Intrastromal corneal implants for ectatic corneal disorders

Systematic Review

Ludwig Boltzmann Institut
Health Technology Assessment

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List of abbreviations

CE	Communauté Européenne
CISIS	Corneal intrastromal implantation system
CCT	Controlled clinical trial
DALK	Deep anterior lamellar keratoplasty
DNA	Deoxyribonucleic acid
FDA	Food and Drug Administration
ICRS	Intracorneal ring segments
LASIK	Laser-assisted in situ keratomileusis
LBI-HTA	Ludwig Boltzmann Institute
n/a	Not applicable
PKT	Penetrating keratoplasty
RCT	Randomised controlled trial
VAEV	Verwaltung von Änderungs- und Ergänzungsvorschlägen zum Leistungskatalog des BMG

Summary

Introduction

Description of technology

Corneal implants are small segments of rings or full rings of synthetic material that are implanted in the corneal stroma to achieve flattening of the surface. In contrast to corneal transplantation that is the most frequent used treatment for ectatic corneal disorders in later stages, corneal implants is a less invasive and reversible intervention.

Implantate aus Kunststoff

In this report we analyse whether corneal implants are more or equally effective and safer than corneal transplantation or no intervention.

Hornhauttransplantation + keine Intervention als Vergleich

Health problem

Originally, intrastromal corneal implants were developed for the treatment of myopia. Later, the implants were also considered for the correction of ectatic corneal disorders such as keratoconus and post-LASIK corneal ectasia.

Implantate bei Keratokonus + Keratektasie nach LASIK

Keratoconus is a non-inflammatory corneal ectasia, characterised by a progressive increase in corneal curvature and thinning of the cornea. Eventually, an obvious cone-shaped protrusion of the corneal surface may develop.

Keratokonus: Krümmung und Ausdünnung Hornhaut

Corneal ectasia is a rare, but serious complication after LASIK (Laser-assisted in situ keratomileusis). The condition is similar to keratoconus where the cornea starts to bulge forwards at a variable time after LASIK.

Keratektasie nach LASIK: ähnlich wie Keratokonus

Methods

Answering the research questions regarding efficacy and safety-related outcomes was based on a systematic literature from different databases. The study selection, data extraction and assessing the methodological quality of the studies was performed by two review authors (SF, IZ), independently from each other.

systematische Literatursuche

Domain effectiveness

The following efficacy-related outcomes were used as evidence to derive a recommendation: length of hospital stay (or time to resume work/normal activities), re-operation rate and change of visual acuity (change of two or more Snellen lines).

entscheidende Endpunkte für Wirksamkeit ...

Domain safety

The following safety-related outcomes were used as evidence to derive a recommendation: intra- and post-operative adverse events.

... und Sicherheit

Results

Available evidence

keine kontrollierten Studien identifiziert, daher Einschluss Ein-Arm-Studien mit ≥50 Augen

We could not identify any controlled trials comparing intrastromal corneal implants with either corneal transplantation or no intervention for the treatment of keratoconus or post-LASIK corneal ectasia. Therefore, we included uncontrolled studies (single-arm studies) with at least 50 eyes for assessing efficacy and safety.

5 Ein-Arm-Studien mit 627 Augen identifiziert

In total, 5 single-arm studies with 627 eyes met our inclusion criteria. The mean age of patients was 26-37 years and the majority were males.

Clinical effectiveness

in mehr Augen *klinisch* relevante Verbesserung Sehstärke, als Verschlechterung

Clinically relevant improvement of visual acuity (*two or more Snellen* lines), occurred in more treated eyes than a worsening of visual acuity (e.g., UCVA improved in 79% and worsened in 0% of the treated eyes). The change from baseline was also considered as statistically significant.

4-23% Reoperationsrate

According to the available data, between 4 and 23% of the eyes with an implanted intrastromal corneal ring had to be re-operated. Length of hospital was not reported in any of the identified studies.

Safety

Komplikationen: 0-2 % während OP; 2-23 % nach OP

Intra-operative adverse events, like difficulties in forming the intrastromal tunnel to implant the rings or anterior perforation, occurred in 0-2% of the eyes. Post-operative adverse events occurred in 2 to 23% of the treated eyes.

Upcoming evidence

keine laufenden Studien Kontrollgruppe Hornhauttransplantation

Currently, there are no registered ongoing or planned controlled trials comparing intrastromal corneal implants with corneal transplantation for a treatment of keratoconus or post-LASIK ectasia.

Reimbursement

Einsatz Ringe in Österreich derzeit nicht erstattet

Currently, the use of intrastromal corneal implants for the treatment of keratoconus or post-LASIK corneal ectasia is not reimbursed by the Austrian health care system.

Discussion

insgesamt geringe Evidenzstärke

Overall, the strength of evidence for efficacy and safety is low to very low. Naturally, this is mainly due to the study design of the single-arm studies.

durchaus Verbesserung Sehschärfe

Considering the findings of the included single-arm studies regarding clinical effectiveness, it seems that the implantation of intrastromal corneal implants can improve visual acuity in a clinically relevant manner. Moreover, a treatment of keratoconus as well as post-LASIK corneal ectasia with intrastromal corneal implants seems relatively safe.

kein Vergleich Wirksamkeit Transplantation

Nevertheless, due to a lack of controlled trials we are not able to draw any conclusions on the clinical effectiveness of intrastromal corneal implants for a treatment of keratoconus or post-LASIK ectasia compared to corneal transplantation or even no intervention.

