UNIVERSITY OF CALGARY | FACULTY OF MEDICINE

# Corneal Crosslinking for Keratoconus and Other Corneal Thinning Disorders

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# CONTENTS

## ABBREVIATIONS

**AHW** Alberta Health and Wellness

**BCVA** Best Corrected Visual Acuity

**CADTH** Canadian Agency for Drugs and Technologies in Health

**CI** Confidence Interval

**CXL** Corneal Crosslinking using riboflavin and ultraviolet-A radiation

**DALK** deep anterior lamellar keratoplasty

**ES** Effect Size

**Kave** Average Keratometry

**KC** Keratoconus

**KE** Keratectasia

**Kmax** Maximum Keratometry

**Kmin** minimum keratometry

**KP** keratoplasty

**LASIK** Laser-Assisted in situ Keratomileusis

**LogMAR** Logarithm of the minimal angle of resolution

**NOS** Newcastle-Ottawa Scale

**PMD** Pellucid Marginal Degeneration

**RCT** Randomized Controlled Trial

**SE** Spherical Equivalent refraction

**UCVA** Uncorrected Visual Acuity

**UVA** Ultraviolet-A

# 1 EXECUTIVE SUMMARY

Introduction

- Corneal thinning disorders are rare progressive disorders that cause the cornea to bow outward into a conical shape.
- Corneal thinning disorders such as keratoconus, keratectasia and pellucid marginal degeneration can result in eye irritation, headaches, eye strain, excessive eye rubbing, light halos, light sensitivity, difficulty with night driving, glare, ghost images, light streaking and worsening myopia.
- KC affects approximately <0.05% of the global population and KE affects approximately 0.01-0.9% of those who undergo LASIK eye surgery. PMD is a rare disease; no incidence or prevalence rates are available.
- These disorders often become symptomatic during early adulthood.
- Gradual loss of visual acuity and other symptoms related to these disorders may heavily impact patient quality of life.
- CXL is under consideration as a method for managing corneal thinning disorders.
- There is no current comparator for CXL.

Methods

- A systematic review of the literature was conducted using nine electronic databases.
- A meta-analysis was conducted based on data from prospective cohort studies.

Results

- There are three previous Health Technology Assessments; none are relevant to the Alberta context.
- There are no systematic reviews or meta-analyses on CXL for management of corneal thinning disorders in the literature.
- 1284 titles and abstracts were retrieved with the systematic search, 103 were reviewed in full-text, and 36 (2 randomized controlled trials and 34 cohort studies) were included. A meta-analysis of the 34 cohort studies was conducted.
- The quality of the cohort studies were assessed using the Newcastle-Ottawa Scale. Twenty-eight of the included studies were considered to be of moderate quality and 6 were high quality according to this scale.
- The RCT quality was assessed using the Jadad scale; both RCTs were classified as moderate quality.
- Although there is the risk of serious adverse events occurring after CXL treatment, these are rare, and CXL is considered to be a safe, minimally invasive procedure.
- The meta-analysis revealed that with keratoconus patients, CXL treatment stops progression and produces statistically significant improvements in Best Corrected Visual Acuity, Uncorrected Visual Acuity, minimum keratometry, average keratometry, maximum keratometry, spherical equivalent and pachymetry outcomes.
- Both RCTs report that CXL results in stabilization of outcomes related to corneal thinning.
- A budget impact analysis based on Alberta costs and global prevalence and incidence data found that provision of CXL would cost $837,052.27- $5,298,846.74 annually when

existing cases are incorporated into the first three years and between $90,855.56 and $344,612.94 annually once existing cases have been treated and only new diagnosis' are undergoing CXL.

## Conclusions

- CXL for the treatment of corneal thinning disorders is an effective treatment.
- However, the long-term effectiveness and CXL's impact on the need for corneal transplant is unknown.

# 2 INTRODUCTION

## 2.1 Purpose of Review

Corneal thinning disorders are rare progressive disorders that can either be caused by a primary disease process (keratoconus) or may be secondary to another process; such as post laser-in-situ-keratomileusis (LASIK) induced keratectasia (KE). It has been estimated that the most common corneal thinning disorder, keratoconus (KC), affects 1 in every 2000 people globally.[1] Non-surgical management of corneal thinning disorders has often been limited to rigid gas permeable glass contact lenses. In advanced stages, corneal transplant has been the standard of care. It has been estimated that corneal transplant is necessary for 10-20% of patients with a corneal thinning disorder.[2] Corneal crosslinking using riboflavin and ultraviolet-A radiation (CXL) is an emerging technology which may be used for managing corneal thinning disorders. The purpose of this review is to determine the safety, clinical efficacy, social impact and economic value of CXL for the management of corneal thinning disorders.

## 2.2 Policy Question

The primary policy question to be answered within this review is:

- Should corneal collagen cross-linking using riboflavin and ultraviolet-A radiation (CXL) be publicly funded for patients with Keratoconus and other progressive corneal thinning disorders in Alberta? If so, what is the optimal clinical situation?

### 2.3 Research Questions

With the overall goal of answering the policy question above, this review will also address the following four research questions:

- What is the burden of Keratoconus and other progressive corneal thinning disorders to patients, the patterns of care and the capacity to deliver care in Alberta?
- How safe and effective is CXL for the treatment of Keratoconus and other progressive corneal thinning disorders?
- What is the cost-effectiveness of CXL for the treatment of Keratoconus and other progressive corneal thinning disorders?
- What is the budget impact of publicly funding CXL for the treatment of Keratoconus and other progressive corneal thinning disorders in Alberta?

## 3 SOCIAL AND SYSTEM DEMOGRAPHICS (S)

### 3.1 Description of Conditions and Disease Progression

#### 3.1.1 Keratoconus

KC is the most common type of degenerative corneal thinning disorder.[1] Prevalence estimates of this disease vary from 1/2000 to 1/500, with incidence ranging from 50/100,000-230/100,000.[3] Alberta-based prevalence and incidence rates are unavailable for this disease. KC has an early onset with the median age being 25 years; progression often slows or stops by the age of 40.[3] Although this disorder often begins at puberty, onset and progression vary greatly amongst

individuals.[3] KC is considered a bilateral disorder, meaning it affects both eyes; however, progression is rarely identical in both eyes.

KC results in non-inflammatory thinning of the cornea, which is the anterior clear portion of the eye covering the pupil and iris. Healthy corneas are approximately half a millimeter (530-550nm) thick, whereas corneas of patients with KC may be as thin as 400nm.[4] As the cornea thins due to KC, the natural pressure within the eye (intraocular pressure) presses the cornea outward, resulting in a conical shape.[3] There are a number of functional and anatomical outcomes of KC.

Symptoms of KC vary greatly across individuals. Initially individuals with KC may be asymptomatic, or the effects may be easily overlooked.[3] Suspicion of KC may arise during a regular eye exam when an ophthalmologist is unable to improve a patient's vision by correcting refractive errors, or when the disease progresses and the patient seeks medical care for their symptoms. Some clinical signs of KC include: evidence of a series of coloured rings (Fleischer's ring) which result from iron deposits; apical scarring; corneal protrusion; vertical stress lines (Vogt's Striae); stromal scars; and corneal thinning.

The first functional symptom of KC is often blurred vision. As the disorder progresses, other symptoms such as eye irritation, headaches, eye strain, excessive eye rubbing, light halos, light sensitivity and difficulty with night driving may develop.[5] With progressive thinning, one's vision will become increasingly blurred. Additional symptoms such as glare, ghost images, light

streaking and worsening myopia may occur as the disorder progresses.[6] In advanced KC, the eye will appear conical in shape.

Currently there is no clear etiology for KC; it is proposed to be a multifactorial process resulting from the numerous pathological pathways. The general pathophysiology of KC shows that affected corneas exhibit high activity and expression of catabolic enzymes, which increase the breakdown of both collagen proteins and the cells that produce these proteins (keratocytes). These changes to the collagen structure and orientation within the cornea ultimately produce the characteristic corneal thinning of KC and the resulting clinical sequelae.

While underlying mechanisms of these alterations remain largely unknown, KC has been shown to have a genetic link, where it is associated with familial inheritance and genetic disorders (such as Marfan's, connective tissue disorders and Down syndrome).[7] A small number of patients exhibit a positive family history, and further clinical studies suggest an autosomal dominant mode of inheritance with a variable phenotype.[7] These studies have been largely been cross-sectional, and limited by ethnicity and gene pools. The resulting point prevalence has also been further confounded by the varying degrees of clinical expression. Monozygotic twin studies have largely supported a genetic basis for KC, however there is evidence that suggests an environmental factor is also required to trigger the genetic susceptibility.[7]

Down syndrome and other genetic diseases have been shown to be associated with KC. Those with Down syndrome have a 0.5-15% chance of having KC; roughly 10-300 fold higher risk than the normal population. There is again discrepancy in the cause of KC within Down syndrome

patients, where some believe there is a genetic link, while others believe there is a link between the disease and eye rubbing. Connective tissue diseases (ex: Marfan's and Ehler's-Danlos syndromes) are also associated with KC. The cause of this link is unknown, but it is believed that the biochemical pathophysiology has a distinctly different underlying collagen abnormality. Prevalence does not differ based on ethnicity, and gender does not appear to impact the chances of getting KC.[3]

### 3.1.2 Keratectasia

KE (also known as iatrogenic keratectasia) is a noninflammatory corneal thinning disorder that can only be induced by LASIK surgery. The first report of this iatrogenic condition was made in 1998, and since then it has been established as a serious post LASIK complication.[8] Incidence estimates of KE vary from 0.01%-0.9% of those who have LASIK surgery.[9] In 2001, it was estimated that approximately 100,000 laser eye surgeries were done annually in Canada.[10] Alberta-based prevalence and incidence rates are unavailable for this disease. KE may manifest one of two ways: it may result in central corneal thinning (similar to KC) with a symmetric astigmatism; or it may result in irregular astigmatism.[11]

Various hypothesis' exist about what causes KE to develop; the two most frequent being that the patient had early (forme fruste) undiagnosed KC prior to LASIK surgery, or that excessive stromal tissue was removed during surgery which causes biochemical instability.[12] KE may begin to affect corneal integrity as soon as a week post-surgery, or as late as several years after the procedure.[13] Once KE begins to manifest, the process cannot be reversed, and is degenerative there forward.

The main risk factor for developing KE is irregular corneal topography prior to surgery. The following factors have also been found to influence development of KE: KC, high myopia, younger age at the time of surgery, deep ablations, thin corneas, excessive ablation or thick flap creation, and thin residual stromal beds.[8] The treatment options for this complication follow along the same pathway as other corneal thinning disorders, where vision can be corrected by contact lens/glasses, and progressing to keratoplasty in the more severe forms.

The management aim in this disease is to identify the risk factors in pre-LASIK screening, and to prevent its development. However, little is currently known about the mechanisms of this disorder; as more is understood, more preventative measures can be taken. Current preventative measures are limited to thorough ophthalmological exam (including assessment of corneal thickness) and flap thickness measurement during surgery.[12]

### 3.1.3 Pellucid Marginal Degeneration

PMD is a bilateral corneal thinning disorder, which is very similar and often confused with KC. It is characterized with peripheral thinning of the inferior lower cornea, resulting in a bulging of the cornea, and formation of atypical astigmatism. This disorder is so rare that incidence estimates are not available.[14] Unlike KC and KE which typically affect the whole cornea, PMD often just results in a small band of thinning cornea.[15] It is often differentiated from other corneal thinning disorders by the shape of astigmatism; rather than progressing in a symmetrical cone in the middle of the cornea, PMD manifests as an uneven bulge towards the bottom of the cornea.[15]

PMD is so rare that very little is known about the mechanics of the condition. It is idiopathic and tends to manifest in early adulthood (with first symptoms appearing in 20-30 year old patients).[14] It tends to affect males more frequently.[14] There have been no epidemiological studies on this disease, and currently there is no evidence to suggest a genetic link.[14]

The net result of PMD is progressive deterioration of visual acuity. However, compared to KE and KC, PMD is slower to progress. As such, the disorder can often go undiagnosed while in early stages, and is often diagnosed during a regular eye exam or during work-up for LASIK or other ophthalmological surgery.[15] A few years after onset, symptoms will often have progressed enough to interfere with usual activities.[15] Ten years after onset, PMD usually stabilizes. After this stabilization, individuals will experience no further mechanical or functional degeneration.[15]

As symptoms are slow to progress and stabilize early, the majority of patient's symptoms can be managed with non-invasive methods such as glasses or rigid gas permeable contact lenses. Very few PMD patients require surgical management (corneal transplant).

### 3.1.4 Tools for Measuring Progression

There are a number of tools which can be used to track and understand the progression of KC, KE and PMD. Some of the most frequently used tools to assess progression include: corneal topography, pachymetry, visual acuity and refractive error. Other less frequently used measures include wavefront aberrometry and endothelial cell density.

Corneal topography is one of the most frequently used methods of assessing corneal thinning. This medical imaging technique allows clinicians to map the curvature of the cornea non-invasively.[16] This procedure is often one of the tools used to confirm a diagnosis of a corneal thinning disorder, and is also used to track the disease progression.[16] This tool is often comprised of three measurements: minimum keratometry (kmin), average keratometry (kave) and maximum keratometry (kmax).[16]

During corneal topography, concentric rings are projected on to the cornea and the image that is reflected back from the cornea is captured by a specialized camera.[16] The images obtained from the camera are analyzed by computer software and can be presented to the practitioner in various formats.[16]

Pachymetry is a method of measuring corneal thickness. There are a variety of types of corneal pachymetry, however ultrasonic pachymetry is the most commonly used.[17] With ultrasonic pachymetry, anesthesia numbs the area of interest while an ultrasound probe is placed on the eye.[18] This procedure usually takes approximately 30 seconds per eye.[18] Normal central corneal thickness is 490-560 um.[19]

Visual acuity, or vision clarity, is often measured in two ways: best corrected visual acuity (BCVA) and uncorrected visual acuity (UCVA). Visual acuity may be used: as a diagnostic screening tool; as baseline data; to measure disease progression; to evaluate treatment; and to determine status as legally blind.[20] BCVA and UCVA are often part of a regular eye exam.[20] Frequently, a Snellen chart is used to measure visual acuity.[20] This chart consists of a series of

letters of decreasing size; each row is referred to as a 'Snell line". When measuring UCVA, the patient is asked to read the Snell chart letters aloud without vision correction, such as glasses or rigid gas permeable contact lenses.[21] BCVA is a measurement of how well a patient can read the letters using optimal correction for nearsightedness (myopia) or farsightedness (hyperopia).[21]

UCVA and BCVA are commonly represented as a number under a numerator of 20 (e.g. 20/18 vision). Fractional visual acuity is determined by placing viewing distance (20 feet) over letter size.[20] When visual acuity is 20/20, an individual has normal vision.[21] A patient is considered to have low vision when their BCVA is 20/70 or worse, and one is considered to be legally blind with BCVA of 20/200 or worse. Clinically, BCVA and UCVA are presented as a logarithm of the minimal angle of resolution (logMAR) rather than as a fraction. On this scale, normal vision is 0 logMAR.[21] Low vision on the logMAR scale is 0.544, and those considered legally blind have a logMAR of 1.

There are three common types of refractive error: myopia, hyperopia and astigmatism.[22] Refractive error occurs when ones eye shape incorrectly bends light, resulting in blurred vision.[22] Refractive errors are commonly corrected through prescription eye glasses, contact lenses or refractive surgery (LASIK).[22] Refractive error is measured as spherical error and cylindrical error. Another measure, spherical equivalent refractive error (SE), is a combination of both spherical and cylindrical error.

### 3.2 Impact of Corneal Thinning on Patient Quality of Life

The impact that unilateral and bilateral low vision has on quality of life has been well studied. Those with low vision often have trouble doing everyday tasks such as reading, watching television, making meals and recognizing faces.[23] It also increases the risk of falls and often results in the individual becoming highly dependent on others for assistance with daily activities.[23] Bilateral vision loss, which is the normal progression for corneal thinning disorders, has significantly more impact of quality of life than unilateral vision loss.[23] In a study by Chia et al, it was found that uncorrectable vision loss had a similar impact on quality of life as a major medical event such as a stroke.[24]

Although corneal thinning disorders are comparable to general uncorrectable vision loss in some respects, an additional factor of consideration is that these disorders primarily affect young adults and often result in life-long symptoms. As Kymes et al note, due to the young age of onset, corneal thinning disorders have a more significant impact on quality of life than would be expected from a disorder of this type.[25] It has been found that keratoconus sufferers had increased prevalence of anxiety disorders, poorer mental health, significant difficulty preforming social duties and high dependency.[25] A study by Wagner et al found that keratoconus patients with less than 20/40 vision (0.3 logMAR, 0.5 decimal acuity) had particularly reduced quality of life.[26] Kymes et al conclude that with keratoconus sufferers, moderate impairment results in disproportionate burden.[25]

Of interest is that a significant correlation has been found between rigid gas permeable contact lens use and quality of life; those with KC who used rigid gas permeable contact lenses reported

significantly better mental health and independence than their non-lens wearing counterparts.[25] However, lens wearers also reported significantly higher discomfort.[25]

In a study assessing quality of life post-corneal transplant, it was found that from a patient perspective, a successful operation was most often defined in terms of relief of pain, improvement in visual acuity and decreased glare; functionality was the most important indicator of post-operative quality of life.[27] Objective outcomes appear to have a significantly smaller impact on satisfaction.[28]

### 3.3 Methods of Managing Mild to Moderate Stage Corneal Thinning Disorders

Various treatment options exist for those suffering from corneal thinning disorders. These range from non-invasive methods of management to invasive forms of treatment. In very early stages of corneal thinning disorders, simple correction with glasses or soft contact lenses is often adequate to correct vision to 20/20. Glasses and soft contacts, however, cannot correct vision change due to astigmatism, and over time they will become ineffective at improving visual acuity. Rigid gas permeable contact lenses are indicated as the next method of management.

Ninety percent of those with corneal thinning disorders will require rigid gas permeable contact lenses. These contact lenses are specially fit to accommodate an irregularly shaped cornea.[29-31] They are made from durable plastic which is designed to allow oxygen to reach the eye. While they are worn, rigid gas permeable contact lenses replace the shape of the cornea and act as a new refracting surface, thereby correcting low vision due to astigmatism. Over time, these lenses can become increasingly difficult to fit due to progression of the irregularity of the cornea. Rigid

gas permeable contact lenses are a way to manage symptoms, but do not slow the disease progression. Soft contacts do not correct for astigmatism, and can only be used to correct visual acuity.

As corneal thinning disorders progress, the minimally invasive forms of treatments no longer have a therapeutic effect due to the increasing corneal irregularity. The next treatment option for these individuals would be the minimally invasive surgical implantation of intrastromal corneal ring segments (Intacs). These devices function to flatten the central cornea, thereby reducing the degree of corneal irregularity.[32-34] Since implantation is a surgical procedure, there are potential side effects such as post-operative infection and epithelial damage.[35;36] It is important to note that this form of treatment may temporarily enhance visual acuity; however, it does not alter the progression of disease. Further treatment options are the more invasive keratoplasty and CXL procedures.

### 3.4 Corneal Crosslinking Procedure

CXL is a process that uses riboflavin (vitamin B2) and ultraviolet A (UVA; 37nm) light to alter and strengthen the cornea. There have been various combinations of other protocols used, but the combination of riboflavin and UVA is safe and practical. Riboflavin is a non-toxic, naturally occurring chemical in the human body; its main function is to metabolize fats, protein and carbohydrates. In the process of CXL it works as a photo-mediator to increase the absorption of UVA light into the corneal stroma.[37] Studies have shown that it can increase the absorption of UVA from 30% to 95%.[38] Since the underlying molecular pathology of the corneal thinning disorders is the breakdown and abnormal structure of the cornea, UVA light functions as an

agent that increases the degree of molecular bonds between collagen type I and other molecules of the extracellular matrix of the cornea. This process of 'Cross-linking' increases the strength and rigidity of the cornea, thereby slowing or even arresting the progression of the disease. The precise mechanism is of CXL is still largely unknown, and apart from the proposed molecular mechanism above, all the results are indirect, with no definitive chemical proof.[37]

The surgical protocol for CXL may vary marginally, although it seldom deviates significantly. CXL is performed in the operating room under sterile conditions and topical anesthesia (ex: proparacaine 0.5%, Oxybuprocaine hydrochloride 0.4%). The central 7.0 to 8.5 mm diameter of the corneal epithelium is then removed from the patient's eye. Photosensitive riboflavin 0.1% solution is instilled every 5 minutes for 20 minutes until the corneal stroma is completely soaked and then every 5 minutes during the 30-minute irradiation with ultraviolet-A (UVA) light. The UVA irradiation is performed using the UV light-emitting diode (370 nm) at a working distance of 5 cm. The correct irradiance density (between 2.7 mW/cm2 and 3.3 mW/cm2) and dose (5.4 J/cm2) are checked before starting with a UVA meter (LaserMate-Q, Laser 2000) at 1 cm and regulated with the potentiometer if required. After treatment, the ocular surface is washed with profuse irrigation using a balanced salt solution and post-procedure topical antibiotic is given.

Surgeons may opt to not remove the epithelium in order to reduce the chance of infection, and to reduce recovery time. This method may be particularly attractive to surgeons performing CXL on young children. There is evidence that CXL without epithelial removal still results in significant improvements in vision and slowed disease progression.[39] Small variations may also exist in the frequency of riboflavin instillation before and during the procedure. In the literature,

studies vary from instilling riboflavin every minute to every 10 minutes prior to the procedure.[40;41] Similarly, during the procedure, the literature suggests a variance from instilling riboflavin from every two to every 10 minutes.[41;42] Depending on the UVA device used, there may be slight variance in the wavelength used for the procedure; as an alternative to 370nm, 365nm wavelength has been used.

After the procedure, the surgeon will apply soft 'bandage' contact lenses to treated eyes, which will be worn for up to four days or until the corneal epithelium has healed.[43] Often, an antibiotic is prescribed to prevent post-surgical infection and pain medication will be provided to ease post-operative discomfort. It is suggested that patients undergoing CXL plan for 2 weeks of recovery before they resume normal activities.[43]

Patients will often gain access to CXL one of two ways in Alberta. Patients may come in for refractive surgery, not knowing that they have early KC or PMD, and will be assessed for CXL after an ophthalmological exam shows signs of a corneal thinning disorder. Alternately, patients will be referred to a clinic by an ophthalmologist after being diagnosed with a corneal thinning disorder.

Within Alberta, there is currently no waitlist for CXL. However, experts in the field indicated that should CXL become publically funded, the number of patients accessing the treatment could increase which may impact the wait time. Currently, there is no comparator for CXL.

### 3.4.1 Frequent Side-Effects of CXL

After the CXL procedure, the patient is expected to experience blurry vision, lacrimation, and the sensation of a foreign body for approximately 24-48 hours. Blurry vision results from corneal edema, and can persist up to 3 months. The edema present in the cornea is due to the thinning and removal of keratocytes, confocal microscopy has verified that the edema is focused in areas devoid of keratocytes. As the edema resolves the patient can expect to have improvement in vision.[44] There are more serious side effects that can occur post-CXL, which can lead to damage ranging from temporary to permanent. These side effects fall under two broad categories, corneal haze and keratitis, which are discussed in the next section.

