“ Magna Graecia ” University, Catanzaro, Italy
Ophthalmology Department

Intraop in-vivo OCT Pachymetric Mapping during epi-off pulsed Accellerated High Fluence Corneal Collagen Cross-Linking with dextran free Riboflavin

Miguel Rechichi MD, PHD

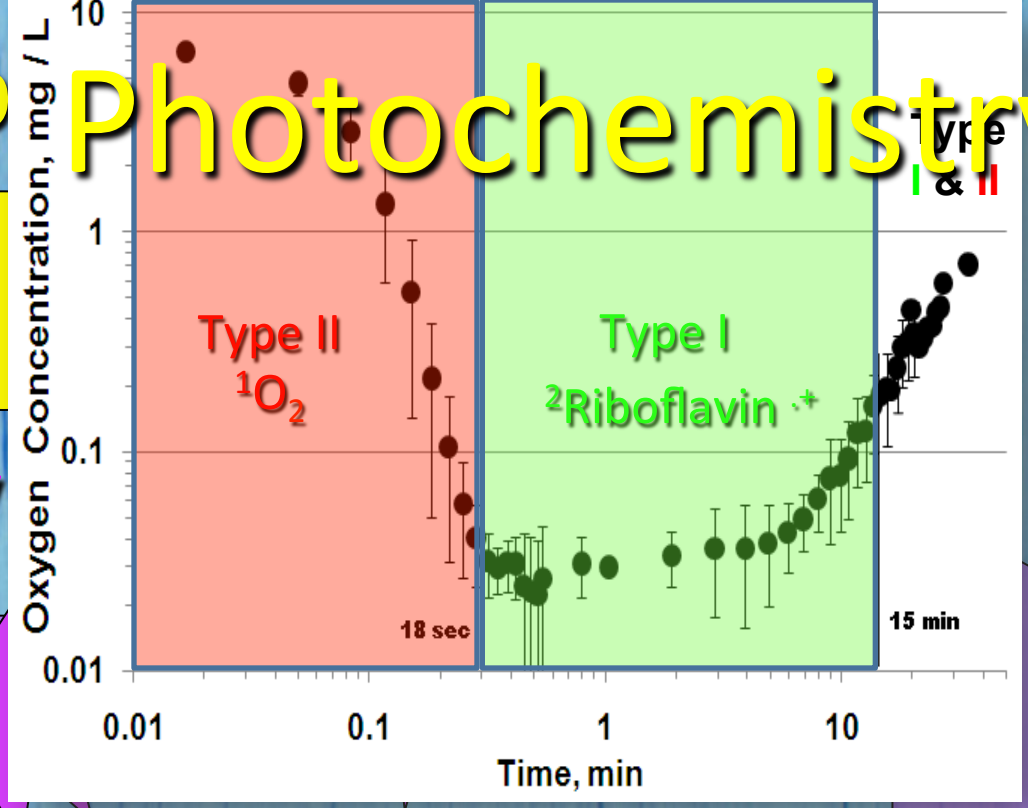
Track 6: Research Trends in Surgical & Medical Ophthalmology

OMICS Group Conferences
Accelerating Scientific Discovery

4th International Conference on
Clinical & Experimental Ophthalmology
July 14-16, 2014 DoubleTree by Hilton Baltimore-BWI Airport, USA

Miguel Rechichi MD, PhD

Rib Photochemistry



UV

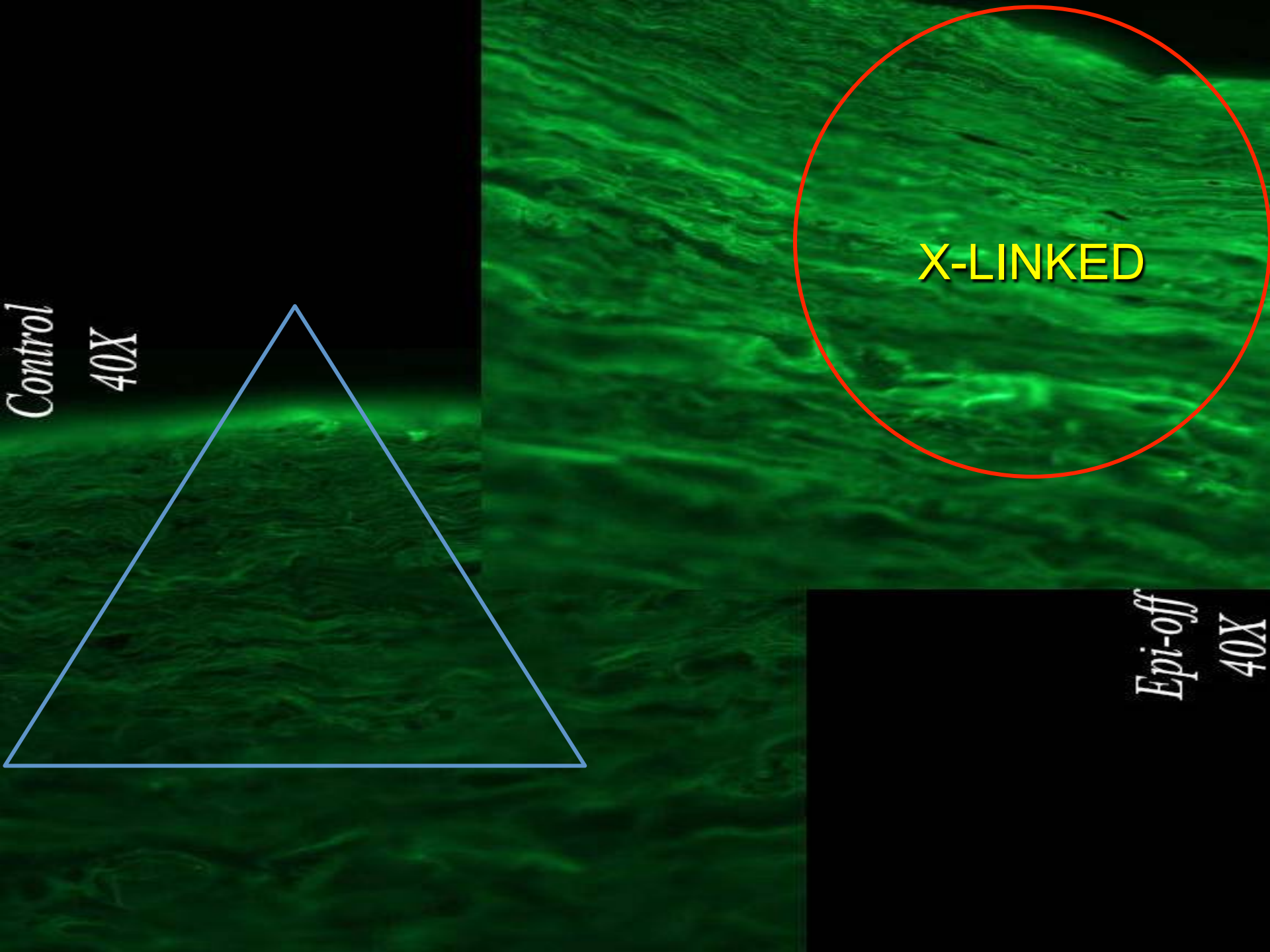
Combination

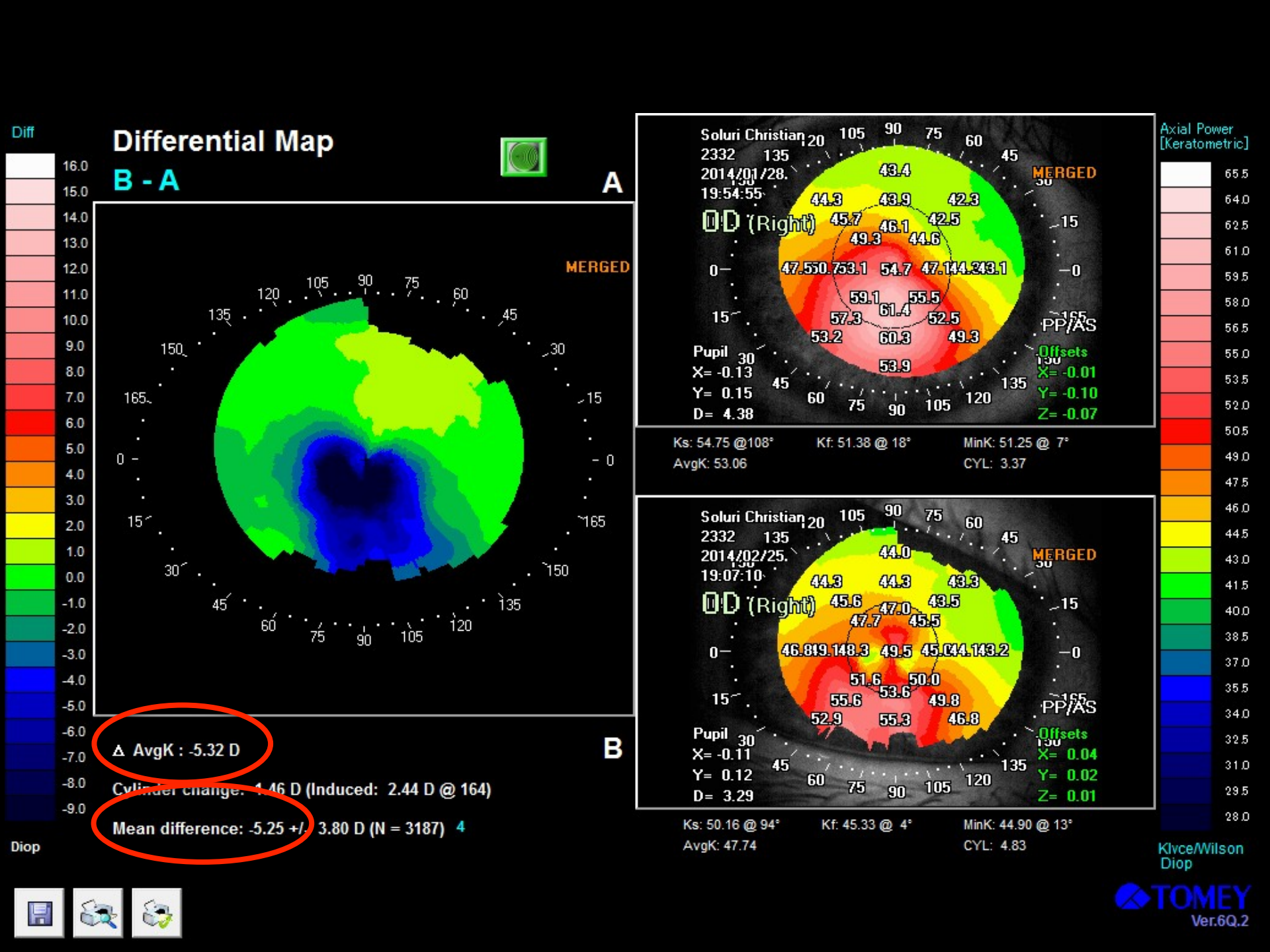
O* O* O*

10%

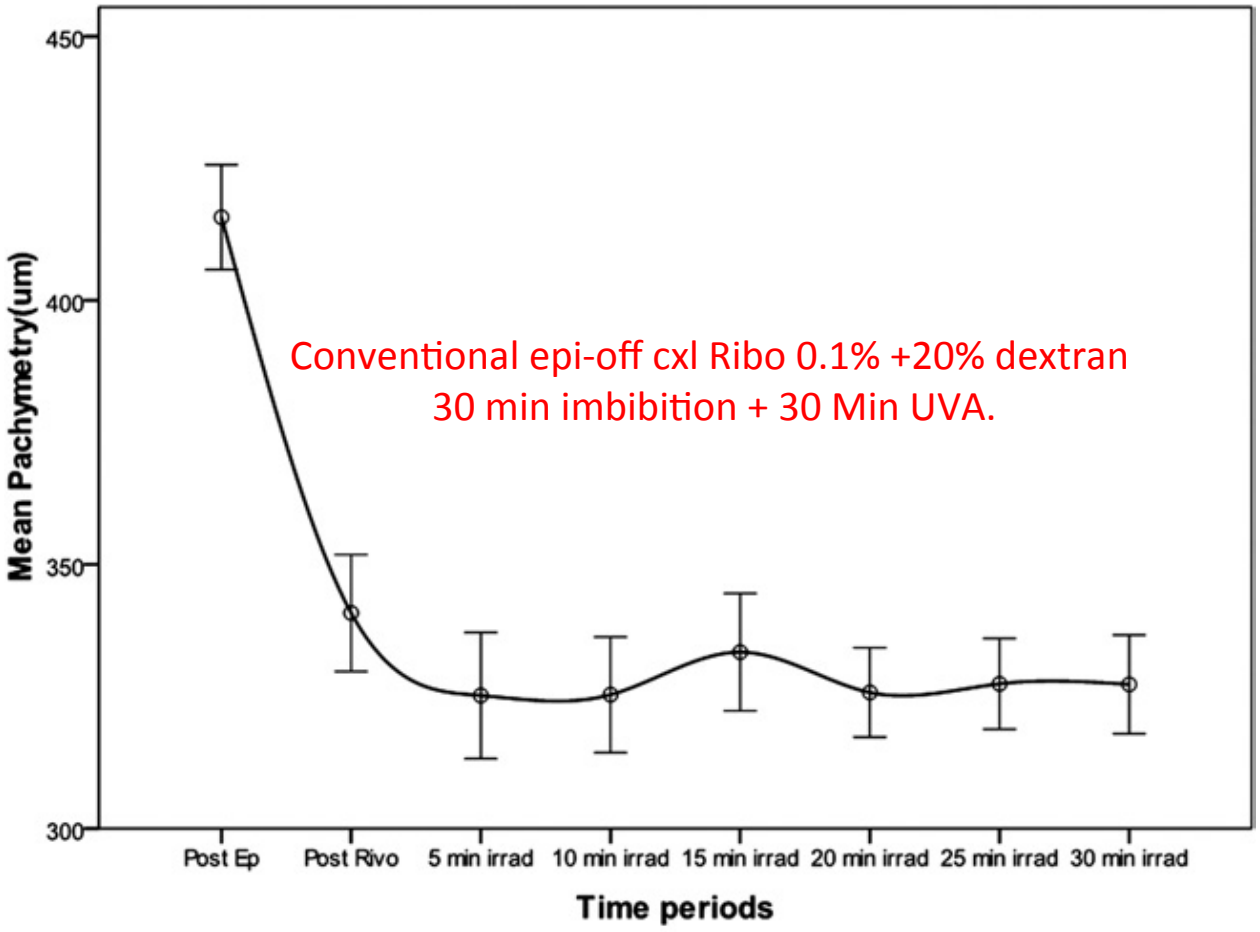
RF* RF* RF*

90%


X-LINKED
Control
40X
Epi-off
40X

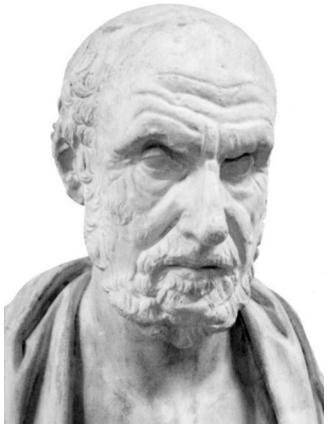

Diff
Differential Map
B - A
A
MERGED
B
Δ AvgK : -5.32 D
Cylinder change: 1.46 D (Induced: 2.44 D @ 164)
Mean difference: -5.25 +/- 3.80 D (N = 3187) 4
Diop
Soluri Christian
2332
2014/01/28.
19:54:55
OD (Right)
MERGED
PP/AS
Pupil
X= -0.13
Y= 0.15
D= 4.38
Offsets
X= -0.01
Y= -0.10
Z= -0.07
Ks: 54.75 @108°
Kf: 51.38 @ 18°
MinK: 51.25 @ 7°
AvgK: 53.06
CYL: 3.37
Soluri Christian
2332
2014/02/25.
19:07:10
OD (Right)
MERGED
PP/AS
Pupil
X= -0.11
Y= 0.12
D= 3.29
Offsets
X= 0.04
Y= 0.02
Z= 0.01
Ks: 50.16 @ 94°
Kf: 45.33 @ 4°
MinK: 44.90 @ 13°
AvgK: 47.74
CYL: 4.83
Axial Power
[Keratometric]
Klvce/Wilson
Diop
TOMEY
Ver.6Q.2

Why intraoperative pachymetry MUST be part of our conventional CXL procedure???



