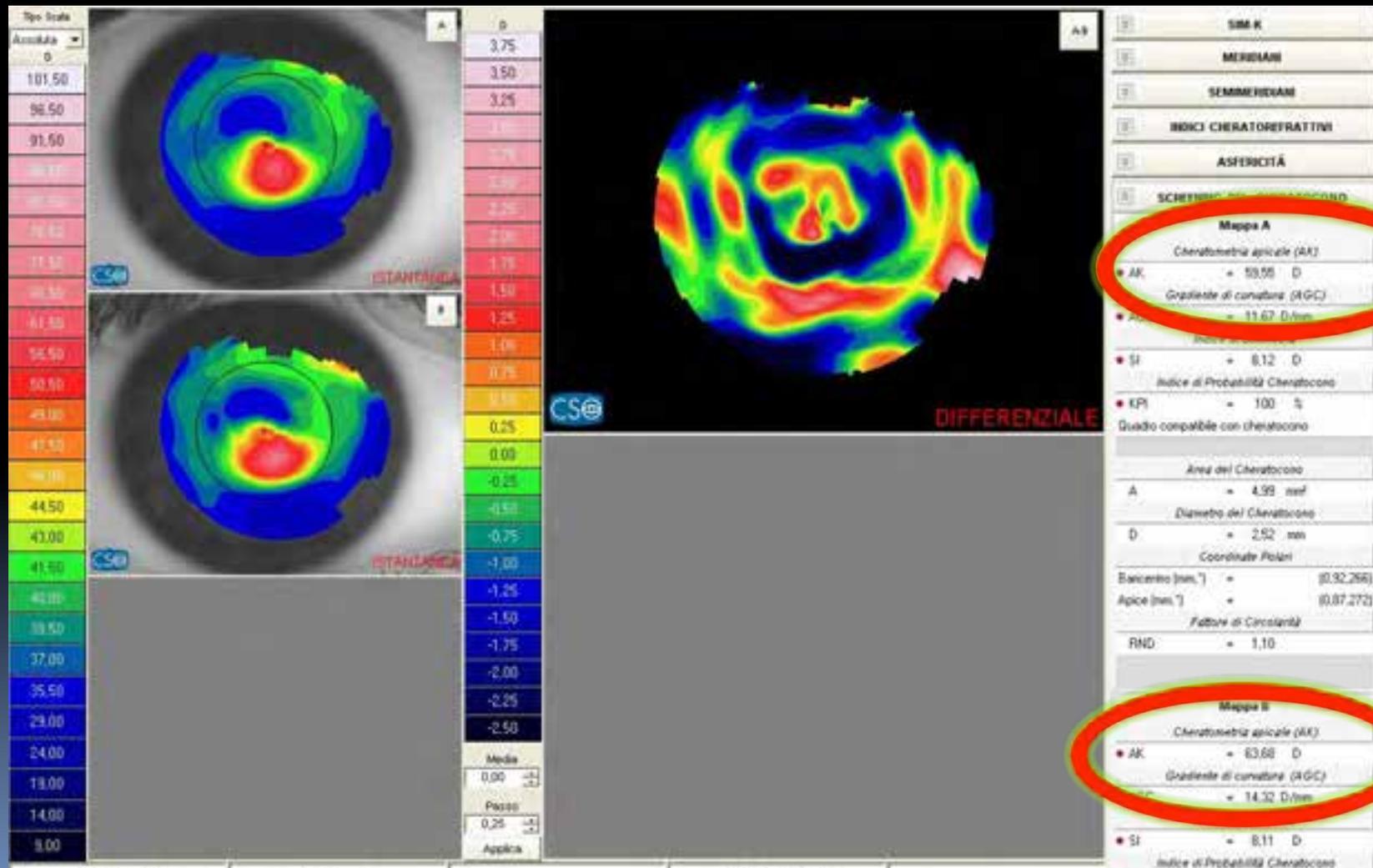
Pachimetria

- Stable pachymetry
- Endothelial cell