### 3.4.2 Serious Post-Procedural Side Effects

**Corneal Haze**

Corneal haze can occur in varying degrees post-CXL. It is a product of corneal scarring resulting in diffuse sub epithelial opacification. Corneal haze was first noted by Herrmann et al in a 41-year-old man, and responded gradually to corticosteroid treatment over a few months.[45] There have been more frequent and numerous observations of this side effect post-CXL since this initial case-report, with estimates of occurrence in 7-8.6% of all patients post-CXL.[46] Greenstein et al found that corneal haze was the worst at one-month post CXL, plateaued at three months post CXL, and significantly dissipated up to one-year post CXL. They also found that the degree of the haze (measured by densitometry) did not correlate with clinical outcomes.[47] Rasikup et al conducted a retrospective study investigating the formation of corneal haze post-CXL. They found that patients with advanced KC are at a higher risk of haze development due to low corneal thickness, and high corneal curvature.[48] Lim et al observed the occurrence of corneal

haze in patients with a mild form of KC, indicating that factors other than severity of KC plays a role in the formation of corneal haze, and that further research is needed into the phenomenon.[46]

**Keratitis**

After any surgical procedure there is the inherit risk of infection, CXL is no exception, especially since there is de-epithelialization of the cornea (removal of a natural defense barrier) and post-procedure use of corticosteroids. There have been significant reports of infection caused by numerous agents within the literature. Microbial Keratitis, has been described in detail, with all cases being successfully treated with antibiotics. [49;50]

However, there have also been more serious and rare cases noted in the literature. Fungal keratitis caused by Fusarium solani, has been reported in a 23-year-old woman, 22 days post-procedure, despite complete re-epithelialization.[51] A case of Acanthamoeba keratitis with corneal melting was described in a 32-year-old woman, five days post procedure. The patient reported to have washed their face with tap water, while unaware of wearing a bandage contact lens. They experienced corneal perforation and required keratoplasty.[52] Herpes keratitis has been reported in patients with no history of herpetic disease. The infection responded to anti-viral and steroid treatment, and showed no relapse 2 months post operation.[53]

There has also been a report of four patients experiencing idiopathic keratitis post-CXL that was characterized by pronounced ciliary redness with cells in the anterior chamber and central keratic precipitates. These patients required treatment with high dose topical corticosteroids, which was successful in resolving the inflammation. However there was permanent damage in two eyes that

clinically manifested as a decrease in BCVA. There has been one further report of keratopathy post CXL that was characterized with corneal infiltrates and no definitive infective agent; resolution was achieved after these patients were treated empirically with antibiotics and corticosteroids.[34] Although there are case studies which describe serious and permanent adverse events due to infection after CXL, there is no data in the literature on the rate at which this occurs. It appears to have a very low incidence rate, however, this is a serious post-operative complication and therefore all patients undergoing CXL require close follow-up post-operatively.

### 3.4.3 Contraindications for CXL

CXL is not indicated for all patients suffering from a corneal thinning disorder. It has been shown to be safe for patients with corneas greater than 400um thick, who have no corneal endothelial damage.[54] The only absolute contraindication for CXL is performing it on corneas thinner than 400um; using CXL on such patients has been shown to cause severe and frequent complications.[54] As many patients with corneal thinning disorders have drastically thin corneas, Hafezi et al developed a modification in which hypo-osmolar saline is added to the 0.1% riboflavin in order to induce temporary corneal thickening.[55] This method has thus far been effective in allowing thin corneas to undergo CXL safely.[54]

## 3.5 Corneal Transplant Procedure

Keratoplasty (KP) is required in 10-20% of patients with KC; this condition is one of the leading indications for KP in the world. The indication for KP is a BCVA below 0.5 (logMAR) despite correction with glasses/contact lens and other therapies. Alternatively, it may be indicated if a

patient cannot tolerate traditional non-invasive methods of management, such as gas permeable contact lenses.[56] Two KP procedures are used: penetrating keratoplasty, and deep anterior lamellar keratoplasty (DALK).[37]

Penetrating keratoplasty is a corneal transplant, or graft where the entire thickness of the cornea is replaced. This has typically been considered the standard of care for patients with advanced corneal thinning disorders. Penetrating keratoplasty requires the availability of a healthy donor cornea from a recently deceased individual. During the procedure, anesthetic and a sedative are given and a speculum is put in place to keep the eye open. A device (trephine) is used to cut the middle two-thirds of the cornea from the donor eye (approximately 8mm), while a similar section is cut from the sedated patient.[56] The donor cornea is placed and sutured to replace the diseased cornea. After the procedure, patients are prescribed antibiotics.[56] Disadvantages to penetrating keratoplasty include: risk of infectious keratitis; astigmatism; graft rejection; graft failure; reoccurrence of KC; and the potential for broken sutures.[57]

DALK is a newer procedure involving only the exchange of the corneal epithelium and stroma. During surgery, the anterior portion of the cornea is removed and replaced with an equal area of healthy cornea from a donor. This procedure requires manual dissection which has been a source of complication in the past; however, improved surgical technique, and instruments have yielded more favorable outcomes. With DALK there is less chance of infection and graft rejection.[58]

Patient visual acuity outcomes are comparable between both procedures, and the choice of procedure is based on complications, contraindications and side effects.

Within Alberta, those needing urgent corneal transplant are usually scheduled for surgery within 6 months. However, the waitlist for elective corneal transplant is upwards of 5 years. An expert in the field noted that this significant wait time is associated with a paucity of donors and funding.

## 3.6 UV-A Devices

There are two devices which are frequently used for CXL: UV-X and VEGA. Within the literature, the most commonly cited device is the UV-X, which is manufactured by IROC Innocross. This device was created by Dr. Theo Seiler and has been produced in Switzerland since 2006.[59] Two generations of this device exist: the UV-X 1000 and the UV-X 2000. The UV-X 2000 boasts to be able to reach greater depths of tissue, thereby having a stronger effect than the first edition.[59] The company website also notes that the UV-X reduces treatment time to 10 minutes by using a more intense beam.[59]

VEGA CBM X-Linker is also used within the literature. This device is manufactured by the Italian company SOOFT Italia which is a division of OFTA hi-tech.[60] It uses 5 diodes to deliver UVA light at 370nm.[60]

### 3.6.1 UV-A Devices Licensed for Use in Canada

Within Canada, there are two devices licensed for use. The UV-X device developed by IROC Innocross was approved for use in Canada, and is produced within the country by ACCUTECH Medical Technologies, a company out of Cambridge, Ontario.

In January, 2012, it was announced that Health Canada would be licensing another UVA device called the Avedro KXL system.[61] With significantly higher UVA power, this device lowers the treatment time to 3 minutes.[61] This device has two uses; it can be used to do CXL procedures for corneal thinning disorders, or can be used at the time of LASIK to strengthen the cornea as a preventative measure, before thinning has occurred.[61] Within Canada, this device will be licensed for the latter use (often called Lasik Xtra).[61]

### 3.7 Current standard of Care in Alberta

In Alberta, there are no known clinical guidelines. However, practitioners follow a similar care pathway. For those with very early stage corneal thinning, glasses and soft contact lenses are used. For mild to moderate management of corneal thinning disorders, rigid gas permeable contact lenses are the current standard of care in Alberta. As thinning progresses and contact lenses become difficult to wear, the patient may be eligible for Intac implants. In advanced stages, the patient will be assessed for corneal transplant. CXL may be used before a patient requires transplant in order to slow progression.

Glasses, soft contacts, rigid gas permeable contact lenses and Intacs are not currently funded or subsidized. Corneal transplant is a funded procedure in Alberta. In Alberta, CXL is currently being offered by private clinics; the procedure is not currently publically funded or subsidized.

# 4 METHODS: TECHNOLOGY EFFECTS AND EFFECTIVENESS (T)

## 4.1.1 Literature Search

For this review and meta-analysis, MEDLINE, EMBASE, PubMED, CINAHL, the Cochrane CENTRAL Registry of Controlled Trials, HTA Health Technology Assessment Database, Cochrane Database of Systematic Reviews, NHSEED and Econlit were searched from 1950-February 26th, 2012. There are many terms used for both CXL and corneal thinning disorders. The search strategy for this review focused on combining these two themes in a comprehensive manner.

Terms such as Keratoconus and corneal opacity were exploded and combined using the Boolean term 'or' with terms such as "keratoconus," "keratoconic," "keratoectasia," "keratoglobus," "pellucid marginal degeneration," and "forme fruste."

To search the intervention, we used the "or" operator to explode and map the MeSH headings "Cross-linking reagents," "ultraviolet therapy," "riboflavin" and "collagen." These results were then combined using the Boolean operator or with terms such as "cross-link*," "crosslink,*" "CXL," "ultraviolet," "riboflavin" and "uvb." To obtain the final results, the CXL terms were combined with the terms describing corneal thinning disorders.

Details of this search are attached as Appendix I. Results were filtered to exclude non-human studies, but no other limits were used.

### 4.1.2 Selection of Literature

The abstracts retrieved were screened in duplicate (LL and SH). Abstracts were included for full-text review if they reported on original data, involved only human subjects, were designed as a Randomized Controlled Trial (RCT) or an observational cohort study and reported on the efficacy of CXL for treatment of KC, PMD or KE. No language restrictions were applied. Abstracts selected for inclusion by either reviewer proceeded to full-text review. This initial screen was intentionally broad to ensure that all relevant literature was captured.

Studies included after the first screen proceeded to full-text review by two reviewers (LL and SH). Studies were included if they met the inclusion criteria presented in Table 1. Any disagreement between reviewers was resolved through discussion and consensus. A kappa statistic for reviewer agreement was calculated.

**Table 1: Inclusion/Exclusion Criteria**

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| Humans participants (any age) | Non-human studies |
| Diagnosed with keratoconus, pellucid marginal degeneration or keratectasia | Combination treatments – assessing CXL in combination with another therapy |
| Original Research | Methodological comparison studies |
| RCT or cohort study | Not RCT or cohort study design |
| Must include relevant outcome data | Post-mortem corneas |
| | Duplicate data |

### 4.1.3 Data Extraction

Data from the included studies was extracted in duplicate (LL, SR) using a standard data extraction form (Appendix II). Any discrepancy was resolved through consensus and discussion.

For this review, seven outcomes were extracted from included studies: Best Corrected Visual Acuity (BCVA), Uncorrected Visual Acuity (UCVA), maximum keratometry (kmax), minimum keratometry (kmin), average keratometry (kave), pachymetry and spherical equivalence (SE). When recorded, mean and standard deviation data was extracted for baseline and all follow-up time points. For follow-up time points, the following additional measurements were recorded when available: change in mean from baseline, change in standard deviation from baseline, p-value and confidence interval.

In addition to outcome data, patient information, procedure methods, safety information and study design details were extracted from each included study.

*4.1.3.1 Quality Assessment*

During data extraction, each included study was assessed for quality. Assessment was completed in duplicate (LL and SH) with discrepancies being resolved through discussion and consensus. Different assessment scales were used depending on study design. The Jadad scale was used to assess the quality of the included RCTs. With this scale, a study is assessed by 7 different criteria. Each study will be given a score between 0 (very poor) and 5 (good quality) based on these criteria.

Cohort studies were assessed using the Newcastle-Ottawa Scale (NOS) which uses 8 questions to evaluate three overall categories: outcome, comparability and selection. For 7 of the questions, one star can be assigned for studies that demonstrate high quality; for the remaining question,

two stars may be assigned. Studies, therefore, may range from having no stars (represents extremely poor quality) to having 9 stars (extremely high quality).

#### 4.1.4 Analysis

All analyses were stratified by time from procedure. Six timepoints were considered: less than 3 months; 3 months; 3-6 months; 6-11 months; 12 months; 18-24 months; and greater than 24 months. If an individual study reported multiple timepoints within the time interval, the latest observation was included (i.e. if a study reported both 4- and 6- month outcomes, the 6 month outcome was include in the 3-6 month analysis). Random effects models were used to calculate the pooled effect size (ES). For each study, the ES was calculated as the ratio of the mean change from baseline to follow-up to the standard deviation of the change.

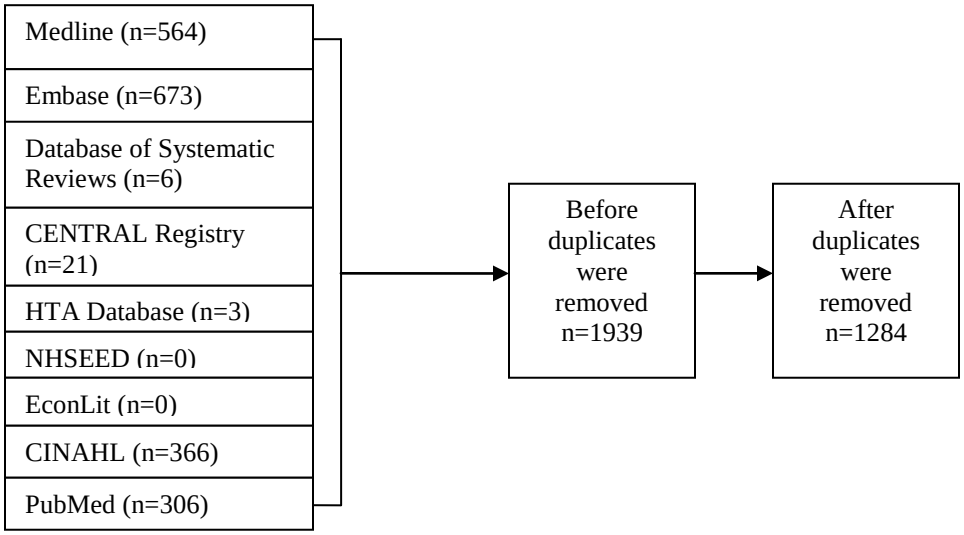
In addition, a meta-regression was completed to evaluate the outcome of progression. All studies reporting at least 3 timepoints were included in the regression. As there are repeated measures within the same patient population, initially a within-study fitted line was calculated using linear regression. Subsequently the fitted lines across studies were meta-analyzed to calculate the pooled estimate of progression. Results were calculated using STATA 12 software.

# 5 RESULTS: TECHNOLOGY EFFECTS AND EFFECTIVENESS (T)

## 5.1 Literature Search

The literature search was conducted on February 26th, 2012 and returned a total of 1939 titles/abstracts before duplicates were removed. The details of the search results can be found in Figure 1. Once duplicates were removed, 1284 abstracts/titles remained.

**Figure 1: Title/Abstract Search Results**




All 1284 titles/abstracts proceeded to duplicate abstract review (LL, SH) and were assessed based on a priori exclusion/inclusion criteria. Consequently, 1181 abstracts were excluded; 103 progressed to full-text review (Figure 2). Based on full-text review, 36 articles were included; 2 randomized controlled trials and 34 cohort studies (Table 2). The two included RCTs used fellow-eye control. The included cohort studies had either no control, a fellow-eye control (an individual's second eye was used as control to treatment eye) or independent eye control.

**Figure 2: Inclusion Flow Chart**

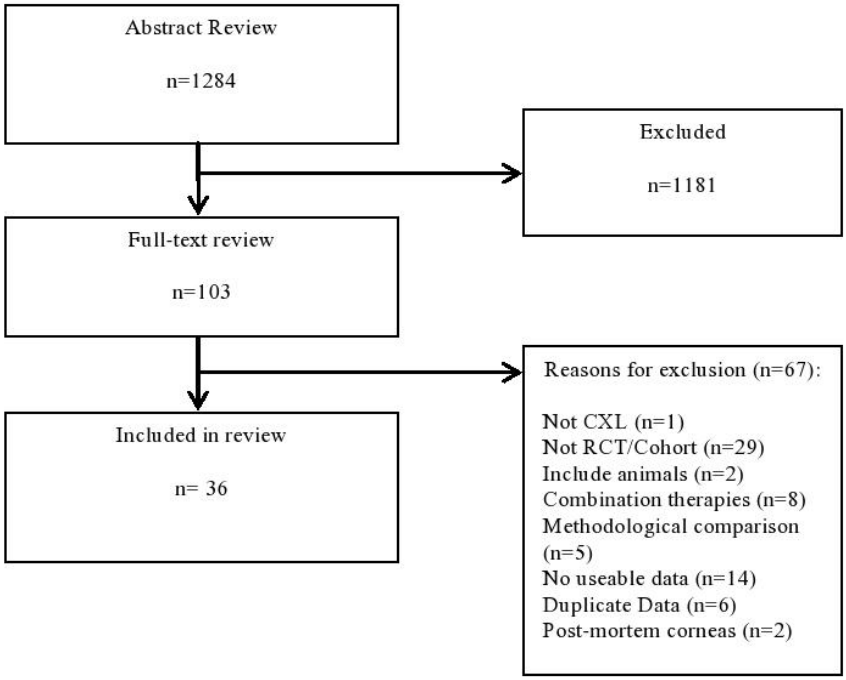


**Table 1: Included/Excluded Studies**

| Included | Excluded During Full-text Review |
|---|---|
| ***KC***<br>Filippello (2012)[41], Caporossi (2011)[64], Saffarian (2010)[65], Arbelaez (2009)[66], El-Raggal (2009)[67], Bikbov (2011)[68], O'Brart (2011)[69], Raiskup (2011)[72], Henriquez (2011)[74], Mate-Istvan (2010)[76], Strmenova (2010)[77], Goldich (2010)[78], Caporossi (2010)[79], Raiskup (2009)[48], Baumeister (2009)[81], Tu (2009)[82], Fournie (2009)[83], Coskunseven (2009)[85], Vinciguerra (2009)[86], Grewal (2009)[87], Agrawal (2009)[88], Jankov (2008)[89], Wittig-Silva (2008)*[90], Raiskup (2008)[91], Mazzota (2007)[92], Caporossi (2006)[93], Wollensak (2003)[94], Derakhshan (2011)[39]<br><br>***KC, KE***<br>Kampik (2011)[63], Hersh (2011)*[75], Doors (2009)[80]<br><br>***KC, KE, PMD***<br>Holopainen (2011)[70]<br><br>***KC, PMD***<br>Koller (2011)[71], Koller (2009)[84]<br><br>***KE***<br>Salgado (2010)[73], Vinciguerra (2010)[40] | **Not CXL:**<br>Abad (2011)[95]<br><br>**Not an RCT/Cohort design:**<br>Guell (2012)[96], Romano (2012)[97], Kanellopoulos (2012)[98], Dhawan (2011)[99], Rama (2011)[100], Beckman (2011)[101], Soeters (2011)[102], Asri (2011)[103], Kymionis (2012)[104], Spadea (2011)[105], Vinciguerra (2011)[106], Saelens (2011)[107], Sueke (2011)[108], Kymionis (2011)[109], Hafezi (2011)[110], Kaya (2011)[111], Kanellopoulos (2011)[112], Reinstein (2011)[113], Sedaghat (2010)[114], Kymionis (2010)[115], Ashar (2010)[116], Constantin (2009)[117], Kymionis (2009)[118], Iovieno (2008)[119], Nassaralla (2007)[120], Wollensak (2003)[121], Labetoulle (2003)[122], Sondergaard (2010)[123], Hafezi (2007)[124]<br><br>**Includes animals:**<br>Spoerl (1999)[38], Raiskup (2010)[125]<br><br>**Combination Treatment:**<br>Iovieno (2011)[126], Koppen (2011)[127], Izquierdo (2011)[128], Vincent (2009)[129], Kymionis (2010)[130], Coskunseven (2009)[131], Kanellopoulos (2009)[132], Stojanovic (2010)[133]<br><br>**Methodological Comparison:**<br>Alio (2011)[134], Vetter (2011)[135], Bakke (2009)[136], Leccisotti (2010)[137], Kanellopoulos (2009)[138]<br><br>**No useable data:** Spoerl (2011)[139], Mikielewcz (2011)[140], Knappe (2011)[141], Renesto (2010)[142], Raiskup (2010)[143], Vinciguerra (2010)[144], Croxatto (2010)[145], Kymionis (2009)[146], Koller (2009)[147], Goldich (2009)[148], Mazzotta (2008)[149], Seiler (2006)[150], Mazzotta (2006)[151], Raiskup (2010)[125]<br><br>**Duplicate data:**<br>Greenstein (2012)[152], Greenstein (2012)[153], Greenstein (2011)[154], Greenstein (2010)[47], Kymionis (2009)[118], Constantin (2009)[155]<br><br>**Post-Mortem Corneas:**<br>Hayes (2011)[156], Cannon (1978)[157] |

*RCT

## 5.2 Systematic Reviews, Meta-analysis and Health Technology Assessments

### 5.2.1 Systematic Reviews

Currently the literature is void of any formal systematic reviews on the topic of corneal cross-linking (CXL) for corneal thinning disorders. There are approximately 25 non-systematic review

articles which broadly cover the topic of CXL, from the biophysical principles of CXL to the clinical management of corneal thinning disorders.

### 5.2.2 Meta-analyses

To date, no meta-analysis on CXL for corneal thinning disorders exist in the literature.

### 5.2.3 Health Technology Assessments

Through the systematic literature search, six Health Technology Assessments (HTAs) on CXL were retrieved. Of these six, two were produced privately and are unavailable; the remaining four have been summarized below. Three review CXL for the management of KC, and one includes other corneal thinning disorders in addition to KC. All vary in terms of comprehensiveness and scope.

#### *5.2.3.1 CADTH*

In April, 2010, the Canadian Agency for Drugs and Technologies in Health (CADTH) released a six page Health Technology Assessment summary on CXL for KC.[158] For this review, a limited literature search was completed, which returned one RCT, one controlled cohort study and six non-controlled cohort studies.[158] All of the studies they included reported either improvement or halted progression.[158]

#### *5.2.3.2 Centre of Region Vastra Gotaland*

The 'HTA Centre of Region Vastra Gotaland,' a Swedish based organization, produced a report reviewing the efficacy of CXL for stabilizing KC in August, 2011.[159] This review returned 247

abstracts and titles and fifty-one were reviewed in full-text. Two RCTs and 5 controlled cohort studies were included in the review. Evidence on clinical efficacy, complications and side-effects was gathered from each of these included studies. This review extracted five primary outcomes to assess clinical efficacy: kmax, kave, corneal radius, BCVA and UCVA. A meta-analysis of the results was not conducted. This HTA notes that the RCTs included were of low to moderate quality.[159] Four of the observational studies that were included were low quality while one was of moderate quality.[159]

All of the studies included in this review reported slight improvement in kmax, kave and corneal radius outcomes.[159] All studies reported slight improvement in both UCVA and BCVA. Based on these outcomes, this HTA concluded that there was limited evidence on whether KC was beneficial. They also stated that there is currently no data about whether CXL may prevent corneal transplants.[159]

*5.2.3.3 Health Quality Ontario*

In November 2011, the Medical Advisory Secretariat (Health Quality Ontario) released a report on CXL as a part of the Ontario Health Technology Assessment Series.[160] This HTA included studies assessing CXL with KC and other corneal thinning disorders such as KE, PMD, bullous keratopathy and infectious keratitis. This review excluded non-English studies and included any study design, including case reports and retrospective designs. This review included studies that used CXL in combination with another therapy, such as intrastromal corneal ring segments and photorefractive keratectomy.

They included 65 reports in their review. They summarized the results of the included studies, but did not conduct a meta-analysis of the outcomes. Based on the evidence found, this report concludes that CXL is effective in stabilizing, and in some cases reversing, corneal thinning disorders.[160] They note that although there are reports of adverse effects with CXL, these are rare, particularly when standard methods are used. This report concludes that there is moderate quality evidence on safety in the literature, moderate quality information on corneal topography outcomes, moderate quality studies assessing visual acuity and low quality longitudinal information.