Kymionis GD, Kounis GA, et al. Intraoperative pachymetric measurements during corneal collagen cross-linking with riboflavin and ultraviolet A irradiation.Ophthalmology. 2009 Dec;116(12):2336-9.

Advice from the past…

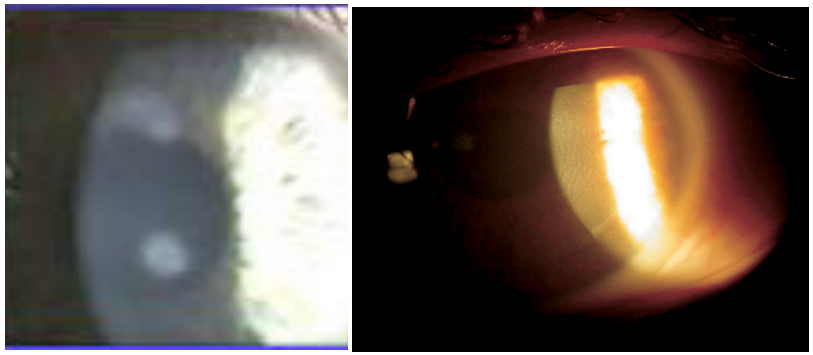


Hippocrates
460-360 BC

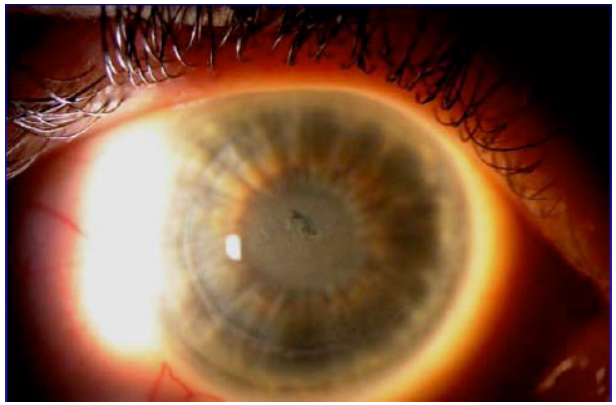
First, do not harm !!!

Epi-off CXL complication...

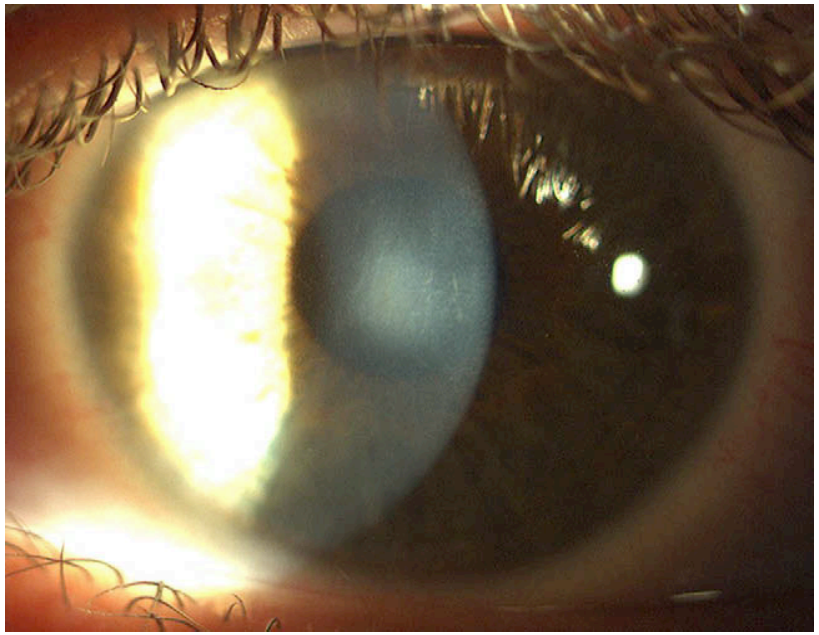
(Dextran 20% riboflavin)



Nummular or lamellar keratitis

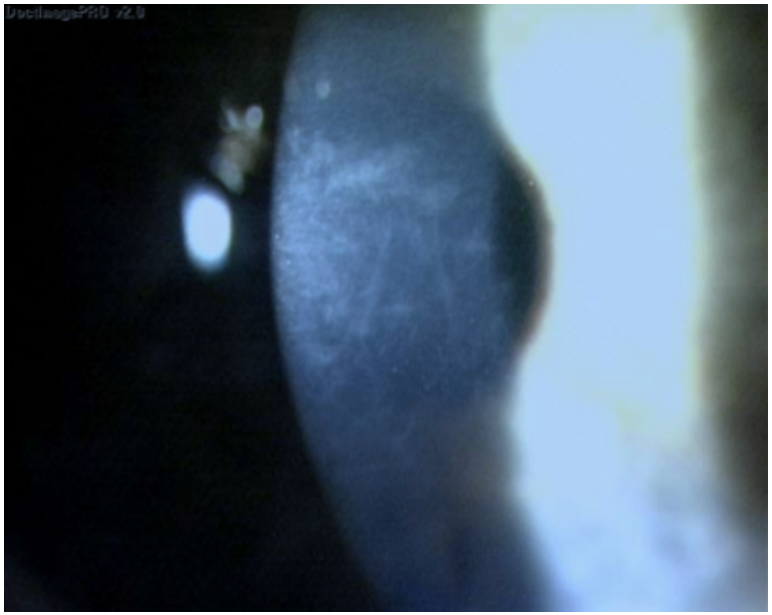


Corneal edema

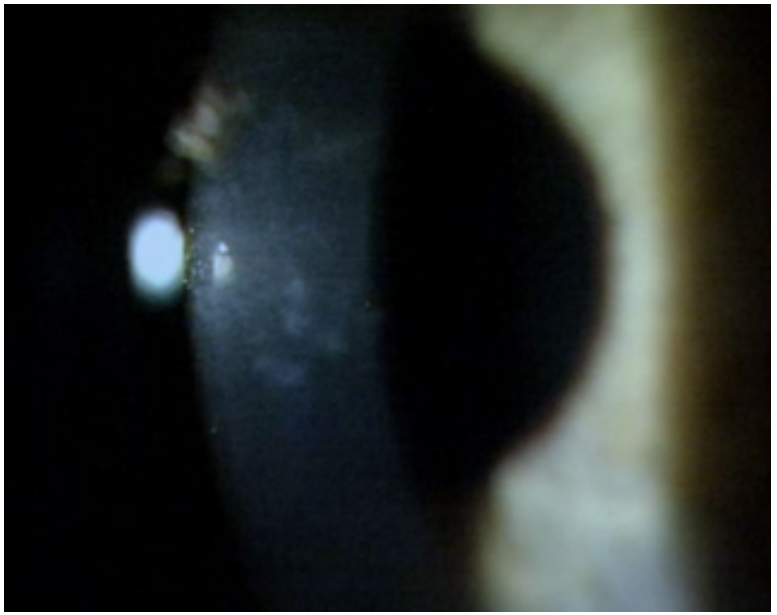


Stromal scar

Early onset Haze after CXL



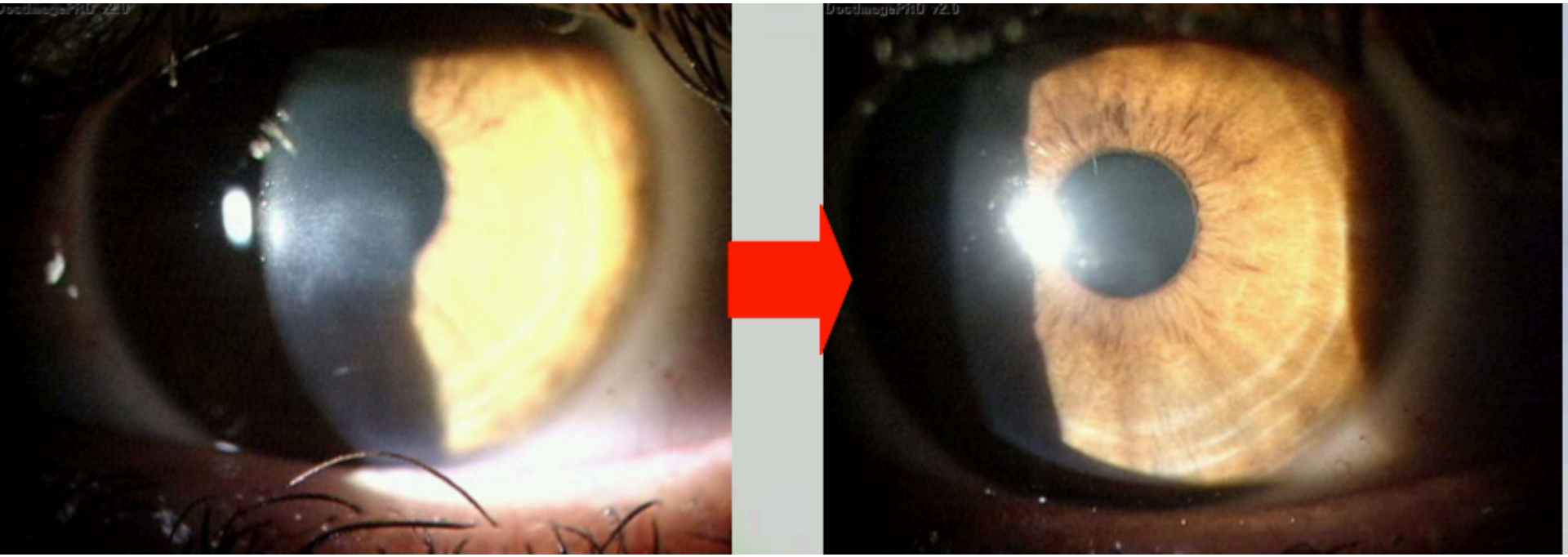
30 days postop



3 months postop

Eyes usually improve
after steroid
treatment !!!

Late onset Haze after CXL



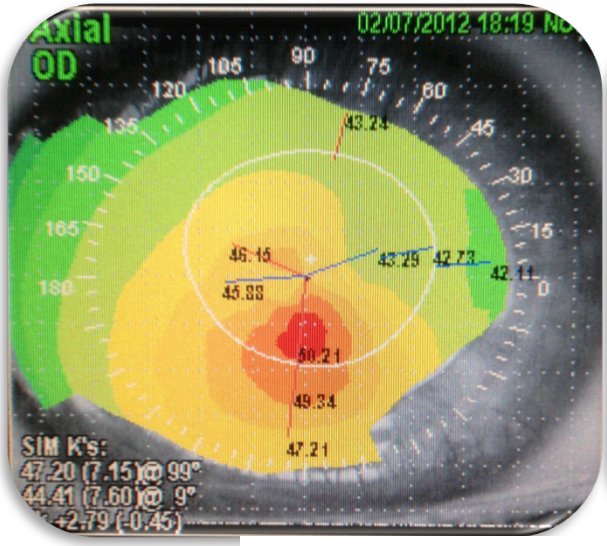
2 months postop

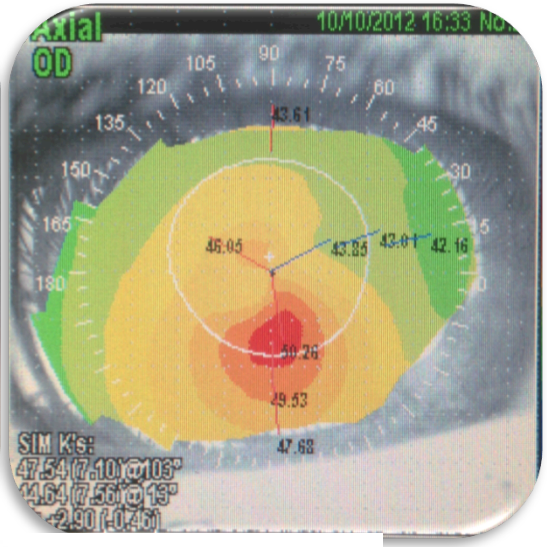
5 months postop

Eyes usually improve
after steroid
treatment !!!