Vorteile intrakorneale Ringe

A major strength of intrastromal corneal implants is their reversibility. Furthermore, after implantation no immunosuppressive drugs are needed, like after corneal transplantation.

Conclusion

The current evidence is not sufficient to prove that intrastromal corneal implants are equally or more effective and safe than corneal transplantation or no intervention for treatingf keratoconus or post-LASIK corneal ectasia.

kein Beweis, dass Ringe wirksamer und sicherer als Transplantation

However, the comparison before and after the ring implantations of the single-arm studies have shown that the visual acuity has improved and that improvement has been clinically relevant in a large proportion of patients. Furthermore, the implantation of intrastromal corneal rings seems to be relatively safe and adverse events were minor.

Vergleich vor und nach Implantation: Verbesserung Sehschärfe; Implantate relativ sicher

The **inclusion** in the catalogue of benefits is recommended **with restrictions.**

Aufnahme mit Einschränkungen

Zusammenfassung

Einleitung

Beschreibung der Technologie

Korneale Ringimplantate aus Kunststoff

Korneale Ringimplantate sind entweder volle Ringe oder Ringsegmente aus Kunststoff, die in das korneale Stroma eingebracht werden, um die Oberfläche zu glätten. Die Implantation erfolgt durch Tunnel, die mechanisch oder durch einen Laser erzeugt werden.

fünf Produkte

Derzeit gibt es fünf Hersteller der Implantate, die alle ein CE-Zertifikat haben:

- Bisantis Segments (Optikon 2000 SpA und Soleko SpA)[1],
- Ferrara Ring™ (gehört zu AJL OPHTHALMIC S.A.),
- Intacs® (gehört zu AJL OPHTHALMIC S.A.),
- Keraring-Intrastromal corneal ring (Mediphacos),
- MyoRing® (DIOPTEX).

Implantate unterscheiden sich in Beschaffenheit

Der Hauptunterschied zwischen den Produkten liegt in deren Beschaffenheit mit verschiedenen Dicken und Durchmessern. Während fast alle Produkte sogenannte Ringsegmente sind, ist der MyoRing® ein voller Ring.

Fokus auf Hornhauttransplantation als Vergleich

Intrakorneale Ringimplantate haben zum Ziel die Sehschärfe zu verbessern. Im Vergleich zur Hornhauttransplantation, die vor allem im späteren Krankheitsstadium am häufigsten bei der Behandlung von Keratokonus oder Keratektasie nach LASIK eingesetzt wird, sind korneale Ringimplantate eine weniger invasive, risikoärmere (z. B. keine Immunsuppressiva nötig) und reversible Technologie. Ein weiterer Vorteil im Vergleich zur Transplantation ist die Möglichkeit einer nachträglichen Adjustierung und die geringere Wartezeit (keine SpenderInnen nötig).

Forschungsfrage

Der Bericht behandelt die Frage, ob die Behandlung von Keratokonus oder Keratektasie nach LASIK mittels intrakornealer Ringimplantate wirksamer und sicherer als (oder zumindest genauso wirksam und sicher wie) die Hornhauttransplantation oder keine Intervention ist.

Indikation und therapeutisches Ziel

Implantate für Behandlung ektatischer Hornhauterkrankungen

Ursprünglich wurden intrakorneale Ringimplantate für die Behandlung der Kurzsichtigkeit entwickelt. Erst später wurden die Implantate auch für die Behandlung ektatischer Hornhauterkrankungen in Betracht gezogen.

Fokus Keratokonus

Der vorliegende Bericht beschränkt sich hierbei auf die Behandlung des Keratokonus und der Keratektasie nach LASIK (Laser-in-situ-Keratomileusis).

Keratokonus + post-LASIK Keratektasie: Hornhautverkrümmung

Der Keratokonus ist eine nicht-entzündliche Hornhauterkrankung, die sich in einer verstärkten Krümmung und gleichzeitiger Ausdünnung der Hornhaut des Auges manifestiert. Die Krankheit tritt oftmals bereits im Jugendalter auf. Die Keratektasie ist eine seltene Komplikation der LASIK, oftmals manifestiert durch Kurzsichtigkeit, und eine Hornhautverkrümmung.

[1] Webseite des Produkts konnte nicht identifiziert werden.

Keratokonus: Zusammenhang systemische Krankheiten möglich

Die Entstehung des Keratokonus ist weitestgehend unklar. Es gilt ein Zusammenhang mit systemischen Erkrankungen (z. B. Trisomie 21) als wahrscheinlich. Oxidativer Stress, aber auch das Reiben der Augen können die Krankheit weiter verschlimmern.

mehrere Risikofaktoren für Keratektasie nach LASIK

Für die Keratektasie nach LASIK gibt es mehrere Risikofaktoren: z. B. abnormale präoperative Topografie des Auges, geringe Dicke der Hornhaut oder starke Kurzsichtigkeit.

seltene Erkrankungen mit erheblichen Einbußen in Lebensqualität

Auch wenn sowohl Keratokonus, als auch post-LASIK Keratektasie selten sind (Prävalenz weniger als 5 pro 10.000 Menschen) und die Konsequenzen für die Gesellschaft eher gering, so führen beide Krankheiten zu erheblichen Seheinschränkungen und damit auch Einschränkungen in der Lebensqualität der Betroffenen.