*5.2.3.4 NICE*

In 2009, NICE prepared a brief technology assessment document based on a rapid literature review.[161] This review assessed the use of CXL for the management of KC. Through the rapid literature review, NICE found 1 RCT, 4 case series, 5 case reports and one multiple case report on this topic. In November 2009, NICE issued a statement noting that there was inadequate information on CXL for KC in the literature, and therefore, it should only be used for research purposes, or with special approval.[162] At this time, NICE indicates that only patients with progressive KC and corneal thickness <400um will be considered for treatment with CXL.[162]

## 5.3 Randomized Controlled Trials

Two RCTs were included in this review: Hersh and Wittig-Silva.[75;90] These two studies represent the most robust data available on this use of CXL for corneal thinning disorders. Both were of moderate quality as assessed by the Jadad scale (Table 3). Due to the nature of the treatment,

neither RCT could be double-blinded. Therefore, both received a score of 3 out of 5 possible points. Blinding was the only area in which these two studies lost points.

**Table 3: RCT Quality Assessment**

| Author | Year | Was the study described as randomized? | Was the method used to generate the sequence of randomization described and appropriate? | Was the study described as double blind? | Was the method of double-blinding described and appropriate? | Was there a description of withdrawals and drop-outs? | Deduct one point of the method used to generate the sequence of randomization was described and was inappropriate | Deduct on point if the study was described as double blind but the method was inappropriate |
|---|---|---|---|---|---|---|---|---|
| Wittig-Silva[90] | 2008 | 1 | 1 | 0 | 0 | 1 | 0 | 0 |
| Hersh[75] | 2011 | 1 | 1 | 0 | 0 | 1 | 0 | 0 |

Hersh et al included 71 eyes of 58 patients in their treatment group; 49 of whom had KC and 22 who had KE.[75] This study used both fellow-eye and sham group controls. There were 30 fellow-eye controls, 21 had KC and 9 had KE, and there were 41 eyes in the sham control group (28 KC eyes and 13 KE eyes). Hersh et al assessed UCVA (logMAR), BCVA (logMAR), refractive error, manifest astigmatism, kmax, kmin and kave. This study found that CXL significantly improved UCVA, BCVA, kmax and kave.[75] UCVA improved by 0.07 logMAR and BCVA improved by 0.12 logMAR.[75] In this study kmax improved by 2 diopters or more in 22 patients and only worsened by 2 diopters or more in 3 patients.[75] It reported that KC patients had more success with the treatment than those with KE, but that it was effective for both.[75] Hersh et al

also found that there was an initial worsening of BCVA and kmax, which subsequently improved.[75]

Wittig-Silva et al included 66 eyes of 49 patients with KC, and randomly assigned them to either the treatment or control group.[90] This paper assessed BCVA (logMAR), UCVA (logMAR), kmin, kave, kmax, pachymetry, refraction, SE, and endothelial cell density.[90] By 6 months, kmax flattened by 0.92 diopters (p=0.002) on average in all treated eyes, and by 1.45 diopters (p=0.002) by 12 months.[90] This study found that on average, BCVA decreased by 0.056 (p=0.092) logMAR by 6 months and 0.12 (p=0.036) by 12 months. [90] Wittig-Silva et al did not find any significant improvements in SE or endothelial cell density. [90] This RCT concludes that within the follow-up period, CXL resulted in a stabilization of all treated eyes. [90]

## 5.4 Observational Studies

### 5.4.1 Quality Assessment

The cohort studies included in this review ranged from six to nine stars (Tables 8 and 9 in Section 8.0). In this scale, 7.5 stars and above indicates good quality, 5-7.5 stars indicates moderate quality and studies awarded less than 5 stars are considered to be poor quality. The area where quality was most often lacking was in question two which probed about control groups. Although some studies included fellow-eye or independent eye controls, many did not include a control, and therefore lost a star for this question. Studies also frequently lost stars in question 8 which asks about participant drop-out rates. Many of the included studies had lengthy follow-up periods, which often resulted in significant loss of patients over the duration of the

study. Long-term studies often had more than 20% loss to follow-up which lost them a star in question 8.

## 5.5 Meta-analysis

An overview of all included studies (including the outcomes they assessed) can be found in Table 10 (Section 8.0). Additionally, the meta-analysis results explained in this section have been summarized by overall pooled ES values and CIs in Table 4. A summary of the meta-regression analysis can be found in Table 5.

**Table 4: Summary of pooled effect size at 1 year by outcome**

| Outcome | Disease | ES | CI | $I^2$ (%) | Significant Improvement | Figure of Forest Plot |
|---|---|---|---|---|---|---|
| BCVA (Decimal Acuity) | KC | 0.10 | 0.05-0.14 | 66 | Yes | Figure 3 |
| BCVA (LogMAR) | KC | -0.09 | -0.13- -0.06 | 89 | Yes | Figure 4 |
| BCVA (LogMAR) | KC, KE, PMD | -0.05 | -0.09- - 0.01 | 46 | Yes | Figure 5 |
| UCVA (Decimal Acuity) | KC | 0.07 | 0.0-0.14 | 93 | Yes | Figure 6 |
| UCVA (LogMAR) | KC | -0.26 | -0.35 - -0.17 | 84 | Yes | Figure 7 |
| UCVA (LogMAR) | KC, KE, PMD | -0.13 | -0.25 - -0.01 | 0 | Yes | Figure 8 |
| Kmin | KC | -1.13 | -1.98 - -0.29 | 83 | Yes | Figure 9 |
| Kave | KC | -1.16 | -1.73 - -0.59 | 92 | Yes | Figure 10 |
| Kave | KC, KE, PMD | -1.42 | -4.57 – 1.72 | 97 | No | Figure 11 |
| Kmax | KC | -1.49 | -2.08 - -0.90 | 93 | Yes | Figure 12 |
| Kmax | KC, KE, PMD | -0.71 | -1.19 - -0.24 | 62 | No | Figure 13 |
| SE | KC | 0.94 | 0.31-1.56 | | Yes | Figure 14 |
| SE | KC, KE, PMD | 0.32 | -0.56 – 1.20 | | No | Figure 15 |
| Pachymetry | KC | -4.79 | -10.1 – 0.52 | | No | Figure 16 |

| | | | | | |
|---|---|---|---|---|---|
| Pachymetry | KC, KE, PMD | -18.89 | -27.3 - -10.5 | Yes | Figure 17 |

**KC** = keratoconus **KE** = keratectasia **PMB** = pellucid marginal degeneration **Kmax** = maximum keratometry **Kmin** = minimum keratometry **Kave** = maximum keratometry **UCVA** = uncorrected visual acuity **BCVA** = best corrected visual acuity **SE** = Spherical Equivalent

**Table 5: Analysis of Progression (Meta-regression)**

| Outcome | Disease | Coefficient | 95% Confidence Interval | P Value | Evidence of Stabilization |
|---|---|---|---|---|---|
| BCVA (Decimal Acuity) | KC | 0.0025 | 0.0006, 0.0044 | 0.008 | Yes |
| BCVA (LogMAR) | KC | -0.0021 | -0.0034 , -0.0008 | 0.002 | Yes |
| BCVA (LogMAR) | KC, KE, PMD | - | - | - | Too few studies assess |
| UCVA (Decimal Acuity) | KC | 0.001 | -0.0001, 0.0021 | 0.078 | Yes |
| UCVA (LogMAR) | KC | - | - | - | Too few studies assess |
| UCVA (LogMAR) | KC, KE, PMD | - | - | - | Too few studies assess |
| Kmin | KC | -0.015 | -0.078 , 0.046 | 0.497 | Yes |
| Kave | KC | -0.040 | -0.12 , 0.04 | 0.266 | Yes |
| Kave | KC, KE, PMD | - | - | - | Too few studies assess |
| Kmax | KC | -0.006 | -0.023 , 0.10 | 0.458 | Yes |
| Kmax | KC, KE, PMD | - | - | - | Too few studies assess |
| SE | KC | 0.05 | 0.013 , 0.090 | 0.024 | Yes |
| SE | KC, KE, PMD | - | - | - | Too few studies assess |

| | | | | | |
|---|---|---|---|---|---|
| Pachymetry | KC | 0.28 | -0.34 , 0.89 | 0.248 | Yes |
| Pachymetry | KC, KE, PMD | - | - | - | Too few studies assess |

**KC** = keratoconus **KE** = keratectasia **PMB** = pellucid marginal degeneration **Kmax** = maximum keratometry **Kmin** = minimum keratometry **Kave** = maximum keratometry **UCVA** = uncorrected visual acuity **BCVA** = best corrected visual acuity **SE** = Spherical Equivalent

### 5.5.1 Best Corrected Visual Acuity

In the included studies, BCVA was reported in two scales: logMAR and decimal acuity (Snellen lines). Due to the nature of these scales, it was not possible to combine the data for the meta-analysis. As such, data was pooled for the studies using logMAR and separately for those using decimal acuity. Additionally, studies were grouped according to disease type based on whether they only looked at KC or whether they looked at KC, KE and PMD combined (mixed disease groups).

Figure 3 shows the studies which looked at KC patients and assessed BCVA using decimal acuity. At all time points considered, the pooled effect size demonstrates improvement with CXL. When a meta-regression was completed to assess progression over time, a statistically significant improvement over time was found (p-value: 0.008) indicating that the improvements in visual acuity increase over time (see Table 5).

Figure 4 shows the forest plot for KC patients, measured in logMAR. At all time points considered, the pooled effect size demonstrates improvement with CXL. When a meta-regression was completed to assess progression over time, a statistically significant improvement over time was found (p-value: 0.002) indicating that the improvements in visual acuity increase over time.

There were a number of studies which included all three disease etiologies, and reported BCVA outcomes in logMAR. This data is shown in Figure 5. At all time points considered, the pooled effect size demonstrates improvement with CXL.

**Figure 3 BCVA: KC Treated with CXL and Assessed by Decimal Acuity, stratified by time**

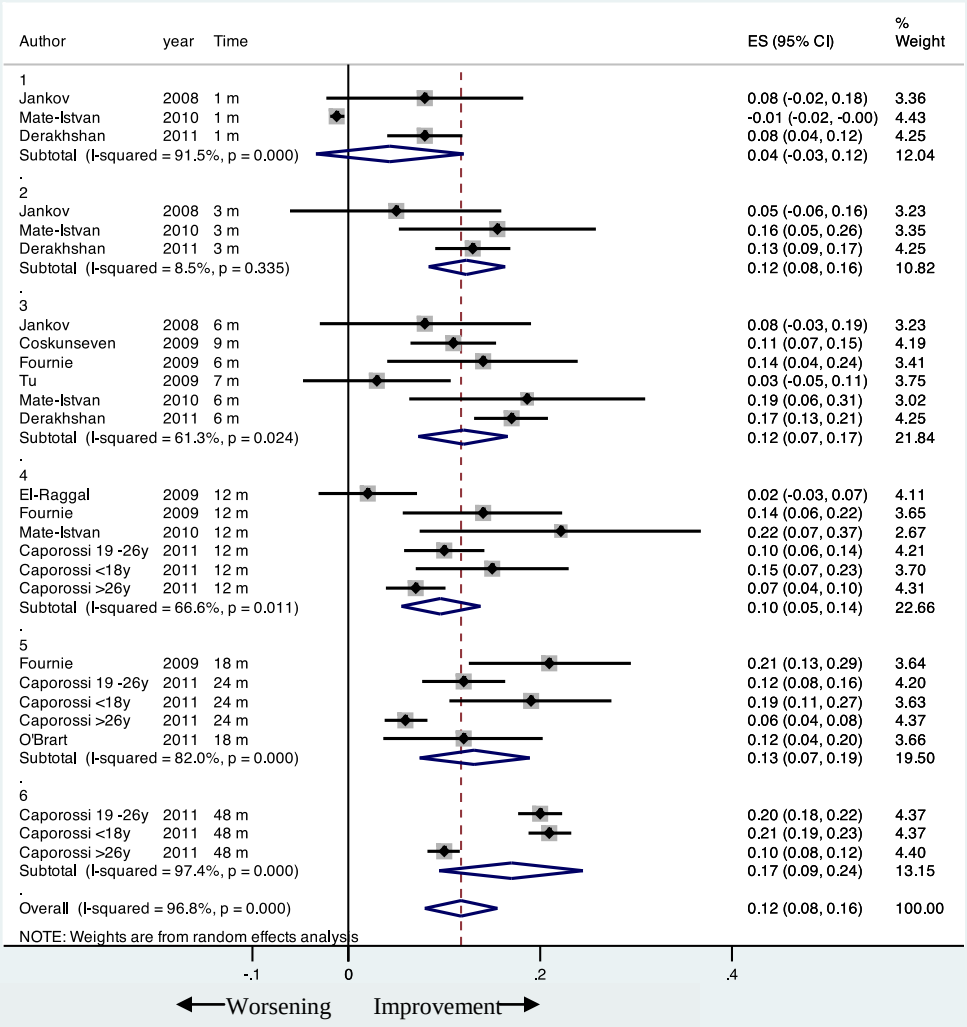


**Figure 4 BCVA: KC Treated with CXL and Assessed by LogMAR, stratified by time**

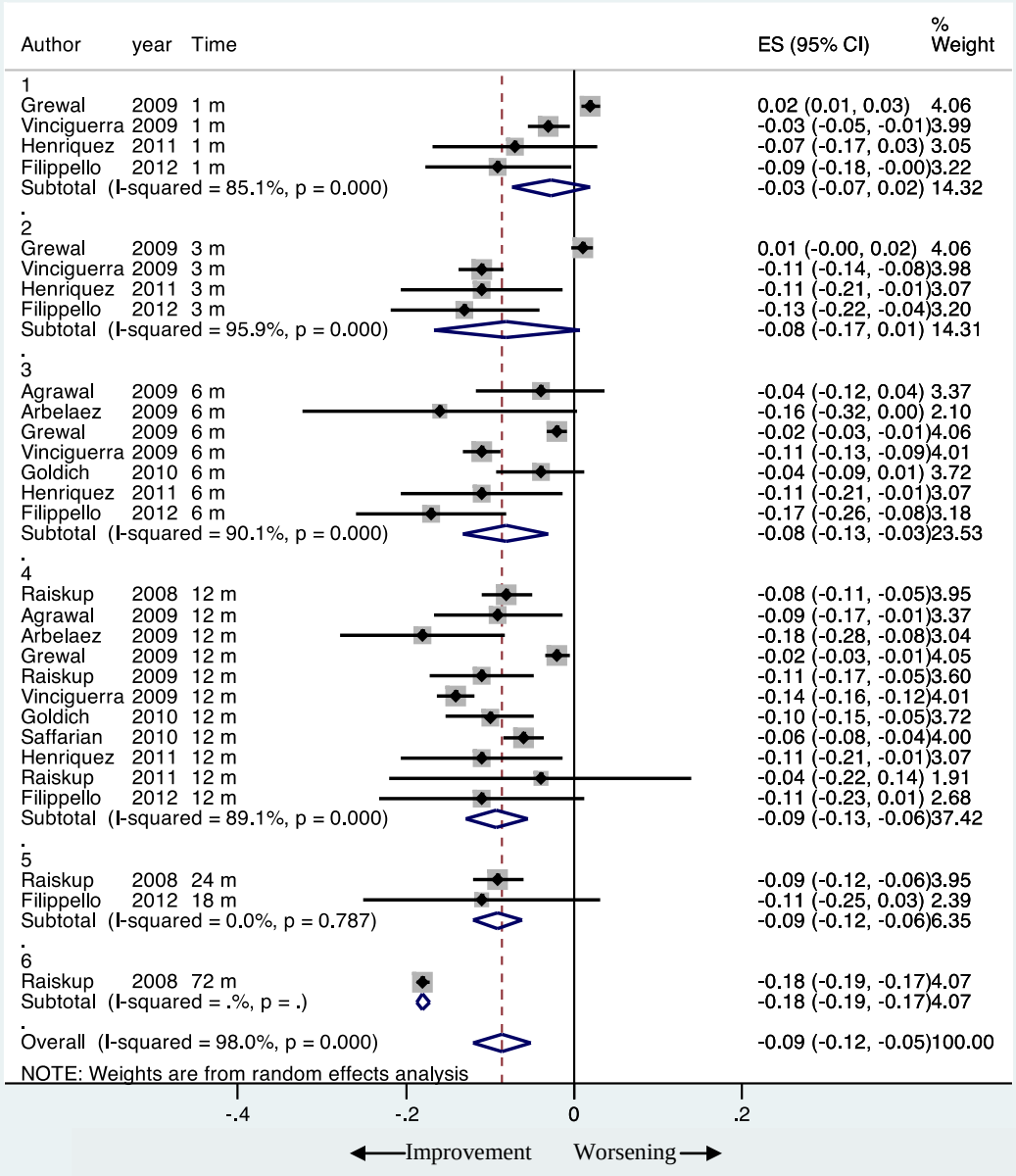
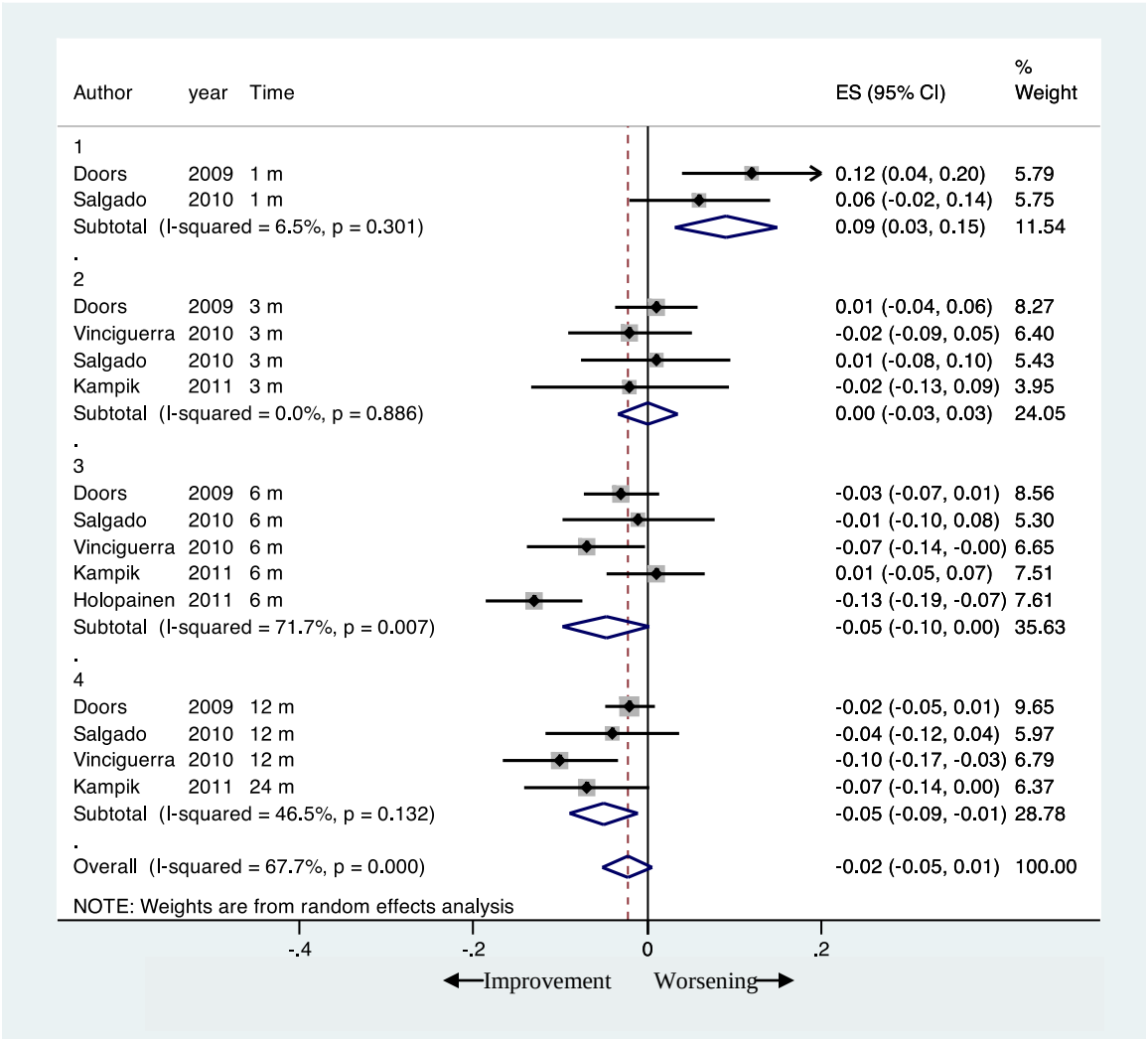


**Figure 5 BCVA: Mixed Disease Treated with CXL and Assessed by LogMAR, stratified by time**




All three meta-analyses of BCVA indicate that this outcome significantly improves after CXL. As BCVA is a measure of functionality, which has been shown to be the most important predictor in patient quality of life, this result is important to consider.

### 5.5.2 Uncorrected Visual Acuity

UCVA was analyzed by disease type and grouped according to outcome measurement used (logMAR or decimal acuity).

In Figure 6, UCVA outcomes, expressed in decimal acuity for KC patients are pooled. At all time points considered, the pooled effect size demonstrates improvement with CXL. When a meta-regression was completed to assess progression over time, a non-statistically significant improvement over time was found (p-value: 0.078) indicating that visual acuity does not improve over time, but remains stable.

Figure 7 shows KC, as assessed by logMAR. At all time points considered, the pooled ES demonstrates improvement with CXL. No meta-regression was completed due to the small number of studies available.

Mixed disease populations, using the logMAR scale have been analyzed in Figure 8. At all time points considered, the pooled ES demonstrates improvement with CXL.

