Keratoconus

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Chairman: Prof. L.E. Pillunat, MD

Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study

- „CLEK Study subjects with keratoconus exhibited a slow but clear decrease in BCVA during follow-up, with low-contrast acuity deteriorating more rapidly than high-contrast.“
- „The 5-year incidence of scarring is 13,7% for the overall sample and 38,0% for those eyes with corneal curvature greater than 52 D that wore contact lenses.“

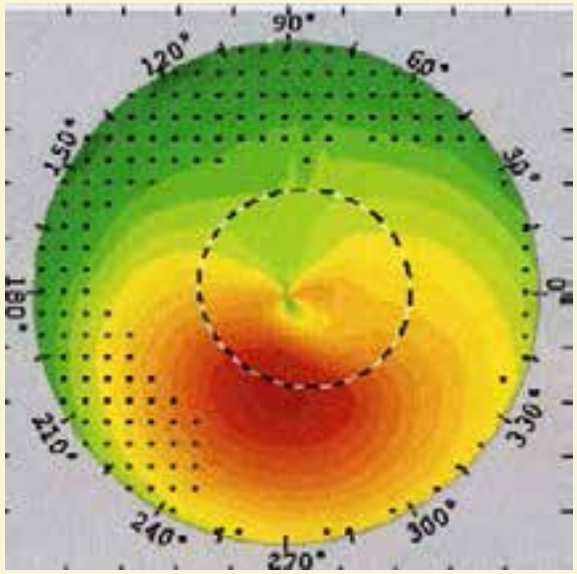
Davis LJ, Schechtman KB, Wilson BS et al. Longitudinal changes in visual acuity in keratoconus. IOVS 2006; 47: 489-500
Batt JT, Wilson BS, Gordon MO et al. Estimation of the incidence and factors predictive of corneal scarring in the collaborative longitudinal evaluation of kertoconus (CLEK) study. Cornea 2005; 25: 16-25

Lifetime economic burden of keratoconus

- **compared to the** expected **cost of the treatment of myopia**:
- included costs of clinic visits, fitting fees, contact lenses, surgical procedures and complications: **25 168 US$**
- the factors that most influenced the lifetime cost were the probability of initial corneal transplant and a subsequent regraft
- the average **annual cost** for individual **routine vision care** is **200 US$**, but **for** patients with **keratoconus**, it is **653 US$**
- combined with the significantly impaired vision-related quality of life and the relatively young onset of disease, the economic burden of the treatment of keratoconus represents a significant public health concern

Rebenitsch RL, Kymes SM, Walline JJ et al. The lifetime economic burden of keratoconus: a decision analysis using a Markov model. Am J Ophthalmol. 2011;151:768-773

Management



- Glasses
- Contact lenses
- Collagen Cross-linking with Riboflavin/ UVA
- Intracorneal rings
- Corneal transplant

Gomes JA, Tan D, Rapuano CJ et al. Global Consensus on Keratoconus and Ectatic Diseases. Cornea 2015; 344(4): 359-369

Global Consensus on Keratoconus and Ectatic Diseases

José A. P. Gomes, MD, PhD, Donald Tan, MD, PhD,† Christopher J. Rapuano, MD,‡ Michael W. Belin, MD,§ Renato Ambrósio, Jr. MD, PhD,¶ José L. Guell, MD,‖ François Malecaze, MD, PhD,** Kohji Nishida, MD,†† and Virender S. Sangwan, MD‡‡, the Group of Panelists for the Global Delphi Panel of Keratoconus and Ectatic Diseases*

CXL is currently available and is performed by the majority of the panelists (83.3%) for keratoconus, using a variety of techniques. The panelists who do not have current access to CXL were willing to use this technique once it becomes available. In addition, it was recognized that *the*

Cornea 2015; 344(4): 359-369

Indication for CXL

- **PROGRESSION !:**

- K-Value
- Astigmatism
- Pachymetry
- Visual acuity

PROGRESSION

- ↑$K_{max\text{-}apex}$ ≥1.0D in 1 y., ↓VA, ↑CL fitting frequence
- ↑Dsph and/or Dcyl ≥3D in 6 mo., or ↑K_{max} ≥1.5D, or mean ↓CT ≥ 5% in 3 consecutive measurements in 6 mo.
- ↑K_{max} ≥1D, or ↑Dcyl ≥1D, or ↑Dsph ≥ 0.5D in 24 mo. (FDA study)

Raiskup F, Hoyer A, Spoerl E, Pillunat LE. Collagen crosslinking with riboflavin and ultraviolet-A light in keratoconus: long-term results. J Cataract Refract Surg. 2008; 34: 796-801
Vinciguerra P, Albe E, Trazza S et al. Refractive, topographic, tomographic, and aberrometric analysis of keratoconic eyes undergoing corneal cross-linking. Ophthalmology 2009; 116: 369-378
Hersh PS, Greenstein SA, Fry KL. Corneal collagen crosslinking for keratoconus and corneal ectasia: One-year results. J Cataract Refract Surg 2011; 37: 149-160

Indication for CXL:
Medical history

- Age, gender
- Sport: body-building, weight-lifting, yoga (upside down standing, pressure breathing)
- Playing wind-instrument
- Pregnancy
- Hormonal therapy (contraceptives, anabolics)
- Thyroid gland dysfunction
- Allergy (Neurodermitis, Steroids)
- Smoking
- Diabetes mellitus

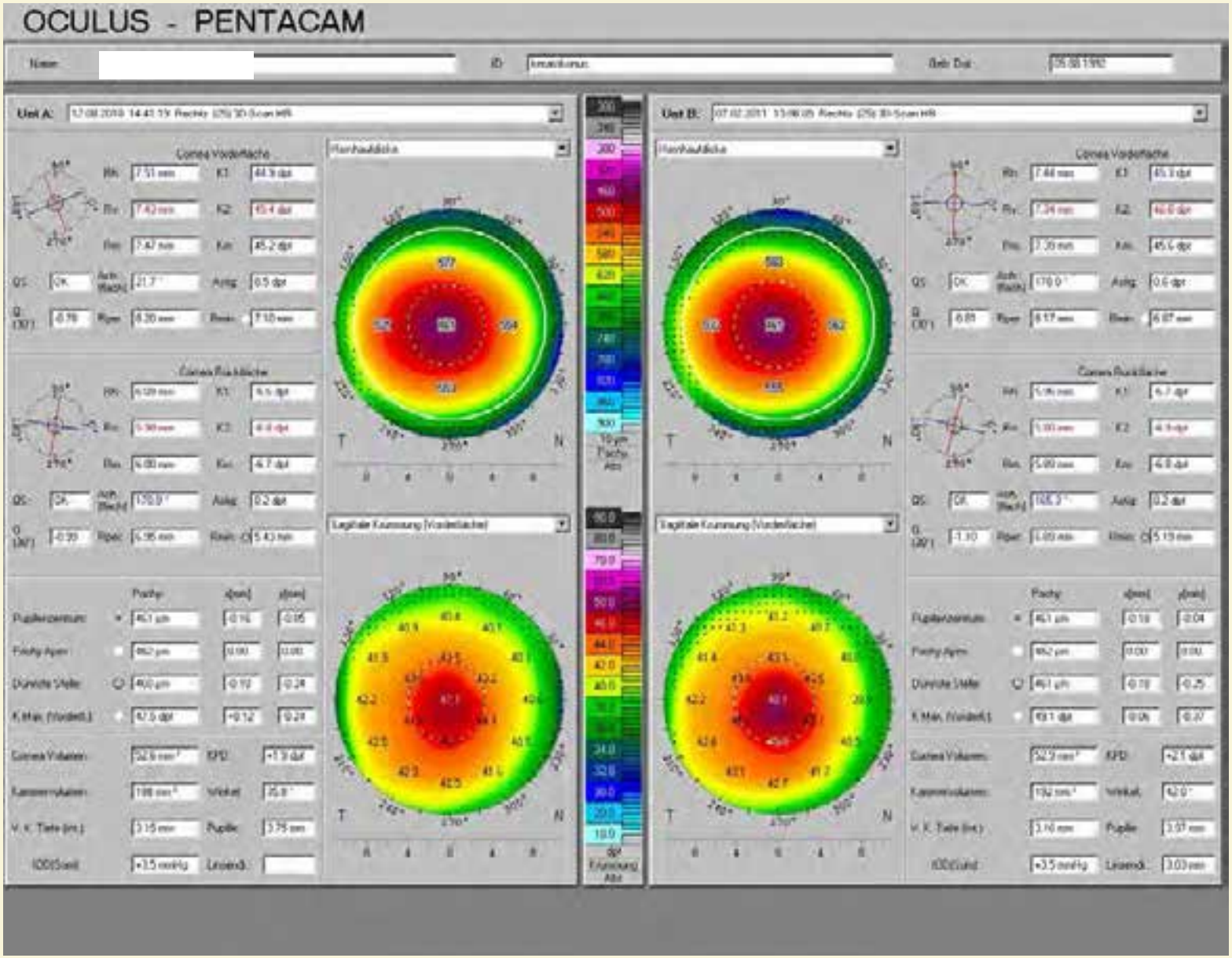
Caporossi A, Mazzotta C, Baiocchi S et al. Age-related long-term functional results after riboflavin UV-A corneal cross-linking. J Ophthalmol 2011: 60804
Spoerl E, Zubaty V, Terai N et al. Influence of high-dose cortisol on the biomechanics of incubated porcine corneal strips. J Refract Surg 2009; 25; S794-798
Spoerl E, Zubaty V, Raiskup F et al. Oestrogen-induced changes in biomechanics in the cornea as a possible reason for keratectasia. Br J Ophthalmol 2007; 91: 1547-50
Bilgihan K, Hondur A, Sul S et al. Pregnancy-induced progression of keratoconus. Cornea 2011; 30: 991-4
Hafezi F, Iseli HP. Pregnancy-related exacerbation of iatrogenic keratectasia despite corneal collagen crosslinking. J Cataract Refract Surg 2008; 34: 219-21

Keratoconus in children

- rapid progression (high risk group)
- Age: 10-18 y.
- Incidence M:F = 4:1
- prompt indication for CXL!