mehrere Behandlungsoptionen für Keratokonus und Keratektasie nach LASIK

Für die Behandlung von Keratokonus und Keratektasie nach LASIK stehen die gleichen Interventionen zu Verfügung: in frühen Stadien werden weiche Kontaktlinsen oder eine Brille eingesetzt, während in mittleren Stadien bereits formstabile Kontaktlinsen zum Einsatz kommen. In späteren Stadien ist ein Tragen von Kontaktlinsen oder Brillen nicht mehr ausreichend und invasive Eingriffe werden notwendig. Dazu zählen die korneale Transplantation, aber auch intrakorneale Ringimplantate und die sogenannte Vernetzungsbehandlung (Collagen Cross-Linking).

gewisse Voraussetzungen Einsatz Ringimplantate

Jedoch setzt die Behandlung des Keratokonus sowie der Keratektasie nach LASIK mittels intrakornealer Ringimplantate vor allem eine gewisse Dicke der Hornhaut (abhängig vom Produkt) und eine Kontaktlinsenunverträglichkeit der PatientInnen voraus.

Methodik

Quellen aus systematischer Literatursuche

Die Beantwortung der Forschungsfragen bezüglich Wirksamkeit und Sicherheit basierte auf einer systematischen Literatursuche in folgenden Datenbanken:

- Medline via Ovid,
- Embase,
- the Cochrane Library,
- CRD (DARE, NHS-EED, HTA).

Handsuche, Anfrage Hersteller

Zusätzlich wurde noch eine Handsuche durchgeführt und es gab eine Anfrage nach Studien bei den einzelnen Herstellern.

Erstautor extrahierte Studiendaten, Zweitautor kontrollierte

Die Studienauswahl erfolgte nach dem 4-Augenprinzip durch den Erstautor (SF) und den Drittautor (EC). Der Erstautor (SF) extrahierte die Studiendaten und die Zweitautorin (IZ) kontrollierte die Daten.

Studienbewertung nach GRADE

Die Daten der für die Entscheidung herangezogenen Endpunkte wurden aus den einzelnen Studien zusammengefasst und nach GRADE (Grading of Recommendations Assessment, Development and Evaluation) bewertet.

Bias-Risiko je Endpunkt

Zusätzlich wurde das Bias-Risiko für jeden entscheidungsrelevanten Endpunkt nach einer Checkliste von zwei AutorInnen (SF, IZ), unabhängig von einander, bewertet.

Klinische Wirksamkeit

entscheidende Endpunkte für Wirksamkeit

Zur Bewertung der Wirksamkeit intrakornealer Ringimplantate wurden die folgenden entscheidenden Endpunkte für eine Empfehlung herangezogen:

- Krankenhausaufenthalt (oder Zeit bis Wiederaufnahme Arbeitstätigkeit/normale Tätigkeiten)
- Reoperationsrate
- Änderung Sehschärfe (Änderung von zwei oder mehr Snellen-Linien)

Sicherheit

entscheidende Endpunkte für Sicherheit

Zur Bewertung der Sicherheit intrakornealer Ringimplantate wurden die folgenden entscheidenden Endpunkte für eine Empfehlung herangezogen:

- intraoperative unerwünschte Ereignisse
- postoperative unerwünschte Ereignisse

Ergebnisse

Verfügbare Evidenz

keine kontrollierten Studien identifiziert, daher Einschluss Ein-Arm-Studien mit ≥50 Augen

Es konnten keine kontrollierten Studien identifiziert werden, die eine Behandlung des Keratokonus oder der Keratektasie nach LASIK mittels intrakornealer Ringimplantate mit einer Hornhauttransplantation oder keiner Intervention verglichen. Daher wurden unkontrollierte Beobachtungsstudien (sogenannte Ein-Arm-Studien) mit 50 Augen oder mehr eingeschlossen.

5 Ein-Arm-Studien mit 627 Augen bei Behandlung Keratokonus eingeschlossen

Insgesamt 5 Ein-Arm-Studien mit 627 Augen entsprachen den Einschlusskriterien. Das Durchschnittsalter der PatientInnen lag zwischen 26 und 37 Jahren mit einem Anteil an Frauen von 30-50 %. Die Nachbetrachtungszeit der meisten Studien lag bei 12 Monaten, wobei es auch jeweils eine Studie mit 24 und 96 Monaten (entspricht 8 Jahren) Nachbetrachtungszeit gab. Die Studien untersuchten (fast) ausschließlich die Behandlung von Keratokonus

Produkte: Intacs® und Keraring

In allen Studien wurde Intacs® implantiert, wobei in zwei Studien auch Keraring implantiert wurden.

keine Studien zu anderen Produkten oder Keratektasie nach LASIK

Es konnten keine Studien identifiziert werden, die andere Produkte (z. B. Ferrara Ring™, MyoRing®) oder die Behandlung von Keratektasie nach LASIK untersuchten.

Klinische Wirksamkeit

in mehr Augen Verbesserung Sehstärke, als Verschlechterung

Die Änderung der Sehschärfe wurde in vier Studien berichtet (eine oder mehr Snellen-Linien). So konnte z. B. die unkorrigierte Sehschärfe nach 12 Monaten in 70-80 % der Augen verbessert werden. Eine Verschlechterung trat in weniger als 10 % der Augen auf.