**Figure 6 UCVA: KC Treated with CXL and Assessed with Decimal Acuity, stratified by time**

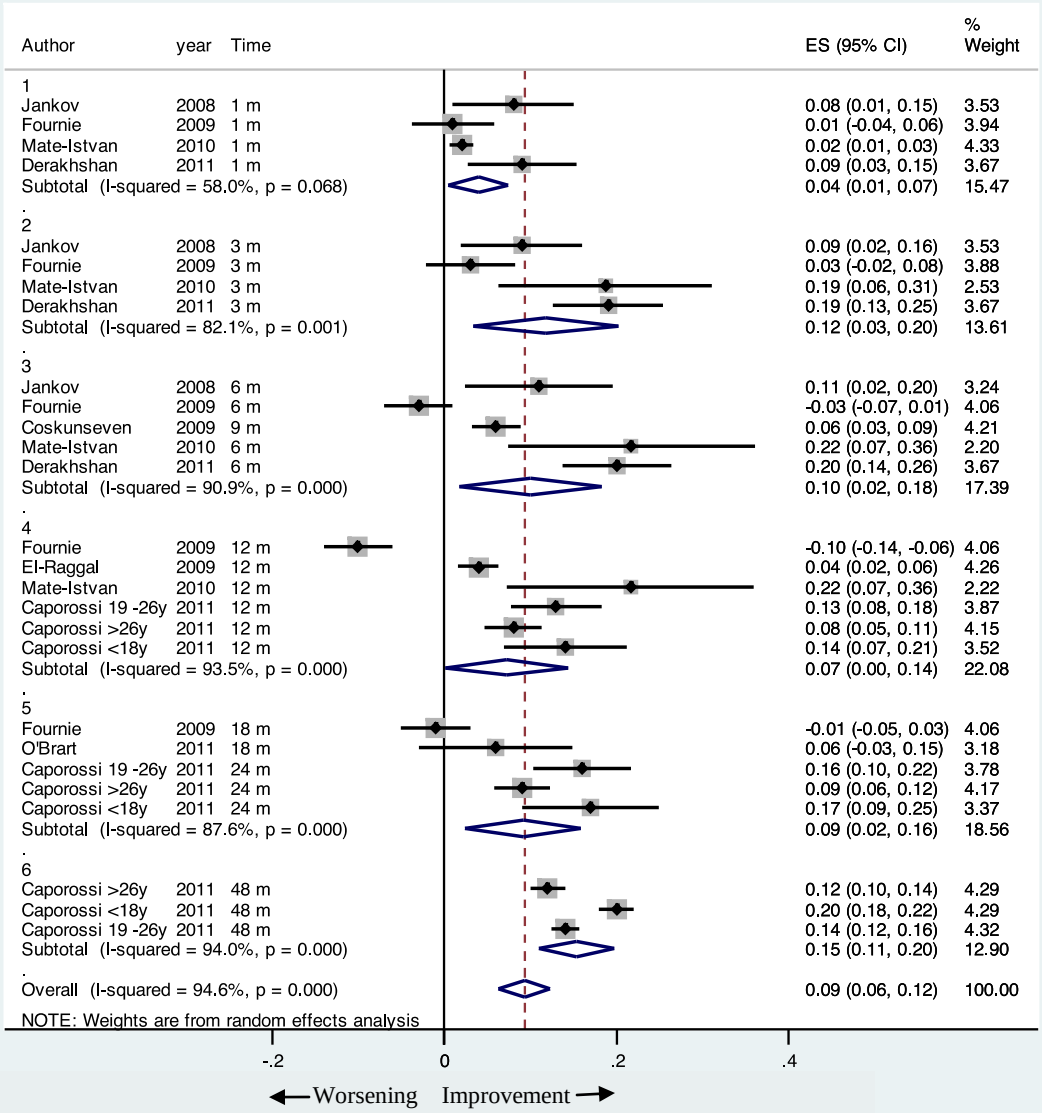


**Figure 7 UCVA: KC Treated with CXL and Assessed by LogMAR, stratified by time**

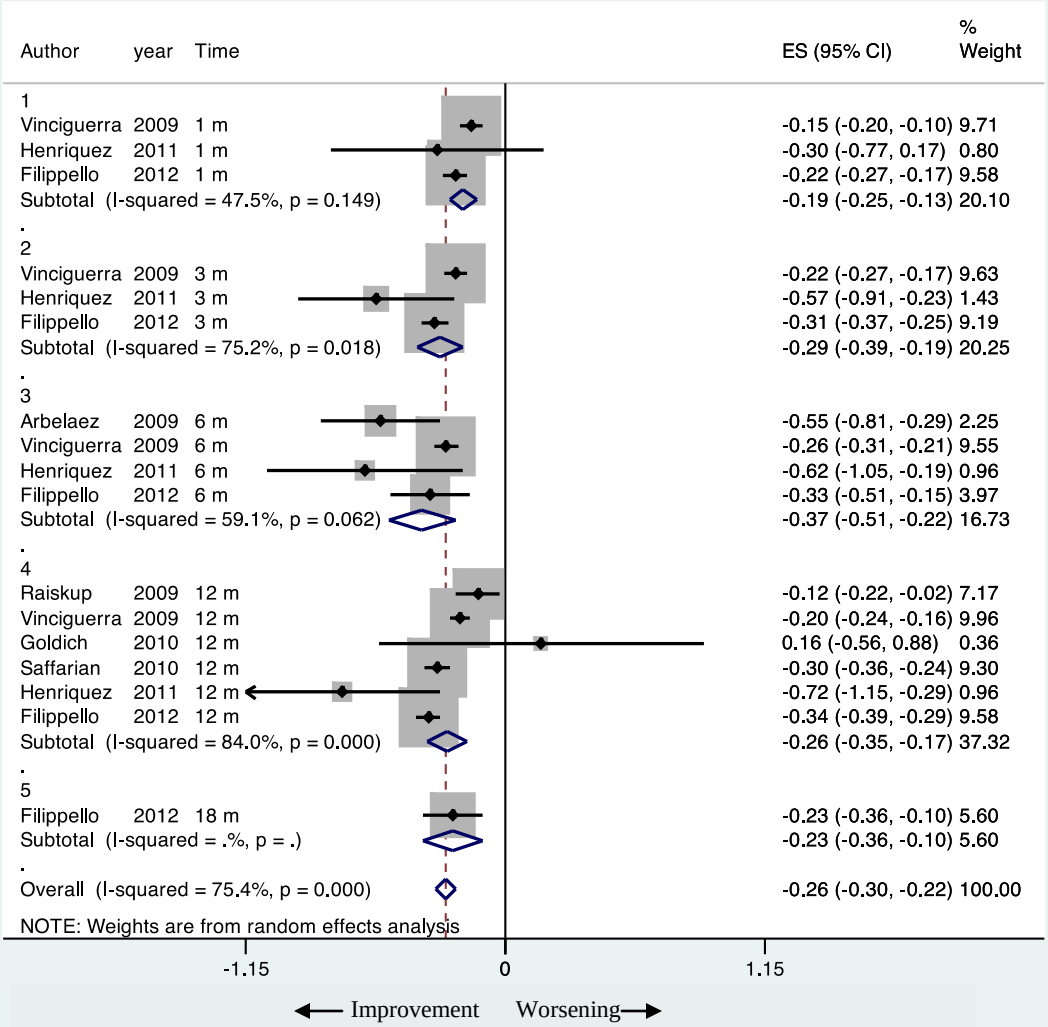
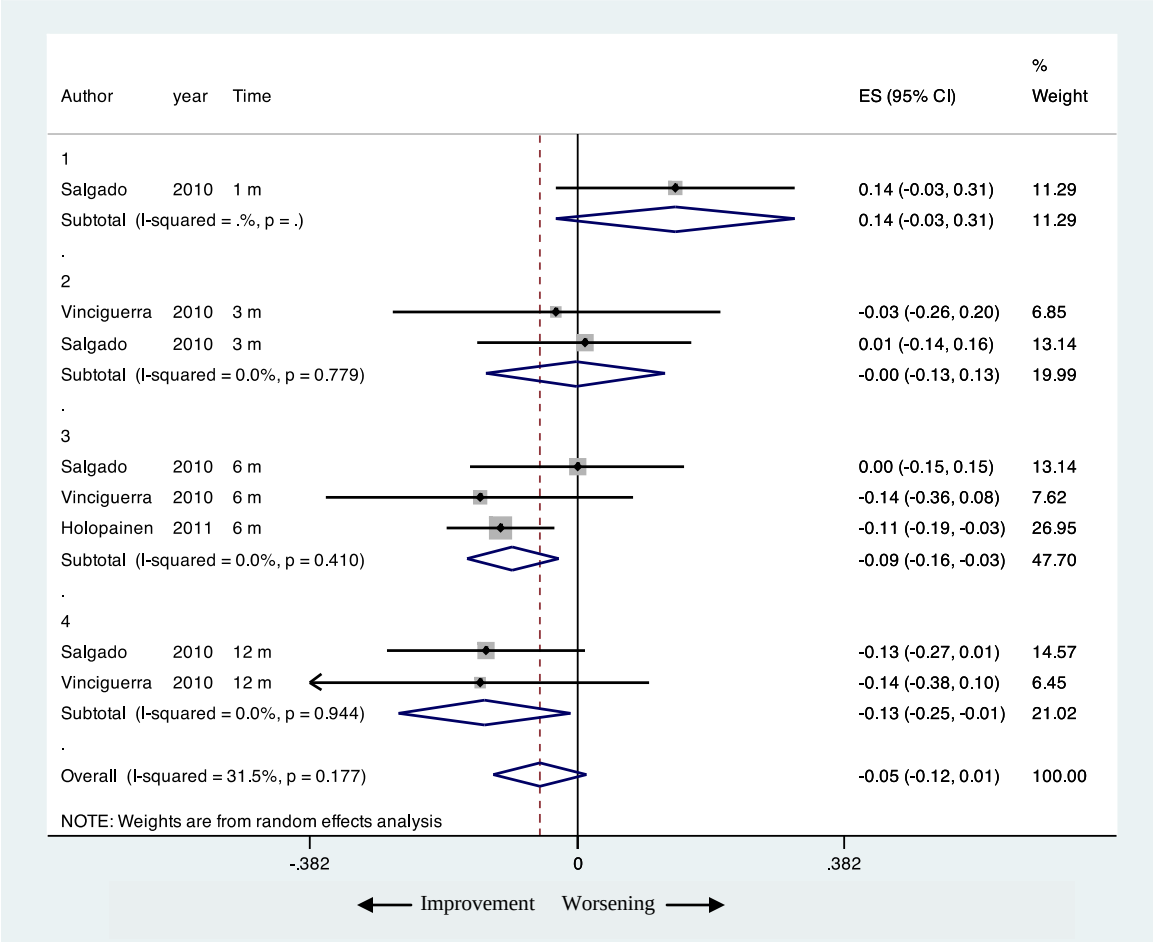


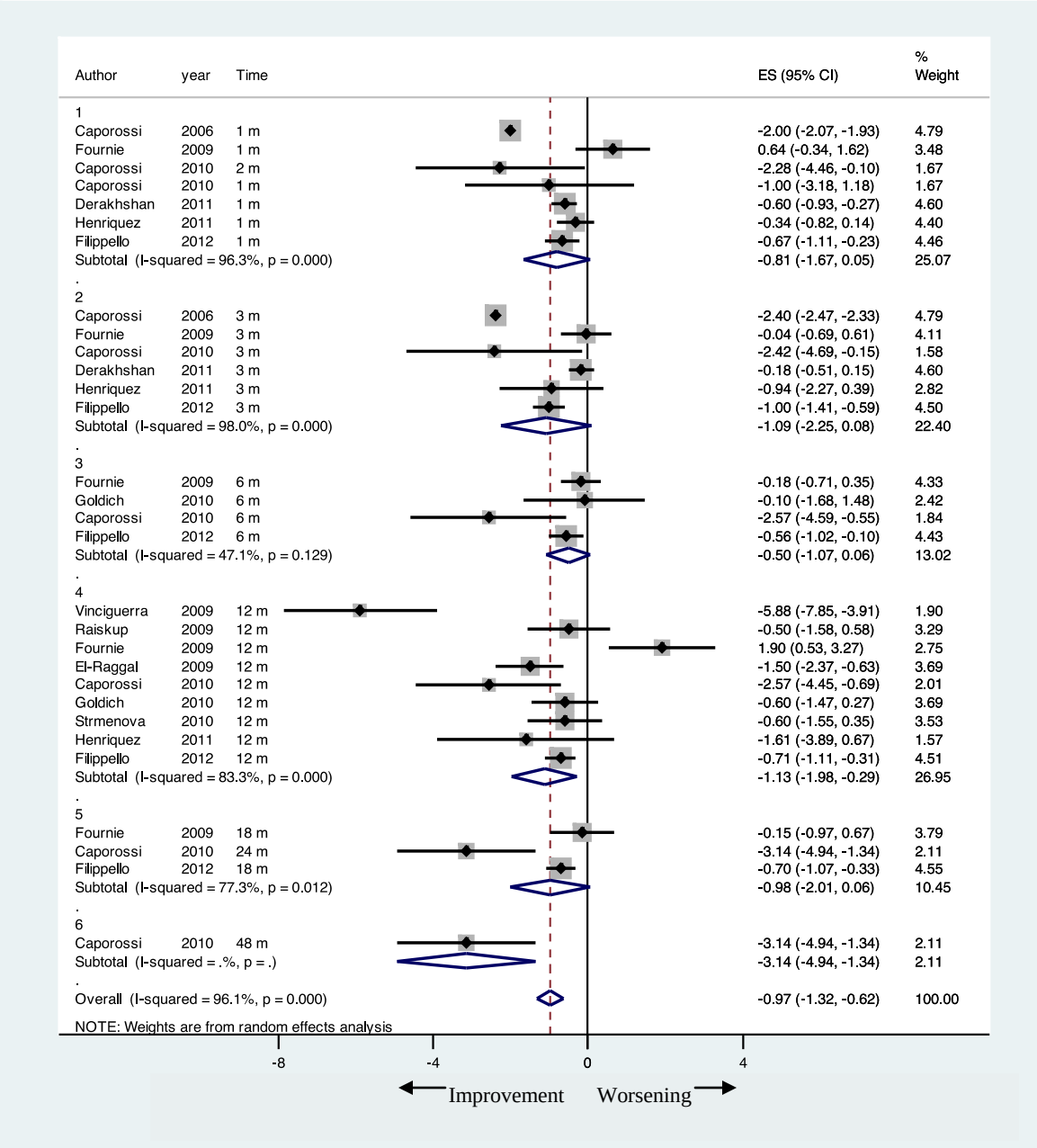
**Figure 8 UCVA: Mixed Disease Assessed by LogMAR, stratified by time**




### 5.5.3 Minimum Keratometry

Figure 9 shows the forest plot for kmin for KC patients. At all time points considered, the pooled effect size demonstrates improvement with CXL. When a meta-regression was completed to assess progression over time, a non-statistically significant improvement over time was found (p-value: 0.497) indicating that kmin does not improve over time but remains stable.

**Figure 9 Kmin: KC, stratified by time**

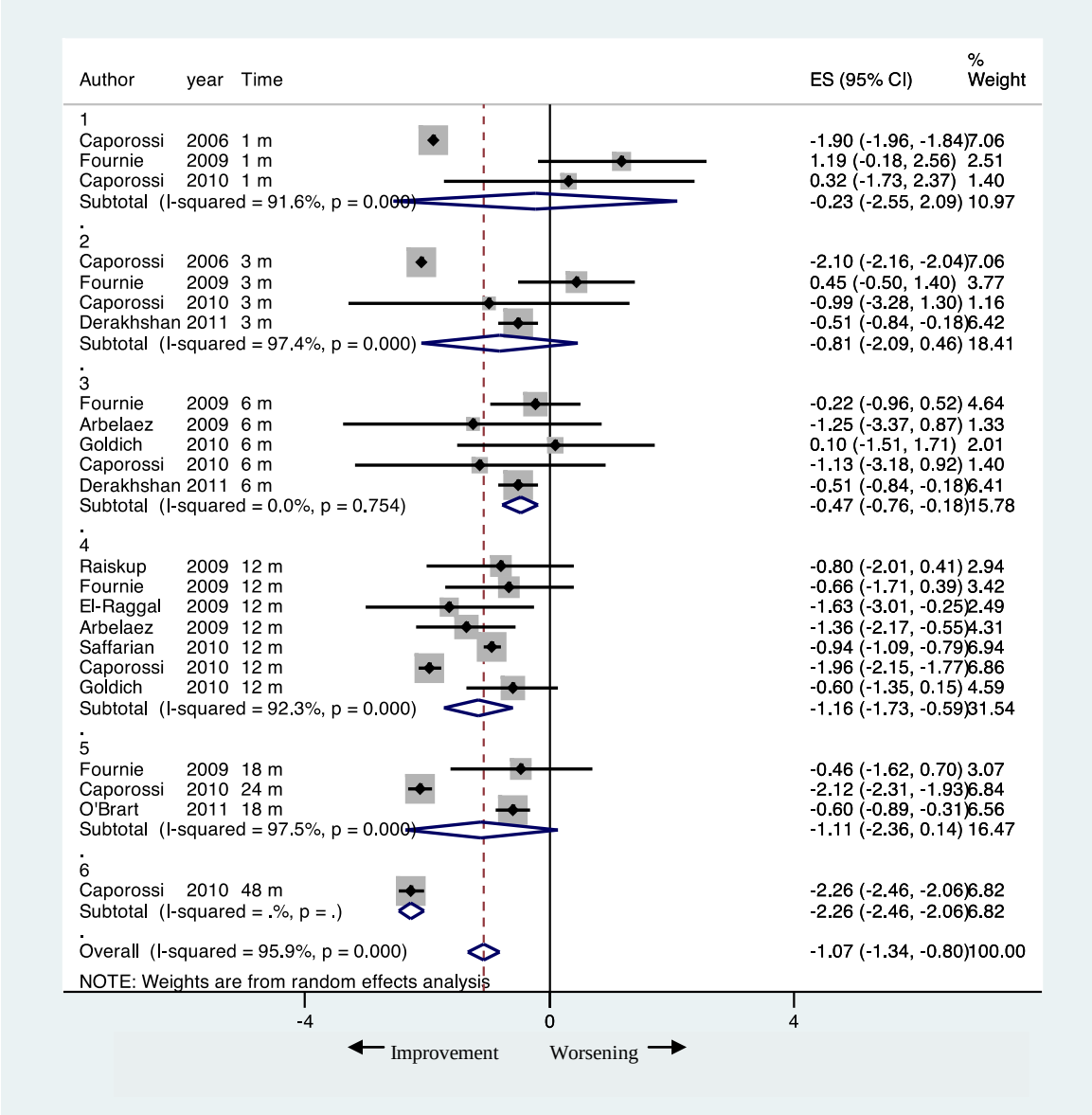



## 5.5.4 Average Keratometry

Figure 10 shows the forest plot for kave for KC patients. At all time points considered, the pooled effect size demonstrates improvement with CXL. When a meta-regression was completed

to assess progression over time, a non-statistically significant improvement over time was found (p-value: 0.266) indicating that this outcome does not improve over time but remains stable.

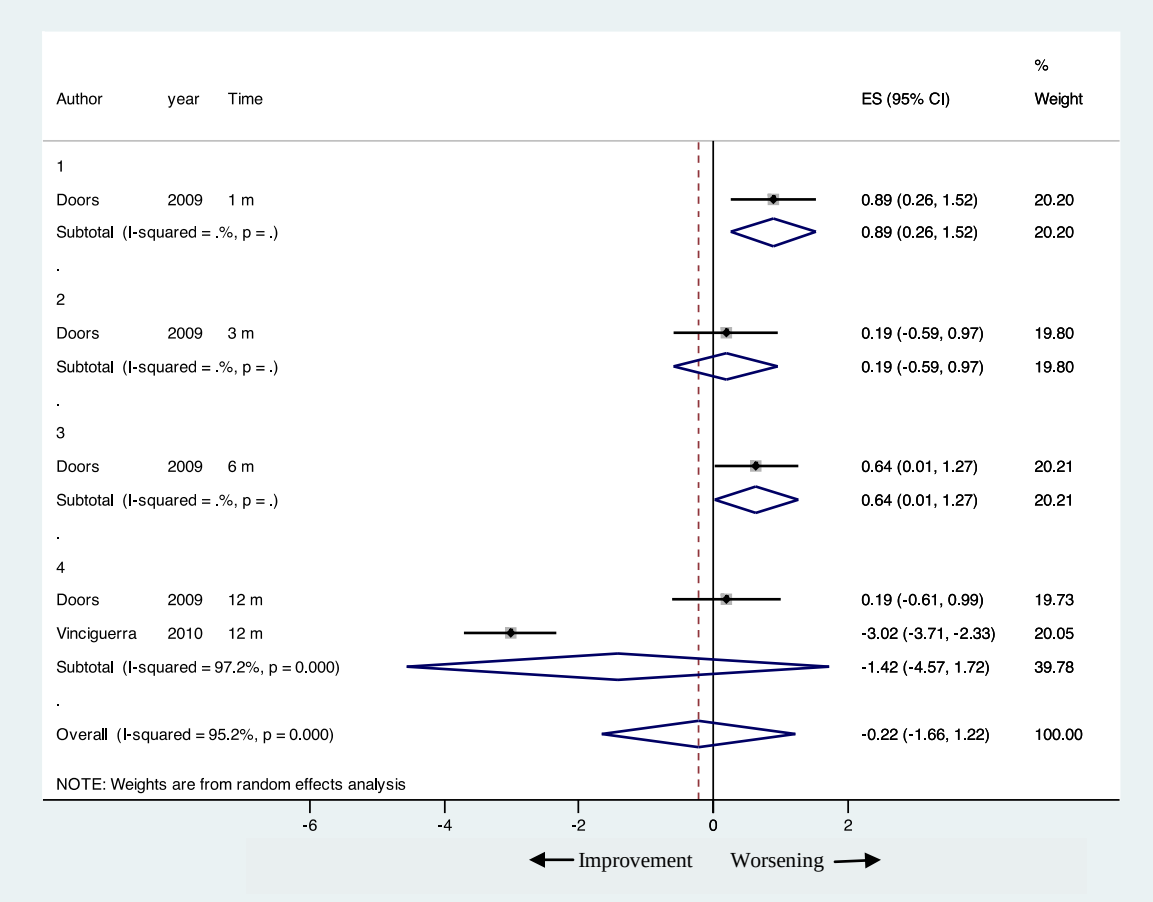
**Figure 10 Kave: KC, stratified by time**




Only two studies reported kave as an outcome for the mixed disease groups (Figure 11). CXL was associated with a worsening of kave at 1 month and 6 months based on one study. However,

at 12 months, one study reported improvement while the other reported worsening. The effect of CXL on kave in mixed disease populations is unclear.

**Figure 11 Kave: Mixed Disease, stratified by Time**




## 5.5.5 Maximum Keratometry

Figure 12 shows studies which included only KC patients. At all time points considered, the pooled effect size demonstrates improvement with CXL. When a meta-regression was completed to assess progression over time, a non-statistically significant improvement over time was found (p-value: 0.458) indicating that kmax does not improve over time but remains stable. For the

mixed disease studies (Figure 13), there was a decrease in kmax at 1 month. However, at 12 months, CXL is associated with an improvement in kmax.