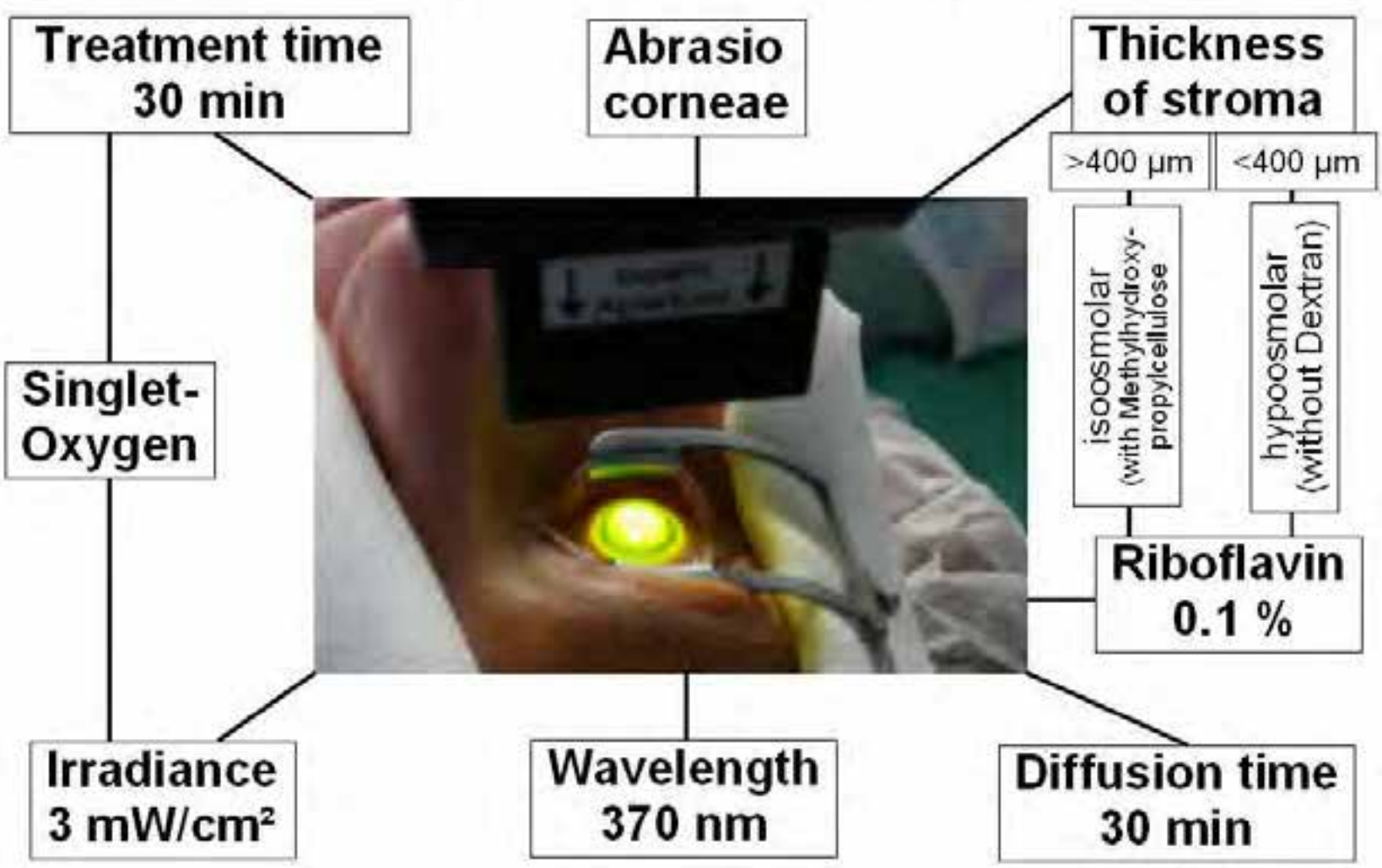
Caporossi A, Mazzotta C, Baiocchi S. Riboflavin-UVA-induced corneal collagen cross-linking in pediatric patients. Cornea 2012; 31:227-31
Caporossi A, Mazzotta C, Baiocchi S, Caporossi T, Denaro R. Age-Related Long-Term Functional Results after Riboflavin UV A Corneal Cross-Linking. J Ophthalmol. 2011;2011:608041.

Progression (F/U 6 mo.)



Epi-off

Standard Treatment Parameters



CXL: Riboflavin + UVA / „Epi-off“

- Topical anaesthesia
- Epithelium removal
- **Pachymetry**
- 0.1% Riboflavin:
  2 Min for 20 Min, Ø Speculum
- **Pachymetry**
- UVA (370nm): 3mW/cm^2 (5.4J/cm^2) for 30 Min.
- CL, ATB, lubricants till epithelialisation
- Steroid drops

Epi-off

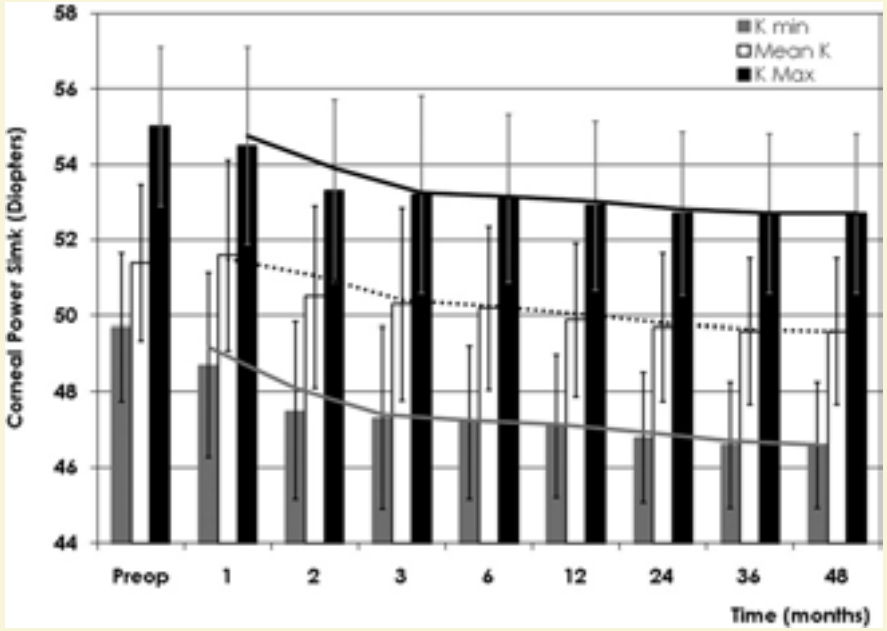
- Caporossi A, Mazzotta C, Baiocchi S, Caporossi T. Long-term results of riboflavin ultraviolet a corneal collagen cross-linking for keratoconus in Italy: the Siena eye cross study. Am J Ophthalmol. 2010 Apr;149(4):585-93. **prospective, non-randomized**
- Hersh PS, Greenstein SA, Fry KL. Corneal collagen crosslinking for keratoconus and corneal ectasia: One-year results. J Cataract Refract Surg. 2011 Jan;37(1):149-60. **multicenter, prospective, randomized controlled trial**
- Wittig-Silva C, Chan E, Islam FM, Wu T, Whiting M, Snibson GR. A randomized, controlled trial of corneal collagen cross-linking in progressive keratoconus: three-year results. Ophthalmology. 2014 Apr;121(4):812-21. **prospective, randomized controlled trial**
- Kymionis GD, Grentzelos MA, Liakopoulos DA et al. Long-term follow-up of corneal collagen cross-linking for keratoconus – the Cretan study. Cornea 2014;33: 1071-1079. **prospective, interventional case series**

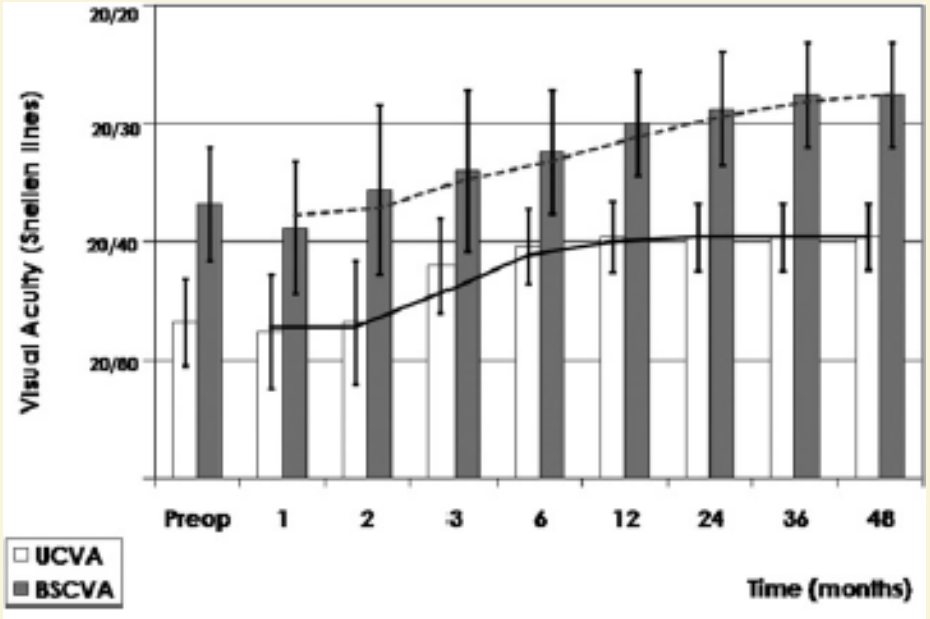
Long-term Results of Riboflavin Ultraviolet A Corneal Collagen Cross-linking for Keratoconus in Italy: The Siena Eye Cross Study

ALDO CAPOROSSI, COSIMO MAZZOTTA, STEFANO BAIOCCHI, AND TOMASO CAPOROSSI

- prospective, nonrandomized, open trial
- 44 eyes
- Age: 10-40 y.
- Follow-up: Ø 52.4 mo. (48-60 mo.)