count stable



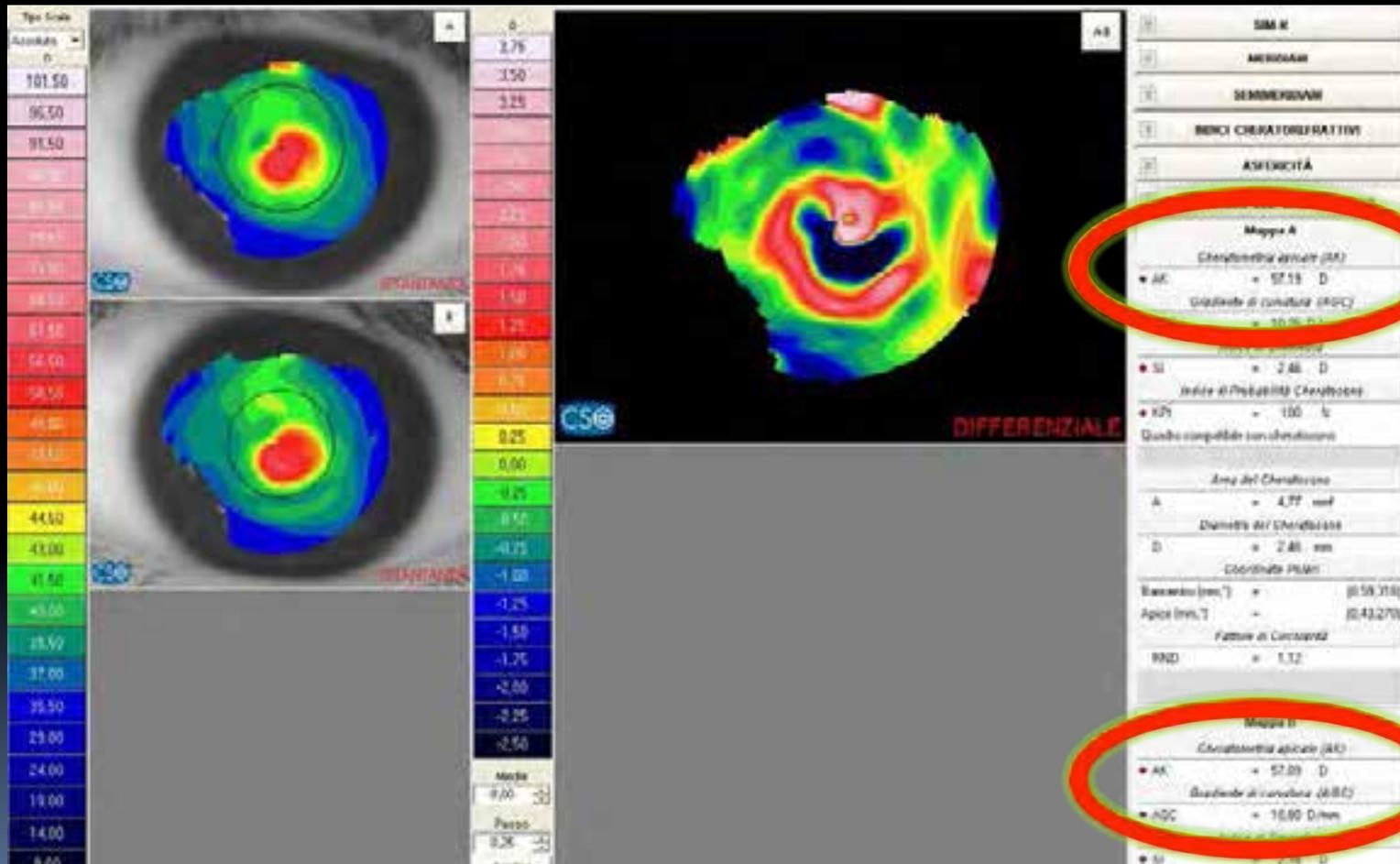
Patients are not only numbers...