**Figure 12 Kmax: KC Treated with CXL, Analyzed by Time**

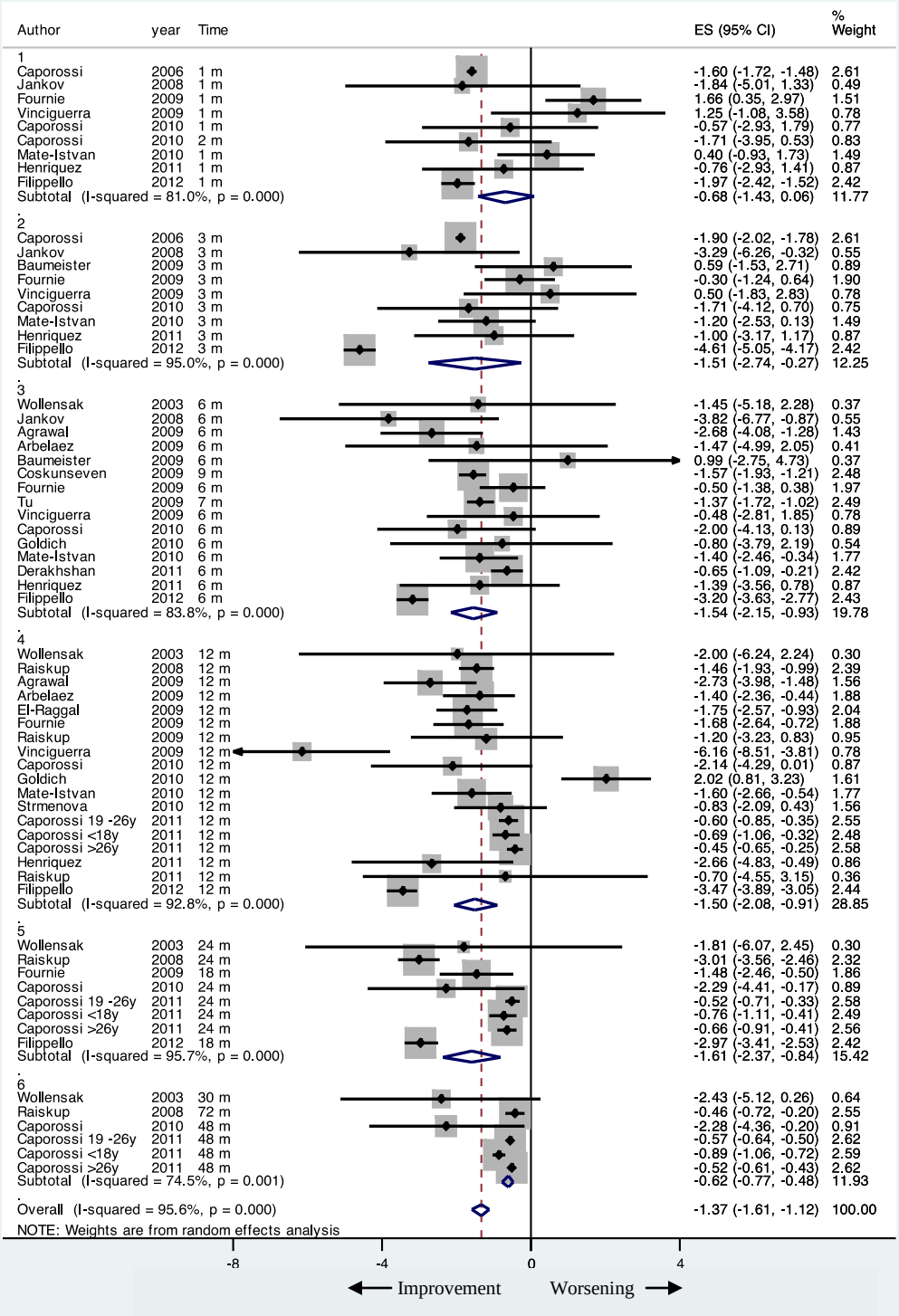
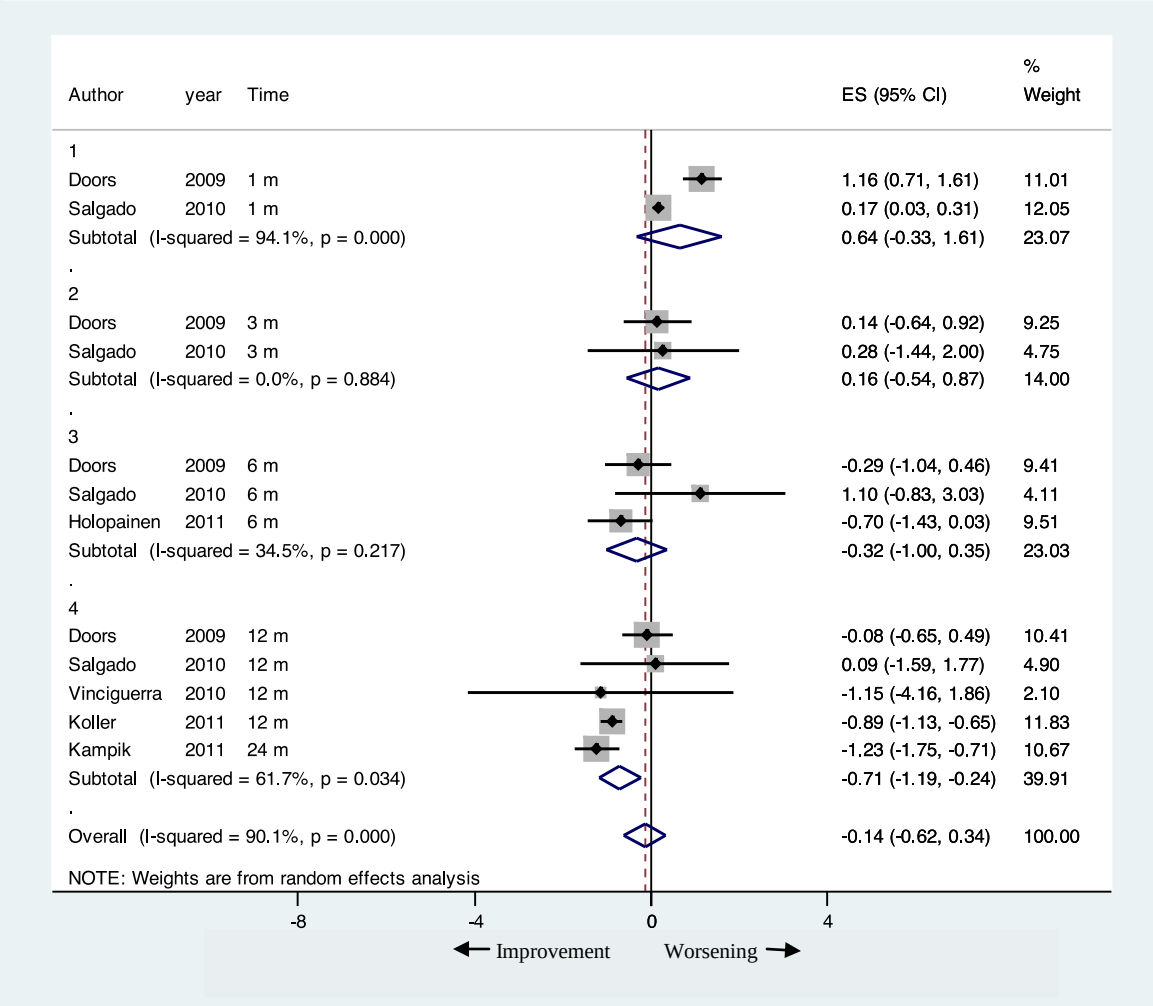


**Figure 13 Kmax: Mixed Disease Treated by CXL, Analyzed by Time**




## 5.5.6 Spherical Equivalent

The forest plot for SE demonstrates that at all time points considered, the pooled ES demonstrates improvement after CXL (Figure 14). When a meta-regression was completed to assess progression over time, a statistically significant improvement over time was found (p-value: 0.024). When the mixed disease studies were analyzed by time, no significant effect was found (Figure 15).

**Figure 14 SE: KC Treated with CXL, Analyzed by Time**

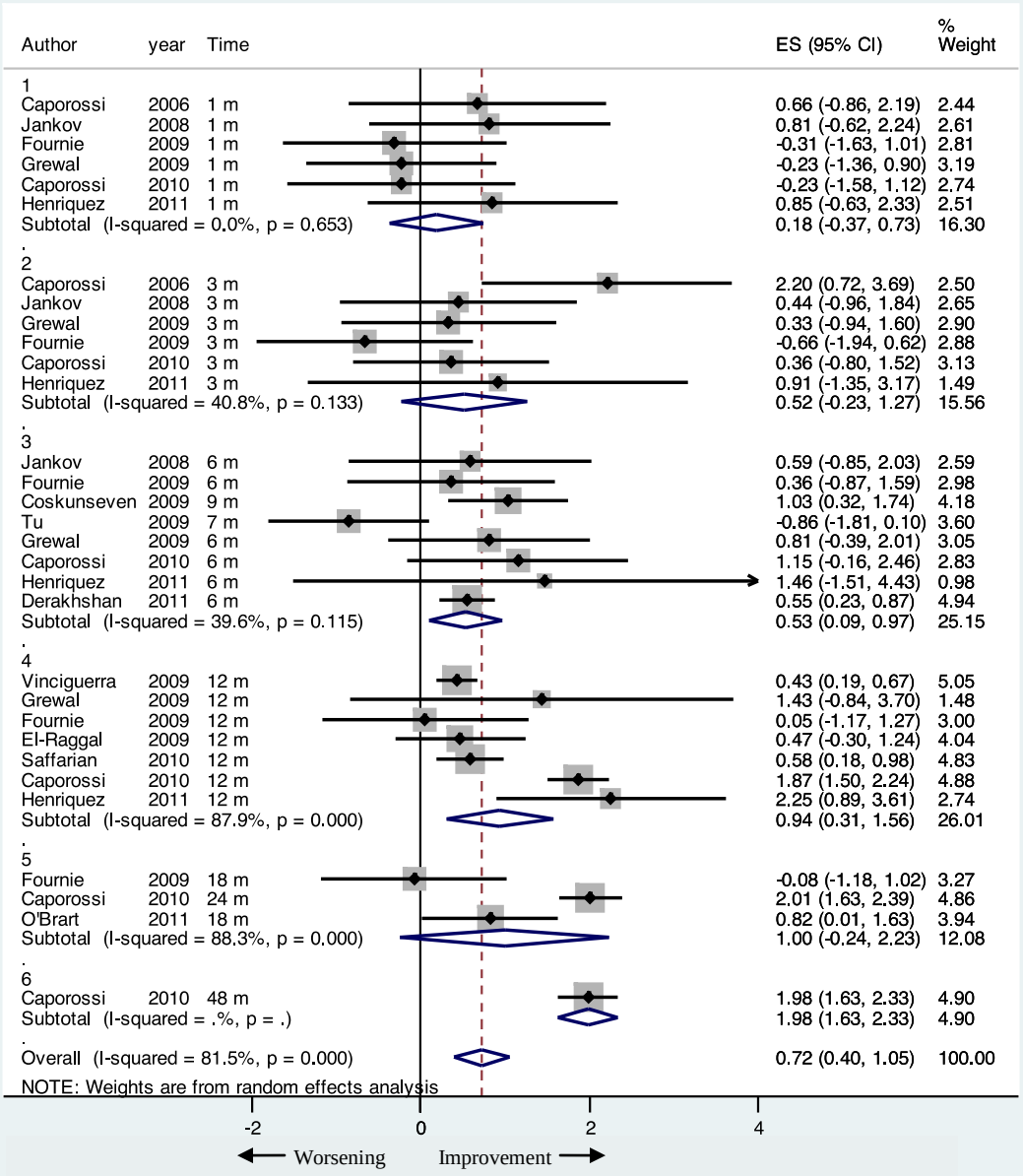
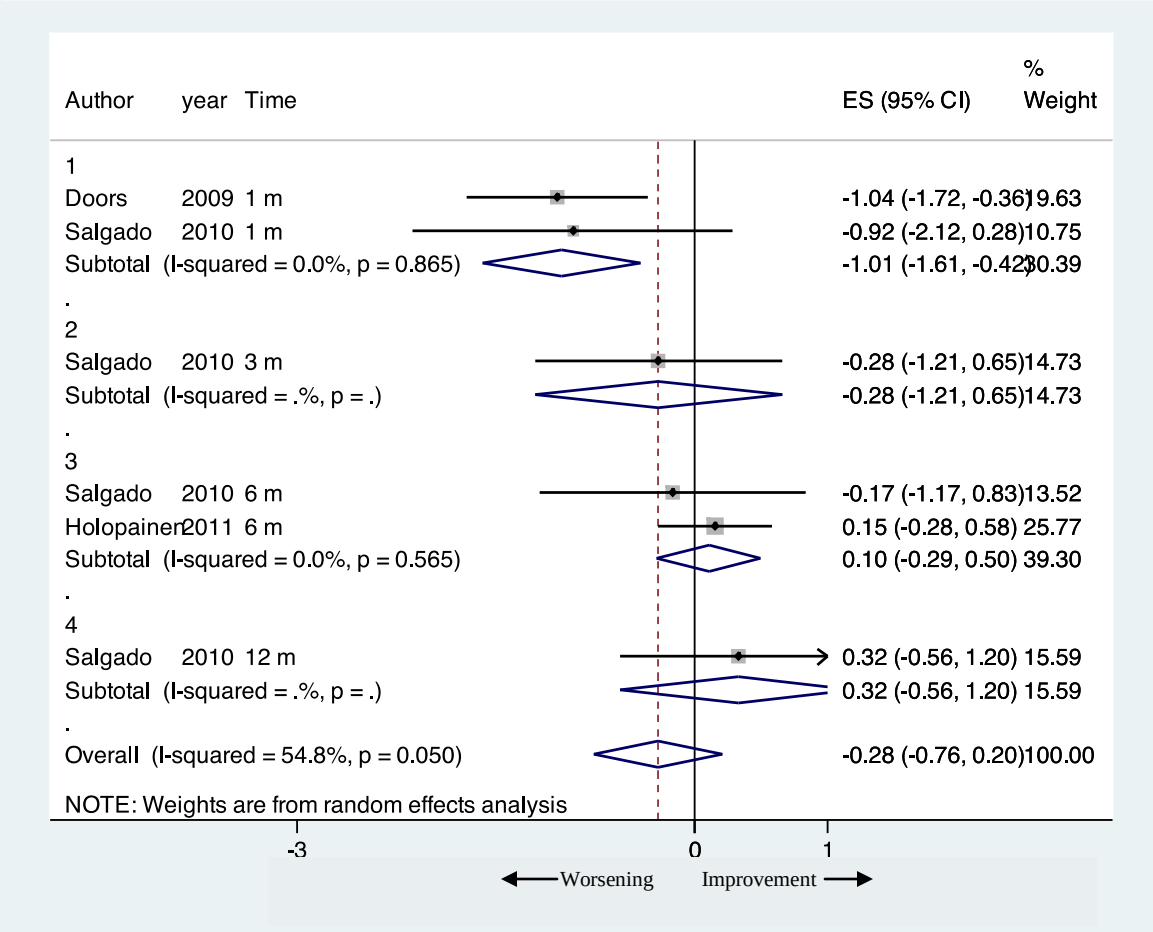


**Figure 15 SE: Mixed Disease, Analyzed by Time**




## 5.5.7 Pachymetry

Figure 16 shows that for KC cases, there was no evidence of worsening or improvement over time. When a meta-regression was completed to assess progression over time, a non-statistically significant improvement over time was found (p-value: 0.248) indicating that pachymetry results do not improve over time but remain stable. Studies which included mixed populations (Figure 17) showed improved pachymetry values.

**Figure 16 Pachymetry: KC by time**

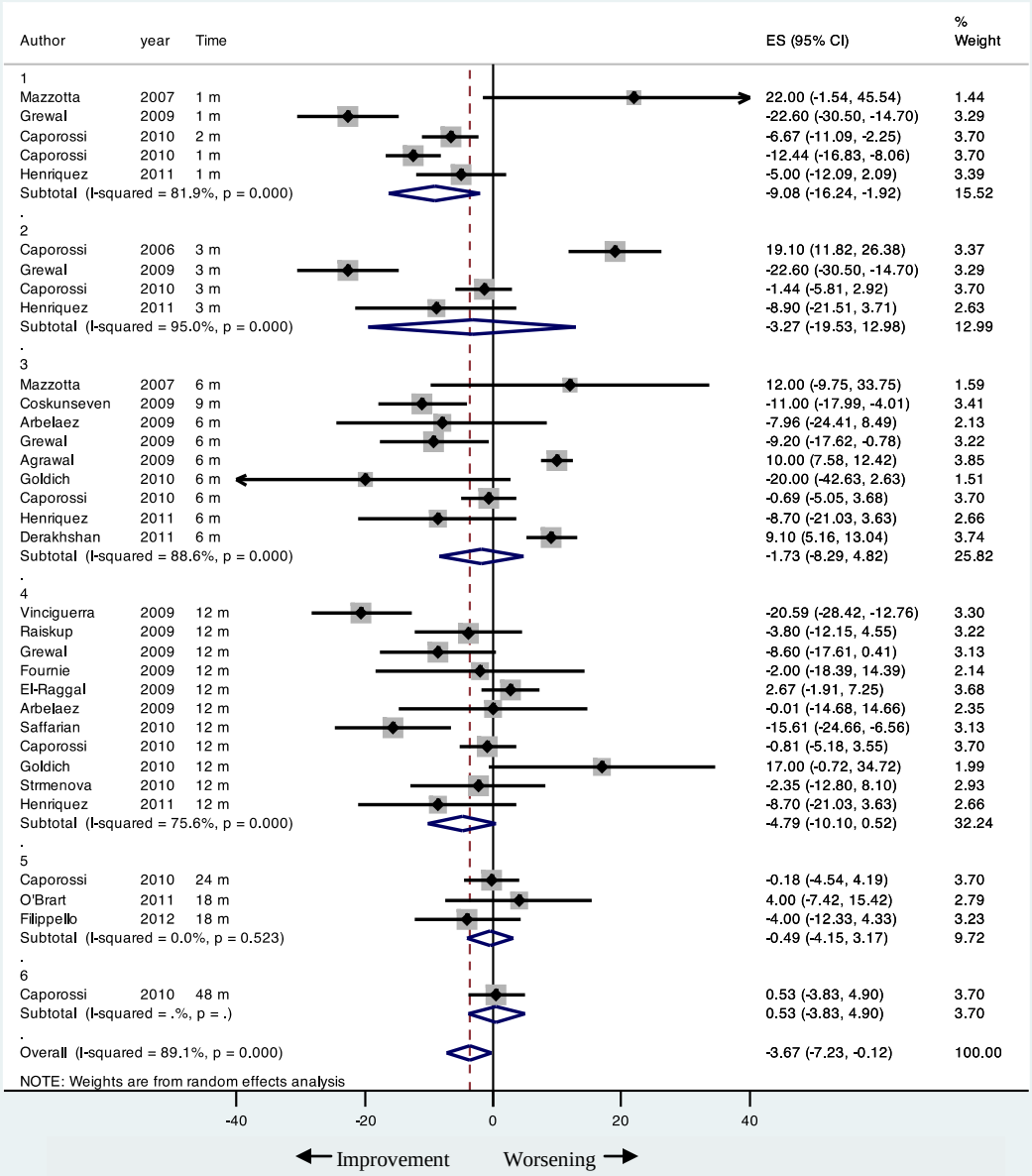
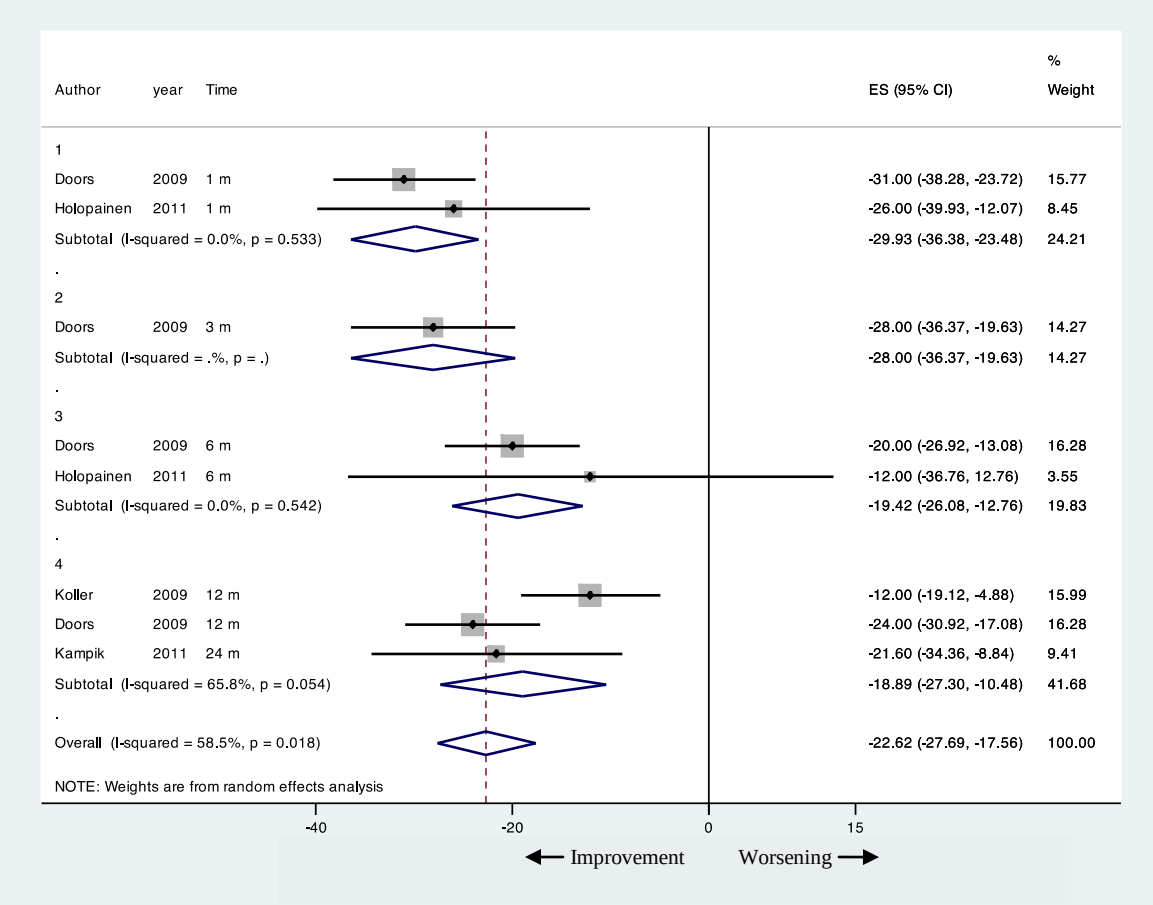


**Figure 17 Pachymetry: Mixed Disease by time**




## *5.6* Technology Effects and Effectiveness Summary (T)

This review identified 36 relevant papers (including 2 RCTs and 34 cohort studies). The 34 cohort studies were meta-analyzed using effect size to estimate clinical efficacy. The RCTs were of moderate quality as assessed by the Jadad scale. The included cohort studies ranged from moderate to excellent quality according to the Newcastle-Ottawa Scale.

No relevant systematic reviews were identified, although a significant number of non-systematic reviews were found. Similarly, there are no known meta-analysis which have previously been

conducted on the efficacy of CXL for corneal thinning disorders. The literature search identified four publically available HTAs on the topic.

The meta-analysis in this report showed that CXL to produces statistically significant improvements in BCVA, UCVA, kmin, kave, kmax, and spherical equivalent outcomes. The only outcome that did not show statistically significant improvement in KC patients was pachymetry. The studies reporting mixed disease groups showed less overall improvement in most measures than studies which only included keratoconus patients. Mixed disease groups showed significant improved in BCVA, UCVA, and pachymetry outcomes. No improvement was seen in kave, kmax, or SE outcomes.

# 6 RESULTS: ECONOMIC (E)

## 6.1 Literature

Very limited literature was found on the economic implications of CXL. Two sources discussed the economic impact of CXL, the HTA produced by Health Quality Ontario, and the Swedish HTA.

The Ontario HTA estimates annual prevalence and incidence rates of KC within Ontario and reports a cost impact analysis based on that data. This analysis took preoperative (consultation, and diagnostic corneal topography), and postoperative treatment (follow-up assessment, corneal topography and prescription medication) into account in addition to addressing the costs of the procedure.[160] This HTA estimated that within Ontario, the CXL process cost $1,036.12 for one eye, or $1,750.55 for both eyes.[160] With an estimated prevalence of 4,047 cases and annual

incidence of 148, it was projected that CXL provision would cost $2.09 million per annum.[160] This report did not assess the comparative costs of CXL and corneal transplant and did not assess how many corneal transplant procedures would be displaced with the provision of CXL.

The Swedish HTA reports the average cost of corneal transplant to be 41 500 SEK per eye (approximately $6,108.74 CAD) in Sweden.[159] In comparison, this report estimates that CXL (including pre- and post-operative follow-up) would cost approximately 30,000 SEK per eye (or $4,415.96 CAD) to provide in Sweden.[159]

The cost estimate from the Swedish HTA is considerably higher than that provided by the Ontario HTA. The reports lack detail necessary to fully understand this difference. One of the reasons for this disparity is that the Swedish report considers it an inpatient procedure whereas the Ontario report assesses it as an outpatient procedure. The Swedish report notes that the costing includes hospitalization and operation room costs compared to the Ontario report which includes only clinic costs.

### 6.2 Economic Evaluation

A primary economic evaluation is not possible. There are two main problems; a lack of data comparing the appropriate treatments and no standard comparator. First, the RCT and cohort data report outcomes in comparison to fellow untreated eyes (similar to placebo). Ideally, clinic inputs into an economic model would compare CXL to other available treatments such as Intacs or corneal transplantation. Second, the relevant comparator is unclear. At the time of CXL,

patients may be offered corneal transplant or this may be offered at a later stage of disease progression.