Am J Opthalmol 2010; 149: 585-593


K min
Mean K
K Max
Corneal Power Simk (Diopters)
58
56
54
52
50
48
46
44
Preop
1
2
3
6
12
24
36
48
Time (months)

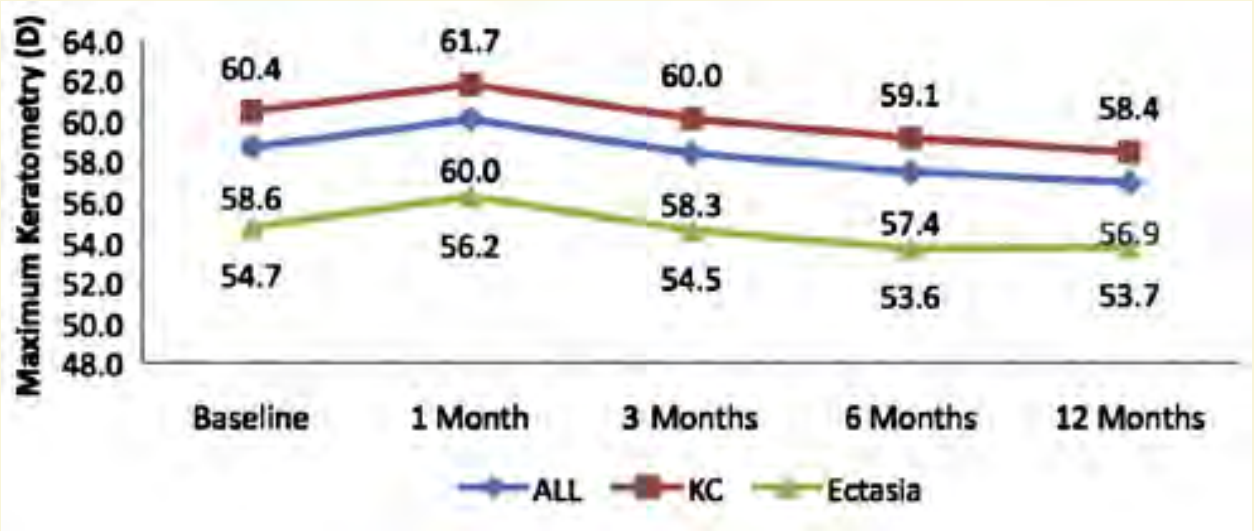

Visual Acuity (Snellen lines)
20/20
20/30
20/40
20/80
Preop
1
2
3
6
12
24
36
48
UCVA
BSCVA
Time (months)

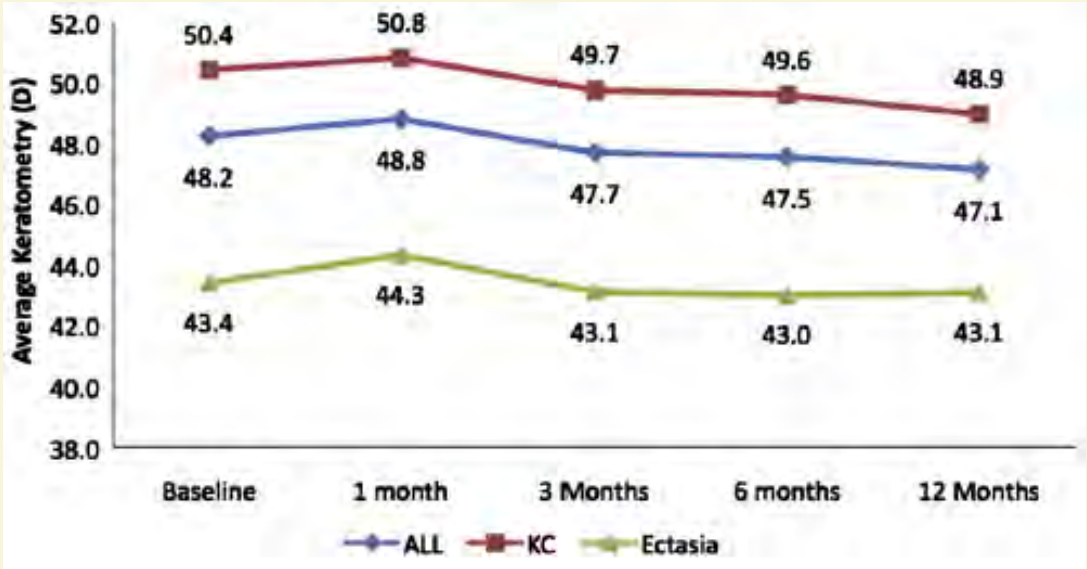
Corneal collagen crosslinking for keratoconus and corneal ectasia: One-year results

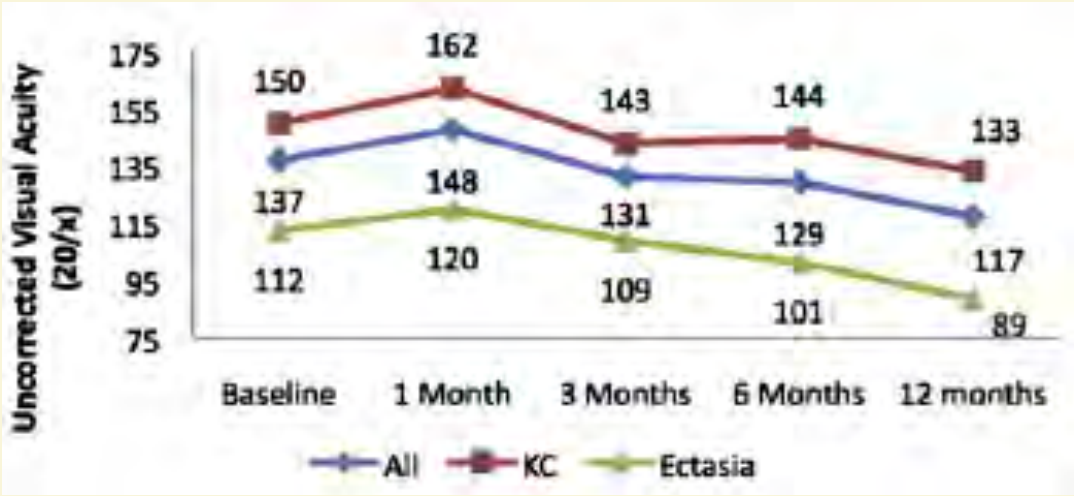
Peter S. Hersh, MD, Steven A. Greenstein, Kristen L. Fry, OD, MS

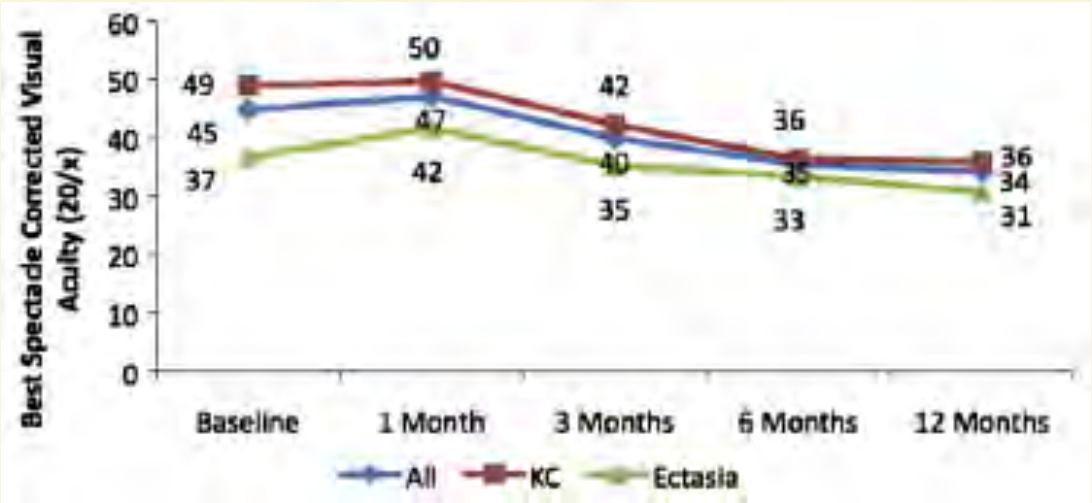
- multicenter, prospective, randomized controlled clinical trial (FDA trial)
- 49 eyes (KCN), 22 eyes (post-LASIK ectasia)
- Age: ≥ 14 y.