A tale of… old epi-off CXL

Female, 33 ys, previous uneventful epi-off cxl in in LE

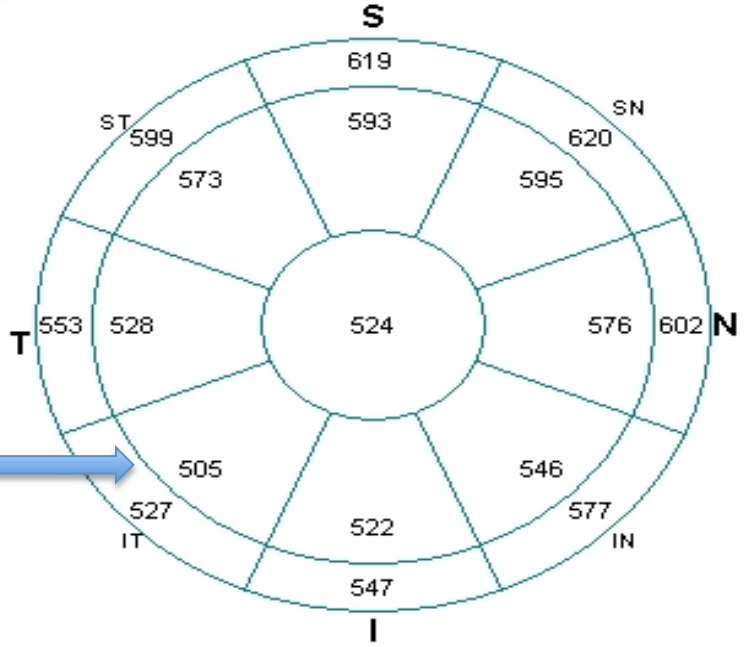


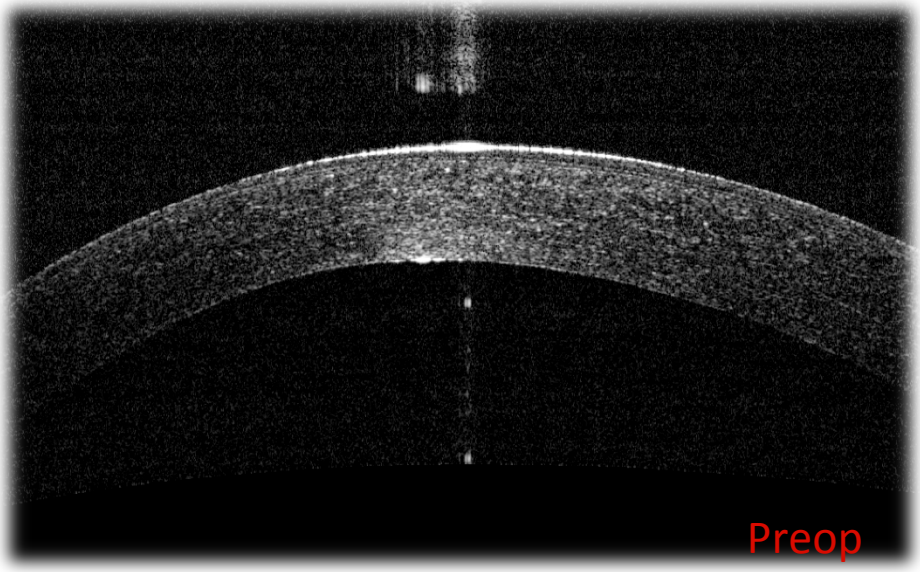


Progressive KC in fellow eye (+0.8 D in 2 months)
CSVA= 0.7

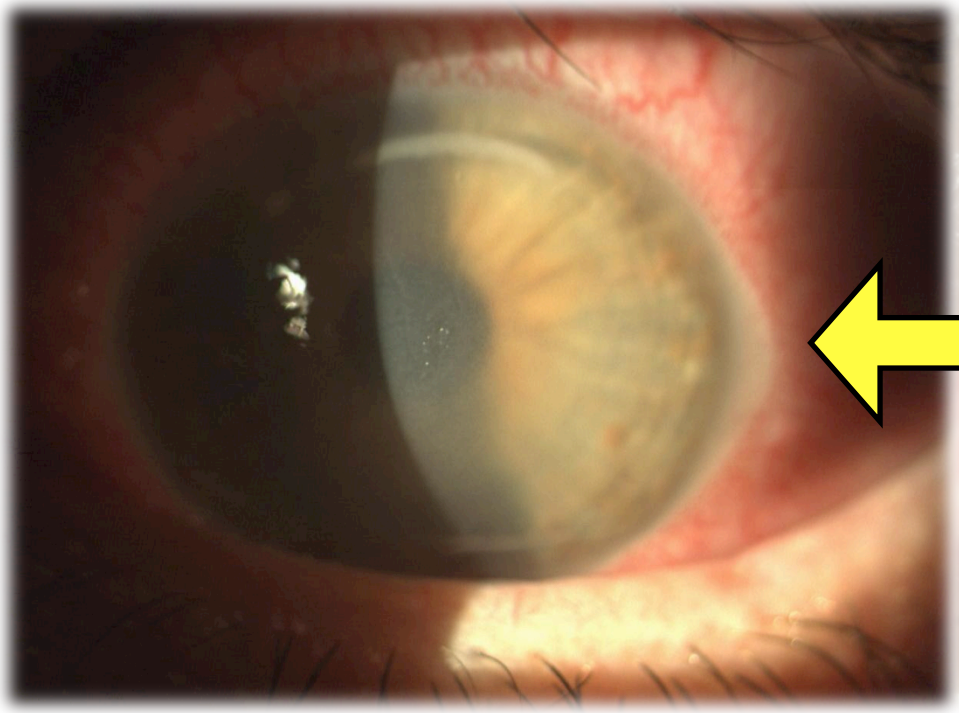
Considering thinnest point > 500 μ

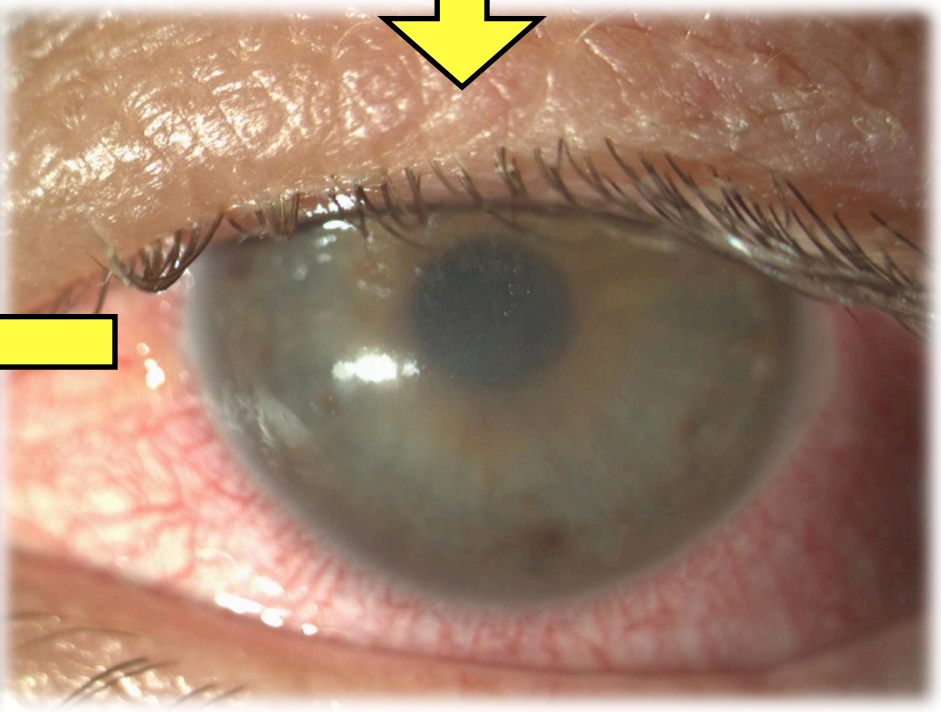
CXL Epi-off was performed with ribo 0.1% + dextran 20% with dextran 30min

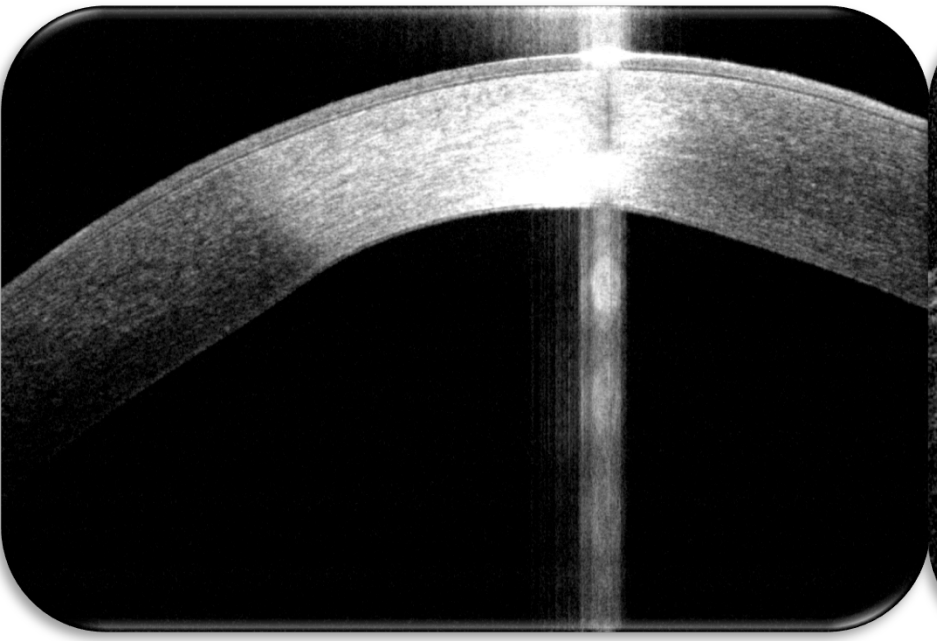


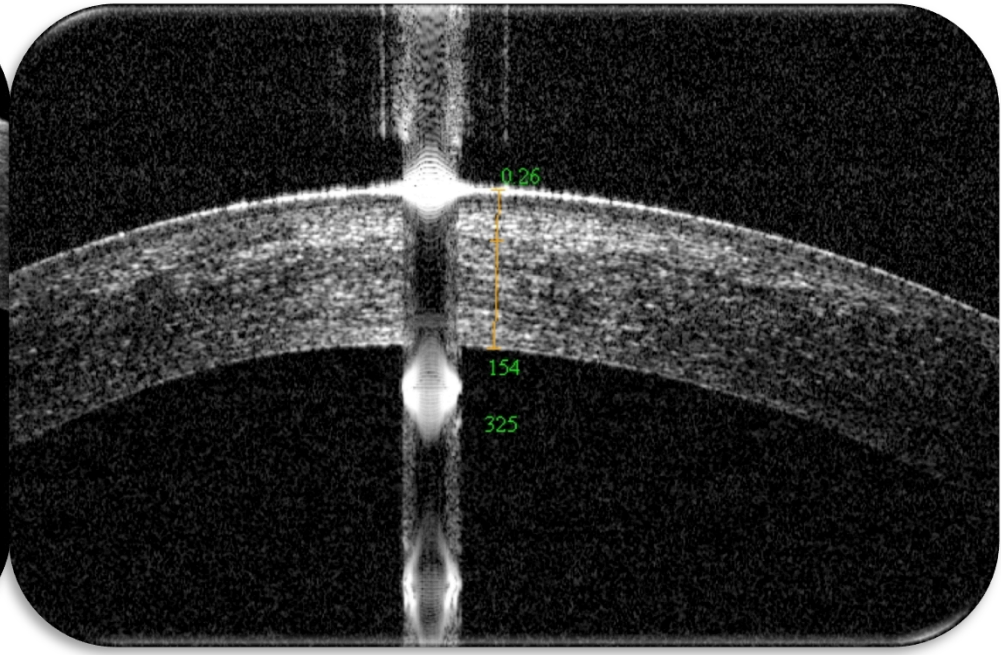


Steroid eyedrops 5 timeday !!!

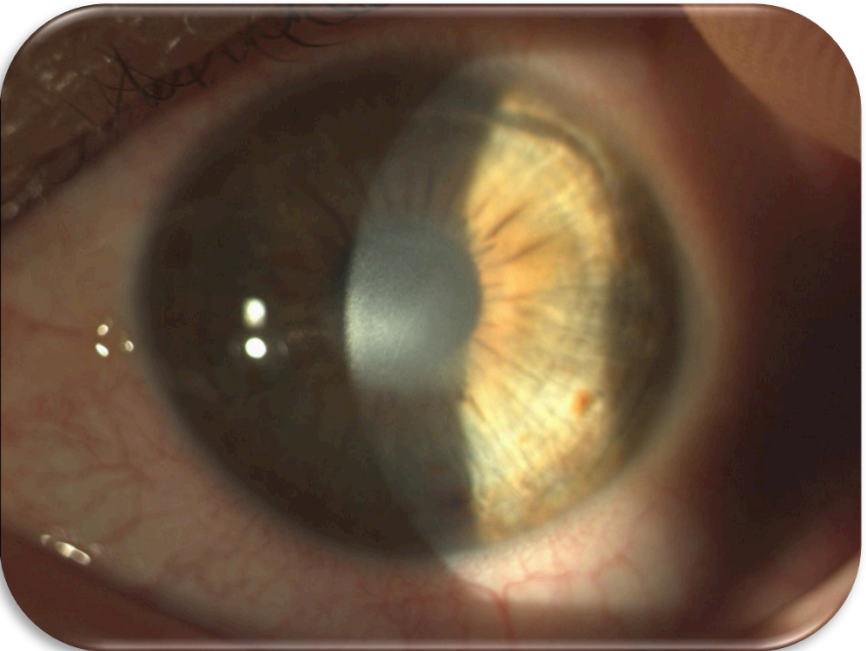


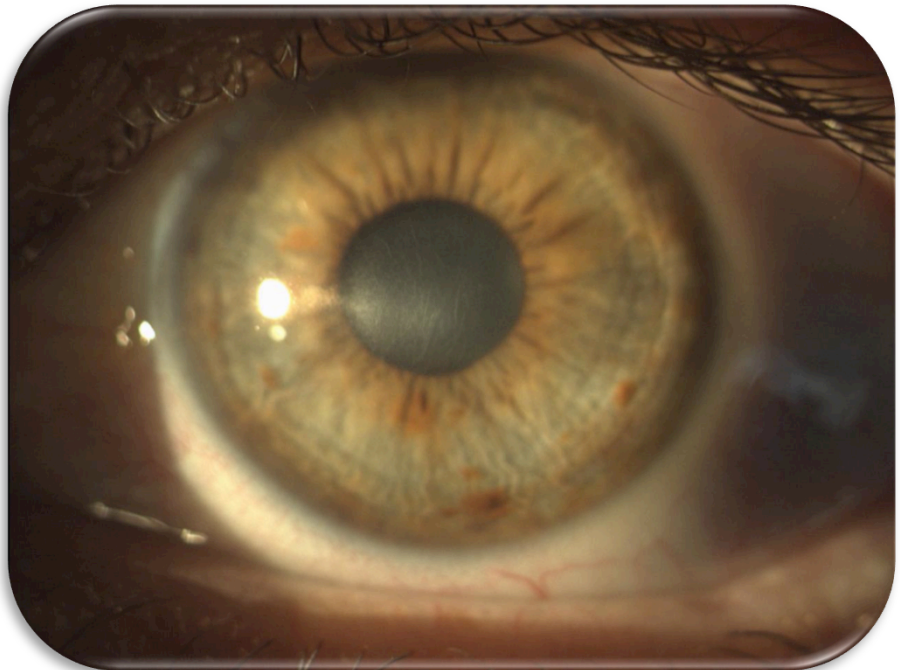






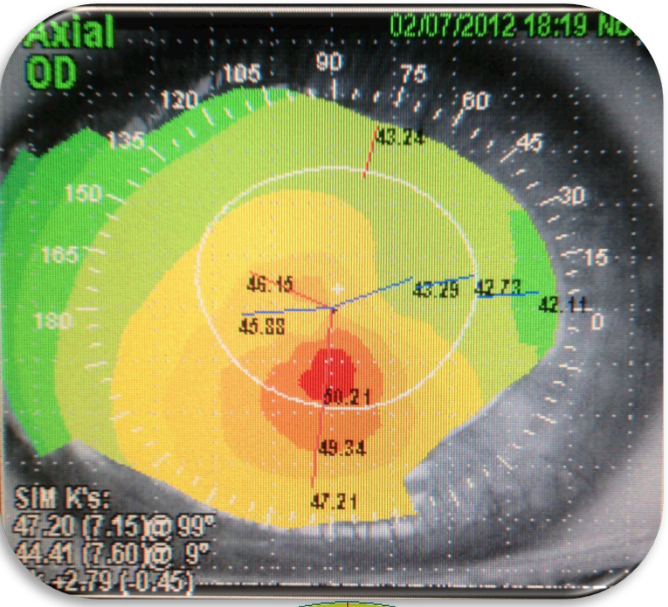
20 days postop… ⇨ Steroid eyedrops tapering… ⇨ 8 Months postop…

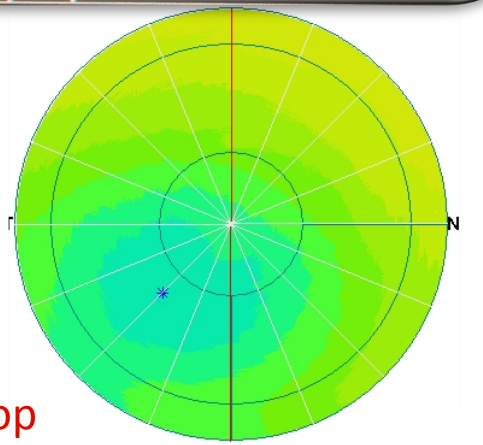




Avoidable complication???