RB



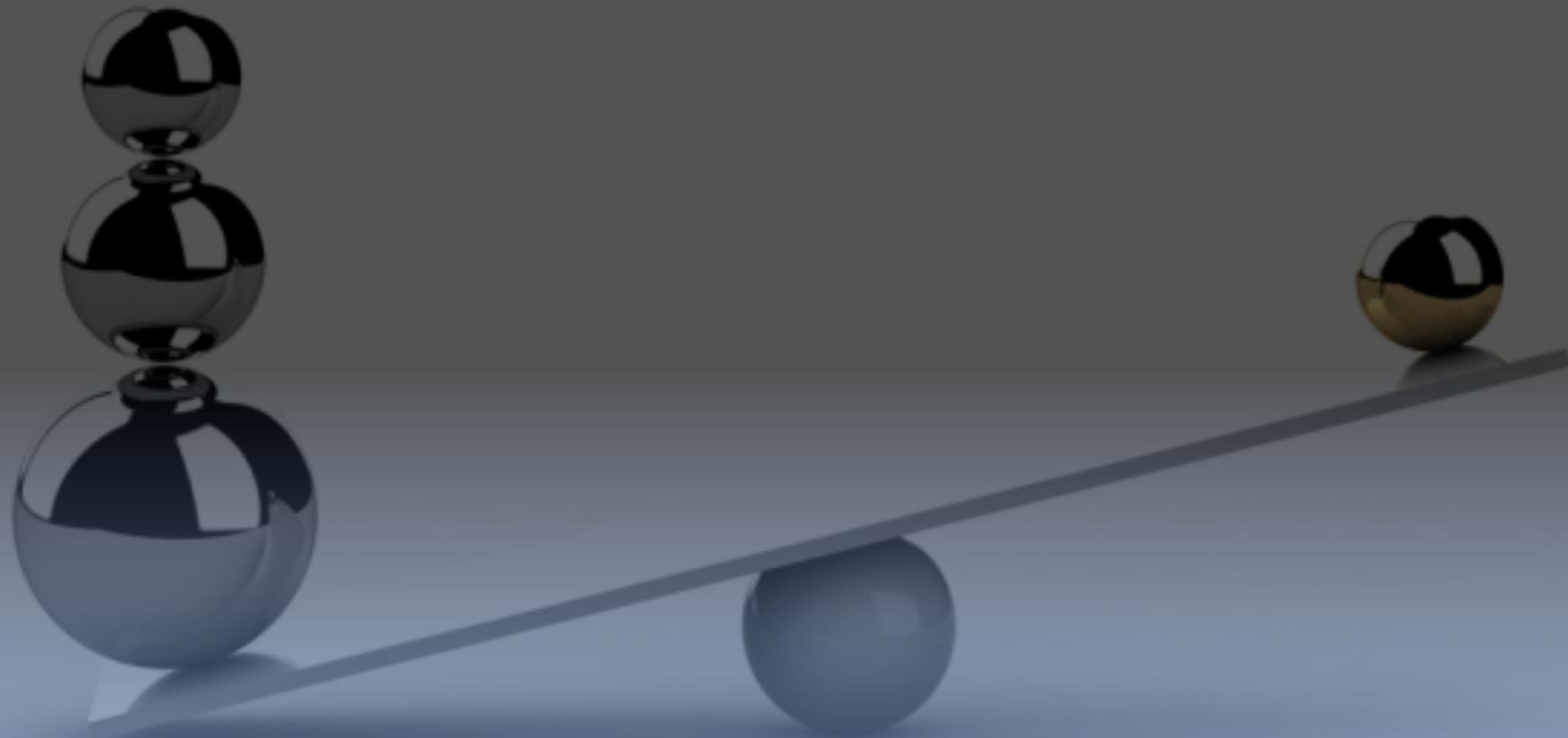
Patients

GF



WHAT'S NEW?

**COMPARISON WITH STANDARD
EPI-OFF**



Transepithelial Iontophoresis Versus Standard Corneal Collagen Cross-linking: 1-Year Results of a Prospective Clinical Study

Paolo Vinciguerra, MD; Vito Romano, MD; Pietro Rosetta, MD; Emanuela F. Legrottaglie, MD; Raffaele Piscopo, MD; Claudia Fabiani, MD; Claudio Azzolini, MD; Riccardo Vinciguerra, MD

ABSTRACT

PURPOSE: To compare 1-year transepithelial corneal collagen cross-linking with iontophoresis (I-CXL) outcomes with standard CXL (S-CXL) epithelium-off for progressive keratoconus.

METHODS: Forty eyes of 40 patients with progressive keratoconus were included in this comparative, prospective clinical study. Corrected distance visual acuity (CDVA), spherical equivalent, cylinder refraction, corneal topography, Scheimpflug tomography, aberrometry, and endothelial cell count were assessed at baseline and at 1, 3, 6, and 12 months of follow-up.