J Cataract Refract Surg 2011; 37: 149-160


Maximum Keratometry (D)
64.0
62.0
60.0
58.0
56.0
54.0
52.0
50.0
48.0
60.4
61.7
60.0
59.1
58.4
58.6
60.0
58.3
57.4
56.9
54.7
56.2
54.5
53.6
53.7
Baseline
1 Month
3 Months
6 Months
12 Months
ALL
KC
Ectasia


Average Keratometry (D)
52.0
50.0
48.0
46.0
44.0
42.0
40.0
38.0
50.4
50.8
49.7
49.6
48.9
48.2
48.8
47.7
47.5
47.1
43.4
44.3
43.1
43.0
43.1
Baseline
1 month
3 Months
6 months
12 Months
ALL
KC
Ectasia


Uncorrected Visual Acuity (20/x)
175
155
135
115
95
75
150
162
143
144
133
137
148
131
129
117
112
120
109
101
89
Baseline
1 Month
3 Months
6 Months
12 months
All
KC
Ectasia


Best Spectacle Corrected Visual Acuity (20/x)
60
50
40
30
20
10
0
49
50
42
36
45
47
40
35
36
37
42
35
33
34
31
Baseline
1 Month
3 Months
6 Months
12 Months
All
KC
Ectasia

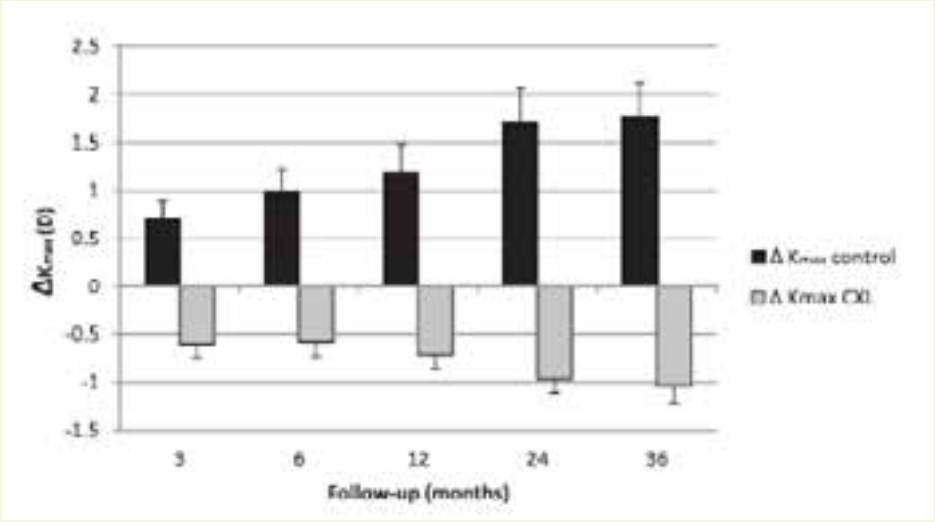
A Randomized, Controlled Trial of Corneal Collagen Cross-Linking in Progressive Keratoconus

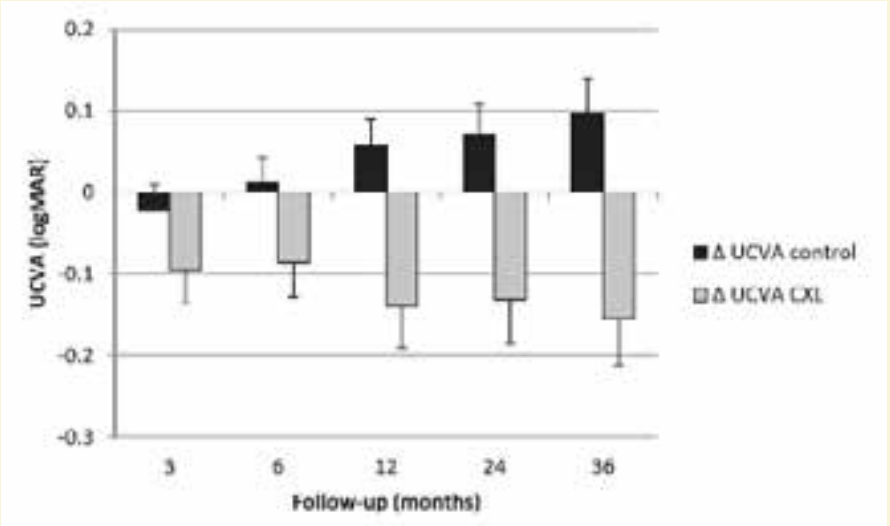
Three-Year Results

Christine Wittig-Silva, MD,[1,2] Elsie Chan, FRANZCO,[1,2] Fakir M.A. Islam, PhD,[1,3] Tony Wu, BSc, BOrth&OphSc,[1] Mark Whiting, FRANZCO,[2] Grant R. Snibson, FRANZCO[1,2]

- prospective, unmasked, randomized controlled trial
- 94 eyes: 48 eyes – control group, 46 eyes – treatment group
- Age: between 16 and 50 years

Ophthalmology 2014; 121: 812-821





CONCLUSIONS: At 36 months, there was a sustained **improvement in Kmax, UCVA, and BSCVA after CXL**, whereas eyes in the **control group demonstrated** further **progression**.

Epithelium-Off Photochemical Corneal Collagen Cross-Linkage Using Riboflavin and Ultraviolet A for Keratoconus and Keratectasia: A Systematic Review and Meta-Analysis

Joyce A. Craig, MA, MSc, MBA,[1] James Mahon, BSc, MSc,[1] Ann Yellowlees, PhD, CStat,[2] Teresa Barata, PhD,[2] Julie Glanville, BA (Hons), MSc,[1] Mick Arber, BA (Hons), MA,[1] Lakshmi Mandava, MSc,[3] John Powell, MB, PhD, MRCPsych, FFPH,[3] and Francisco Figueiredo, MD, PhD, FRCOphth[4]

- 49 papers included: 8 reported 4 RCTs, 29 prospective, 12 retrospective studies
- the majority of **evidence** graded as „**low**“ (trial design, no comparator, large drop-out rate, incomplete reporting)
- „…uncertainty remains about duration of benefit…“

The Ocular Surface 2014; 12(3): 202-214

ARTICLE

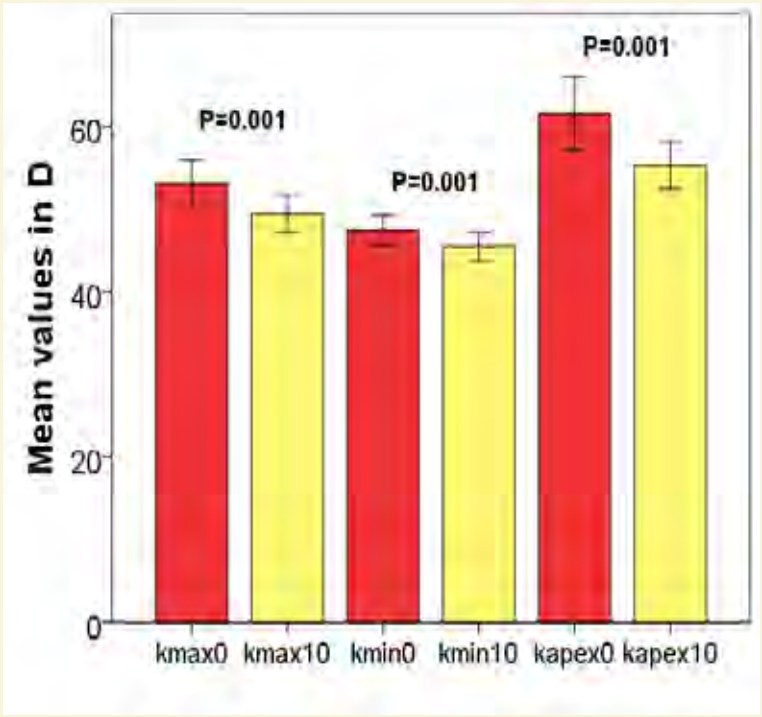
Corneal collagen crosslinking with riboflavin and ultraviolet-A light in progressive keratoconus: Ten-year results

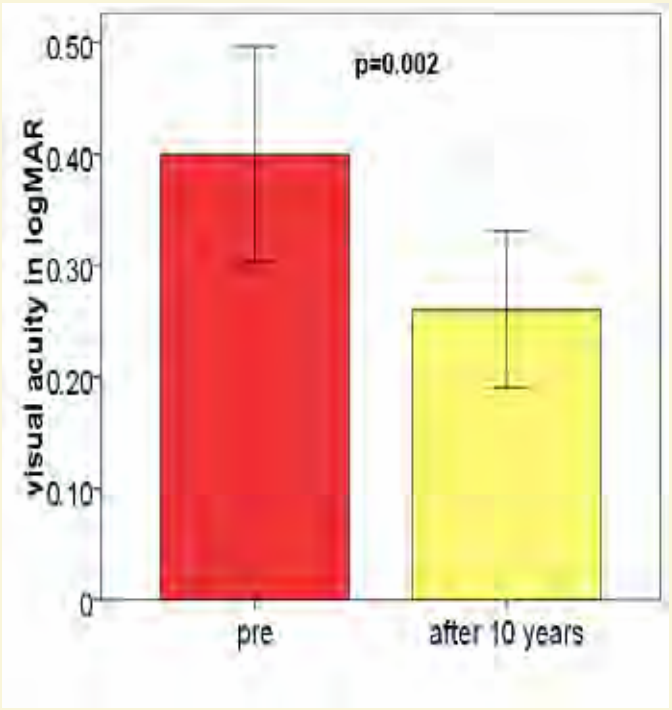
Frederik Raiskup, MD, PhD, FEBO, Anja Theuring, MD, Lutz E. Pillunat, MD, Eberhard Spoerl, PhD

- retrospective, non-randomized
- 34 eyes/24 pat.
- ♀:6, ♂:18
- Age: 28.4 ± 7.3y.
- F/U: 131.91 ± 20.13 mo.