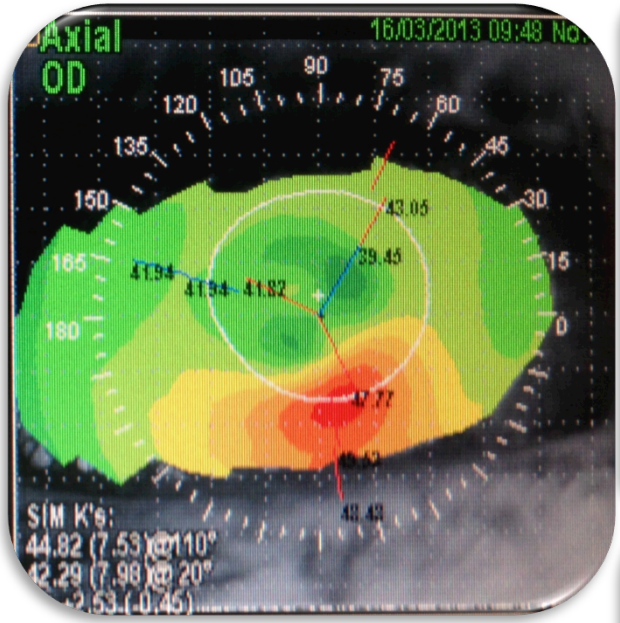
Preop CSVA 0.7
-1.25<> -1.75 (180)

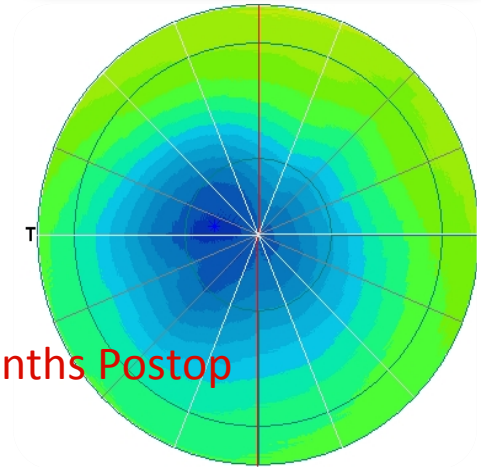




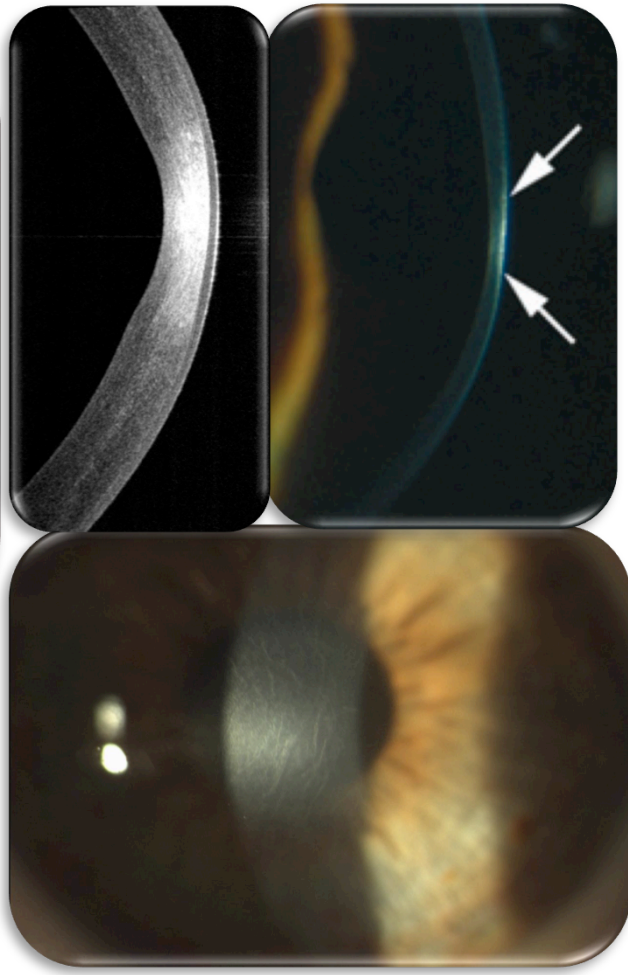
Preop

8 M PostopCSVA 0.6
Cyl +1.75 (130)

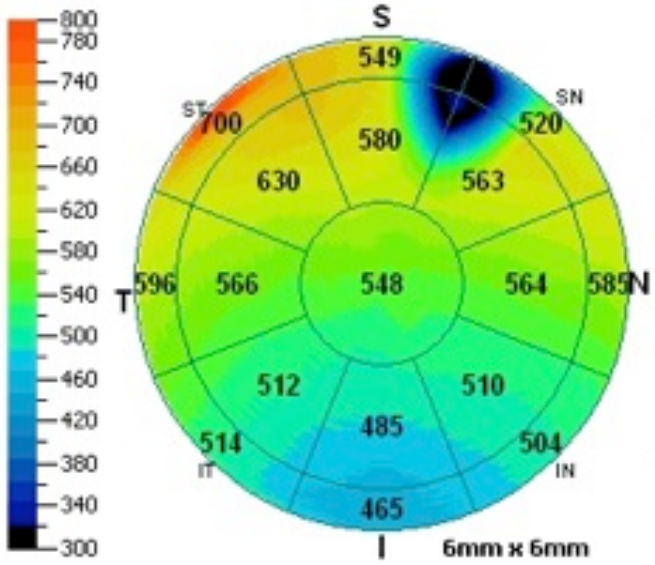


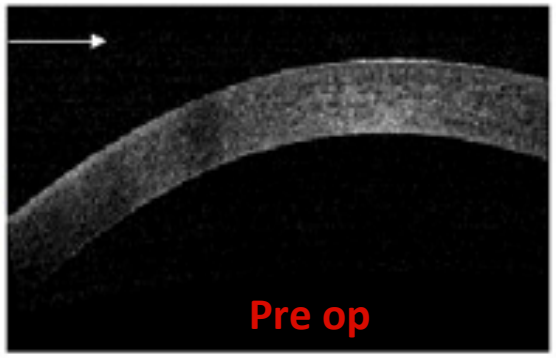


8 months Postop

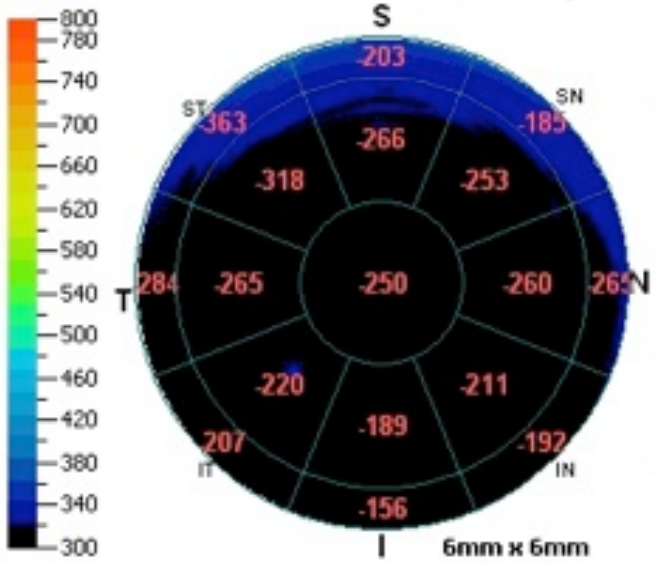


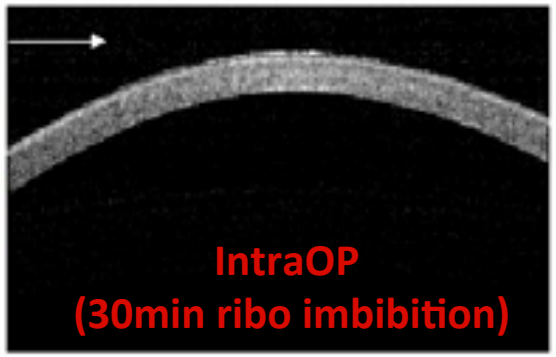
8 months Postop





30 min imb
+
30 min UVA 3MW





Uncooperative patient

Frequent recentering

Procedure > 60 min

…probably if I had changed protocol
looking at intraop pachymetric mapping !!!

CXL in Thin Corneas

Soaking the cornea in a hypoosmolar riboflavin solution increases central corneal thickness.

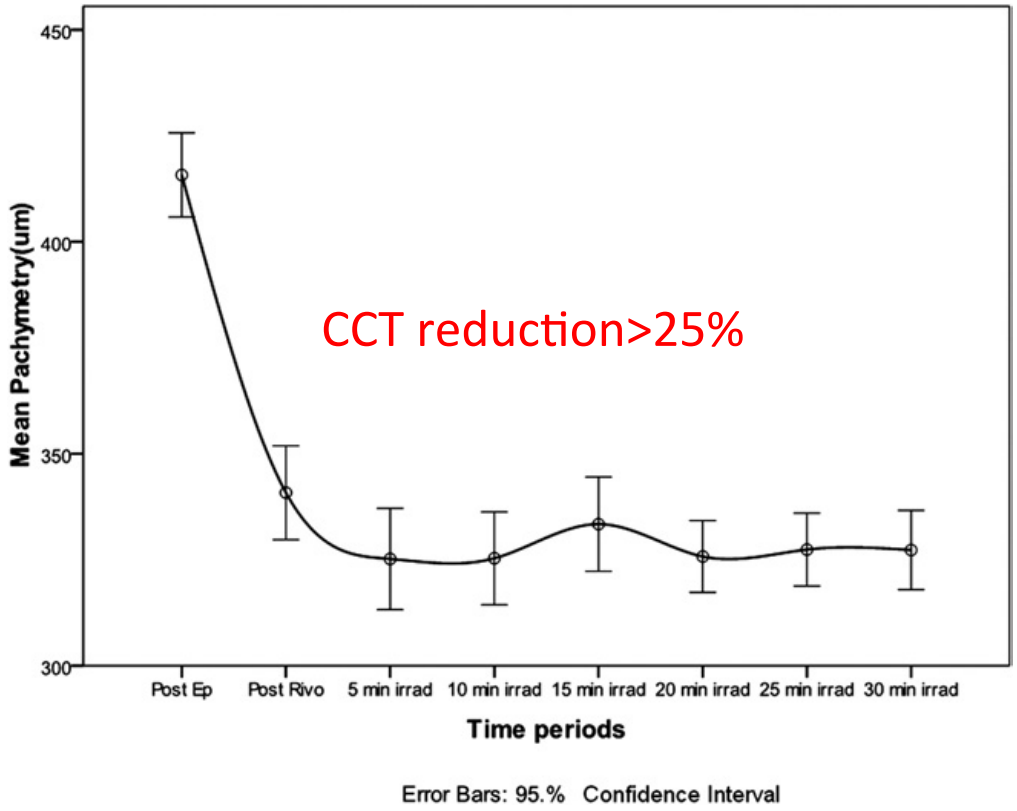
BY ELENA ALBÉ, MD

It is also interesting to note that the thickest corneas thin at a higher rate than the thinnest, probably because thick corneas have more interlamellar and interfibrillar spaces and become more dehydrated during the CXL procedure.[6,7] ■

TAKE-HOME MESSAGE

- Infusion of a hypoosmolar riboflavin solution can protect corneal tissue from stromal opacities.
- CCT reduction during the soaking phase could be a predictive factor for the development of stromal opacity after CXL.

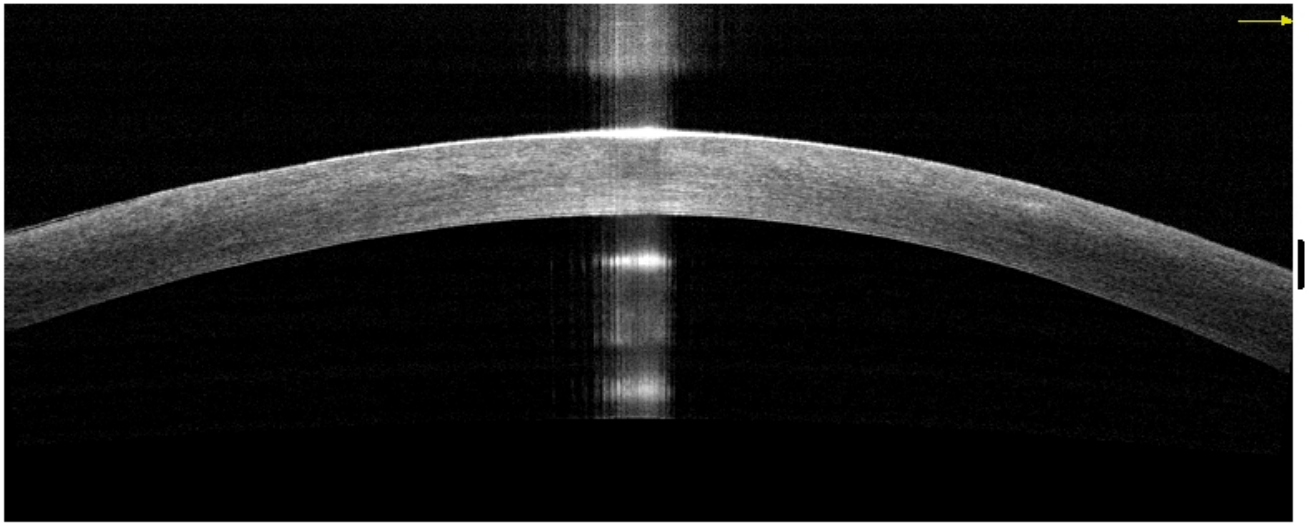
Why intraoperative pachymetry MUST be part of our conventional CXL procedure???



…because of consistent and unpredictable corneal shrinking!!!

Kymionis GD, Kounis GA, et al. Intraoperative pachymetric measurements during corneal collagen cross-linking with riboflavin and ultraviolet A irradiation.Ophthalmology. 2009 Dec;116(12):2336-9.

Why intraop pachymetric mapping SHOULD be part of CXL procedure???