RESULTS: Patients received either I-CXL (20 eyes) or S-CXL (20 eyes). Functional parameters (visual acuity and aberrometry) showed a significant improvement ($P < .05$) after 6 and 12 months of follow-up in both groups. In the I-CXL group, the CDVA showed a rapid recovery of vision after 3 months ($P = .01$). AQ1 Morphological parameters showed a significant reduction of maximum keratometry in the S-CXL group by -1.05 ± 1.51 D after 12 months, whereas the I-CXL group curvature was stable (-0.31 ± 1.87 D). Minimum pachymetry values were stable even after 12 months of follow-up in the I-CXL group, whereas a significant corneal thinning 12 months following treatment was recorded in the S-CXL group ($P < .001$). None of the patients had continuous progression of keratoconus or had to repeat CXL procedures. Endothelial cell counts did not change significantly ($P > .05$).

CONCLUSIONS: The 1-year outcomes suggest that I-CXL might be comparable to S-CXL in stabilizing the progression of the degenerative ectatic disease. Additionally, quicker improvement of functional parameters was reported in the I-CXL group.

[J Refract Surg. 201X;(X(X)):XX-XX.]

Corneal collagen cross-linking (CXL) is currently the only treatment able to slow or halt the progression of ectatic disease.¹⁻⁴ Long-term follow-up studies on CXL refer to the standard technique (S-CXL), which entails epithelial debridement to allow riboflavin (hydrophilic) penetration in the corneal stroma; otherwise the corneal epithelium (lipophilic) reduces its permeability.⁵ Nevertheless, epithelial removal causes postoperative pain,⁶ delayed visual recovery,^{1,7,8} and increased risks of infection. Transepithelial cross-linking (TE-CXL) was introduced to avoid these threats. The original dextran-containing solutions have been reported to be ineffective for TE-CXL,⁹⁻¹¹ but other formulations of riboflavin (with chemical enhancers)¹² showed equivocal results in clinical studies.¹³⁻¹⁵ Conversely, preliminary results have shown that transepithelial cross-linking with iontophoresis (I-CXL) is able to increase the riboflavin concentration inside the stroma compared to other TE-CXL techniques together with histological changes.¹⁶⁻¹⁸ Pilot clinical findings using I-CXL have also reported encouraging results.¹⁹ In this study, we compared 1-year results of two groups of patients with keratoconus who were treated with I-CXL and S-CXL (epithelium-off Dresden protocol).

From Humanitas Clinical and Research Center, Milan, Italy (PV, PR, EFL, RP, CF); Humanitas University, Rozzano, Milan, Italy (PV); the Department of Corneal and External Eye Diseases, St. Paul's Eye Unit; Royal Liverpool University Hospital, Liverpool, United Kingdom (VR); and the Department of Surgical Sciences, Division of Ophthalmology, University of Insubria, Varese, Italy (CA, RV).

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Dr. Paolo Vinciguerra is a consultant for Nidek and Oculus Optikgeräte, GmbH. The remaining authors have no financial or proprietary interest in the materials presented herein.

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Aim

- To compare 1-year transepithelial corneal collagen cross-linking with iontophoresis (I-CXL) outcomes with standard CXL (S-CXL) epithelium-off for progressive keratoconus.