Änderung ≥2 Snellen-Linien in zwei Fallserien berichtet

Für Empfehlung der Aufnahme der Leistung, wurde lediglich der Endpunkt „Änderung der Sehschärfe“ von 2 oder mehr Snellen-Linien für eine Entscheidung herangezogen (berichtet in 2 Studien). Denn erst eine Änderung von 2 Snellen-Linien gilt als klinisch relevant:

in mehr Augen *klinisch* relevante Verbesserung Sehstärke, als Verschlechterung

So konnte z. B. die unkorrigierte Sehschärfe nach 6 Monaten in 79 % der Augen um 2 oder mehr Snellen-Linien verbessert werden, während es bei keinen der behandelten Augen eine Verschlechterung gab. Nach 12 Monaten konnte die korrigierte Sehschärfe in 42 % verbessert werden. Eine Verschlechterung gab es bei 8 % der behandelten Augen.

Die Reoperationsrate lag bei 4-23 %. Ein direkter Vergleich mit der Hornhauttransplantation oder keiner Behandlung lag nicht vor.

4-23 % Reoperationsrate

Die Dauer des Krankenhausaufenthalts (oder Zeit bis Wiederaufnahme Arbeitstätigkeit/normale Tätigkeiten) wurde in keiner der Studien berichtet.

KH-Aufenthalt nicht berichtet

Sicherheit

Während der Operation traten in 0-2 % der behandelten Augen Komplikationen auf: z. B. Schwierigkeiten bei der Formung der Tunnel zur Implantation der Ringe. Nach dem operativen Eingriff gab es in 2 bis 23 % der Augen unerwünschte Ereignisse, wie Wanderung des Implantats, Infektion oder Perforation der Hornhaut.

Komplikationen während OP: in 0-2 % Augen
Komplikationen nach OP: in 2-23 % Augen

Laufende Studien

Aktuell sind keine laufenden kontrollierten Studien registriert, die die Behandlung ektatischer Hornhauterkrankungen mittels intrakornealer Ringimplantate mit einer Hornhauttransplantation vergleichen.

keine laufenden Studien
Kontrollgruppe Hornhauttransplantation

Zwei registrierte randomisierte kontrollierte Studien vergleichen verschiedene intrakorneale Ringimplantate bei Keratokonus miteinander (siehe Appendix).

zwei RCTs vergleichen Implantate miteinander

Kostenerstattung

Derzeit werden in Österreich die Kosten für den Einsatz intrakornealer Ringe bei der Behandlung ektatischer Hornhauterkrankungen nicht separat erstattet.

Einsatz Ringe in Österreich derzeit nicht erstattet

Diskussion

Ziel des Berichts war es die Wirksamkeit und Sicherheit intrakornealer Ringimplantate bei der Behandlung von Keratokonus oder Keratektasie nach LASIK im Vergleich zu einer Hornhauttransplantation oder keiner Intervention zu untersuchen.

Ziel: Wirksamkeit und Sicherheit intrakornealer Ringe

Nachdem keine kontrollierten Studien identifiziert wurden, wurden 5 Ein-Arm-Studien für die Bewertung herangezogen. Aufgrund des unkontrollierten Studiendesigns ist die Stärke der Evidenz jedoch nur gering bis sehr gering.

5 Beobachtungsstudien mit geringer Evidenzstärke

Auch wenn die Studienlage nicht eindeutig die Wirksamkeit und Sicherheit der kornealen Ringimplantate belegen kann, so gibt es immerhin Anzeichen, dass eine Verbesserung der Sehschärfe erreicht werden kann – auch wenn es durchaus bei einigen Augen eine Verschlechterung der Sehschärfe gab.

Ein-Arm-Studien: durchaus Verbesserung Sehschärfe

Ein entscheidender Vorteil der Implantate ist deren Reversibilität. Die notwendigen Reoperationen konnten ohne bleibende Schäden durchgeführt werden. Außerdem sind nach dem Eingriff keine Immunsuppressiva nötig, wie es bei der Hornhauttransplantation der Fall ist und der Eingriff ist weniger invasiv als eine Hornhauttransplantation.

Vorteile intrakorneale Ringe

Nicht zuletzt scheinen die Implantate – zumindest kurzfristig gesehen – relativ sicher.

Implantate relativ sicher

Kritikpunkte der Studien sind vor allem die relativ kurzen Nachbeobachtungszeiträume in der Mehrzahl der Studien, nicht berichtete PatientInneneigenschaften in einigen Studien (z. B. Alter), die Tatsache, dass nicht alle Studien Rückschlüsse auf eine klinisch relevante Änderung der Sehschärfe zuließen und in zwei Studien war der Erstautor Berater bei einem der Hersteller sowie Editor des Journals in dem die Studie publiziert wurde.

einige Kritikpunkte der Studien

Schwächen des Reviews

Entscheidende Schwächen des vorliegenden Berichts sind insbesondere: der konsequente Ausschluss von Studien, die weniger als 50 Augen untersuchten, der Ausschluss von Studien die retrospektiv angelegt waren (dazu zählten auch Studien mit einer historischen Kontrollgruppe) und bei zwei der eingeschlossenen Studien war nicht eindeutig klar, ob diese prospektiv durchgeführt wurden.