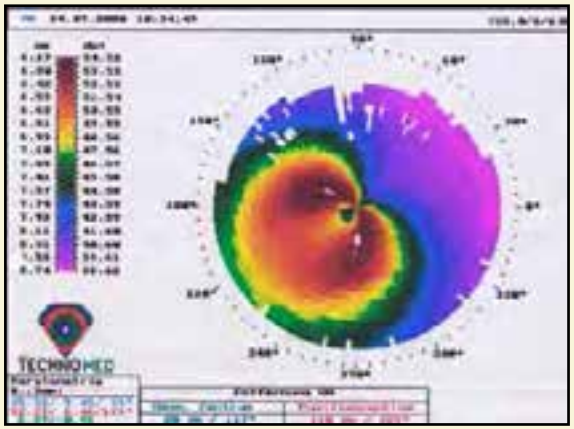
J Cataract Refract Surg. 2015; 41(1): 41-46

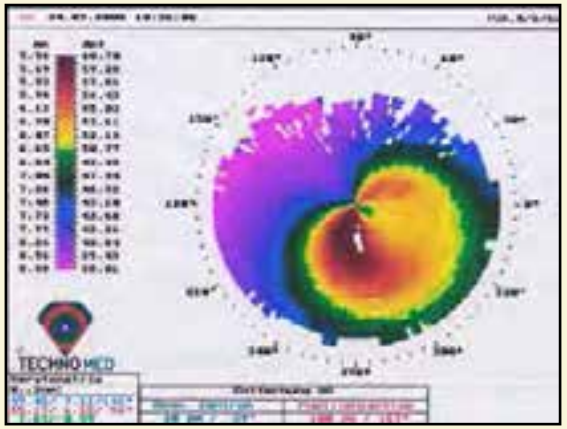
Ten-year results

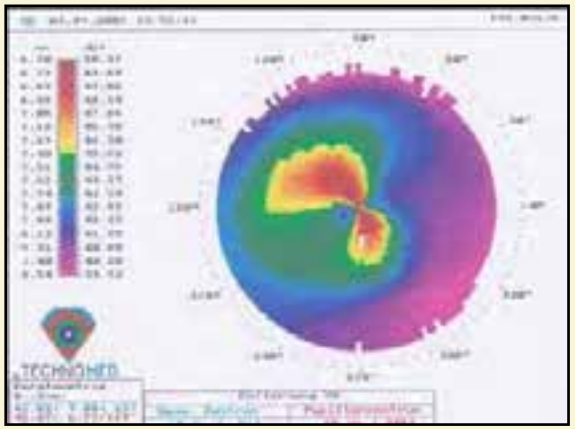


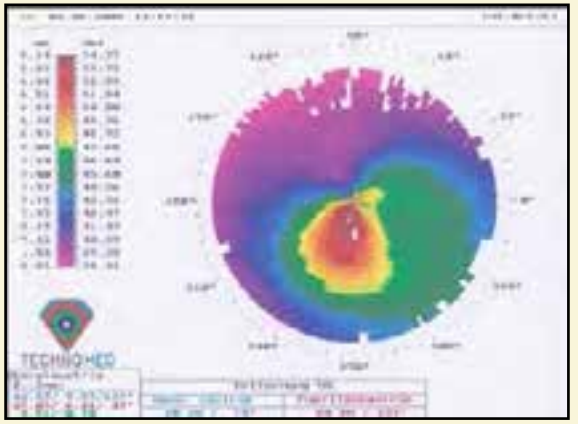


CXL – F/U: 10 y.







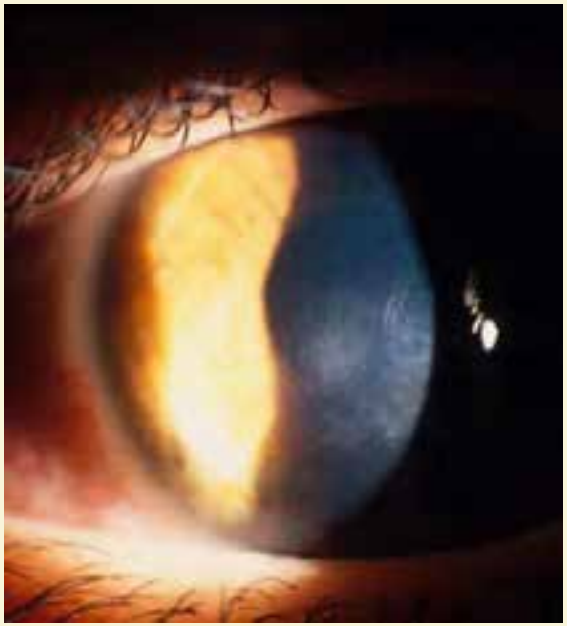


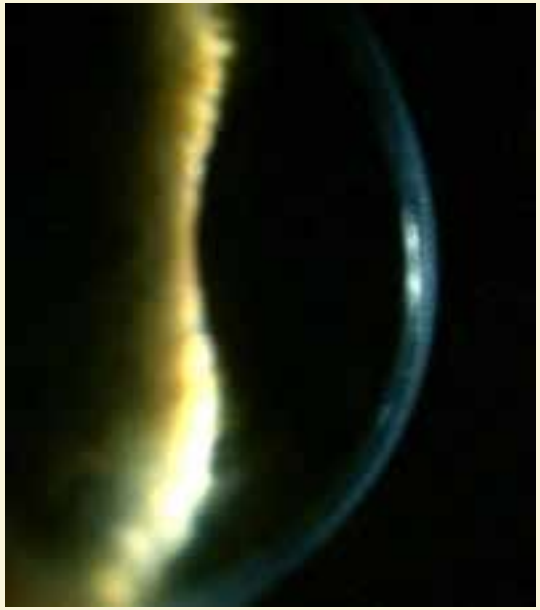
BDCVA: RE: 0,9 LE: 0,8

Complications after CXL

- Faschinger C, Kleinert R, Wedrich A. **Corneal melting in both eyes** after simultaneous corneal cross-linking in a patient with keratoconus and Down syndrome. Ophthalmologe. 2010; 107: 951-2, 954-5
- Zamora KV, Males JJ. **Polymicrobial keratitis** after a collagen cross-linking procedure with postoperative use of a contact lens: a case report. Cornea. 2009; 28: 474-476
- Hermann CI, Hammer T, Duncker GI. **Hazeformation** (corneal scarring) after cross-linking therapy in keratoconus. Ophthalmologe. 2008; 105 (5): 485-487
- Eberwein P, Auw-Hädrich C, Birnbaum F, Maier PC, Reinhard T. **Corneal melting** after cross-linking and deep lamellar keratoplasty in a keratoconus patient. Klin Monatsbl Augenheilkd. 2008; 22 (1): 96-8
- Kymionis GD, Bouzoukis DI, Diakonis VF, Portaliou DM, Pallikaris AI, Yoo SH. **Diffuse lamellar keratitis** after corneal crosslinking in a patient with post-laser in situ keratomileusis corneal ectasia. J Cataract Refract Surg. 2007; 33(12): 2135-7
- Kymionis GD, Portaliou DM, Bouzoukis DI, Suh LH, Pallikaris AI, Markomanolakis M, Yoo SH. **Herpetic keratitis with iritis** after corneal crosslinking with riboflavin and ultraviolet A for keratokonus. J Cataract Refract Surg. 2007; 33(11): 1982-4
- Mazzotta C, Balestrazzi A, Baiocchi S, Traversi C, Caporossi A. **Stromal haze** after combined riboflavin-UVA corneal collagen cross-linking in keratoconus: in vivo confocal microscopic evaluation. Clin Experiment Ophthalmol. 2007; 35(6): 580-2

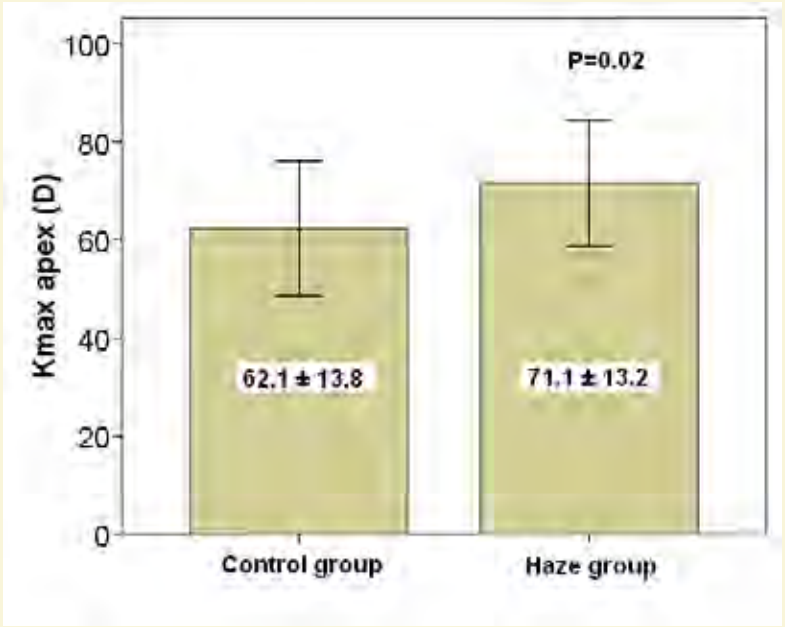
Corneal scars

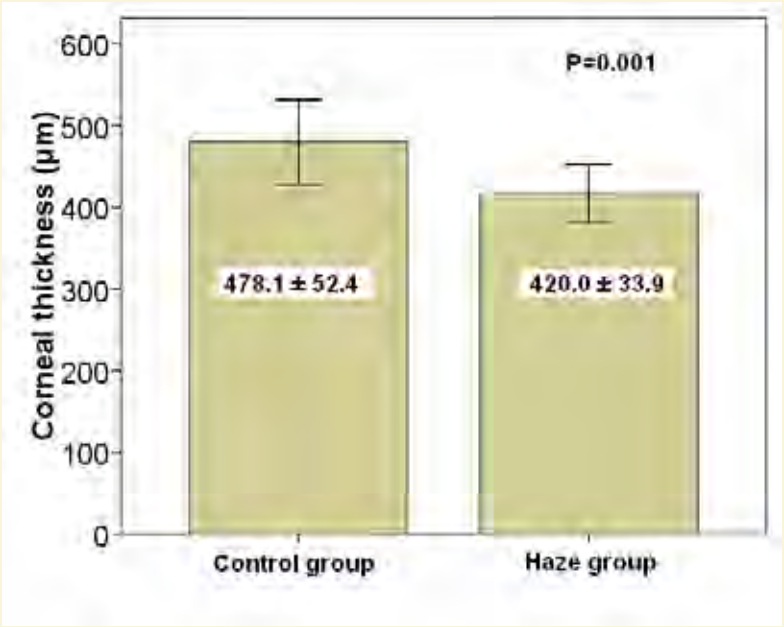




Raiskup F, Hoyer A, Spoerl E. Permanent corneal haze after riboflavin-UVA-induced cross-linking in keratoconus. J Refract Surg. 2009; 25: S824-828