### 6.3 Budget Impact Assessment

Table 6 presents a rough estimate of the costs involved in providing CXL within Alberta. Data is divided into pre-procedure, procedure and post-procedure costs incurred; each includes costs for clinical expertise, pharmaceuticals and procedure/equipment costs. Medication costs were derived from the Alberta Blue Cross Drug Benefits List [163]. These costs were calculated based on the assumption that one milliliter of solution would provide 20 drops. Costs for clinical expertise and the procedure/equipment were estimated using the schedule of medical benefits and expert consultation. Cost estimates have been reported for one and two eye procedures. Costs for a complete oculo-visual examination were used pre- and post-operatively, although, in some cases, a full examination may not be necessary. Using costs for a complete examination rather than a partial exam provides a conservative estimate.

Estimates for proparacaine, riboflavin and vigamox were unavailable from Alberta data; Ontario data was used for these three costs. [160] Costs for corneal topography were also unavailable from Alberta-based data; Ontario data was used for these estimates.[160] None of these fours expenses are significant cost-drivers in this estimate, so slight variation is unlikely to significantly impact the overall cost.

It is estimated that to provide CXL in Alberta for one eye, it would cost approximately $1167.44 per person, with two eyes per person costing $1937.75.

**Table 6:** CXL Cost Estimates Per Patient

| Clinical Phase | Item | Cost |
|---|---|---|
| ***Preoperative*** | | |
| Ophthalmologist Consultation | Complete oculo-visual examination (09.01F) | $47.40 |
| Ophthalmologist Repeat Visit | Complete oculo-visual examination (09.01F) | $47.40 |
| Corneal Topography | First Visit | $50.00 |
| | Second Visit | $50.00 |
| *Cost for 1 or 2 eyes* | | *$194.80* |
| ***CXL Procedure*** | | |
| Medication | Proparacaine 0.5% | $10.13 |
| | Riboflavin 0.1% | $19.50 |
| Technical/Ophthalmologist Procedure | Superficial Keratectomy (25.39C) | $297.99 |
| | Anterior Chamber Laser (26.52) | $405.49 |
| *Cost for 1 eye* | | *$733.11* |
| *Cost for 2 eyes* | | *$1456.09* |
| ***Post-Operative*** | | |
| Ophthalmologist Repeat Visit | First day - complete oculo-visual examination (09.01F) | $47.40 |
| | First week - Complete oculo-visual examination (09.01F) | $47.40 |
| | First month- Complete oculo-visu examination (09.01F) | $47.40 |
| Corneal Topography | First month measurement | $50 |
| Medication | Antibiotic – Moxifloxacin (Vigamox) | $30.00 |
| | Anti-inflammation – dexamethasone (Ophthalmic Suspension) | $17.33/eye |
| *Cost for 1 eye* | | *$239.53* |
| *Cost for 2 eyes* | | *$286.86* |
| **TOTAL COST 1 eye** | | **$1167.44** |
| **TOTAL COST 2 eyes** | | **$1937.75** |

Prevalence and incidence estimates are varied in the literature. Through expert opinion, it was confirmed that the prevalence of KC can range from 1/2000 up to 1/500 (personal communication). Based on the estimate that there are currently 3,835,041 people in Alberta, it can be estimated that there are between 1917.5 and 7670.1 people in Alberta currently living with KC. The Ontario HTA report estimated that the incidence of KC is 2/100,000; this estimate has been adopted in this budget impact analysis.[3] It therefore can be estimated that approximately 77 people are diagnosed with KC every year in Alberta.

KE develops in approximately 0.01-0.9% of those who undergo LASIK eye surgery [9]; or an estimated 1.1-99 people annually in Alberta. There are no estimates available for PMD, so costs could not be determined for this disease group. Due to the extreme rarity of this disease, the exclusion of this disease from cost estimates is unlikely to significantly affect the overall estimate.

Table 7 presents estimated costs for conducting CXL on patients with KC and KE within Alberta. The existing cases (prevalence) were incorporated into the annual average over a span of three years (1/3 added every year); thereafter, the annual averages were derived solely from incidence rates. Both low and high annual averages are reported based on high and low prevalence and incidence rates.

**Table 7**: Prevalence, Incidence and Annual costs

| | | All prevalence cases completed within 3 years and incident cases completed annually | | Incident cases completed annually | |
|---|---|---|---|---|---|
| | | *Low estimate* | *High estimate* | *Low estimate* | *High estimate* |
| **KC** | # Patients (n) | 716 | 2633 | 77 | 77 |
| | Annual average cost, 1 Eye per Patient ($) | $835,740.32 | $3,074,330.45 | $89,543.61 | $89,543.61 |
| | Annual average cost, 2 Eyes per Patient ($) | $1,387,185.46 | $5,102,860.81 | $148,627.01 | $148,627.01 |
| **KE** | # Patients (n) | 1 | 101 | 1 | 101 |
| | Annual average cost, 1 Eye per Patient ($) | $1,311.96 | $118,076.02 | $1,311.96 | $118,076.02 |
| | Annual average cost, 2 Eyes per Patient ($) | $2,177.62 | $195,985.92 | $2,177.62 | $195,985.92 |
| **Total** | # Patients (n) | 717 | 2,734 | 78 | 178 |
| | Annual average cost, 1 Eye per Patient ($) | $837,052.27 | $3,192,406.47 | $90,855.56 | $207,619.62 |
| | Annual average cost, 2 Eyes per Patient ($) | $1,389,363.08 | $5,298,846.74 | $150,804.64 | $344,612.94 |

Based on the above prevalence and incidence rates, it can be estimated that during the first three years, provision of CXL for all patients with KC and KE would cost between $837,052.27 and $3,192,406.47 for one eye per patient or $1,389,363.08-$5,298,846.74 for two eyes per patient

annually. After existing cases have been treated, annual treatment cost will be between $90,855.56 and $207,619.62 for one eye and between $150,804.64 and $344,612.94 for treating two eyes per patient. This estimate is limited by a lack of Alberta prevalence and incidence rates for each disease, by large ranges in the literature, and by four missing Alberta-based costs.

# 7 CONCLUSIONS OF THE STE ANALYSIS

Using CXL for the treatment of corneal thinning disorders is a relatively new innovation which has been approved for use in many countries. Surprisingly, no systematic reviews or meta-analyses have been completed on this topic, despite the availability of a number of cohort and RCT studies. Similarly, only two HTAs outline the economic implications of publically funding this technology, however, neither is relevant to the Alberta context.

Although there is the risk of serious adverse events occurring after CXL treatment, these are rare. Post-procedure side-effects are frequent, but are either treatable or resolve with time. CXL is considered to be a safe, minimally invasive procedure.

The meta-analysis in this report shows that CXL stabilizes the cornea. With keratoconus patients, CXL treatment was shown to produce statistically significant improvements in all outcomes considered except pachymetry. The studies reporting mixed disease groups showed less overall improvement in most measures but still demonstrated significant improvement in BCVA, UCVA, and pachymetry. Both of the included RCTs reported that CXL resulted in stabilization of corneal thinning.

A budget impact analysis based on Alberta costs and global prevalence and incidence data found that provision of CXL would cost between $837,052.27 and $5,298,846.74 annually when existing cases are incorporated into the first three years and between $90,855.56 and $344,612.94 annually once existing cases have been treated and only new diagnosis' are undergoing CXL. This estimate is limited by a lack of Alberta prevalence and incidence rates for each disease.

There are a number of gaps in the literature that limit this report. As of yet, long-term effects of CXL are not known. Since this technology is new, there is no outcome or safety data over a long follow-up time. Similarly, there is also no data on whether CXL will replace or delay the need for corneal transplant; this information would likely result from studies with long follow-up periods. There is also a lack of RCTs and high quality cohort studies. More RCT data would improve the quality of efficacy estimates. Overall, CXL appears to be effective and safe. However, the total cost, cost-effectiveness and long-term outcomes of the procedure are unknown.

Reference List

(1) Rabinowitz YS. Keratoconus. [Review] [164 refs]. *Survey of Ophthalmology* 1998;42:297-319.

(2) Tuft S, Moodaley L, Gregory W, Davison C, Buckley R. Prognostic Factors for the Progression of Keratoconus. *Ophthalmology* 1994;439-447.

(3) Yaron S. RM. Keratoconus. *Survey of Ophthalmology* 1998;42:297-319.

(4) Kwon Y, Fingert J, Greenlee E. Intraocular pressure and corneal pachymetry. 2006.

(5) National Keratoconus Foundation. What is Keratoconus? 2012.

(6) Accuvision. Keratoconus Diagnosis and Treatment - Do you have Keratoconus? 2011.

(7) Edwards M, McGhee C, Dean S. The Genetics of Keratoconus. *Clinical and Experimental Ophthalmology* 2001;29:345-351.

(8) Randleman JB. Post-laser in-situ keratomileusis ectasia: current understanding and future directions. [Review] [59 refs]. *CURR OPIN OPHTHALMOL* 2006;17:406-412.

(9) Binder PS. Analysis of ectasia after laser in situ keratomileusis: Risk factors. *Journal of Cataract & Refractive Surgery* 2007;33:1530-1538.

(10) CBC News. Woman Awarded $1.7M for Laser Eye Surgery Blindness. 2001.

(11) Comaish IF, Lawless MA. Progressive post-LASIK keratectasia: Biomechanical instability or chronic disease process? *Journal of Cataract & Refractive Surgery* 2002;28:2206-2213.

(12) Agarwal A. Keratectasia after LASIK. 2006.

(13) Meghpara B, Nakamura H, Macsai M et al. Keratectasia after laser in situ keratomileusis: a histopathologic and immunohistochemical study. *Arch Ophthalmol* 2008;126:1655-1663.

(14) Jinabhai A, Radhakrishnan H, O'Donnel C. Pellucid Corneal Marginal Degeneration: A Review. *Contact Lens and Anterior Eye* 2011;34:56-63.

(15) Lens Design. Pellucid Marginal Degereation - Correction and Treatment with Contact Lenses. 2011.

(16) Fung M, Hampton R. Corneal Topography and Imaging. 2012.

(17) O'Donnel C, Maldonado-Codina C. Agreement and Repeatability of Central Thickness Measurement in Normal Corneas Using Ultrasound Pachymetry and the OCULUS Pentacam. *Cornea* 2004;24.

(18) Clinical Policy Bulletin: Corneal Pachmetry. 2011.

(19) Shafiq I, Hashmani S. Comparison Between Central Corneal Thickness Measurements Obtained with Orbscan II Topographer and Ultrasonic Pachymeter. *Pak J Ophthalmol* 2007;23.

(20) Grasso J, Long J, McCulloch J, Moore C. Visual Acuity. 2011.

(21) Precision Vision: Visual Acuity. 2012.

(22) WHO: What is refractive error? 2012.

(23) Vu HTV, Keeffe JE, McCarty CA, Taylor HR. Impact of unilateral and bilateral vision loss on quality of life. *British Journal of Ophthalmology* 2005;89:360-363.

(24) Chia EM, Wang JJ, Rochtchina E, Smith W, Cumming RR, Mitchell P. Impact of Bilateral Visual Impairment on Health-Related Quality of Life: the Blue Mountains Eye Study. *Investigative Ophthalmology & Visual Science* 2004;45:71-76.

(25) Kymes SM, Walline JJ, Zadnik K, Gordon MO. Quality of life in keratoconus. *AM J OPHTHALMOL* 2004;138:527-535.

(26) Wagner H, Barr JT, Zadnik K. Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study: Methods and findings to date. *Contact Lens and Anterior Eye* 2007;30:223-232.

(27) Mendes F, Schaumberg DA, Navon S et al. Assessment of visual function after corneal transplantation: the quality of life and psychometric assessment after corneal transplantation (Q-PACT) study. *AM J OPHTHALMOL* 2003;135:785-793.

(28) Uiters E, van den Borne B, van der Horst FG, V+¦lker-Dieben HJM. Patient Satisfaction After Corneal Transplantation. *Cornea* 2001;20.

(29) Jhanji V, Sharma N, Vajpayee RB. Management of keratoconus: current scenario. [Review]. *British Journal of Ophthalmology* 2011;95:1044-1050.

(30) Randleman JB. Post-laser in-situ keratomileusis ectasia: Current understanding and future directions. *Current Opinion in Ophthalmology 17 (4) (pp 406-412), 2006 Date of Publication: Aug 2006*:Aug.

(31) Kompella VB, Aasuri MK, Rao GN. Management of Pellucid Marginal Corneal Degeneration with Rigid Gas Permeable Contact Lenses. *Eye & Contact Lens* 2002;28.

(32) Pi+¦ero DP, Alio JL. Intracorneal ring segments in ectatic corneal disease ΓÇô a review. *Clinical & Experimental Ophthalmology* 2010;38:154-167.

(33) Siganos CS, Kymionis GD, Kartakis N, Theodorakis MA, Astyrakakis N, Pallikaris IG. Management of keratoconus with Intacs. *AM J OPHTHALMOL* 2003;135:64-70.

(34) Rodriguez-Ausin P, Gutierrez-Ortega R, Arance-Gil A, Romero-Jimenez M, Fuentes-Paez G. Keratopathy after cross-linking for keratoconus. *Cornea* 2011;30:1051-1053.

(35) Pi+¦ero DP, Alio JL, Kady BE et al. Refractive and Aberrometric Outcomes of Intracorneal Ring Segments for Keratoconus: Mechanical versus Femtosecond-assisted Procedures. *Ophthalmology* 2009;116:1675-1687.

(36) Bourcier T, Borderie V, Laroche L. Late bacterial keratitis after implantation of intrastromal corneal ring segments. *Journal of Cataract & Refractive Surgery* 2003;29:407-409.

(37) Hovakimyan M, Guthoff RF, Stachs O. Collagen cross-linking: current status and future directions. *Journal of ophthalmology* 2012;2012:406850.

(38) Spoerl E, Seiler T. Techniques for stiffening the cornea. *Journal of Refractive Surgery* 1999;15:711-713.

(39) Derakhshan A, Shandiz J, Ahadi M, Daneshvar R, Esmaily H. Short-term Outcomes of Collagen Crosslinking for Early Keratoconus. *Journal of Ophthalmic & Vision Research* 2011;6:155-159.

(40) Vinciguerra P, Camesasca FI, Albe E, Trazza S. Corneal collagen cross-linking for ectasia after excimer laser refractive surgery: 1-year results. *Journal of Refractive Surgery* 2010;26:486-497.

(41) Filippello M, Stagni E, O'Brart D. Transepithelial corneal collagen crosslinking: Bilateral study. *Journal of Cataract & Refractive Surgery* 2012;38:283-291.

(42) Raiskup F, Spoerl E. Corneal cross-linking with hypo-osmolar riboflavin solution in thin keratoconic corneas. *AM J OPHTHALMOL* 2011;152:28-32.

(43) Corneal Collagen Cross-Linking with Riboflavin and UV light in Keratoconus and related corneal ectasia. 2011.

(44) Dahl BJ, Spotts E, Truong JQ. Corneal collagen cross-linking: an introduction and literature review. *Optometry (St Louis, Mo )* 2012;83:33-42.

(45) Herrmann CI, Hammer T, Duncker GI. [Hazeformation (corneal scarring) after cross-linking therapy in keratoconus]. [German]. *Ophthalmologe* 2008;105:485-487.

(46) Lim LS, Beuerman R, Lim L, Tan DT. Late-onset deep stromal scarring after riboflavin-UV-A corneal collagen cross-linking for mild keratoconus. *Arch Ophthalmol* 2011;129:360-362.

(47) Greenstein SA, Fry KL, Bhatt J, Hersh PS. Natural history of corneal haze after collagen crosslinking for keratoconus and corneal ectasia: Scheimpflug and biomicroscopic analysis. *Journal of Cataract & Refractive Surgery* 2010;36:2105-2114.

(48) Raiskup F, Hoyer A, Spoerl E. Permanent corneal haze after riboflavin-UVA-induced cross-linking in keratoconus. *Journal of Refractive Surgery* 2009;25:S824-S828.

(49) 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.

(50) Pollhammer M, Cursiefen C. Bacterial keratitis early after corneal crosslinking with riboflavin and ultraviolet-A. *Journal of Cataract & Refractive Surgery* 2009;35:588-589.

(51) Garcia-Delpech S, Diaz-Llopis M, Udaondo P, Salom D. Fusarium keratitis 3 weeks after healed corneal cross-linking. *Journal of Refractive Surgery* 2010;26:994-995.

(52) Rama P, Di MF, Matuska S, Paganoni G, Spinelli A. Acanthamoeba keratitis with perforation after corneal crosslinking and bandage contact lens use. *Journal of Cataract & Refractive Surgery* 2009;35:788-791.

(53) Kymionis GD, Portaliou DM, Bouzoukis DI et al. Herpetic keratitis with iritis after corneal crosslinking with riboflavin and ultraviolet A for keratoconus. *Journal of Cataract & Refractive Surgery* 2007;33:1982-1984.

(54) Samaras KE, Lake DB. Corneal Collagen Cross Linking (CXL): A Review. *International Ophthalmology Clinics* 2010;50.

(55) Hafezi F, Mrochen M, Iseli HP, Seiler T. Collagen crosslinking with ultraviolet-A and hypoosmolar riboflavin solution in thin corneas. *Journal of Cataract & Refractive Surgery* 2009;35:621-624.

(56) Lim L, Pesudovs K, Coster DJ. Penetrating keratoplasty for keratoconus: visual outcome and success. *Ophthalmology* 2000;107:1125-1131.

(57) Bahar I, Kaiserman I, McAllum P, Slomovic A, Rootman D. Comparison of Posterior Lamellar Keratoplasty Techniques to Penetrating Keratoplasty. *Ophthalmology* 2008;115:1525-1533.

(58) Reinhart WJ, Musch DC, Jacobs DS, Lee WB, Kaufman SC, Shtein RM. Deep Anterior Lamellar Keratoplasty as an Alternative to Penetrating Keratoplasty: A Report by the American Academy of Ophthalmology. *Ophthalmology* 2011;118:209-218.

(59) Innocross. 2012.

(60) OFTA Hi-Tech. VEGA. 2012.

(61) KXL: the first true breakthrough in corneal cross-linking. 2012.

(62) Egger M, Smith D, Altman DG. *Systematic Reviews in Health Care: Meta-analysis in Context*. London: BMJ Publishing Group, 2001.

(63) Kampik D, Koch M, Kampik K, Geerling G. [Corneal riboflavin/UV-A collagen cross-linking (CXL) in keratoconus: two-year results]. [German]. *Klinische Monatsblatter fur Augenheilkunde* 2011;228:525-530.

(64) Caporossi A, Mazzotta C, Baiocchi S, Caporossi T, Denaro R. Age-Related Long-Term Functional Results after Riboflavin UV A Corneal Cross-Linking. *Journal of ophthalmology* 2011;2011:608041.

(65) Saffarian L, Khakshoor H, Zarei-Ghanavati M, Esmaily H. Corneal Crosslinking for Keratoconus in Iranian Patients: Outcomes at 1 year following treatment. *Middle East African journal of ophthalmology* 2010;17:365-368.

(66) Arbelaez MC, Sekito MB, Vidal C, Choudhury SR. Collagen cross-linking with riboflavin and ultraviolet-A light in keratoconus: One-year results. *Oman Journal of Ophthalmology* 2009;2:33-38.

(67) El-Raggal TM. Riboflavin-Ultraviolet A Corneal Cross-linking for Keratoconus. *Middle East African journal of ophthalmology* 2009;16:256-259.

(68) Bikbov MM, Bikbova GM, Khabibullin AF. [Corneal collagen cross-linking in keratoconus management]. [Russian]. *Vestnik Oftalmologii* 2011;127:21-25.

(69) O'Brart DP, Chan E, Samaras K, Patel P, Shah SP. A randomised, prospective study to investigate the efficacy of riboflavin/ultraviolet A (370 nm) corneal collagen cross-linkage to halt the progression of keratoconus. *British Journal of Ophthalmology* 2011;95:1519-1524.

(70) Holopainen JM, Krootila K. Transient corneal thinning in eyes undergoing corneal cross-linking. *AM J OPHTHALMOL* 2011;152:533-536.

(71) Koller T, Pajic B, Vinciguerra P, Seiler T. Flattening of the cornea after collagen crosslinking for keratoconus. *Journal of Cataract & Refractive Surgery* 2011;37:1488-1492.

(72) Raiskup F, Kissner A, Spoerl E, Pillunat LE. [Corneal cross-linking with hypo-osmolar riboflavin solution for keratoconus with thin corneas]. [German]. *Ophthalmologe* 2011;108:846-851.

(73) Salgado JP, Khoramnia R, Lohmann CP, Winkler von MC. Corneal collagen crosslinking in post-LASIK keratectasia. *British Journal of Ophthalmology* 2011;95:493-497.

(74) Henriquez MA, Izquierdo L, Jr., Bernilla C, Zakrzewski PA, Mannis M. Riboflavin/Ultraviolet A corneal collagen cross-linking for the treatment of keratoconus: visual outcomes and Scheimpflug analysis. *Cornea* 2011;30:281-286.

(75) Hersh PS, Greenstein SA, Fry KL. Corneal collagen crosslinking for keratoconus and corneal ectasia: One-year results. *Journal of Cataract & Refractive Surgery* 2011;37:149-160.

(76) Mate-Istvan I, Tomi T, Borda A, Vultur F. [Corneal collagen cross-linking in the treatment of keratoconus--preliminary results]. [Romanian]. *Oftalmologia* 2010;54:86-90.

(77) Strmenova E, Vlkova E, Hlinomazova Z et al. [Corneal cross-linking--modern method of keratoconus treatment]. [Slovak]. *Ceska a Slovenska Oftalmologie* 2010;66:248-253.

(78) Goldich Y, Marcovich AL, Barkana Y, Avni I, Zadok D. Safety of corneal collagen cross-linking with UV-A and riboflavin in progressive keratoconus. *Cornea* 2010;29:409-411.

(79) 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;149:585-593.

(80) Doors M, Tahzib NG, Eggink FA, Berendschot TT, Webers CA, Nuijts RM. Use of anterior segment optical coherence tomography to study corneal changes after collagen cross-linking. *AM J OPHTHALMOL* 2009;148:844-851.

(81) Baumeister M, Klaproth OK, Gehmlich J, Buhren J, Kohnen T. [Changes in corneal first-surface wavefront aberration after corneal collagen cross-linking in keratoconus]. [German]. *Klinische Monatsblatter fur Augenheilkunde* 2009;226:752-756.

(82) Tu KL, Aslanides IM. Orbscan II anterior elevation changes following corneal collagen cross-linking treatment for keratoconus. *Journal of Refractive Surgery* 2009;25:715-722.

(83) Fournie P, Galiacy S, Arne JL, Malecaze F. [Corneal collagen cross-linking with ultraviolet-A light and riboflavin for the treatment of progressive keratoconus]. [French]. *Journal Francais d Opthalmologie* 2009;32:1-7.

(84) Koller T, Iseli HP, Hafezi F, Vinciguerra P, Seiler T. Scheimpflug imaging of corneas after collagen cross-linking. *Cornea* 2009;28:510-515.

(85) Coskunseven E, Jankov MR, Hafezi F. Contralateral eye study of corneal collagen cross-linking with riboflavin and UVA irradiation in patients with keratoconus. *Journal of Refractive Surgery* 2009;25:371-376.

(86) 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.

(87) Grewal DS, Brar GS, Jain R, Sood V, Singla M, Grewal SP. Corneal collagen crosslinking using riboflavin and ultraviolet-A light for keratoconus: one-year analysis using Scheimpflug imaging. *Journal of Cataract & Refractive Surgery* 2009;35:425-432.