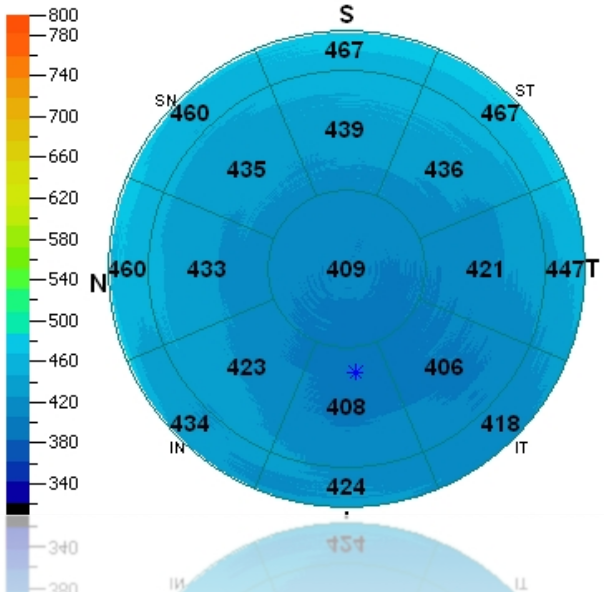


Pachymetry Assessment

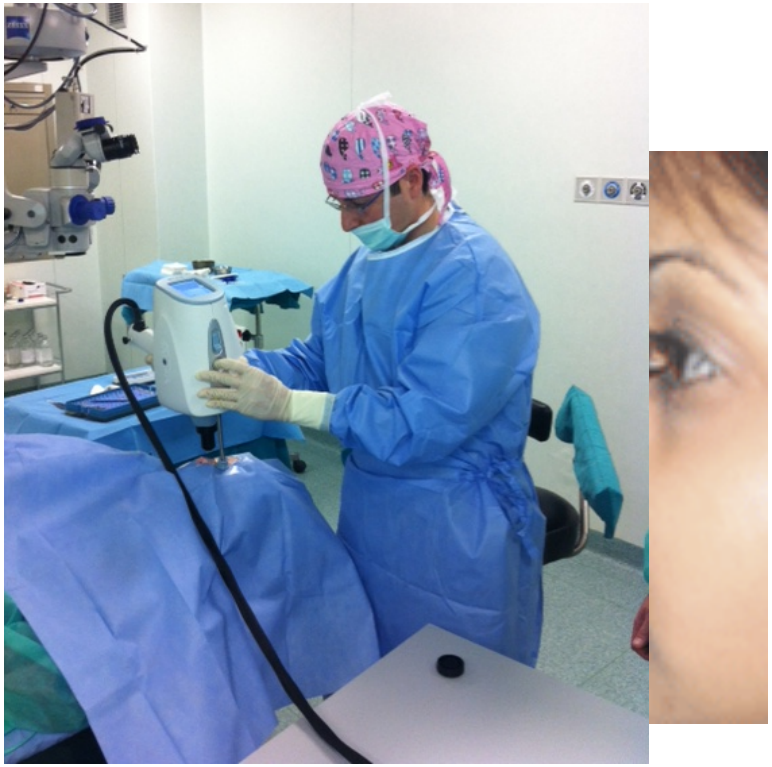
Superior - Inferior Comparison within 5mm zone

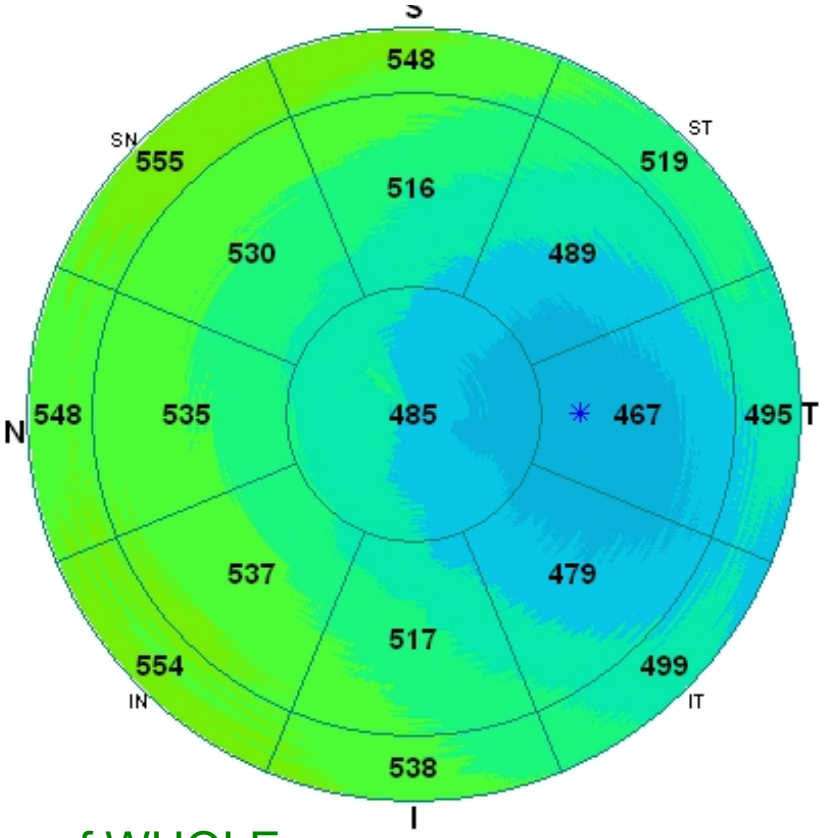
SN-IT(2-5mm):	29	S-I(2-5mm):	31
Min-Median:	-22	Min-Max:	-55
Min:	398	Location Y:	-1313

Min thickness (x, y) 0.123mm, -1.313mm shown as *



Intraop US-pachymetry vs HD-OCT pachymetric mapping





- ✓ Non-contact pachymetric mapping of WHOLE corneal cornea
- ✓ Repeatable
- ✓ Precise intraop definition of thinnest point/area
- ✓ In-vivo imaging of cxl process

~~Hand held pachymeter mapping of WHOLE corneal cornea~~

~~Repeatability???~~

~~In KC thinnest point is eccentric and variable~~

Why cornea shrink??

Look at eccipients…

HYPEROSMOLAR!!!!

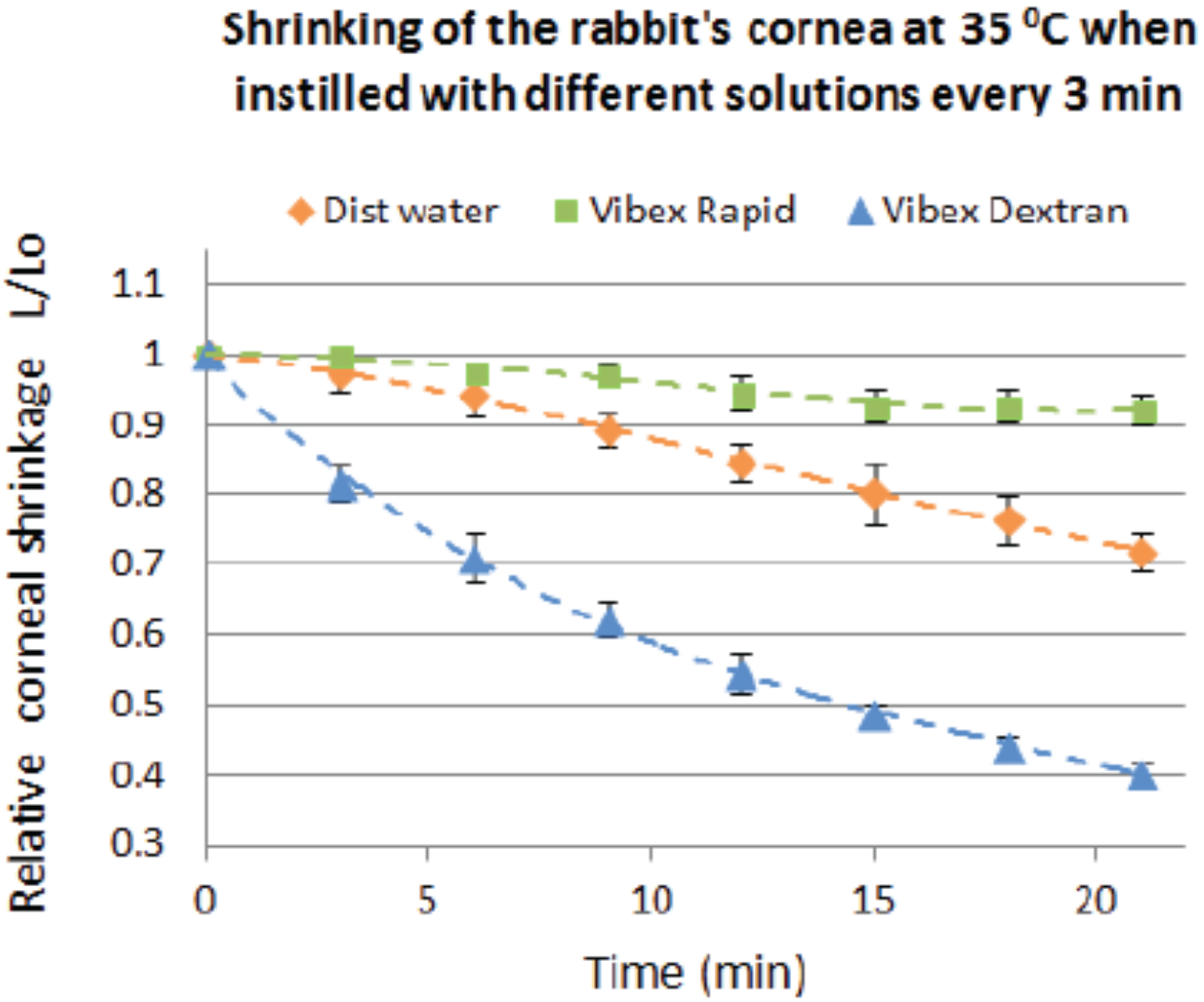
Dextran 20% was originally chosen for the original riboflavin formulations used in cross-linking in part for its viscosity, which allowed the riboflavin to remain in place on the eye for delivery during an extended soak time.

ISOSMOLAR!!!!

(HPMC), a water-soluble viscoelastic polymer commonly used as an ophthalmic lubricant.

These formulations diffuse more quickly into the corneal stroma during epithelium-off corneal cross-linking, requiring shorter pre-soaking times to achieve the same riboflavin concentration in the respect to dextranformulations

Suggestions from Avedro's lab…



How to solve corneal shrinking??

- REMOVE DEXTRAN!!!!
- Use dextran-free iso-osmolar solution!!!

Expert Opinion on Orphan Drugs (2013) 1(3):235-240

Drug Evaluation

EXPERT OPINION

1. Introduction
2. Keratoconus

Riboflavin 0.1% (VibeX) for the treatment of keratoconus

Cosimo Mazzotta†, Stefano Baiocchi, Tomaso Caporossi, Stefano Caragiuli, Anna Lucia Paradiso & Aldo Caporossi

†*Siena University, Policlinico Santa Maria alle Scotte, Department of Ophthalmology, Siena, Italy*

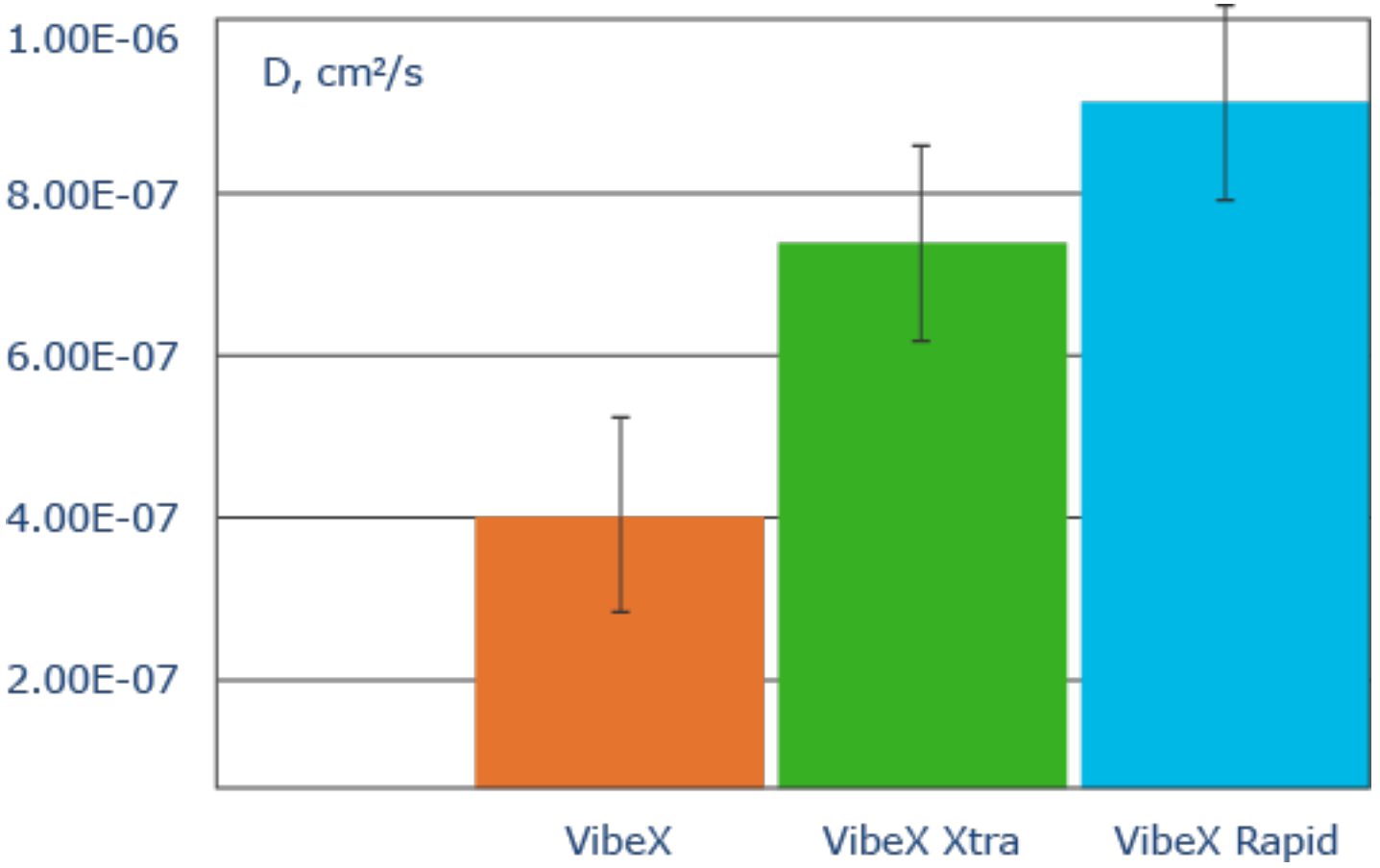
Box 2. Drug summary.

Drug name	VibeX Rapid™
Pharmaceutical company	Avedro, Inc. (Waltham, Massachusetts, MA, USA)
Indication	Keratoconus and secondary corneal ectasia
Composition	100 mL of solution contains: riboflavin 0.1 g, HPMC, disodium hydrogen phosphate, sodium phosphate monobasic dihydrate, sodium chloride, water for injectable solution
Mechanism of action	Ophthalmic medical device used for corneal crosslinking treatment
Route of administration	Topically

Compared with VibeX riboflavin 0.1% – dextran 20% formula, the VibeX Rapid has been proposed for a faster and homogeneous corneal soaking, avoiding the intraoperative corneal thinning often occurring with the standard riboflavin solutions containing high molecular weight dextran as excipient.

VibeX Rapid™ dextran-free Riboflavin 0.1% plus HPMC solution

Mean diffusivities for VibeX, VibeX Xtra, VibeX Rapid Corneal flaps without epithelium.



ACXL: EPI-OFF protocols

Name	Formulation	Procedure	Protocol
[redacted]	0.1% Riboflavin 20% Dextran	KXL for Keratoconus & Post Lasik Ectasia Lasik Xtra for Corneal Strengthening During Lasik	***Epi-Off*** • Vibex Soak Time - 20 min. • UVA Time - 4 min. @ 30mw/cm²
 • 2X Faster Diffusion than Vibex • Dextran Free	0.1% Riboflavin HPMC	KXL for Keratoconus & Post Lasik Ectasia	***Epi-Off*** • Vibex Rapid Soak Time - 10 min. • UVA Time - 4 min. @ 30mw/cm²

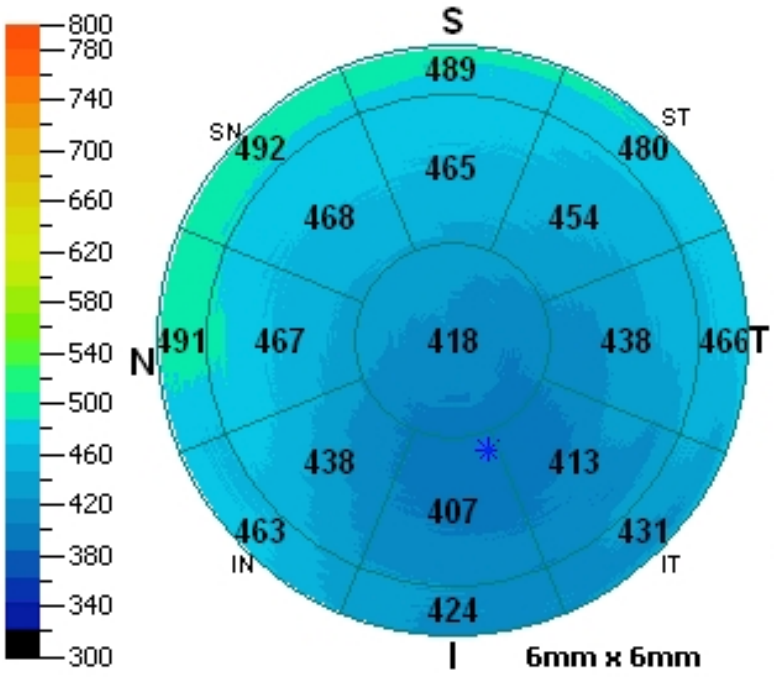
Study design

- 25 eye of 25 patients (15 M, 10 F) affected by bilateral progressive keratoconus. Mean age 26.9 ys.