Problem: Durchführung prospektive kontrollierte Studien bei seltenen Erkrankungen

Ein generelles Problem ist, dass Keratokonus und Keratektasie nach LASIK seltene Erkrankungen sind. Dies bedingt geringe PatientInnenzahlen und gestaltet es durchaus schwierig, prospektive kontrollierte Studien durchzuführen. Zudem ist die Wahl der Hornhauttransplantation als Vergleichsintervention kritisch, da einer Behandlungsgruppe der weniger invasive Eingriff der intrakornealen Ringimplantate vorenthalten würde.

dennoch: es wurden RCTs durchgeführt, aber nicht veröffentlicht

Ungeachtet der etwaigen, oben genannten, Schwierigkeiten, wurden bei der Literatursuche zwei Abstracts von randomisierten kontrollierten Studien identifiziert, die die Behandlung des Keratokonus durch intrakorneale Ringimplantate mit der Hornhauttransplantation verglichen. Jedoch wurden die Ergebnisse der beiden Studien scheinbar nie veröffentlicht.

Empfehlung

kein Beweis, dass Ringe wirksamer und sicherer als Transplantation

Die gegenwärtige Studienlage lässt keine Rückschlüsse zu, ob eine Behandlung des Keratokonus oder Keratektasie nach LASIK mittels intrakornealer Ringimplantate wirksamer oder sicherer als andere Alternativen ist.

Vermutung, dass wirksam + sicher

Ein Vergleich der Sehschärfe vor und nach der Implantation lässt vermuten, dass die Sehschärfe durchaus verbessert werden kann. Außerdem scheinen die Implantate relativ sicher. Aufgrund der geringeren Invasivität und Reversibilität ist die Ringimplantation jedenfalls vor einer Hornhauttransplantation in Betracht zu ziehen.

Implantate haben viele Vorteile Aufnahme in Leistungskatalog mit Einschränkungen empfohlen

Aus den oben genannten Gründen wird daher eine Aufnahme in den Katalog medizinischer Einzelleistung empfohlen – jedoch unter folgenden Einschränkungen:

- Es besteht eine Kontaktlinsenunverträglichkeit oder eine Behandlung mit Kontaktlinsen ist nicht (mehr) möglich
- Die individuellen Indikationen und Kontra-Indikationen der einzelnen Produkte müssen beachtet werden.
- Die Leistung sollte nur in größeren Krankenhäusern (z. B. Universitätskliniken) durchgeführt werden.
- Die Sicherheit der Implantate sollte in einer nationalen Datenbank dokumentiert und überwacht werden.

1 Scope

1.1 Research question

PIKO-Frage

Are intrastromal corneal implants (rings/ring segments) in comparison to corneal transplants (or no intervention) in patients with keratoconus or post-LASIK[2] iatrogenic corneal ectasia equally or more effective and safe concerning length of hospital stay (or time to work resumption), quality of life, re-operation rate, patient satisfaction, change of visual acuity and adverse events?

1.2 Inclusion criteria

Einschlusskriterien

Inclusion criteria for relevant studies are summarised in Table 1.2-1.

Table 1.2-1: Inclusion criteria

Population	❁ Patients with: ❁ Keratoconus (ICD-10 code: H18.6) [1] ❁ who are not able to wear glasses or contact lenses (due to intolerance) or ❁ who show an unsatisfactory visual acuity with glasses or contact lenses ❁ Post-LASIK[3] iatrogenic corneal ectasia (ICD-10 code: Q13.4), ❁ MeSH-terms: C11 Eye Diseases, C11.204 Corneal Diseases, C11.204.627 Keratoconus [1]
Intervention	❁ Intracorneal ring segments (ICRS) or intracorneal rings or intrastromal corneal rings or intrastromal corneal implants ❁ Product names: Ferrara Ring™ (Ferrara Ophthalmics™) Intacs® (Addition Technology™), Keraring (Mediphacos), MyoRing® (DIOPTEX), [Bisantis Segments (Optikon), probably not available anymore] ❁ MeSH-terms: E07.695 Prostheses and Implants, E07.695.225 Eye, Artificial
Control	❁ Corneal transplantation ❁ No intervention[4]
Outcomes	
Efficacy	❁ Length of hospital stay (or time to work resumption) ❁ Quality of life (health- or vision-related) ❁ Re-operation rate ❁ Patient satisfaction ❁ Change of visual acuity
Safety	❁ Adverse events (intra- and post-operative)

[2] Laser-assisted in situ keratomileusis

[3] Laser-assisted in situ keratomileusis

[4] In addition, "no intervention" was considered as comparator. This decision was made, just in case there are no appropriate controlled trials.

Study design	
Efficacy	❁ Randomised controlled trials ❁ Prospective non-randomised controlled trials ❁ Prospective single-arm studies (with 50 and more eyes)[5]
Safety	❁ Randomised controlled trials ❁ Prospective non-randomised controlled trials ❁ Prospective single-arm studies (with 50 and more eyes)

1.3 Literature search

systematische Literaturssuche in Datenbanken

The systematic literature search was conducted on the 29th of December 2014 in the following databases:

- Medline via Ovid
- Embase
- The Cochrane Library
- CRD (DARE, NHS-EED, HTA)

In addition, these websites were searched for relevant assessments on the 12th of January 2015 (without any hits):

- Canadian Agency for Drugs and Technologies in Health (http://www.cadth.ca/index.php/en/home)
- NIHR Health Technology Assessment Programme (http://www.hta.ac.uk/)
- NHS Institute for Health and Clinical Excellence (http://www.nice.org.uk/)
- WHO Health Evidence Network (http://www.euro.who.int/en/what-we-do/data-and-evidence)

systematische Literatursuche: 201 Treffer

The systematic search was limited to clinical trials in Medline and Embase. After deduplication, 201 citations were available. The specific search strategy employed can be found in the Appendix.

167 weitere Studien von Herstellern

A total of 167 new citations were identified through studies sent by the manufacturers.