Scars

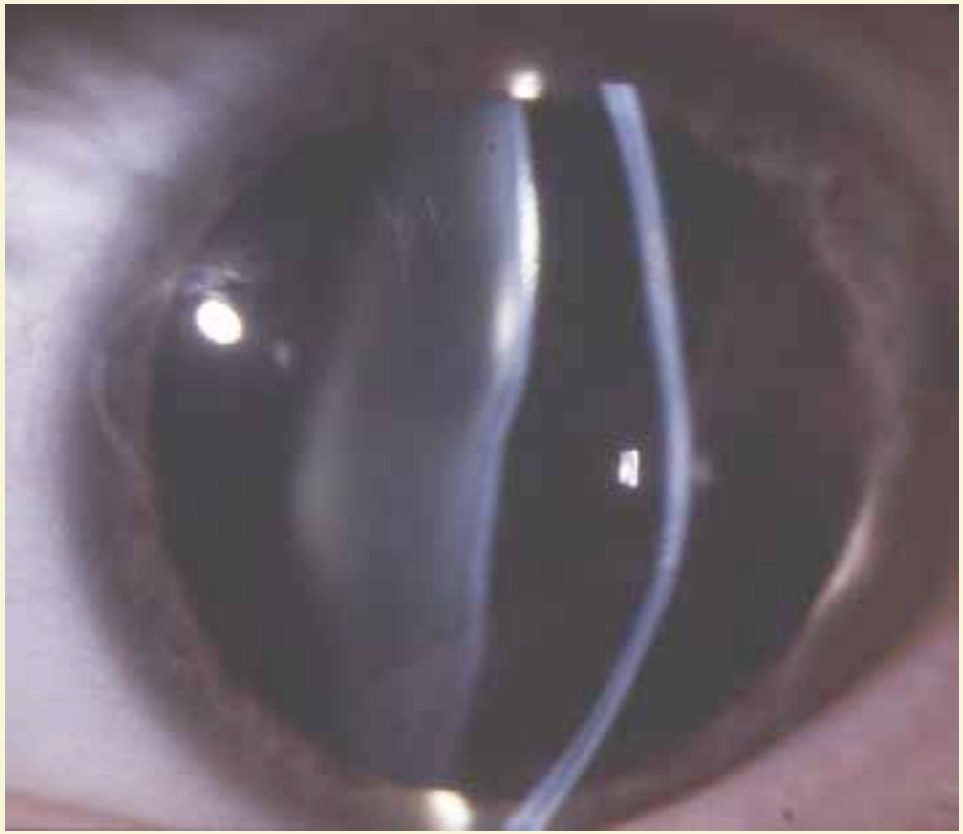

Kmax apex (D)
100
80
60
40
20
0
P=0.02
62.1 ± 13.8
71.1 ± 13.2
Control group
Haze group


Corneal thickness (µm)
600
500
400
300
200
100
0
P=0.001
478.1 ± 52.4
420.0 ± 33.9
Control group
Haze group

Corneal scar development after CXL:

- Risk factors: ↑K-values, ↓corneal thickness
- Advanced keratoconus: ↑ Risk for scar development

Thin corneas



CXL and corneal thickness < 400µm

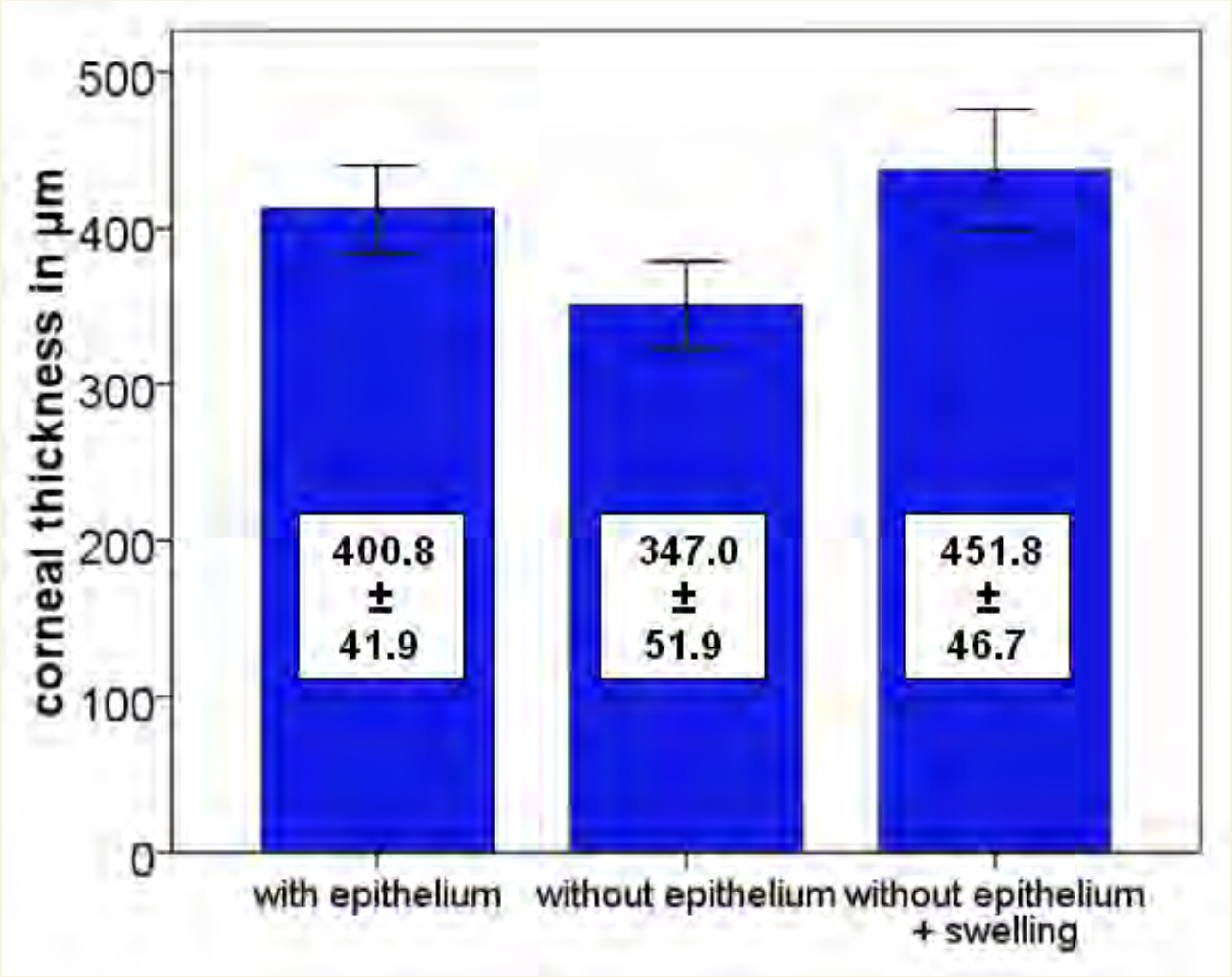
- local anaesthesia
- **Epithelium removal**
- **Pachymetry**
- **hypoosmolar 0.1% riboflavin solution**:
  2 Min/30 Min, Ø speculum
- **Pachymetry**
- UVA (370nm): 3mW/cm^2 (5.4J/cm^2)/30 Min.
- CL, ATB, Lubricant
- Steroids

Thin corneas

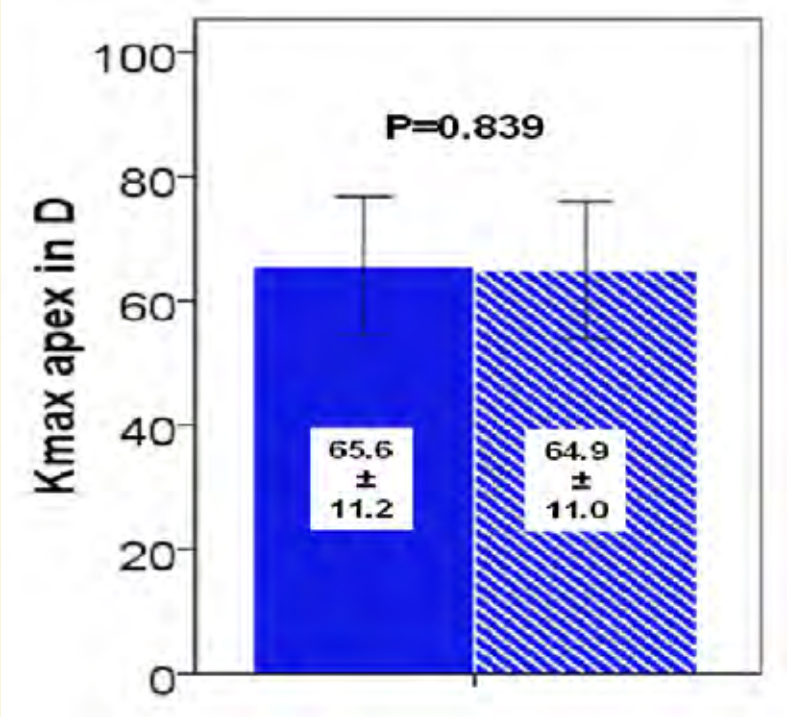
- 29 eyes
- Pat.: 29
- 20♂, 9♀
- Age: 27.4±9.4J.
- Follow-up: 1y.