- Preop maximum K reading less than 58 D. No Vogt's striae or corneal opacity. Corneal thickness > 325 micron.

- Intraop OCT was performed Preoperatively **(PREOP)**, after epithelium removal **(Epi-R),** after 10 min riboflavin soaking with VibexRapid **(RS),** after 8 min irradiation **(IR).**

- Pachymetric Parameters measured: Central corneal thickness **(CCT),**inferior paracentral corneal thickness **(IPCT)** (average of three inferior paracentral octants), superior-inferior **SI** , **Min-Max, Min**



Accellerated CXL protocol (7.2 J)

Dr. Rechichi's
VibeX Rapid Protocol
For corneas 325 microns or greater, after epithelial removal

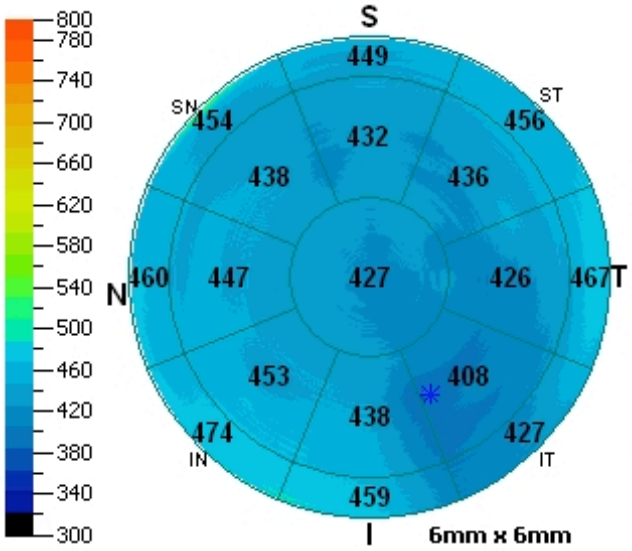
1. After epithelial removal, apply VibeX Rapid. Soak for up to 10 minutes, reapplying every 1-2 minutes.

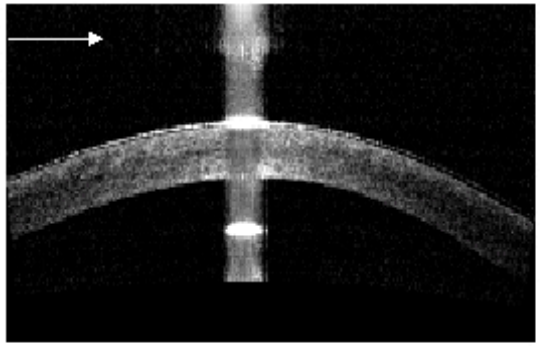
2. Following completion of the soak, rinse VibeX Rapid from the eye with BSS.

3. Treat with 7.2 J/cm², using an irradiance of 30mW/cm2 with pulsed illumination [1,1].

Previous Scan 12/04/2013 08:46:50

Scan Quality Index Good 58





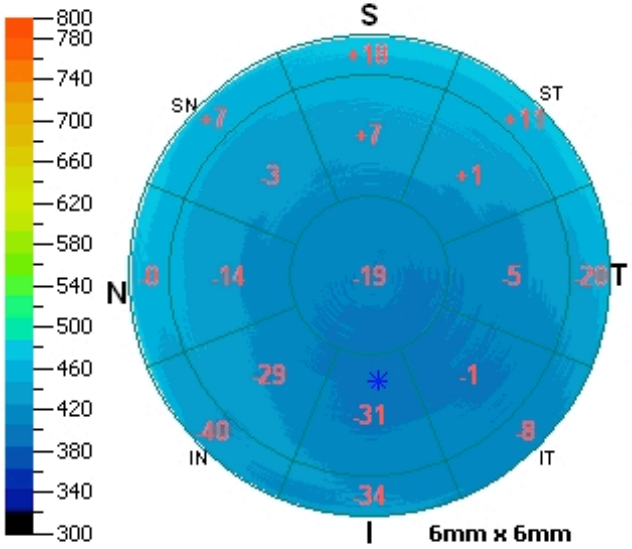
Pachymetry Assessment

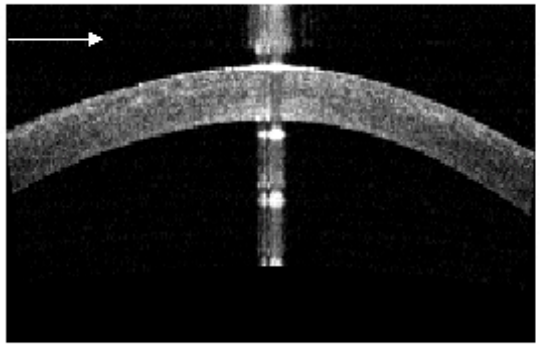
Superior - Inferior Comparison within 5mm zone

SN-IT(2-5mm):	30	S-I(2-5mm):	-6
Min-Median:	-40	Min-Max:	-75
Min:	392	Location Y:	-1482

Min thickness (x, y) 0.762mm, -1.482mm shown as *

Show Original





Pachymetry Assessment

Superior - Inferior Comparison within 5mm zone

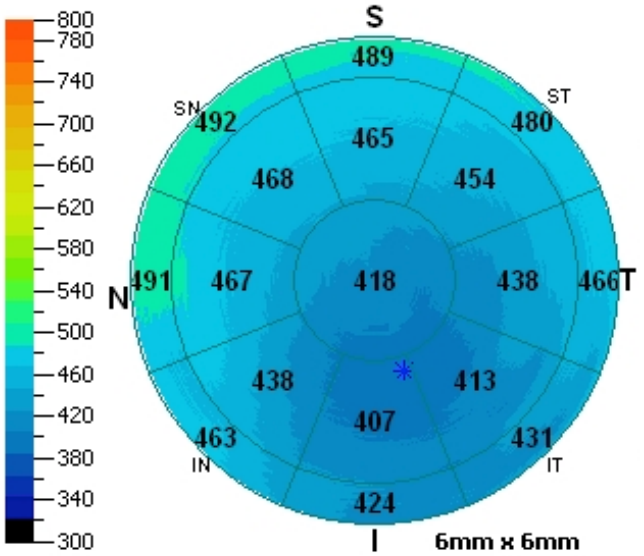
SN-IT(2-5mm):	29	S-I(2-5mm):	31
Min-Median:	-22	Min-Max:	-55
Min:	398	Location Y:	-1313

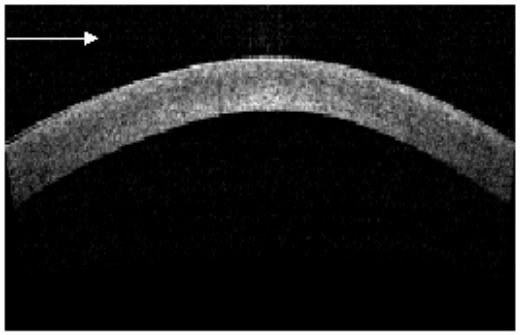
Min thickness (x, y) 0.123mm, -1.313mm shown as *

Recent Scan 12/04/2013 08:55:18

Scan Quality Index Good 63

Previous Scan 12/04/2013 08:12:23





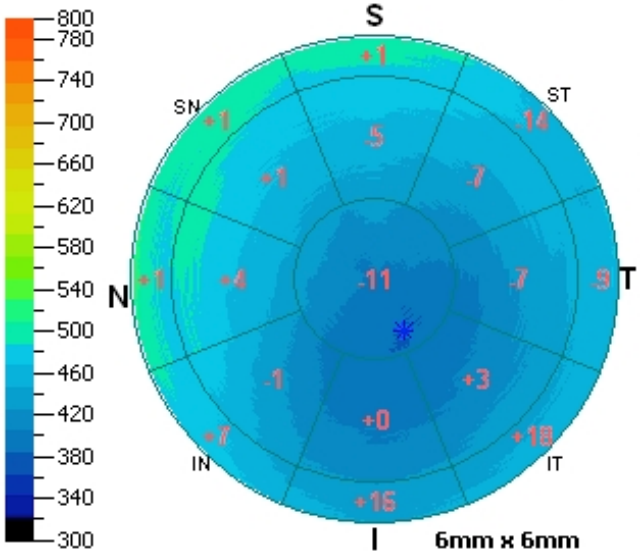
Pachymetry Assessment

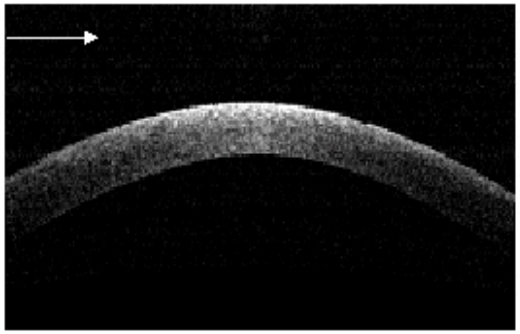
Superior - Inferior Comparison within 5mm zone

SN-IT(2-5mm):	55	S-I(2-5mm):	58
Min-Median:	-44	Min-Max:	-91
Min:	395	Location Y:	-1113

Min thickness (x, y) 0.369mm, -1.113mm shown as *

Show Original





Pachymetry Assessment

Superior - Inferior Comparison within 5mm zone

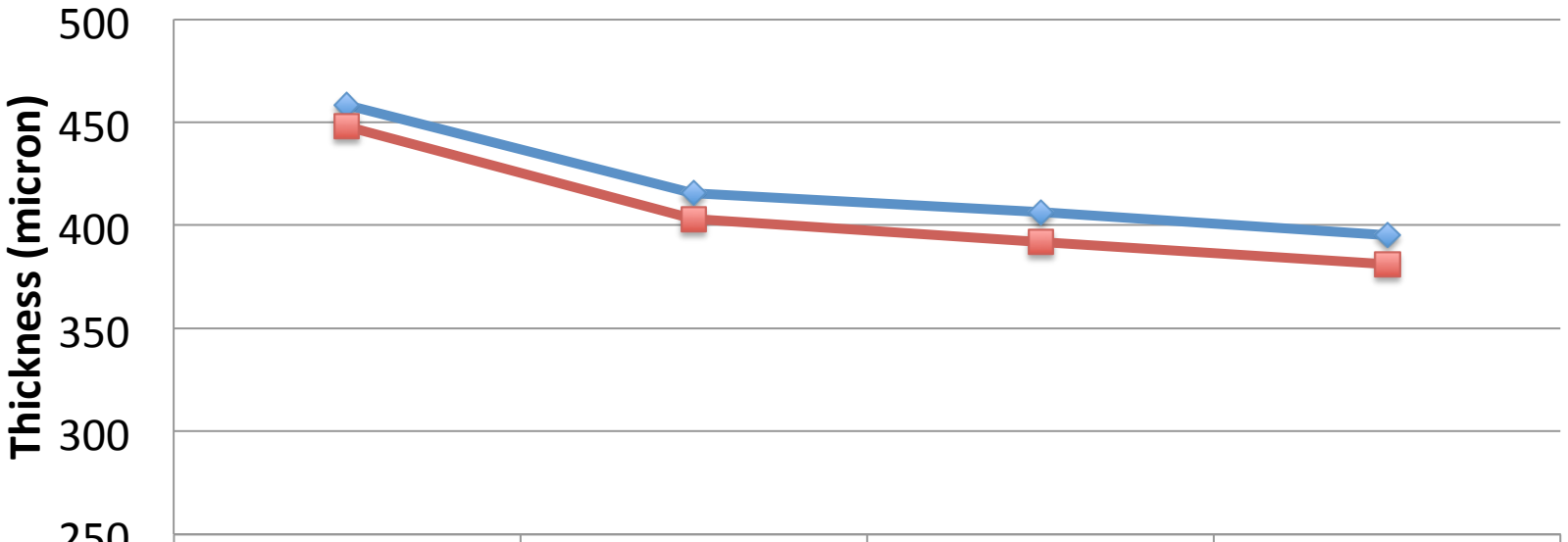
SN-IT(2-5mm):	54	S-I(2-5mm):	54
Min-Median:	-49	Min-Max:	-107
Min:	387	Location Y:	-633