(88) Agrawal VB. Corneal collagen cross-linking with riboflavin and ultraviolet - a light for keratoconus: results in Indian eyes. *INDIAN J OPHTHALMOL* 2009;57:111-114.

(89) Jankov MR, Hafezi F, Beko M et al. [Corneal Cross-linking for the treatment of keratoconus: preliminary results]. [Portuguese]. *Arquivos Brasileiros de Oftalmologia* 2008;71:813-818.

(90) Wittig-Silva C, Whiting M, Lamoureux E, Lindsay RG, Sullivan LJ, Snibson GR. A randomized controlled trial of corneal collagen cross-linking in progressive keratoconus: preliminary results. *Journal of Refractive Surgery* 2008;24:S720-S725.

(91) Raiskup-Wolf F, Hoyer A, Spoerl E, Pillunat LE. Collagen crosslinking with riboflavin and ultraviolet-A light in keratoconus: long-term results. *Journal of Cataract & Refractive Surgery* 2008;34:796-801.

(92) Mazzotta C, Balestrazzi A, Traversi C et al. Treatment of progressive keratoconus by riboflavin-UVA-induced cross-linking of corneal collagen: ultrastructural analysis by Heidelberg Retinal Tomograph II in vivo confocal microscopy in humans. *Cornea* 2007;26:390-397.

(93) Caporossi A, Baiocchi S, Mazzotta C, Traversi C, Caporossi T. Parasurgical therapy for keratoconus by riboflavin-ultraviolet type A rays induced cross-linking of corneal collagen: preliminary refractive results in an Italian study. *Journal of Cataract & Refractive Surgery* 2006;32:837-845.

(94) Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. *AM J OPHTHALMOL* 2003;135:620-627.

(95) Abad JC, Arango J, Tobon C. Comparison of astigmatism correction using shorter arc length 90degrees/120degrees asymmetric intacs severe keratoconus versus 150degrees single-segment intacs severe keratoconus in asymmetric keratoconus. *Cornea* 2011;30:1201-1206.

(96) Guell JL, Morral M, Malecaze F, Gris O, Elies D, Manero F. Collagen crosslinking and toric iris-claw phakic intraocular lens for myopic astigmatism in progressive mild to moderate keratoconus. *Journal of Cataract & Refractive Surgery* 2012;38:475-484.

(97) Romano MR, Quaranta G, Bregu M, Albe E, Vinciguerra P. No retinal morphology changes after use of riboflavin and long-wavelength ultraviolet light for treatment of keratoconus. *Acta Opthalmologica* 2012;90:e79-e80.

(98) Kanellopoulos AJ. Long term results of a prospective randomized bilateral eye comparison trial of higher fluence, shorter duration ultraviolet A radiation, and riboflavin

collagen cross linking for progressive keratoconus. *Clinical Ophthalmology* 2012;6:97-101.

(99) Dhawan S, Rao K, Natrajan S. Complications of corneal collagen cross-linking. *Journal of ophthalmology* 2011;2011:869015.

(100) Rama P, Di MF, Matuska S, Insacco C, Paganoni G. Severe keratitis following corneal cross-linking for keratoconus. *Acta Opthalmologica* 2011;89:e658-e659.

(101) Beckman RJ, Janbaz CC, Behndig A, Linden C. Spatial distribution of corneal light scattering after corneal collagen crosslinking. *Journal of Cataract & Refractive Surgery* 2011;37:1939-1944.

(102) Soeters N, Van der Lelij A, van d, V, Tahzib NG. Corneal crosslinking for progressive keratoconus in four children. *Journal of Pediatric Ophthalmology & Strabismus* 2011;48:Online-9.

(103) Asri D, Touboul D, Fournie P et al. Corneal collagen crosslinking in progressive keratoconus: multicenter results from the French National Reference Center for Keratoconus. *Journal of Cataract & Refractive Surgery* 2011;37:2137-2143.

(104) Kymionis GD, Portaliou DM, Diakonis VF, Kounis GA, Panagopoulou SI, Grentzelos MA. Corneal collagen cross-linking with riboflavin and ultraviolet-A irradiation in patients with thin corneas. *AM J OPHTHALMOL* 2012;153:24-28.

(105) Spadea L, Mencucci R. Corneal collagen cross-linking. *Ophthalmology* 2011;118:2520-2524.

(106) Vinciguerra P, Camesasca FI, Romano MR. Corneal crosslinking and lens opacity. *Ophthalmology* 2011;118:2519-2.

(107) Saelens IE, Bartels MC, Bleyen I, Van RG. Refractive, topographic, and visual outcomes of same-day corneal cross-linking with Ferrara intracorneal ring segments in patients with progressive keratoconus. *Cornea* 2011;30:1406-1408.

(108) Sueke H, Ramasamy B, Tey A, Kaye S. Methodological issues in corneal collagen crosslinking in post-LASIK keratectasia. *British Journal of Ophthalmology* 2011;95:1759-1760.

(109) Kymionis GD, Kontadakis GA, Kounis GA et al. Simultaneous topography-guided PRK followed by corneal collagen cross-linking for keratoconus. *Journal of Refractive Surgery* 2009;25:S807-S811.

(110) Hafezi F, Koller T, Vinciguerra P, Seiler T. Marked remodelling of the anterior corneal surface following collagen cross-linking with riboflavin and UVA. *British Journal of Ophthalmology* 2011;95:1171-1172.

(111) Kaya V, Utine CA, Yilmaz OF. Efficacy of corneal collagen cross-linking using a custom epithelial debridement technique in thin corneas: a confocal microscopy study. *Journal of Refractive Surgery* 2011;27:444-450.

(112) Kanellopoulos AJ, Binder PS. Management of corneal ectasia after LASIK with combined, same-day, topography-guided partial transepithelial PRK and collagen cross-linking: the athens protocol. *Journal of Refractive Surgery* 2011;27:323-331.

(113) Reinstein DZ, Gobbe M, Archer TJ, Couch D. Epithelial thickness profile as a method to evaluate the effectiveness of collagen cross-linking treatment after corneal ectasia. *Journal of Refractive Surgery* 2011;27:356-363.

(114) Sedaghat M, Naderi M, Zarei-Ghanavati M. Biomechanical parameters of the cornea after collagen crosslinking measured by waveform analysis. *Journal of Cataract & Refractive Surgery* 2010;36:1728-1731.

(115) Kymionis GD, Grentzelos MA, Kounis GA et al. Intraocular pressure measurements after corneal collagen crosslinking with riboflavin and ultraviolet A in eyes with keratoconus. *Journal of Cataract & Refractive Surgery* 2010;36:1724-1727.

(116) Ashar JN, Vadavalli PK. Long-term results of riboflavin ultraviolet A corneal collagen cross-linking for Keratoconus in Italy: the Siena eye cross study. *AM J OPHTHALMOL* 2010;150:588-589.

(117) Constantin M, Corbu C. [Corneal collagen cross-linking--results in keratoconus]. [Romanian]. *Oftalmologia* 2009;53:85-88.

(118) Kymionis GD, Diakonis VF, Kalyvianaki M et al. One-year follow-up of corneal confocal microscopy after corneal cross-linking in patients with post laser in situ keratosmileusis ectasia and keratoconus. *AM J OPHTHALMOL* 778;147:774-778.

(119) Iovieno A, Oechsler RA, Yoo SH. Long-term results of collagen crosslinking with riboflavin and UVA in keratoconus. *Journal of Cataract & Refractive Surgery* 2008;34:1616-1617.

(120) Nassaralla BA, McLeod SD, Nassaralla JJ, Jr. Prophylactic mitomycin C to inhibit corneal haze after photorefractive keratectomy for residual myopia following radial keratotomy. *Journal of Refractive Surgery* 2007;23:226-232.

(121) Wollensak G, Sporl E, Seiler T. [Treatment of keratoconus by collagen cross linking]. [German]. *Ophthalmologe* 2003;100:44-49.

(122) Labetoulle M. An alternative to transplantation for keratoconus?. [French]. *Journal Francais d'Ophtalmologie 26 (10) (pp 1097-1098), 2003 Date of Publication: Dec 2003*:Dec.

(123) Sondergaard AP, Ivarsen A, Hjortdal J. [UVA riboflavin-crosslinking: promising keratoconus treatment]. [Danish]. *Ugeskrift for Laeger* 2010;172:946.

(124) Hafezi F, Kanellopoulos J, Wiltfang R, Seiler T. Corneal collagen crosslinking with riboflavin and ultraviolet A to treat induced keratectasia after laser in situ keratomileusis. *Journal of Cataract & Refractive Surgery* 2007;33:2035-2040.

(125) Raiskup F, Kissner A, Hoyer A, Sporl E, Pillunat LE. Corneal scar development after cross-linking in keratoconus. [German, English]. *Ophthalmologe 107 (9) (pp 837-842), 2010 Date of Publication: 2010*:2010.

(126) Iovieno A, Legare ME, Rootman DB, Yeung SN, Kim P, Rootman DS. Intracorneal ring segments implantation followed by same-day photorefractive keratectomy and corneal collagen cross-linking in keratoconus. *Journal of Refractive Surgery* 2011;27:915-918.

(127) Koppen C, Gobin L, Mathysen D, Wouters K, Tassignon MJ. Influence of contact lens wear on the results of ultraviolet A/riboflavin cross-linking for progressive keratoconus. *British Journal of Ophthalmology* 2011;95:1402-1405.

(128) Izquierdo L, Jr., Henriquez MA, McCarthy M. Artiflex phakic intraocular lens implantation after corneal collagen cross-linking in keratoconic eyes. *Journal of Refractive Surgery* 2011;27:482-487.

(129) Vincent AL, Markie DM, De KB et al. Exclusion of known corneal dystrophy genes in an autosomal dominant pedigree of a unique anterior membrane corneal dystrophy. *Molecular Vision 15 (pp 1700-1708), 2009 Date of Publication: 26 Aug 2009*:26.

(130) Kymionis GD, Portaliou DM, Diakonis VF et al. Posterior linear stromal haze formation after simultaneous photorefractive keratectomy followed by corneal collagen cross-linking. *Investigative Ophthalmology & Visual Science* 2010;51:5030-5033.

(131) Coskunseven E, Jankov MR, Hafezi F, Atun S, Arslan E, Kymionis GD. Effect of treatment sequence in combined intrastromal corneal rings and corneal collagen crosslinking for keratoconus. *Journal of Cataract & Refractive Surgery* 2009;35:2084-2091.

(132) Kanellopoulos AJ. Collagen cross-linking in early keratoconus with riboflavin in a femtosecond laser-created pocket: initial clinical results. *Journal of Refractive Surgery* 2009;25:1034-1037.

(133) Stojanovic A, Zhang J, Chen X, Nitter TA, Chen S, Wang Q. Topography-guided transepithelial surface ablation followed by corneal collagen cross-linking performed in a single combined procedure for the treatment of keratoconus and pellucid marginal degeneration. *Journal of Refractive Surgery* 2010;26:145-152.

(134) Alio JL, Toffaha BT, Pinero DP, Klonowski P, Javaloy J. Cross-linking in progressive keratoconus using an epithelial debridement or intrastromal pocket technique after

previous corneal ring segment implantation. *Journal of Refractive Surgery* 2011;27:737-743.

(135) Vetter JM, Tubic-Grozdanis M, Faust M, Lorenz K, Gericke A, Stoffelns BM. [Effect of various compositions of riboflavin eye drops on the intraoperative corneal thickness during UVA-cross-linking in keratoconus eyes]. [German]. *Klinische Monatsblatter fur Augenheilkunde* 2011;228:509-514.

(136) Bakke EF, Stojanovic A, Chen X, Drolsum L. Penetration of riboflavin and postoperative pain in corneal collagen crosslinking: excimer laser superficial versus mechanical full-thickness epithelial removal. *Journal of Cataract & Refractive Surgery* 2009;35:1363-1366.

(137) Leccisotti A, Islam T. Transepithelial corneal collagen cross-linking in keratoconus. *Journal of Refractive Surgery* 2010;26:942-948.

(138) Kanellopoulos AJ. Comparison of sequential vs same-day simultaneous collagen cross-linking and topography-guided PRK for treatment of keratoconus. *Journal of Refractive Surgery* 2009;25:S812-S818.

(139) Spoerl E, Terai N, Scholz F, Raiskup F, Pillunat LE. Detection of biomechanical changes after corneal cross-linking using Ocular Response Analyzer software. *Journal of Refractive Surgery* 2011;27:452-457.

(140) Mikielewicz M, Kotliar K, Barraquer RI, Michael R. Air-pulse corneal applanation signal curve parameters for the characterisation of keratoconus. *British Journal of Ophthalmology* 2011;95:793-798.

(141) Knappe S, Stachs O, Zhivov A, Hovakimyan M, Guthoff R. Results of confocal microscopy examinations after collagen cross-linking with riboflavin and UVA light in patients with progressive keratoconus. *Ophthalmologica* 2011;225:95-104.

(142) Renesto AC, Barros JN, Campos M. Impression cytologic analysis after corneal collagen cross-linking using riboflavin and ultraviolet-A light in the treatment of keratoconus. *Cornea* 2010;29:1139-1144.

(143) Raiskup F, Kissner A, Hoyer A, Sporl E, Pillunat LE. [Corneal scar development after cross-linking in keratoconus]. [German]. *Ophthalmologe* 2010;107:837-842.

(144) Vinciguerra P, Albe E, Mahmoud AM, Trazza S, Hafezi F, Roberts CJ. Intra- and postoperative variation in ocular response analyzer parameters in keratoconic eyes after corneal cross-linking. *Journal of Refractive Surgery* 2010;26:669-676.

(145) Croxatto JO, Tytiun AE, Argento CJ. Sequential in vivo confocal microscopy study of corneal wound healing after cross-linking in patients with keratoconus. *Journal of Refractive Surgery* 2010;26:638-645.

(146) Kymionis GD, Kounis GA, Portaliou DM et al. Intraoperative pachymetric measurements during corneal collagen cross-linking with riboflavin and ultraviolet A irradiation. *Ophthalmology* 2009;116:2336-2339.

(147) Koller T, Mrochen M, Seiler T. Complication and failure rates after corneal crosslinking. *Journal of Cataract & Refractive Surgery* 2009;35:1358-1362.

(148) Goldich Y, Barkana Y, Morad Y, Hartstein M, Avni I, Zadok D. Can we measure corneal biomechanical changes after collagen cross-linking in eyes with keratoconus?--a pilot study. *Cornea* 2009;28:498-502.

(149) Mazzotta C, Traversi C, Baiocchi S et al. Corneal healing after riboflavin ultraviolet-A collagen cross-linking determined by confocal laser scanning microscopy in vivo: early and late modifications. *AM J OPHTHALMOL* 2008;146:527-533.

(150) Seiler T, Hafezi F. Corneal cross-linking-induced stromal demarcation line. *Cornea* 2006;25:1057-1059.

(151) Mazzotta C, Traversi C, Baiocchi S, Sergio P, Caporossi T, Caporossi A. Conservative treatment of keratoconus by riboflavin-uva-induced cross-linking of corneal collagen: qualitative investigation. *European Journal of Ophthalmology* 2006;16:530-535.

(152) Greenstein SA, Fry KL, Hersh MJ, Hersh PS. Higher-order aberrations after corneal collagen crosslinking for keratoconus and corneal ectasia. *Journal of Cataract & Refractive Surgery* 2012;38:292-302.

(153) Greenstein SA, Fry KL, Hersh PS. In vivo biomechanical changes after corneal collagen cross-linking for keratoconus and corneal ectasia: 1-year analysis of a randomized, controlled, clinical trial. *Cornea* 2012;31:21-25.

(154) Greenstein SA, Fry KL, Hersh PS. Corneal topography indices after corneal collagen crosslinking for keratoconus and corneal ectasia: one-year results. *Journal of Cataract & Refractive Surgery* 2011;37:1282-1290.

(155) Constantin M, Corbu C. Evolutive aspects in keratoconus patients after collagen cross-linking. [Romanian]. *Oftalmologia (Bucharest, Romania : 1990) 53 (2) (pp 88-91), 2009 Date of Publication: 2009* 2009;1990-1991.

(156) Hayes S, Boote C, Kamma-Lorger CS et al. Riboflavin/UVA collagen cross-linking-induced changes in normal and keratoconus corneal stroma. *PLoS ONE [Electronic Resource]* 2011;6:e22405.

(157) Cannon DJ, Foster CS. Collagen crosslinking in keratoconus. *Investigative Ophthalmology & Visual Science* 1978;17:63-65.

(158) Canadian Agency for Drugs and Technologies in Health. Corneal Cross-linking with Riboflavin for Keratoconus: Clinical and Cost-effectiveness. 2010.

(159) Stenevi U, Claesson M, Holmberg Y et al. Corneal Crosslinking in Keratoconus. 2011.

(160) Pron G, Ieraci L, Kaulback K. Collagen Cross-Linking Using Riboflavin and Ultraviolet-A for Corneal Thinning Disorders: An Evidence-Based Analysis. 2011.

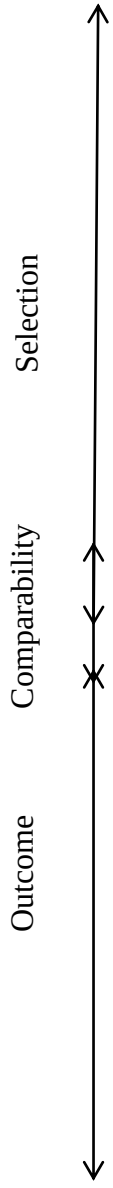
(161) National Institute for Health and Clinical Excellence. Interventional Procedure Overview of Photochemical Corneal Collagen Crosslinking using Riboflacin and Ultraviolet A for Keratoconus. 2009.

(162) National Institute for Health and Clinical Excellence. Photochemical Corneal Collagen Cross-linkage using Riboflavin and Ultraviolet A for Keratoconus. 2012.

(163) Alberta Health & Wellness - Drug Benefit List.

# 8 TABLES

**Table 8: Newcastle Ottawa Scale for Cohort Study Quality Assessment**




| Questions | Options (Circle) |
|---|---|
| Q1 Representativeness of the exposed cohort? | a) Truly representative of the average in the community*<br>b) Somewhat representative of the average in the community*<br>c) Selected group<br>d) No description of the derivation of the cohort |
| Q2 Selection of the non-exposed cohort | a) Drawn from the same community as the exposed cohort*<br>b) Drawn from a different source<br>c) No description of the derivation of the non-exposed cohort |
| Q3 Ascertainment of Exposure | a) Secure record*<br>b) Structured interview*<br>c) Written self-report<br>d) No description |
| Q4 Demonstration that outcome of interest was not present at the start of the study | a) Yes*<br>b) No |
| Q5 Comparability of cohorts on the basis of the design or analysis | a) Study controls for _____ (Select most appropriate factor)*<br>b) Study controls for any additional factor* |
| Q6 Assessment of outcome | a) Independent blind assessment*<br>b) Record linkage*<br>c) Self-report<br>d) No description |
| Q7 Was follow-up long enough for outcomes to occur? | a) Yes*<br>b) No |
| Q8 Adequacy of follow-up of cohorts | a) Complete follow-up (all subjects accounted for)*<br>b) Subjects lost to follow-up unlikely to introduce bias (less than 5%)*<br>c) Follow up rate more than 20% and no description of those lost<br>d) No statement |

**Table 9: Cohort Quality Assessment**

| Author | Year | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| Filippello[41] | 2012 | * | * | * | * | ** | * | * | * | 9 |
| Kampik[63] | 2011 | * | | * | * | * | * | * | | 6 |
| Caporossi[64] | 2011 | * | | * | * | * | * | * | | 6 |
| Saffarian[65] | 2010 | * | | * | * | * | * | * | * | 7 |
| Arbelaez[66] | 2009 | * | | * | * | * | * | * | * | 7 |
| El-Raggal[67] | 2009 | * | | * | * | * | * | * | * | 7 |
| Bikbov[68] | 2011 | * | | * | * | * | * | * | * | 7 |
| O'Brart[69] | 2011 | * | * | * | * | ** | * | * | * | 9 |
| Holopainen[70] | 2011 | * | | * | * | * | * | * | * | 7 |
| Koller[71] | 2011 | * | | * | * | * | * | * | * | 7 |
| Raiskup[72] | 2011 | * | | * | * | * | * | * | * | 7 |
| Salgado[73] | 2010 | * | | * | * | * | * | * | * | 7 |
| Henriquez[74] | 2011 | * | | * | * | * | * | * | * | 7 |
| Vinciguerra[40] | 2010 | * | | * | * | * | * | * | | 6 |
| Mate-Istvan[76] | 2010 | * | | * | * | * | * | * | * | 7 |
| Strmenova[77] | 2010 | * | | * | * | * | * | * | * | 7 |
| Goldich[78] | 2010 | * | | * | * | * | * | * | * | 7 |
| Caporossi[79] | 2010 | * | | * | * | * | * | * | * | 7 |
| Doors[80] | 2009 | * | | * | * | * | * | * | | 6 |
| Raiskup[48] | 2009 | * | | * | * | * | * | * | * | 7 |
| Baumeister[81] | 2009 | * | | * | * | * | * | * | * | 7 |
| Tu[82] | 2009 | * | | * | * | * | * | * | * | 7 |
| Fournie[83] | 2009 | * | | * | * | * | * | * | | 6 |
| Koller[84] | 2009 | * | * | * | * | ** | * | * | * | 9 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Coskunseven[85] | 2009 | * | * | * | * | ** | * | * | * | 9 |
| Vinciguerra[86] | 2009 | * | * | * | * | ** | * | * | * | 9 |
| Grewal[87] | 2009 | * | | * | * | * | * | * | * | 7 |
| Agrawal[88] | 2009 | * | | * | * | * | * | * | * | 7 |
| Jankov[89] | 2008 | * | | * | * | * | * | * | * | 7 |
| Raiskup[91] | 2008 | * | | * | * | * | * | * | | 6 |
| Mazzotta[92] | 2007 | * | | * | * | * | * | * | * | 7 |
| Caporossi[93] | 2006 | * | * | * | * | ** | * | * | * | 9 |
| Wollensak[94] | 2003 | * | | * | * | * | * | * | * | 7 |
| Derakhshan[39] | 2011 | * | | * | * | * | * | * | * | 7 |