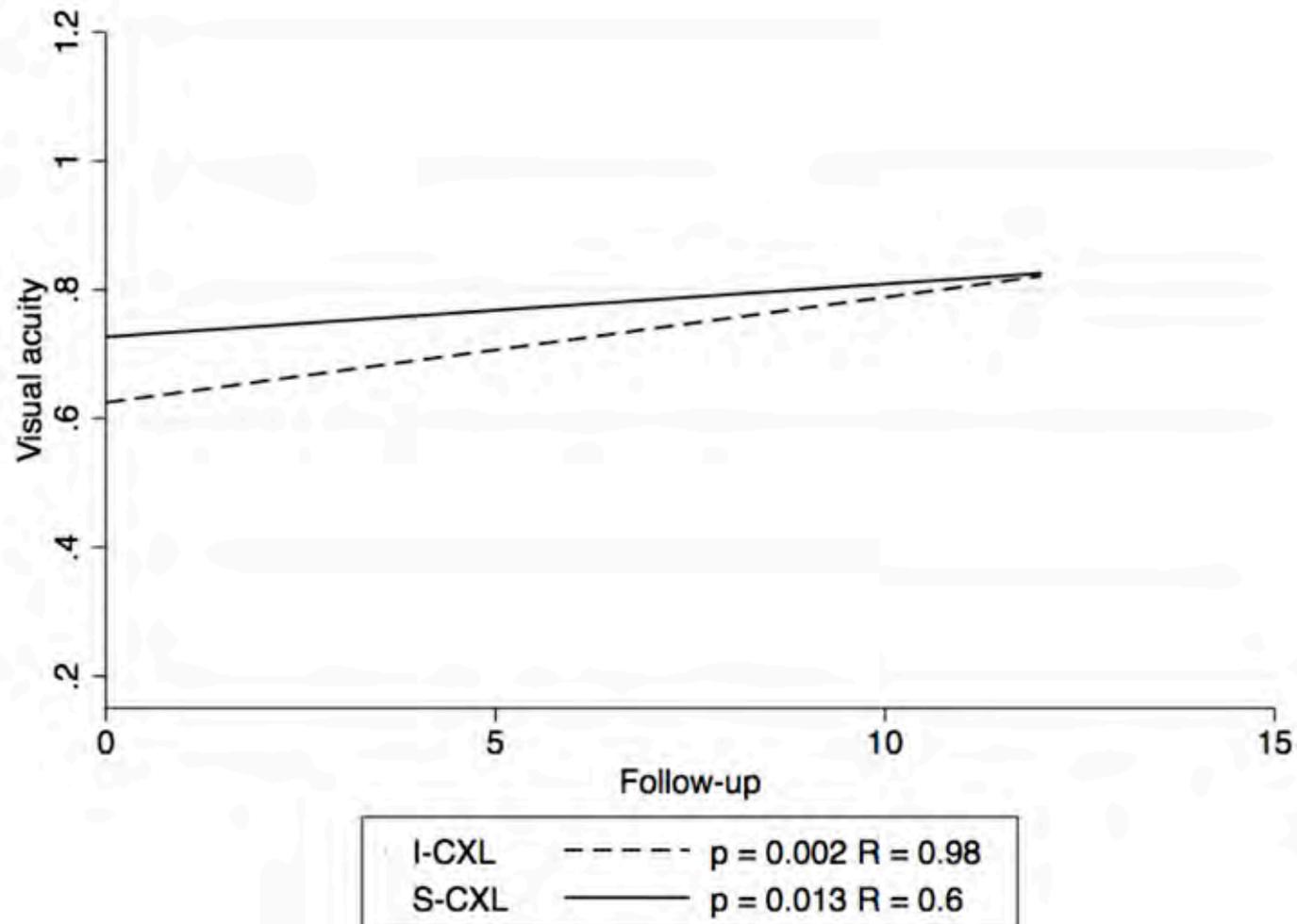
Study design

- Prospective comparative
 - 20 eyes of 20 patients Ionto (I-CXL)
 - 20 eyes of 20 patients Stadard 3 mW (S-CXL)
- 12 months of follow up
- Corrected distance visual acuity (CDVA), spherical equivalent, cylinder refraction, corneal topography, Scheimpflug tomography, aberrometry, and endothelial cell count were assessed.