Min thickness (x, y) 0.357mm, -0.633mm shown as *

Recent Scan 12/04/2013 08:20:46

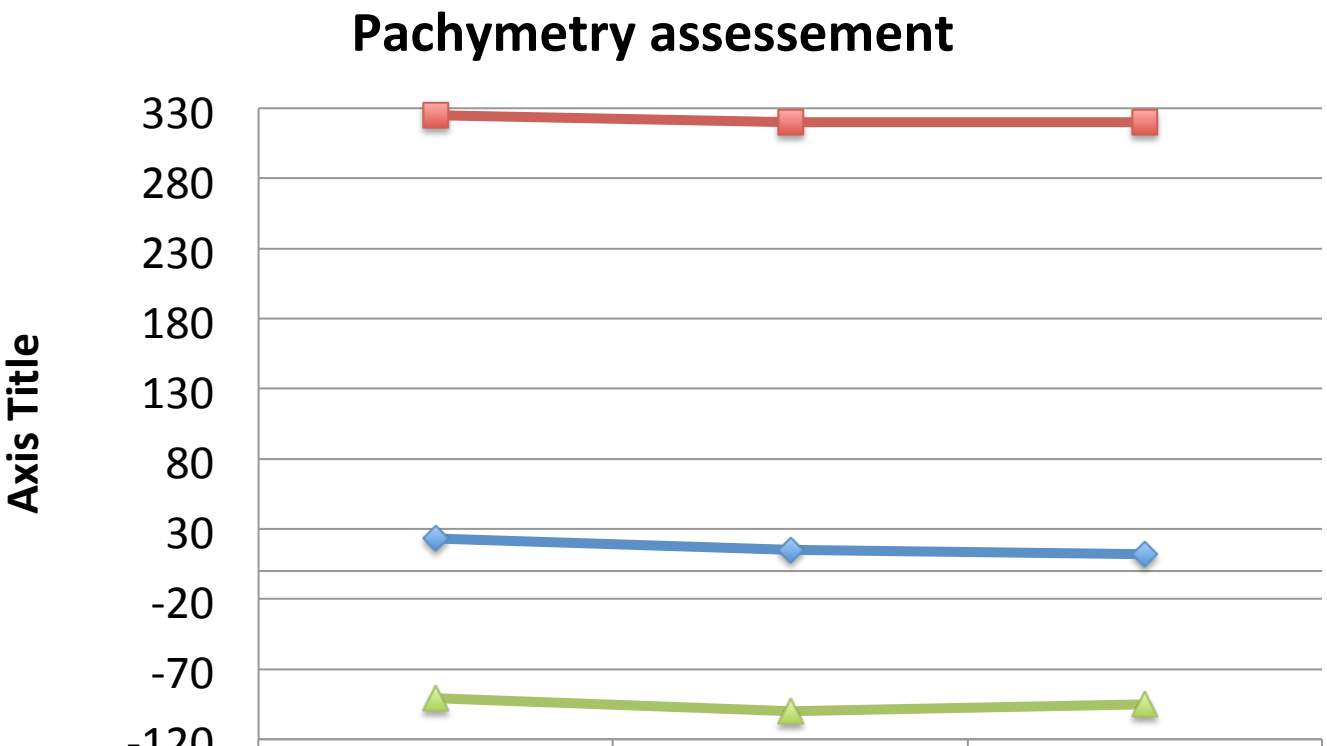
Results

30 mw, 7.2 mJ Pulsed 1:1 protocol
10 minVibrapid Imbibition + 8min irradiation



	Preop	Epi-r	RS	IR
CCT	458,5	415,7	406,4	395
IPCT	448	403	392	381

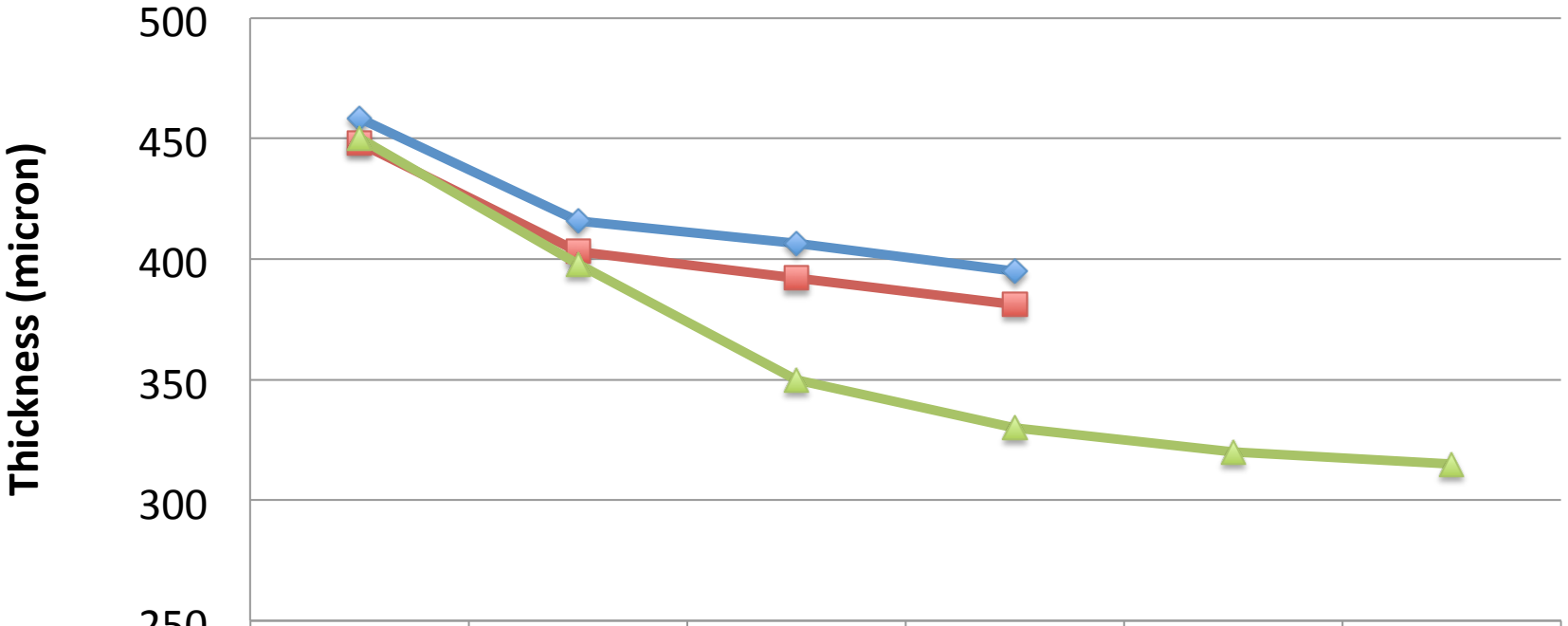
Results



	Epi-r	RS	IR
S-I	23	15	12
Min	325	320	320
Min-Max	-91	-100	-95

Results

Comparison between old and new cxl protocol



	Preop	Epi-r	RS	IR	RS 30m	IR 30 m
CCT	458,5	415,7	406,4	395		
IPCT	448	403	392	381		
Conv CXL	450	398	350	330	320	315

Why use newer cxl machine?

•Fully Customizable power, from 15 to 45 mW/ cm2

Customizable 5.4 J or 7.2 J energy delivered to cornea

• Superior top hat beam profile

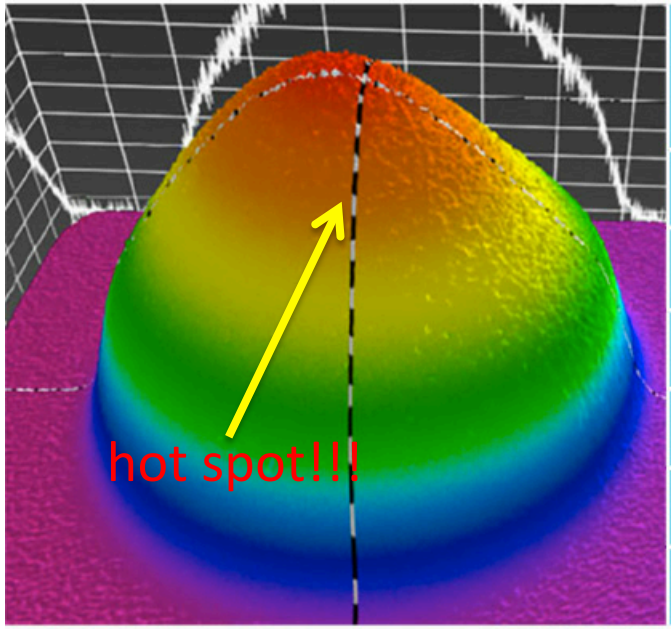
• Precise focusing of the spot

Why use newer cxl machine?

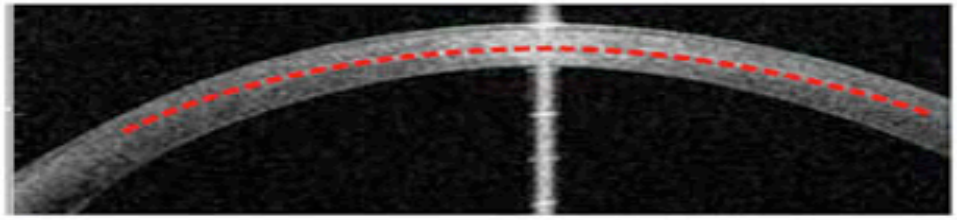
Flat Non-optimized

Beam profile

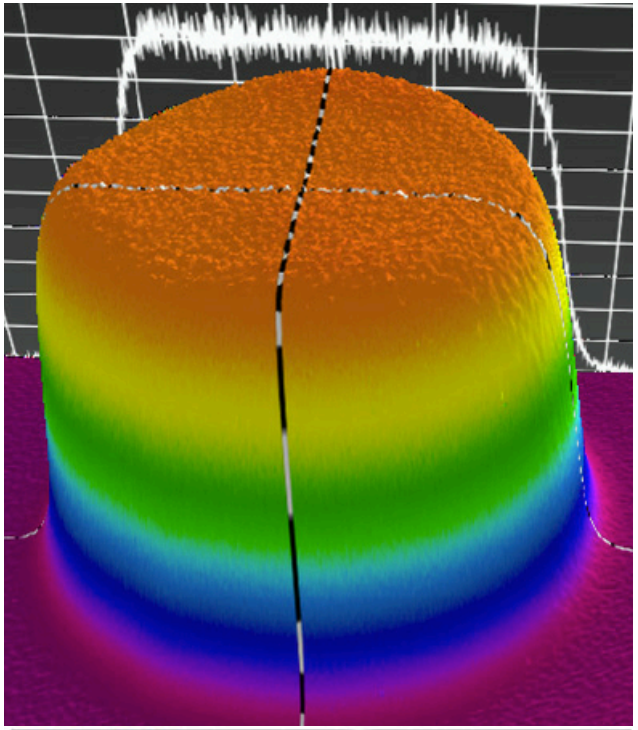
TopHat Optimized

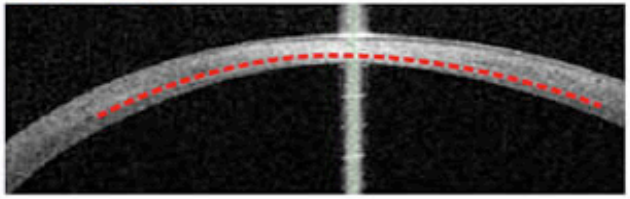


Annulus (mm)	Total Surface Exposure Energy (J)
Central 2	8.4
2 to 4	6.5
4 to 6	5.9
6 to 7	5.9
7 to 9	5.0
9 to 11	3.7



Less cross-linking in periphery





Improved cross-linking in periphery

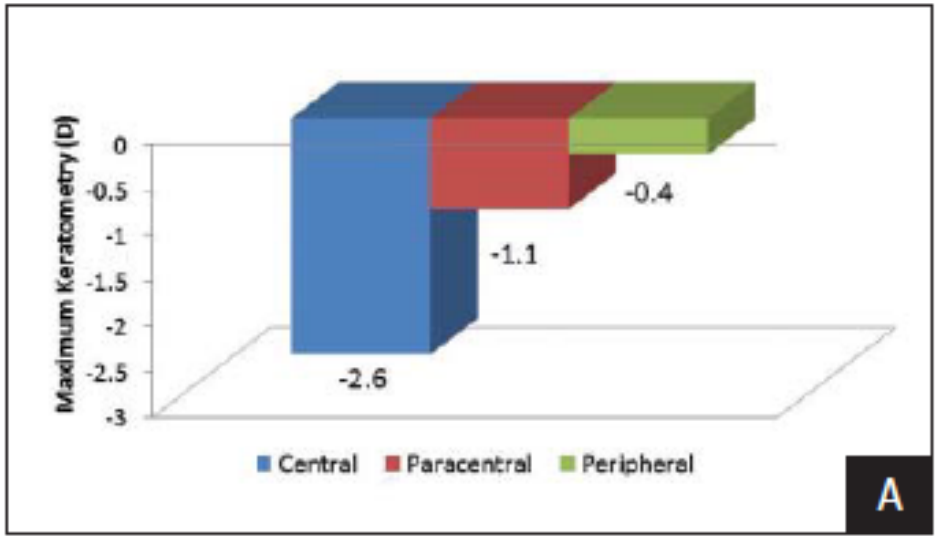
uneven energy distribution
Energy delivery greatly affected by defocus (>10% over 1mm)

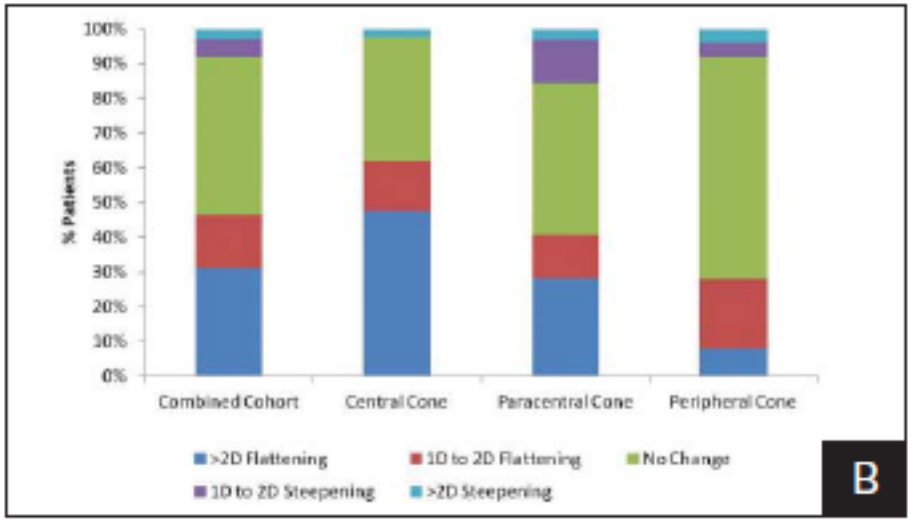
More homogeneous energy delivery

Why use newer cxl machine?

Effect of Topographic Cone Location on Outcomes of Corneal Collagen Cross-linking for Keratoconus and Corneal Ectasia

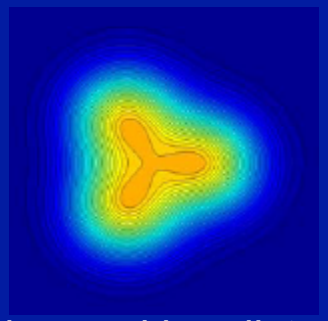
Steven A. Greenstein, MD; Kristen L. Fry, OD, MS; Peter S. Hersh, MD



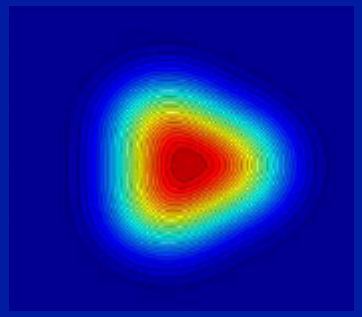


CONCLUSIONS: After CXL, more topographic flattening occurs in eyes with centrally located cones and the least flattening effect occurs when the cone is located peripherally. This cone-location effect is found in eyes with both keratoconus and ectasia. [*J Refract Surg.*

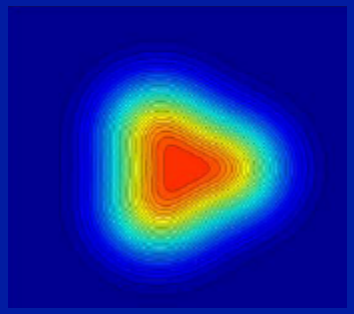
Why use newer cxl machine?



Excessive working distance
Ineffective treatment!!!



Neat working distance
HOT-SPOT danger!!!