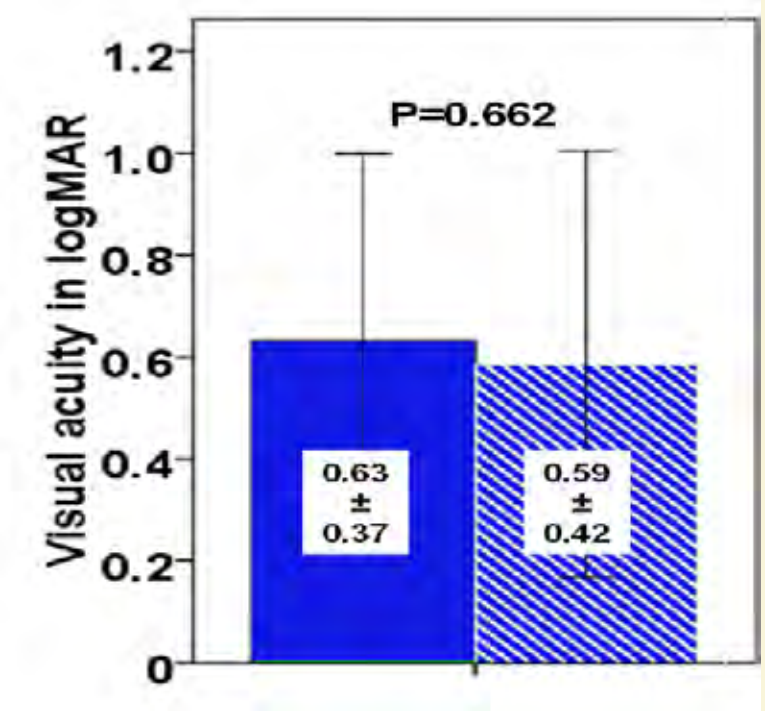
Raiskup F, Spoerl E. Corneal cross-linking with hypoosmolar riboflavin solution in thin keratoconic corneas. Am J Ophthalmol. 2011; 152:28-32

CXL and hypoosmolar 0.1% riboflavin solution



Kapex, CDVA


Kmax apex in D
100
80
60
40
20
0
P=0.839
65.6
±
11.2
64.9
±
11.0


Visual acuity in logMAR
1.2
1.0
0.8
0.6
0.4
0.2
0
P=0.662
0.63
±
0.37
0.59
±
0.42

CXL and hypoosmolar 0.1% riboflavin solution in thin corneas

- **No scars**

Does Corneal Collagen Cross-linking Reduce the Need for Keratoplasties in Patients With Keratoconus?

Gunhild Falleth Sandvik, MPhil, Andreas Thorsrud, MD,* Marianne Råen, MPhil,* Atle E. Østern, MD, PhD,* Marit Sæthre, MD, PhD,* and Liv Drolsum, MD, PhD*†*

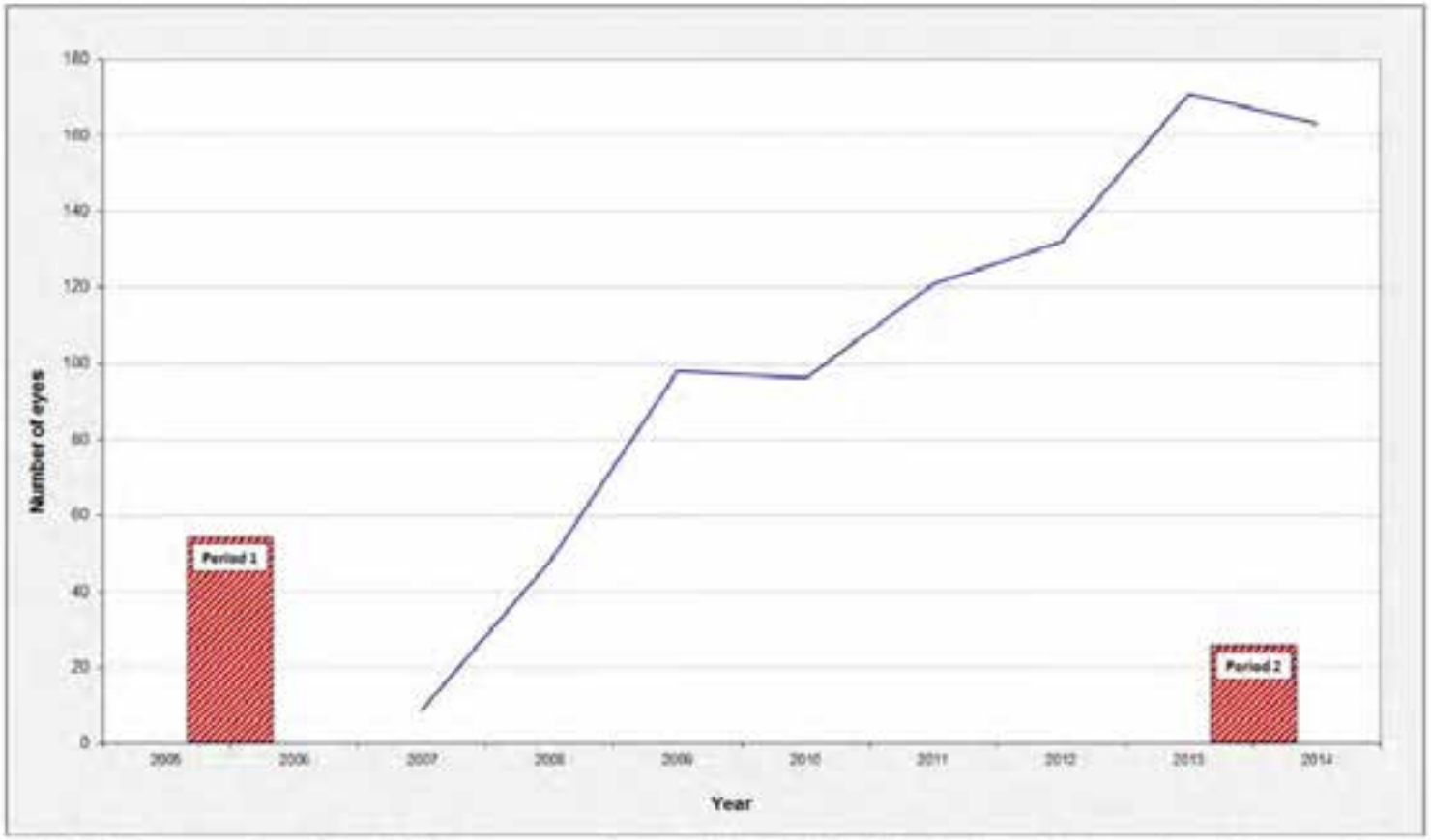


FIGURE 1. The annual number of CXL treatments from 2007 to 2015 (blue line), and the number of keratoplasties for keratoconus in period 1 (2005–2006) and period 2 (2013–2014).

Cornea 2015; 34(9): 991-995

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Conclusions: The frequency of keratoplasty for keratoconus has been more than halved in our department over the last decade. There is reason to believe that this reduction is for a great part caused by the introduction of CXL treatment.

Gomes JA, Tan D, Rapuano CJ et al. Global Consensus on Keratoconus and Ectatic Diseases. Cornea 2015; 344(4): 359-369

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A Multi-Center, Randomized, Placebo-Controlled Evaluation of the Safety and Efficacy of the [redacted] (Riboflavin Ophthalmic Solution) for Corneal Collagen Cross-Linking in Eyes With Keratoconus

This study is ongoing, but not recruiting participants.

ClinicalTrials.gov Identifier:
NCT01972854

Purpose

The objectives of this study are to evaluate the safety and efficacy of corneal collagen cross-linking performed with [redacted] (riboflavin ophthalmic solution) [redacted] compared to placebo in impeding the progression of, and/or reducing, maximum corneal curvature.

Condition	Intervention	Phase
Keratoconus	Drug: riboflavin: 0.12% riboflavin ophthalmic solution [redacted] Drug: placebo: 0.0% riboflavin opthalmic solution [redacted]	Phase 3

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Parallel Assignment
Masking: Single Blind (Outcomes Assessor)
Primary Purpose: Treatment

Primary Outcome Measures:

- Change in Kmax from baseline [Time Frame: 12 months] [Designated as safety issue: No]

  The primary endpoint is the mean change from baseline to 12 months in maximum corneal curvature (Kmax) between [redacted] treatment group and the Placebo control group.