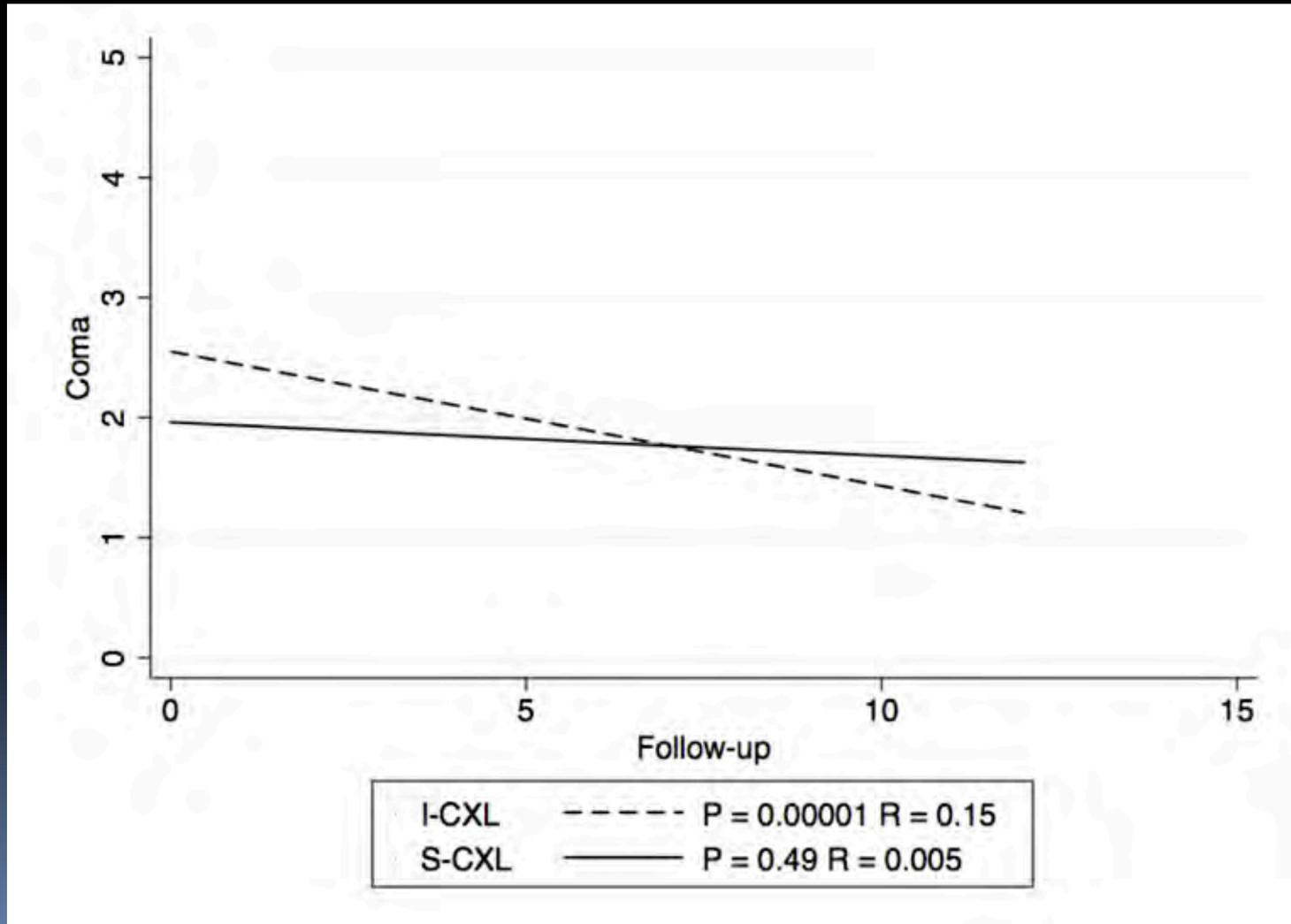
Results

- BCVA
 - I-CXL e S-CXL were comparable, both inducing a significant increase in BCVA
 - I-CXL induces a faster recovery (already at month 3)
- HOA
 - I-CXL is able to significantly reduce HOA and Coma (month 6 and 12)
 - S-CXL group showed an improvement only in coma after 6 and 12 months