Zusätzliche Handsuche mit 61 Resultaten

By hand search (internet and Scopus), 61 additional citations were found, resulting in a total of 429 hits.

[5] Single-arm studies are only considered for assessing the clinical effectiveness when no controlled studies are available.

1.4 Flow chart study of selection

Literaturauswahl

Overall, 429 hits were identified. The references were screened by two independent researchers (SF, CE) and in case of disagreement a third researcher was involved to solve the differences. The selection process is displayed in Figure 1.4-1. Articles that were excluded due to several reasons but still used as background are categorised under "background literature". Furthermore, we were not able to order five articles. These are categorised under "not available".

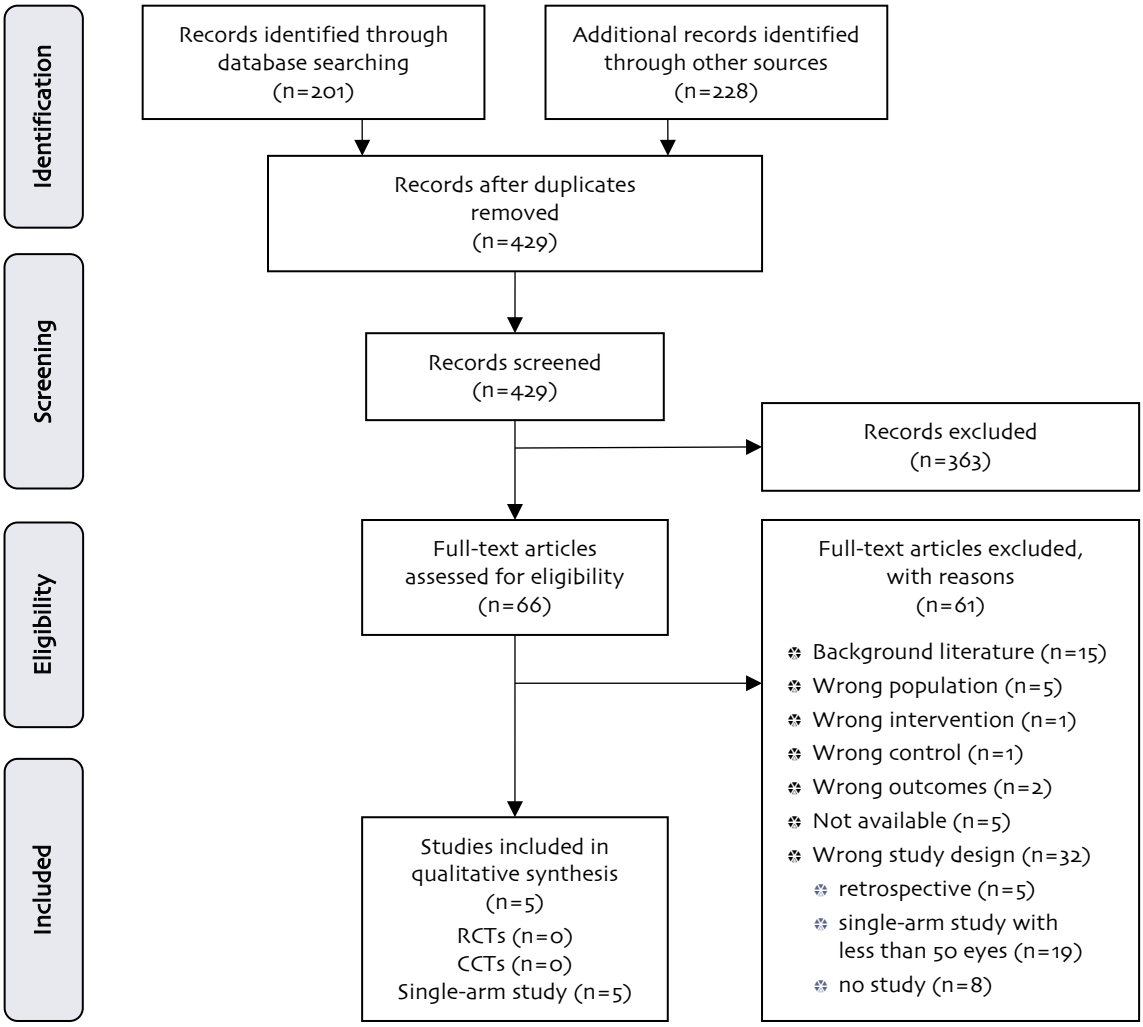

Figure 1.4-1: Flow chart of study selection (PRISMA Flow Diagram)

2 Description and technical characteristics of technology

2.1 Methods

Research questions

Element ID	Research question	Importance 2 = critical 1 = optional
B0001	What are intrastromal corneal implants and the comparators?	2
B0002	What is the claimed benefit of intrastromal corneal implants in relation to the comparators?	2
B0003	What is the phase of development and implementation of intrastromal corneal implants and the comparators?	1
B0004	Who administers intrastromal corneal implants and the comparators and in what context and level of care are they provided?	2
B0008	What kind of special premises are needed to use intrastromal corneal implants and the comparators?	2
B0009	What supplies are needed to use intrastromal corneal implants and the comparators?	2
A0020	For which indications have intrastromal corneal implants received marketing authorisation or CE marking?	1
A0021	What is the reimbursement status of intrastromal corneal implants?	1

Sources

Quellen aus systematischer und händischer Literatursuche

To answer the research questions regarding the description and technical characteristics of the technology, the results from the systematic literature search (see Chapter 1.3) in Medline via Ovid, Embase, the Cochrane Library plus CRD (DARE, NHS-EED, HTA) and from the hand search were used.