Correct working distance:
Optimal treatment

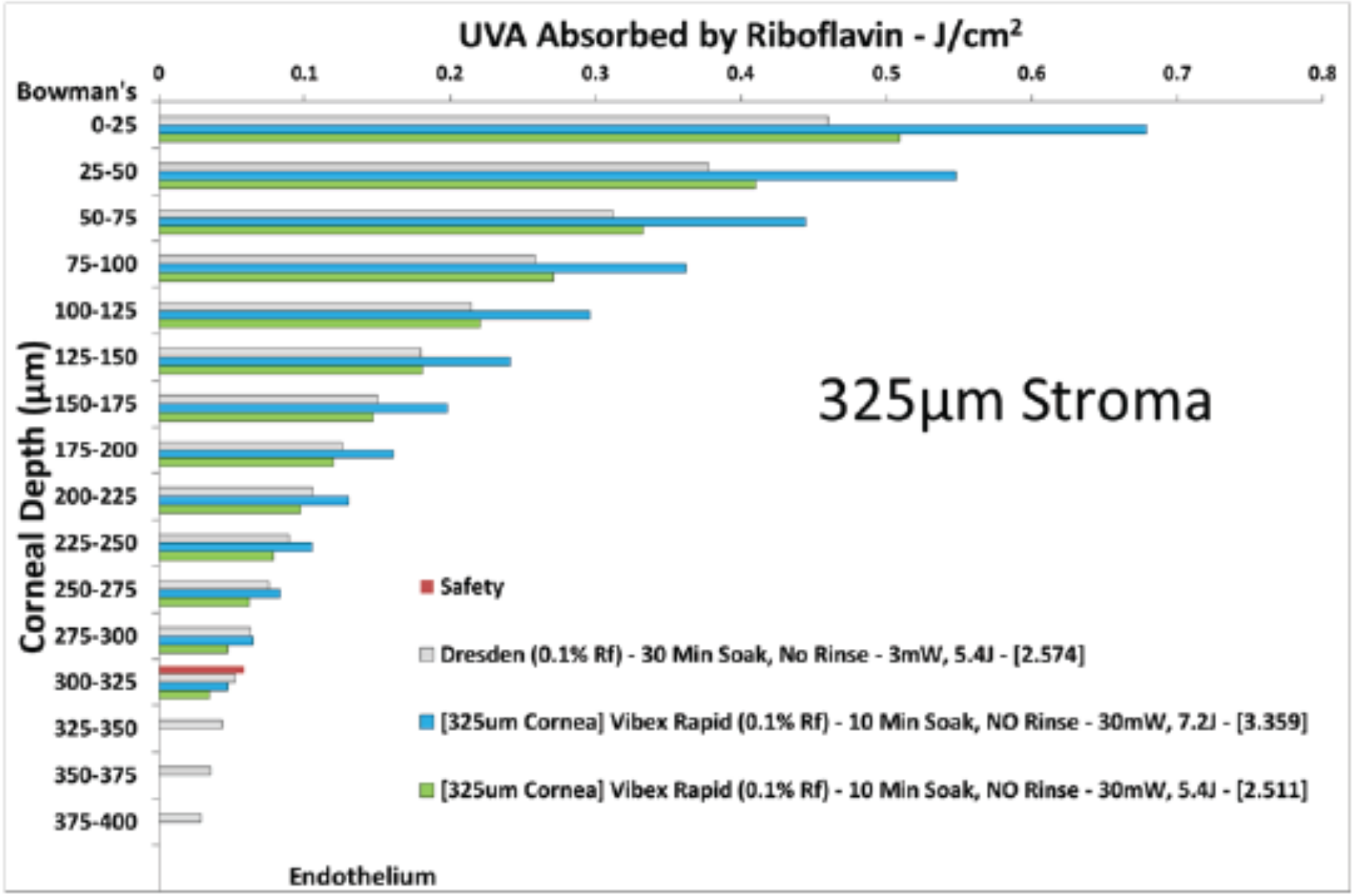
Defocus issue

Defocus ± 1mm = 8-10% reduction in energy delivered to the cornea

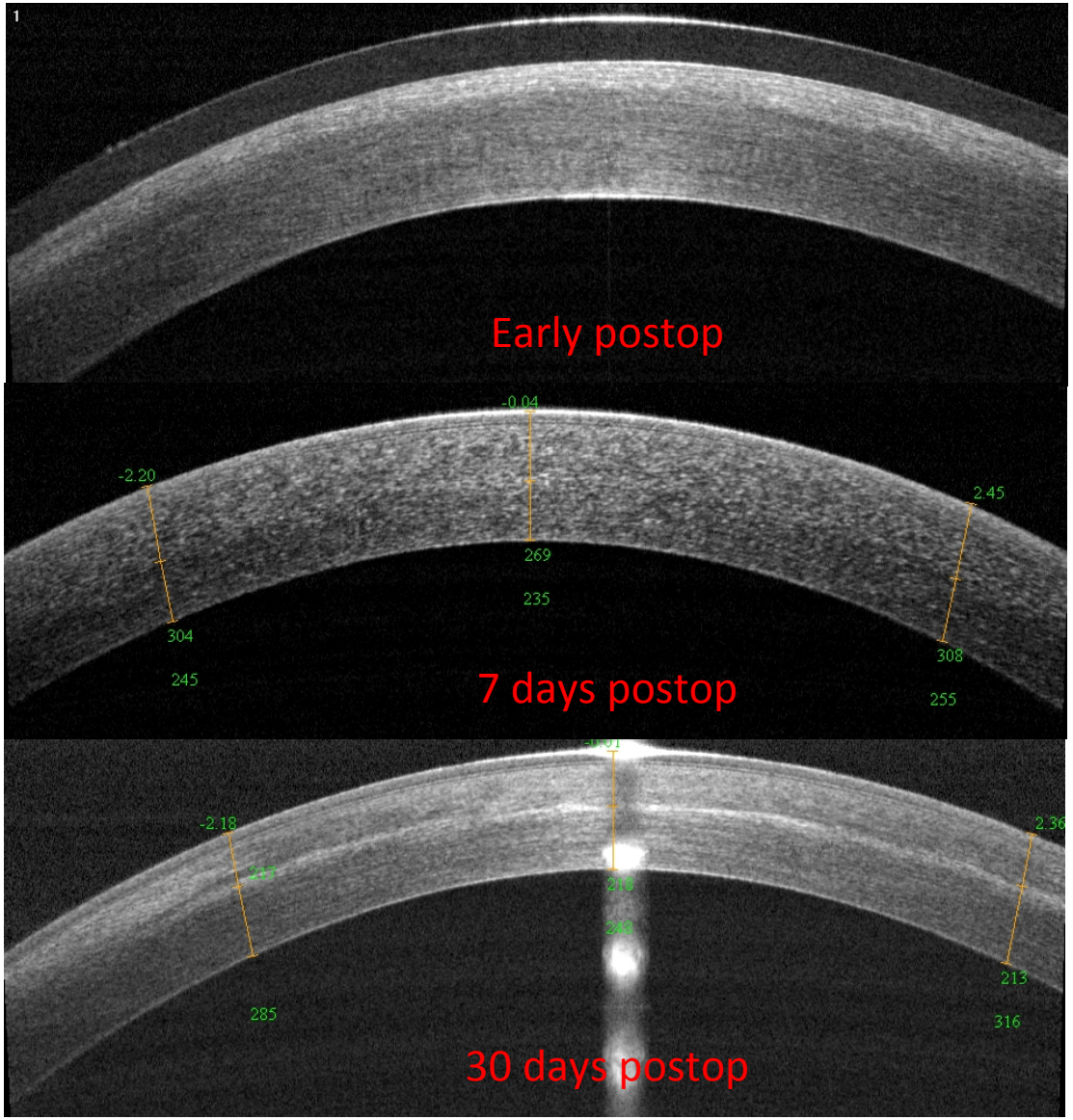
Decentering of 0.2 mm = 8-10% reduction in energy delivered to the cornea

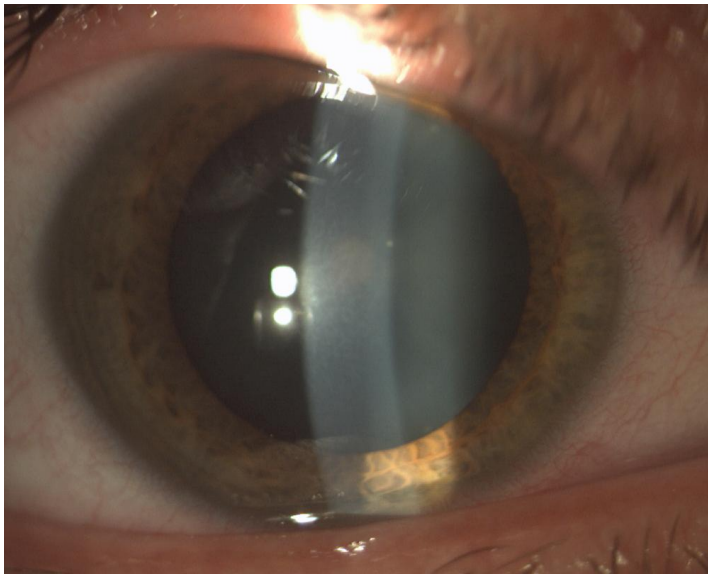
Decentering of 0.5 mm = 20% reduction in energy delivered to the cornea

What about safety shifting from 5.4 to 7.2 J ?

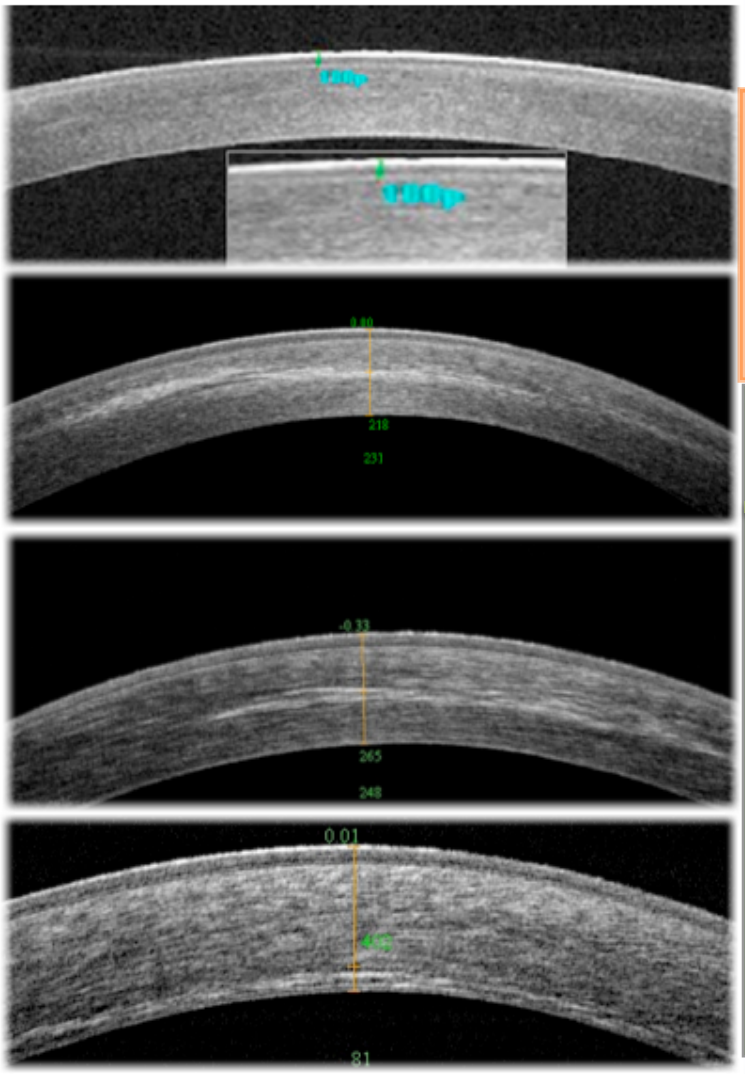


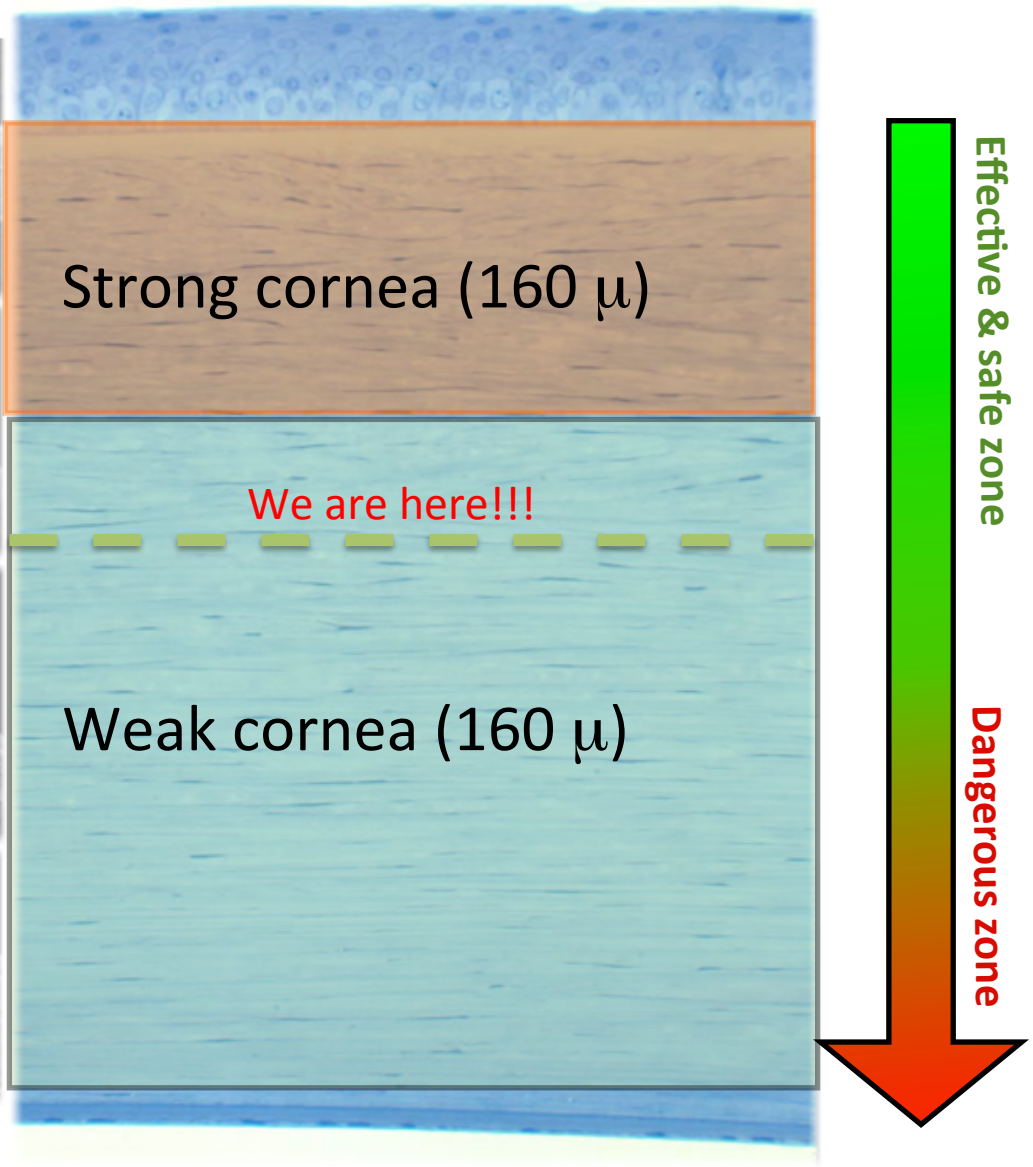
What about safety?





What about safety?





Conclusion

- ✓ *Epi-off* accellerated pulsed corneal CXL with the use of dextran-free riboflavin limited central and paracentral corneal thinning during the procedure.

- ✓ After epithelium removal a mild but statistically significant decrease of CCT was demonstrated only after irradiation phase.

- ✓ Wide-angle pachymetryc mapping showed a smooth thickness variation in whole corneal during procedure

- ✓ The safety of this new cxl protocol respect to conventional is supported by these objective findings

avedro

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May, 2013 Vol. 3, No. 3

"To improve overall safety of epi-off procedures, the use of VibeX Rapid and accelerated protocols may reduce corneal dehydration and preserve original corneal thickness."

Miguel Rechichi, MD

Thank you !!!