## Table 10: Summary of Included Studies

| Reference | Number of Eyes Enrolled | Mean Age | Type of Control | Disease | Follow-up length | Change in Treatment Group Outcome Measures (Change of Final Follow-up Period from Baseline) | Overall Conclusions |
|---|---|---|---|---|---|---|---|
| Filippello | 20 | 27 | Fellow-eye | KC | 18 months | BCVA (logMAR) -0.21<br>UCVA (logMAR) -0.04<br>Kmax 0.3<br>Kmin 0.47<br>Pachymetry -25 | Stabilization of cornea |
| Kampik | 46 | 33.5 | None | KC<br>KE | 24 months | BCVA -0.05<br>Kmax -1.23<br>Pachymetry -21.6 | Stabilization of cornea |
| Caporossi | 516 | NR | None | KC | 48 months | Pediatric BCVA (Snellen) 0.21<br>Pediatric UCVA (Snellen) 0.2<br>Pediatric Kmax -0.89<br>Young adult BCVA (Snellen) 0.2<br>Young adult UCVA (Snellen) 0.14<br>Young adult Kmax -0.57<br>Adult BCVA (Snellen) 0.1<br>Adult UCVA (Snellen) 0.12<br>Adult Kmax -0.52 | Stabilization of cornea, particularly in patients under 26 years old |
| Saffarian | 92 | 21.5 | None | KC | 12 months | BCVA (logMAR) -0.06<br>UCVA (logMAR) -0.3<br>Kave -0.94<br>Pachymetry -15.61<br>SE 0.58 | Stabilization of cornea |
| Arbelaez | 19 | 24.4 | None | KC | 12 months | BCVA (logMAR) -0.18<br>UCVA (logMAR) -0.63<br>Kmax -1.4<br>Kave -1.36 | Stabilization of cornea |
| El-Raggal | 15 | 26.4 | None | KC | 12 months | BCVA (Snellen) 0.02<br>UCVA (Snellen) 0.04<br>Kmax -1.75<br>Kmin -1.5<br>Kave -1.63<br>Pachmetry 2.67<br>SE 0.47 | Stabilization of cornea |
| O'Brart | 24 | 49.6 | Fellow-eye | KC | 18 months | BCVA (Snellen) 0.12<br>UCVA (Snellen) 0.06<br>Kave -0.6<br>Pachymetry +4<br>SE +0.82 | Stabilization of cornea |
| Holopainen | 30 | 38 | None | KC, KE,<br>PMD | 6 months | BCVA (logMAR) -0.13<br>UCVA (logMAR) -0.01<br>Kave -0.7<br>Pachymetry -12<br>SE +0.15 | Stabilization of cornea |
| Koller | 151 | 29.3 | None | KC, PMD | 12 months | Kmax +0.89 | Stabilization of cornea |
| Raiskup | 32 | 27.4 | None | KC | 12 months | BCVA (logMAR) -0.04 | Stabilization of cornea |
| Salgado | 22 | NR | None | KE | 12 months | BCVA (logMAR) -0.04<br>UCVA (logMAR) -0.13<br>Kmax 0.31<br>Kmin 0.26<br>SE 0.32 | Stabilization of cornea |
| Henriquez | 10 | 29.7 | None | KC | | BCVA (logMAR) -0.11<br>UCVA (logMAR) -0.72<br>Kmax -2.667<br>Kmin -1.609<br>SE 2.25 | Stabilization of cornea |
| Hersh* | 71 | NR | Fellow-eye and | KC, KE | 12 months | BCVA (logMAR) -0.12<br>UCVA (logMAR) -0.07<br>Kmax -1.7 | Stabilization of cornea |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | Sham Control<br><br>Group | | | Kave -1.1<br>SE 0.86 | |
| Vinciguerra | 13 | 42 | None | KE | 12 months | BCVA (logMAR) -0.1<br>UCVA (logMAR) -0.14<br>Kmax -3.44<br>Kmin -2.61<br>Kave -3.02<br>SE 0.91 | Stabilization of cornea |
| Mate-Istvan | 27 | 28.45 | None | KC | 12 months | BCVA (snellen) 0.1866<br>UCVA (snellen) 0.2159<br>Kave -1.67<br>SE -0.69 | Stabilization of cornea |
| Strmenova | 40 | 28.45 | None | KC | 12 months | Kmax -0.83<br>Kmin -0.6<br>Kave -2.35 | Stabilization of cornea |
| Goldich | 14 | 28.2 | None | KC | 12 months | BCVA (logMAR) -0.1<br>UCVA (logMAR) 0.16<br>Kmax -1.8<br>Kmin -0.6<br>Kave -0.6<br>Pachymetry 17 | Stabilization of cornea |
| Caporossi | 44 | NR | None | KC | 48 months | BCVA (snellen) 1.04<br>UCVA (snellen) 0.81<br>Kave -2.26<br>Pachymetry 0.534<br>SE 1.98 | Stabilization of cornea |
| Doors | 29 | 35.1 | None | KC, KE | 12 Months | BCVA (logMAR) -0.02<br>Kmax -0.08<br>Kave 2.21<br>Pachymetry -24 | Stabilization of cornea |
| Raiskip | 163 | 31.52 | None | KC | 12 months | BCVA (logMAR, no haze) -0.11<br>UCVA (logMAR, no haze) -0.12<br>Pachymetry no haze -3.8<br>BCVA (logMAR, haze) 0.2<br>UCVA (logMAR, haze) 0.23<br>Pachymetry haze 35 | Stabilization of cornea |
| Baumeister | 20 | 32.2 | None | KC | 6 months | Kmax 0.99 | Stabilization of cornea |
| Tu | 14 | 29.5 | None | KC | 7 months | BCVA (snellen, pattern 1 eyes) 0.03<br>Kmax (pattern 1 eyes) -1.37<br>SE (pattern 1 eyes) 0.54<br>BCVA (snellen, pattern 2 eyes) 0.02<br>Kmax (pattern 2 eyes) 0.64<br>SE (pattern 2 eyes) -1.83 | Stabilization of cornea |
| Fournie | 20 | 23.7 | None | KC | 18 months | BCVA (Snellen) 0.21<br>UCVA (Snellen) 0.01<br>Kmax -1.48<br>Kmin -0.15<br>Kave -0.46<br>Pachymetry +4<br>SE -3.21 | Stabilization of cornea |
| Koller | 42 | NR | Fellow-eye<br><br>Control | KC, PMD | 12 months | Pachymetry -12 | Stabilization of cornea |
| Coskunseven | 38 | 38 | Fellow-eye<br><br>Control | KC | 9 months | BCVA (Snellen) 0.11<br>UCVA (Snellen) 0.06<br>Kmax -1.57<br>Pachymetry -11<br>SE 1.03 | Stabilization of cornea |
| Vinciguerra | 56 | NR | Fellow-eye<br><br>Control | KC | 12 months | BCVA (logMAR) -0.14<br>UCVA (logMAR) -0.2<br>Kmax -6.16<br>Kmin -5.88<br>Pachymetry -20.59<br>SE 0.43 | Stabilization of cornea |
| Grewal | 102 | 25.6 | None | KC | 12 months | BCVA (logMAR) -0.02<br>Pachymetry -8.6<br>SE 1.43 | Stabilization of cornea |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Agrawal | 37 | 16.9 | None | KC | 12 months | BCVA (logMAR) -0.09<br>Kmax -2.47 | Stabilization of cornea |
| Jankov | 25 | 28 | None | KC | 6 months | BCVA (Snellen) 0.08<br>UCVA (Snellen) 0.11<br>Kmax -2.14<br>SE 0.59 | Stabilization of cornea |
| Wittig-Silva* | 66 | NR | Sham Control | KC | 12 months | BCVA (logMAR) -0.12<br>Kmax 1.45<br>Kmin -5.88<br>Pachymetry -20.59<br>SE 0.43 | Stabilization of cornea |
| Raiskup | 241 | 30.04 | None | KC | 72 months | BCVA (logMAR) -0.18<br>Kmax -2.44 | Stabilization of cornea |
| Mazzotta | 10 | NR | None | KC | 6 months | Pachymetry 12 | Stabilization of cornea |
| Caporossi | 18 | 31.4 | Fellow-Eye Control | KC | 3 months | Kmax -1.9<br>Kmin -2.4<br>Kave -2.1<br>Pachymetry 19.1<br>SE 2.205 | Stabilization of cornea |
| Derakhshan | 31 | 22.3 | None | KC | 6 months | BCVA (Snellen) 0.17<br>UCVA (Snellen) 0.02<br>Kmax -0.65<br>Kave -0.51<br>Pachymetry 30.8<br>SE 0.55 | Stabilization of cornea |

*RCT **KC** = keratoconus **KE** = keratectasia **PMB** = pellucid marginal degeneration **D.A.** Decimal Acuity **LogMAR** Log of the minimum angle of refraction **Kmax** = maximum keratometry **Kmin** = minimum keratometry **Kave** = maximum keratometry **UCVA** = uncorrected visual acuity **BCVA** = best corrected visual acuity **SE** = Spherical Equivalent

## APPENDIX I: SEARCH STRATEGY

Databases Searched:

- MEDLINE
- EMBASE
- PubMED
- CINAHL
- Cochrane CENTRAL Registry of Controlled Trials
- Cochrane Database of Systematic Reviews
- NHSEED
- Econlit
- HTA Health Technology Assessment Database

Preliminary MEDLINE Search Strategy:

1. exp Keratoconus/ or exp Corneal Opacity/
2. (keratoconus or keratoconic or keratoectasia or keratectasia or keratoglobus or pellucid or marginal furrow or pellucid marginal degeneration or forme fruste).tw.
3. ((cone or conical) adj5 (ectasia* or cornea*)).tw.
4. (cornea* adj5 ectasia*).tw.
5. (cornea* adj5 thin*).tw.
6. 1 or 2 or 3 or 4 or 5
7. exp Cross-Linking Reagents/ or exp ultraviolet therapy/ or ultraviolet rays/ or exp riboflavin/ or collagen/
8. ((cross-link* or crosslink* or bifunct*) adj5 reagent*).tw.
9. (cross-link* or crosslink*).tw.
10. cxl.tw.
11. (vitamin b or ultraviolet or riboflavin or collagen or uvb or puva).tw.
12. 7 or 8 or 9 or 10 or 11
13. 6 and 12
14. limit 13 to animals
15. limit 13 to (animals and humans)
16. 14 not 15
17. 13 not 16

Embase

1. exp Keratoconus/ or exp Cornea Opacity/
2. (keratoconus or keratoconic or keratoectasia or keratectasia or keratoglobus or pellucid or marginal furrow or pellucid marginal degeneration or forme fruste).tw.
3. ((cone or conical) adj5 (ectasia* or cornea*)).tw.
4. (cornea* adj5 ectasia*).tw.
5. (cornea* adj5 thin*).tw.
6. 1 or 2 or 3 or 4 or 5
7. exp Cross-Linking Reagent/ or exp phototherapy/ or ultraviolet radiation/ or exp riboflavin/ or collagen/
8. ((cross-link* or crosslink* or bifunct*) adj5 reagent*).tw.
9. (cross-link* or crosslink*).tw.
10. cxl.tw.
11. (vitamin b or ultraviolet or riboflavin or collagen or uvb or puva).tw.
12. 7 or 8 or 9 or 10 or 11
13. 6 and 12
14. limit 13 to animals
15. limit 13 to (animals and humans)
16. 14 not 15
17. 13 not 16

Systematic reviews

1. (keratoconus or corneal opacity or keratoconic or keratoectasia or keratectasia or keratoglobus or pellucid or marginal furrow or pellucid marginal degeneration or forme fruste).tw.
2. ((cone or conical) adj5 (ectasia* or cornea*)).tw.
3. (cornea* adj5 ectasia*).tw.
4. (cornea* adj5 thin*).tw.
5. 1 or 2 or 3 or 4
6. (Cross-Linking Reagents or ultraviolet therapy or ultraviolet rays or riboflavin or collagen)
7. ((cross-link* or crosslink* or bifunct*) adj5 reagent*).tw.

8. (cross-link* or crosslink*).tw.
9. cxl.tw.
10. (vitamin b or ultraviolet or riboflavin or collagen or uvb or puva).tw.
11. 6 or 7 or 8 or 9 or 10
12. 5 and 11

Central RCT

1. exp Keratoconus/ or exp Corneal Opacity/
2. (keratoconus or keratoconic or keratoectasia or keratectasia or keratoglobus or pellucid or marginal furrow or pellucid marginal degeneration or forme fruste).tw.
3. ((cone or conical) adj5 (ectasia* or cornea*)).tw.
4. (cornea* adj5 ectasia*).tw.
5. (cornea* adj5 thin*).tw.
6. 1 or 2 or 3 or 4 or 5
7. exp Cross-Linking Reagents/ or exp ultraviolet therapy/ or ultraviolet rays/ or exp riboflavin/ or collagen/
8. ((cross-link* or crosslink* or bifunct*) adj5 reagent*).tw.
9. (cross-link* or crosslink*).tw.
10. cxl.tw.
11. (vitamin b or ultraviolet or riboflavin or collagen or uvb or puva).tw.
12. 7 or 8 or 9 or 10 or 11
13. 6 and 12

HTA Database

1. exp Keratoconus/ or exp Corneal Opacity/
2. (keratoconus or keratoconic or keratoectasia or keratectasia or keratoglobus or pellucid or marginal furrow or pellucid marginal degeneration or forme fruste).tw.
3. ((cone or conical) adj5 (ectasia* or cornea*)).tw.
4. (cornea* adj5 ectasia*).tw.
5. (cornea* adj5 thin*).tw.
6. 1 or 2 or 3 or 4 or 5
7. exp Cross-Linking Reagents/ or exp ultraviolet therapy/ or ultraviolet rays/ or exp riboflavin/ or collagen/

8. ((cross-link* or crosslink* or bifunct*) adj5 reagent*).tw.
9. (cross-link* or crosslink*).tw.
10. cxl.tw.
11. (vitamin b or ultraviolet or riboflavin or collagen or uvb or puva).tw.
12. 7 or 8 or 9 or 10 or 11
13. 6 and 12

NHSEED

1. exp Keratoconus/
2. (keratoconus or corneal opacity or keratoconic or keratoectasia or keratectasia or keratoglobus or pellucid or marginal furrow or pellucid marginal degeneration or forme fruste).tw.
3. ((cone or conical) adj5 (ectasia* or cornea*)).tw.
4. (cornea* adj5 ectasia*).tw.
5. (cornea* adj5 thin*).tw.
6. 1 or 2 or 3 or 4 or 5
7. exp ultraviolet therapy/ or ultraviolet rays/ or exp riboflavin/ or collagen/
8. (Cross-Linking Reagents).tw.
9. ((cross-link* or crosslink* or bifunct*) adj5 reagent*).tw.
10. (cross-link* or crosslink*).tw.
11. cxl.tw.
12. (vitamin b or ultraviolet or riboflavin or collagen or uvb or puva).tw.
13. 7 or 8 or 9 or 10 or 11 or 12
14. 6 and 13

Pubmed

1. Search Keratoconus [MeSH terms] or Corneal Opacity [MeSH terms]
2. Search keratoconus[Title/Abstract] or keratoconic[Title/Abstract] or keratoectasia[Title/Abstract] or keratectasia[Title/Abstract] or keratoglobus[Title/Abstract] or pellucid[Title/Abstract] or marginal furrow[Title/Abstract] or pellucid marginal degeneration[Title/Abstract] or forme fruste[Title/Abstract] or cornea* thin*[Title/Abstract] or cornea* ectas*[Title/Abstract]
3. Search cross-linking reagents [MeSH terms] or ultraviolet therapy [MeSH terms] or ultraviolet rays [MeSH terms] or riboflavin [MeSH terms] or collagen [MeSH terms]
4. Search cross-link*[Title/Abstract] or crosslink*[Title/Abstract]
5. Search #1 or #2

6. Search #3 or #4
7. Search #5 and #6
8. Search #5 and #6 Limits: Humans

Econlit

1. (keratoconus or corneal opacity or keratoectasia or keratectasia or pellucid marginal degeneration or forme fruste or ectasia*).TI.
2. (cornea* adj5 ectasia*).TI.
3. (cornea* adj5 thin*).TI.
4. 1 or 2 or 3
7. exp Cross-Linking Reagents/ or exp ultraviolet therapy/ or ultraviolet rays/ or exp riboflavin/ or collagen/
8. ((cross-link* or crosslink* or bifunct*) adj5 reagent*).tw.
9. (cross-link* or crosslink*).tw.
10. cxl.tw.
11. (vitamin b or ultraviolet or riboflavin or collagen or uvb or puva).tw.
12. 7 or 8 or 9 or 10 or 11
13. 6 and 12
14. limit 13 to animals
15. limit 13 to (animals and humans)
16. 14 not 15
17. 13 not 16

CINAHL

1. (TX (keratoconus or corneal opacity or keratoconic or keratoectasia or keratectasia or pellucid or marginal furrow or pellucid marginal degeneration or forme fruste or cornea* thin* or cornea* ectasia*))
2. (MW (riboflavin or collagen or ultraviolet)) or (TX (cross-link* or crosslink* or cxl or vitamin b or ultraviolet or riboflavin or uvb or puva or cross-linking reagents))

## APPENDIX II: DATA EXTRACTION FORM

**Data Extraction Form**

Author: _____ Ref ID: _____

Journal: _____

Publication Year: _____

Country: _____

Recruitment Period: _____ - _____

Publication Language: _____

**Study Design**

RCT (fellow eye control) ___

RCT (independent eye control) ___

Cohort (no control) ___

Cohort (fellow eye control) ___

Cohort (independent eye control) ___

**Population Demographics**

| | |
|---|---|
| Number of Included Participants | ____ |
| Number of included eyes | ____ |
| Number of Participants Excluded at each time point | ____ |

| | |
|---|---|
| Number of Eyes excluded at each time point | ____ |
| Mean Age of Participants | ____ +/- __ |
| Age range | _____-_____ |
| Percent Males | _____% |
| Disease | KC__<br>KE__<br>PMD__ |

**Procedure Information**

- Corneal expansion using hypo-osmolar riboflavin? YES NO
- Corneal removal method:
  - __ Complete
  - __ Partial
- Riboflavin concentration: _____%
- Before procedure, riboflavin applied every ____mins for ____(total time)
- During procedure, riboflavin applied every ____mins for ____(total time)
- UV device:
  - __ IROC (UVX 1000 or 2000)
  - __ ACCUTECH
  - __ Other (Specify: _____)
- Ultraviolet exposure time _____mins
- UV wavelength _____nm
- Irridance ____$mW/cm^2$
- Distance from apex of cornea ____cm

## Study Outcomes

Follow-up length (months): _____

## Baseline data (before procedure)

| | Treatment (mean+/ SD) | Control |
|---|---|---|
| **BCVA** | ± | ± |
| **UCVA** | ± | ± |
| **K-Max** | ± | ± |
| **K-Ave** | ± | ± |
| **K-min** | | |
| **Spherical Equivalent** | ± | ± |
| **Pachymetry** | ± | ± |

## Follow-up point 1 (_____months post-procedure)

| | Treatment | | | Control | | |
|---|---|---|---|---|---|---|
| | **Mean +/- SD** | **P-value** | **Change in mean from baseline and SD** | **Mean +/- SD** | **P-value** | **Change in mean from baseline and SD** |
| **BCVA** | ± | | ± | ± | | ± |
| **UCVA** | ± | | ± | ± | | ± |
| **K-Max** | ± | | ± | ± | | ± |
| **K-Ave** | ± | | ± | ± | | ± |
| **K-Min** | | | ± | | | ± |
| **Spherical Equivalent** | ± | | ± | ± | | ± |
| **Pachymetry** | ± | | ± | ± | | ± |

## Follow-up point 2 (_____months post-procedure)

| | Treatment | | | Control | | |
|---|---|---|---|---|---|---|
| | **Mean +/- SD** | **P-value** | **Change in mean from baseline and SD** | **Mean +/- SD** | **P-value** | **Change in mean from baseline and SD** |
| **BCVA** | ± | | ± | ± | | ± |
| **UCVA** | ± | | ± | ± | | ± |
| **K-Max** | ± | | ± | ± | | ± |
| **K-Ave** | ± | | ± | ± | | ± |
| **K-Min** | | | ± | | | ± |
| **Spherical Equivalent** | ± | | ± | ± | | ± |
| **Pachymetry** | ± | | ± | ± | | ± |

## Follow-up point 3 (_____months post-procedure)

| | Treatment | | | Control | | |
|---|---|---|---|---|---|---|
| | **Mean +/- SD** | **P-value** | **Change in mean from baseline and SD** | **Mean +/- SD** | **P-value** | **Change in mean from baseline and SD** |
| **BCVA** | ± | | ± | ± | | ± |
| **UCVA** | ± | | ± | ± | | ± |
| **K-Max** | ± | | ± | ± | | ± |
| **K-Ave** | ± | | ± | ± | | ± |
| **K-Min** | | | ± | | | ± |
| **Spherical Equivalent** | ± | | ± | ± | | ± |
| **Pachymetry** | ± | | ± | ± | | ± |

## Follow-up point 4 (_____months post-procedure)

| | Treatment | | | Control | | |
|---|---|---|---|---|---|---|

| | Mean +/- SD | P-value | Change in mean from baseline and SD | Mean +/- SD | P-value | Change in mean from baseline and SD |
|---|---|---|---|---|---|---|
| **BCVA** | ± | | ± | ± | | ± |
| **UCVA** | ± | | ± | ± | | ± |
| **K-Max** | ± | | ± | ± | | ± |
| **K-Ave** | ± | | ± | ± | | ± |
| **K-Min** | | | ± | | | ± |
| **Spherical Equivalent** | ± | | ± | ± | | ± |
| **Pachymetry** | ± | | ± | ± | | ± |

## Follow-up point 5 (_____months post-procedure)

| | Treatment | | | Control | | |
|---|---|---|---|---|---|---|
| | **Mean +/- SD** | **P-value** | **Change in mean from baseline and SD** | **Mean +/- SD** | **P-value** | **Change in mean from baseline and SD** |
| **BCVA** | ± | | ± | ± | | ± |
| **UCVA** | ± | | ± | ± | | ± |
| **K-Max** | ± | | ± | ± | | ± |
| **K-Ave** | ± | | ± | ± | | ± |
| **K-Min** | | | ± | | | ± |
| **Spherical Equivalent** | ± | | ± | ± | | ± |
| **Pachymetry** | ± | | ± | ± | | ± |

## Safety

Total number of patients reporting adverse effects in study: ____

Total number treated successfully: _____

Total number requiring corneal transplant due to CXL adverse effects: ___

Adverse event (record number of each case):

Corneal Edema: ___

Corneal nerve damage: ___

Treatment Failure: ___

Postoverative infection/ulcer[1]: ___

Stromal Haze: ___

Stromal Haze for longer than 12 months: ___

Increased intraocular pressure: ___

Cataract: _____

Photokeratitis: _____

Non-infectious Keratitis: ____

Corneal Melting: ___

Corneal erosion: ___

[1] Acanthameoba keratitis, bacterial keratitis, herpetic keratitis, neurodermatitis,

## APPENDIX III: INTERVIEW QUESTIONS FOR CXL PRACTITIONERS

1. Where does CXL fit within the clinical pathway for Keratoconus and other progressive corneal thinning disorders (i.e., at what point in the keratoconus disease trajectory is the optimal time for a patient to undergo a CXL procedure)?

2. What do you think of CXL in terms of its clinical utility?

3. What are the alternative options to CXL?
    a. How does CXL compare to alternative options with respect to safety, effectiveness, cost-effectiveness and quality of life?

4. Please describe your practice –do you bill privately, publically, or both?
    a. Approximately how many CXL procedures would you do in any given year?
    b. Which thinning disorders do you see the most of?
    c. Are there wait lists for patients to access CXL at your clinic? If yes, how long is the wait?
    d. Are there waitlists for corneal transplant? If yes, how long is the wait?

5. How is CXL currently being provided in Alberta (i.e., is it being provided publically and/or privately), and by whom?

6. If CXL were to become completely publically funded, would the number of people having the procedure increase?
    a. Do we have capacity in Alberta to deliver the service if it became publically funded?
    b. Would the provision of CXL need to change in order to accommodate public provision of this service? (for example, more trained clinicians would be needed or it would have to become a within hospital procedure to keep up with volume)

7. What is the unit cost of CXL and the unit cost of delivering the associated service (including equipment, facility, healthcare provider fees etc.)?
        i. What ICD9, SOMB codes do you use (if publically provided)? OR
        ii. Does the Government of Alberta (GoA) or AHS pay for any portion of that service at present (perhaps through restricted government programs)?
        iii. If the patient is paying directly for a CXL procedure, what is the cost to them per eye?
        iv. Did you purchase the CXL equipment?
            1. How much does this equipment cost to maintain?
            2. How often must it be replaced?

8. Is there anything else you would like to say about CXL and its provision in Alberta that we haven't asked directly about?

**Thank you so much!**