2.2 Results

Features of the technology and comparators

B0001 – What are intrastromal corneal implants and the comparators?

Korneale Ringimplantate aus Kunststoff

Corneal implants are small segments of rings or full rings of synthetic material (e.g., polymethyl methacrylate or acrylic polymers) that are implanted in the corneal stroma to achieve flattening of the surface. The rings are implanted in channels created mechanically or by means of a laser [2, 3].

fünf Hersteller von Implantaten

Currently, five products of intrastromal corneal implants are marketed by five manufacturers [2, 3]:

- Bisantis Segments (Optikon 2000 SpA and Soleko SpA, Italy)[6],
- Ferrara Ring™ (former Ferrara Ophthalmics™, Brazil, belongs now to AJL OPHTHALMIC S.A., Spain)[7],
- Intacs® (former Addition Technology™, USA, belongs now to AJL OPHTHALMIC S.A., Spain)[8],
- Keraring-Intrastromal corneal ring (Mediphacos, Brazil)[9],
- MyoRing® (DIOPTEX, Austria)[10].

Implantate unterscheiden sich in Beschaffenheit

The main difference between these products is their design (full rings or segments) with different shapes, diameters and thicknesses [3]. Bisantis Segments, Ferrara Ring™, Intacs® and Keraring are arc segments and therefore called intracorneal ring segments (ICRS). The MyoRing® is a full ring and therefore called a corneal intrastromal implantation system (CISIS). In the following, "rings" is used to designate both full rings and ring segments.

verschiedene Behandlungsalternativen

Generally, optical corrections, such as contact lenses (used in early stages of keratoconus) and corneal transplantation, are treatment options for ectatic corneal disorders [4, 5]. Collagen cross-linking is a relatively new treatment option that is supposed to slow the progression of the disease [5, 6]. However, intrastromal corneal implants are indicated when patients show contact lens intolerance (preferably in the absence of corneal disorders) [4].

Fokus auf Hornhauttransplantation als Vergleich

Corneal transplantation has been used for many decades to treat ectatic corneal disorders and is the most frequent used treatment for ectatic corneal disorders [5, 6]. Furthermore, in the description of the application form we received from the Austrian Ministry of Health ("Verwaltung von Änderungs- und Ergänzungsvorschlägen zum Leistungskatalog des BMG", VAEV) the only treatment alternative that is mentioned is corneal transplantation. In addition, several papers defined intrastromal corneal implants as an alternative to keratoplasty [7]. Thus, corneal transplantation was exclusively chosen as a comparator, even though it is more invasive than the use of intrastromal corneal implants [4, 8].

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[6] It seems very likely that this product is not available anymore, since the manufacturer's website could not be identified (access date: 20th January 2015).

[7] See also http://www.ferrararing.com.br/en/products and http://www.ajlsa.com

[8] See also http://www.additiontechnology.com and http://www.ajlsa.com

[9] See also http://www.mediphacos.com/en/medico/produtos/

[10] See also http://www.dioptex.com/products/myoring-corneal-implant/

verschiedene Hornhauttrans-plantationsverfahren

Corneal transplantation, also known as corneal grafting, consists in the replacement of the diseased cornea by corneal tissues from a suitable, deceased donor. There are several methods of transplantations: e.g., penetrating keratoplasty (PKP) designates the transplantation of the entire corneal tissue, deep anterior lamellar keratoplasty (DALK) the transplantation of the anterior corneal layers while preserving Descement's membrane and endothelium [4, 5].

keine Intervention als zusätzlicher Vergleich

In addition, "no intervention" was considered as a secondary comparator besides corneal transplantation.

B0002 – What is the claimed benefit of intrastromal corneal implants in relation to the comparators?

Verbesserung Sehschärfe

Intrastromal corneal implants for the treatment of keratoconus and post-LASIK corneal ectasia are intended to improve visual acuity – like corneal transplantation as well [4, 9].

intrakorneale Ringe relativ einfach entfernbar

The main expected advantage of intrastromal corneal implants over other surgical interventions like corneal transplantation is that the implants can be removed relatively easily. This allows a (partial) reversal of the correction or the replacement with different rings to further adapt the needed correction [5, 10].

Intervention gilt als minimal-invasiv

Furthermore, the intervention is a minimally invasive surgical option. Thus, a possibly resulting strength is that patients are allowed to quickly resume work or normal activities, as compared to corneal transplantation [3, 10].

Hornhauttransplantation birgt viele Nachteile ...

A major issue of corneal transplantation is that an adequate donor is required. This implicates waiting times, the matching of human leukocyte antigen (HLA), the use of immunosuppressive drugs (even only local), the life expectancy of the transplant (approximately ten years) and a more complicated re-operation [4-6, 8].

... und höhere Risiken

Since corneal transplantation is a more invasive intervention, it entails higher intra-operative and post-operative risks as well as higher risks for secondary trauma due to a weakening of the structure of the eye ball [4-6, 8].

B0003 – What is the phase of development and implementation of intrastromal corneal implants and the comparators?

Ringe und Hornhauttransplantation seit mehreren Jahren etabliert

Since the early 1990s for myopia and since 2004 for ectatic corneal disorders, intrastromal corneal implants have been sold and in use. Thus, the device is not in a phase of development anymore and – more or less –fully developed. Similarly, corneal transplantation has already been in use for many decades and is a well-established technique [2, 4].