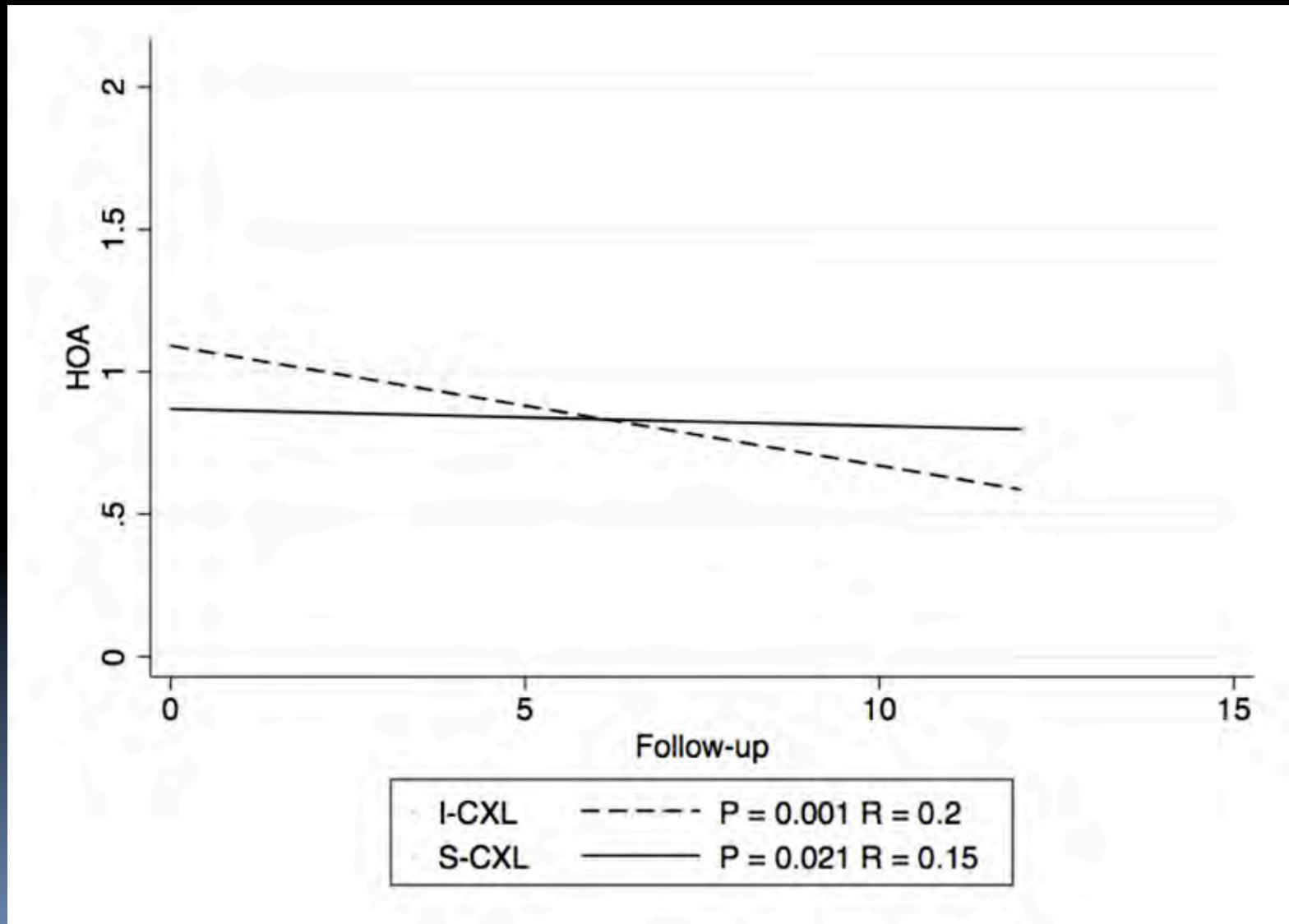
Visual acuity linear regression



Coma linear regression



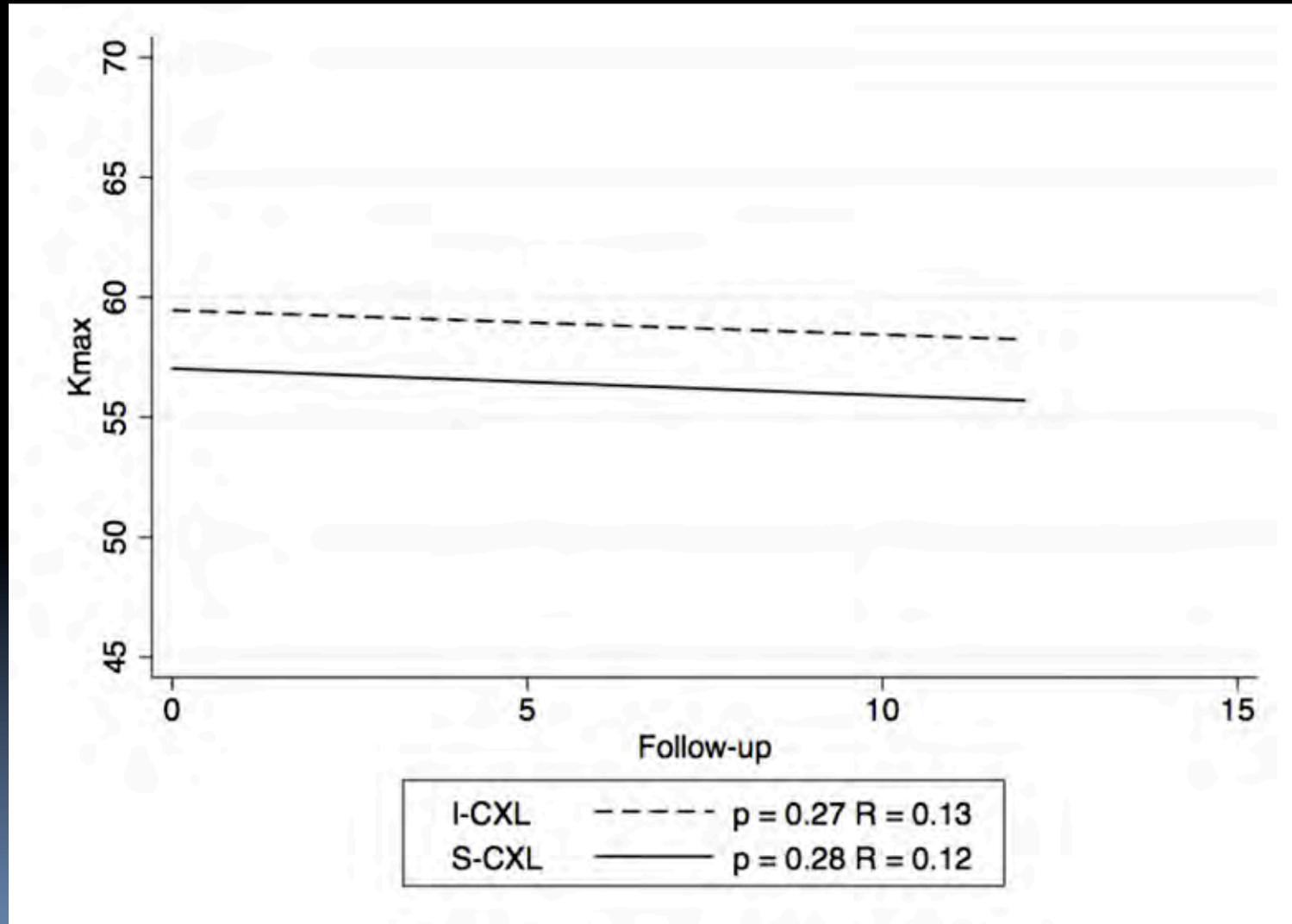
HOA linear regression



Results

- Kmax
 - S-CXL induced a significant improvement of numerous topographic indices during the follow-up (such as CKI)
 - Kmax was reduced significantly by -1.05 ± 1.51 D after 12 months after S-CXL.
 - I-CXL only showed a significant improvement of corneal symmetry index after 12 months of follow-up.
 - The reduction of -0.31 ± 1.87 of Kmax did not reach statistical significance in I-CXL group.

However, linear regression analysis for Kmax was not significant in either group



Results

- Pachymetry
 - The main result of this analysis is that there is a statistically significant thinning of the minimum corneal thickness in the S-CXL group ($P = .0001$), whereas this did not occur after I-CXL.
 - Even after 12 months of follow-up; this difference was statistically significant

Discussion

- These results highlight the clinical efficacy of I-CXL to overcome the problems of TE-CXL: the penetration of riboflavin through the epithelium.
- It is known from preclinical reports that the biomechanical effect, riboflavin penetration, and distribution of I-CXL are higher than in TE-CXL but lower when compared to S-CXL.
- We will continue the follow-up of the patients to determine whether this stiffening effect, even if reduced, will be enough to halt the ectatic disease in the long term.

Conclusions

- At 12 months follow up
 - I-CXL is not inferior to S-CXL
 - Faster recovery of BCVA
 - More reduction of HOA and Coma
 - Does not induce thinning
- Only 12 months! Follow up continues!

Conclusions

- Iontophoresis is a safe technique
- It appears effective in arresting the progression of the disease
- Significant improvements of functional parameters
- Reduction of pain