- Safety Endpoints [Time Frame: 12 months] [Designated as safety issue: Yes]
  - Loss of BSCVA (Best Spectacle-Corrected Visual Acuity) beginning at the 6 month follow-up examination, specifically, the percentage of eyes that have a loss of 15 or more letters in BSCVA on the ETDRS (Early Treatment Diabetic Retinopathy Study) chart as compared to baseline
  - The incidence of serious ophthalmic adverse events

Estimated Enrollment:	200
Study Start Date:	November 2013
Estimated Study Completion Date:	December 2016
Primary Completion Date:	March 2016 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Experimental: 0.12% riboflavin ophthalmic solution	Drug: riboflavin: 0.12% riboflavin ophthalmic solution with the [redacted] Subjects will receive 0.12% riboflavin ophthalmic solution [redacted] followed by irradiation with the [redacted] at 30mW/cm2 intensity for 8 minutes with an on/off cycle of 1 second UVA on/1 second UVA off, for a total radiant exposure of 7.2 J /cm2.
Placebo Comparator: Placebo 0.0% riboflavin ophthalmic solution	Drug: placebo: 0.0% riboflavin ophthalmic solution with the [redacted] Subjects will receive 0.0% riboflavin ophthalmic solution (Placebo) followed by irradiation with the [redacted] at 30mW/cm2 intensity for 8 minutes with an on/off cycle of 1 second UVA on/1 second UVA off, for a total radiant exposure of 7.2 J /cm2.

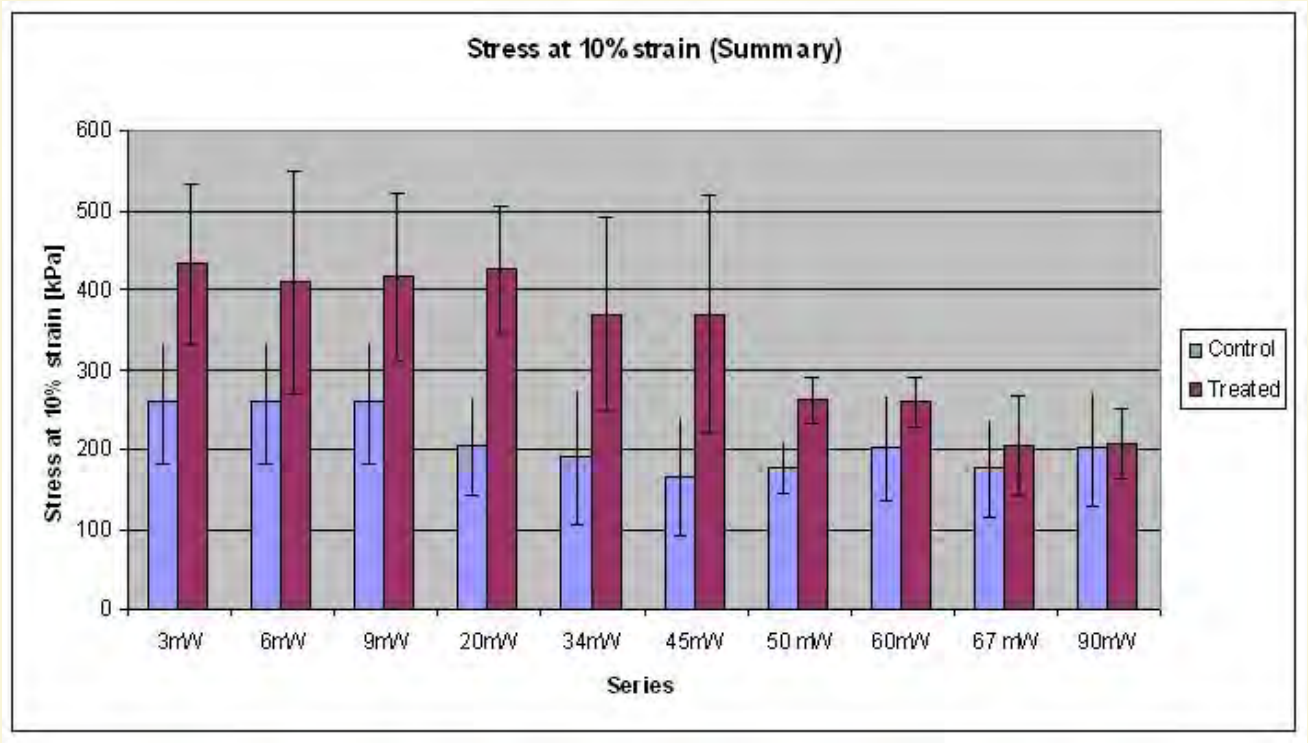
Eligibility

Ages Eligible for Study:	12 Years and older (Child, Adult, Senior)
Genders Eligible for Study:	Both
Accepts Healthy Volunteers:	No

Accelerated CXL

- shortens the illumination time by increasing the illumination intensity (Bunsen-Roscoe law of reciprocity)
- reduces the overall treatment time

Accelerated CXL

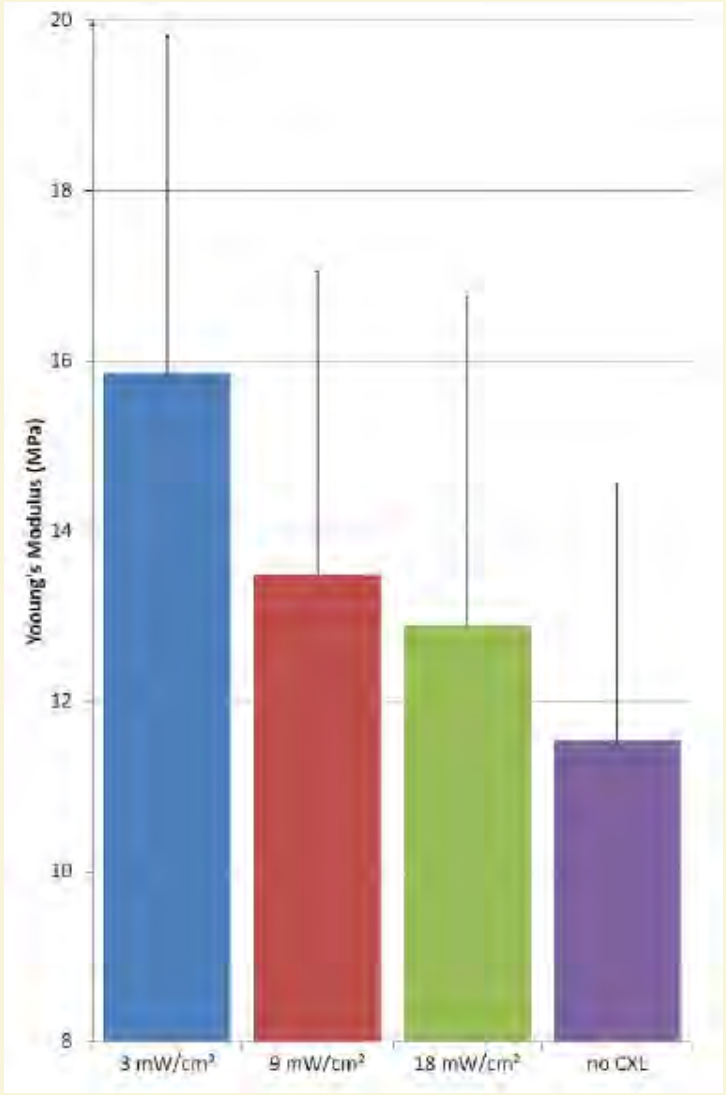


- The ex vivo results in porcine corneas show that the Bunsen-Roscoe reciprocity law is only **valid for illumination intensities up to 40 to 50mW/cm^2** and illumination time of more than 2 min.

Wernli J, Schumacher S, Spoerl E et al. The efficacy of corneal cross-linking shows a sudden decrease with a very high intensity UL light and short treatment time. IOVS 2013; 54: 1176-1180

Accelerated CXL

- The **biomechanical effect of CXL decreased significantly when using high irradiance/ short irradiation time settings.** Intrastromal oxygen diffusion capacity and increased oxygen consumption associated with higher irradiances may be a limiting factor leading to reduced treatment efficiency.



Hammer A, Richoz O, Mosquera SA et al. Corneal biomechanical properties at different corneal CXL irradiances. IOVS 2014; 55: 2881-2884

Accelerated CXL

- Sherif AM. Accelerated versus conventional corneal colagen cross-linking in the treatment of mild keratoconus: a comparative study. Clinical Ophthalmology 2014; 8: 1435-1440. **prospective randomized interventional case-control clinical trial: „ … appears to show comparable results to conventional CXL…“**
- Elbaz U, Shen C, Lichtinger A et al. Accelerated corneal collagen crosslinking for keratoconus – A 1- year follow-up. Cornea 2014; 33: 769-773. **retrospective study: „…is effective in stabilizing topographic parameters…“**
- Kymionis GD, Tsoulnaras KI, Grentzelos MA et al. Evaluation of corneal stromal demarcation line depth following standard and modified-accelerated collagen cross-linking protocol. Am J Ophthalmol 2014; 158: 671-675. **prospective, comparative study: „…provided the same treatment depth as the classic Dresden protocol…“**

Accelerated CXL

- Studies comparing the demarcation line depth between conventional and accelerrated CXL showed that the **demarcation line** was consistently **deeper with the „traditional“ protocol**.

Ozurhan EB, Sezgin Akcay BI, Yildirim Y et al. Evaluation of corneal stromal demarcation line after two different protocols of accelerated corneal collagen cross-linking procedures using anterior segment optical coherence tomography and confocal microscopy. Journal of ophthalmology 2014; 2014: 981893
Kymionis GD, Tsoulnaras KI, Grentzelos MA et al. Corneal stroma demarcation line after standard and high-intensity collagen crosslinking determined with anterior segment optical coherence tomography. JCRS 2014; 40: 736-740
Bouheraoua N, Jouve L, El Sanharawi M et al. Optical coherence tomography and confocal microscopy following 3 different protocols of corneal collagen-crosslinking in keratoconus. IOVS 2014

Accelerated CXL

- summarizing all studies on accelerated CXL, **no consistent findings** could be concluded regarding its effect in the treatment of keratoconus
- this could be explained by the **different riboflavin preparation, different CXL protocols, variable total energy** of irradiation and **different stage of disease**