Administration, investments, personnel and tools required to use the technology and the comparator(s)

B0004 – Who administers intrastromal corneal implants and the comparators and in what context and level of care are they provided?

Ringimplantation durch Hornhaut-/ RefraktivchirurgIn

The implantation of intrastromal corneal implants should be performed by an eye surgeon (or corneal surgeon) with the support of two persons of the nursing staff. The procedure can be done under topical or general anaesthetics in an inpatient setting or in an outpatient facility [4, 9, 10].

Eingriff unter lokaler oder allgemeiner Narkose

For the corneal transplantation, general anaesthesia or local anaesthesia and a sedative are needed. The operation itself requires a corneal surgeon with a supporting team. It can be performed in an inpatient setting or in an outpatient facility [4].

B0008 – What kind of special premises are needed to use intrastromal corneal implants and the comparators?

siehe B0009

See Element ID B0009.

B0009 – What supplies are needed to use intrastromal corneal implants and the comparators?

Eingriff unter sterilen Bedingungen

For intrastromal corneal implants as well as corneal transplantation a sterile operation theatre is suggested [4, 10]. However, since for inserting intrastromal corneal implants the eye ball needs not to be opened, the operation can also performed in a "Behandlungsraum-invasiv" [11].

Ringimplantation durch Tunnel

In addition, for the implantation of intrastromal corneal implants, a channel has to be created to insert the device. This can be done with a femtosecond laser or mechanically; thus, several instruments are needed for the intervention (e.g., a Sinsky hook, a knife, etc.) [2].

bei Hornhauttransplantation geeigneter Spender nötig

Several instruments are likewise required for corneal transplantation, as is a transplant from an adequate donor (requiring a donor management system, immunosuppressive drugs, etc.) [5].

Regulatory & reimbursement status

A0020 – For which indications have intrastromal corneal implants received marketing authorisation or CE marking?

intrakorneale Ringe zunächst für Behandlung von Myopie in Europa zugelassen

Initially, intrastromal corneal implants were developed for the treatment of myopia and several products received market authorisation in Europe (CE marking) for this indication. However, at the same time another intervention for this disease arose and overshadowed intrastromal corneal rings: laser-assisted in situ keratomileusis (LASIK). Therefore, intrastromal corneal implants never achieved commercial success for the treatment of myopia [3].

später auch Behandlung Keratokonus

In addition, intrastromal corneal implants were also considered to be a therapeutic alternative for the correction of ectatic corneal disorders such as keratoconus and post-LASIK corneal ectasia [3].

alle erwerbbare Produkte CE-Zertifikat, Intacs® FDA-Zulassung

Thereafter, all products of intrastromal corneal implants mentioned at the beginning of Chapter 2.2 that are actually available are approved by the Communauté Européenne (CE) for the treatment of keratoconus (and post-LASIK ectasia). Intacs® is also approved by the US FDA –however, as a Humanitarian Use Device (HUD)[11].

Überblick Zulassungsstatus

An overview of the different intrastromal corneal ring products based on the information of the manufacturers' websites is listed in the table below.

[11] An HUD is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year.

Table 2.2-1: Overview of marketing authorisation of intrastromal corneal rings for keratoconus

Manufacturer	FDA-approval	CE-marking
Bisantis Segments (Optikon 2000 SpA and Soleko SpA, Italy)	No information found[12]	No information found[12]
Ferrara RingTM (Ferrara OphthalmicsTM, Brazil)	No	Yes
Intacs® (Addition TechnologyTM, USA)	Yes	Yes
Keraring – Intrastromal corneal ring (Mediphacos)	No	Yes
MyoRing® (DIOPTEX)	No	Yes

References: individual manufacturers' websites

A0021 – What is the reimbursement status of intrastromal corneal implants?

Einsatz Ringe in Österreich derzeit nicht erstattet

Actually, the use of intrastromal corneal implants for the treatment of keratoconus or post-LASIK corneal ectasia is not included in the Austrian hospital benefit catalogue. Therefore, the intervention itself is not reimbursed by the Austrian health care system.

[12] Since we could not identify the website of the manufacturer, we were not able to find any information regarding FDA and CE approval.

3 Health problem and current use

3.1 Methods

Research questions

Element ID	Research question	Importance 2 = critical 1 = optional
A0001	For which health conditions, and for what purposes is intrastromal corneal implants used?	2
A0002	What is the disease or health condition in the scope of this assessment?	2
A0003	What are the known risk factors for keratoconus or post-LASIK corneal ectasia?	2
A0004	What is the natural course of keratoconus or post-LASIK corneal ectasia?	2
A0005	What is the burden of keratoconus or post-LASIK corneal ectasia?	2
A0006	What are the consequences of keratoconus or post-LASIK corneal ectasia for society?	2
A0024	How is keratoconus or post-LASIK corneal ectasia currently diagnosed according to published guidelines and in practice?	2
A0025	How is keratoconus or post-LASIK corneal ectasia currently managed according to published guidelines and in practice?	2
A0007	What is the target population in this assessment?	2
A0023	How many people belong to the target population?	1
A0011	How much is intrastromal corneal implants utilised?	2

Sources

Quellen aus systematischer und händischer Literatursuche

To answer the research questions regarding the health problem and current use, the results from the systematic literature search (see Chapter 1.3) in Medline via Ovid, Embase, the Cochrane Library plus CRD (DARE, NHS-EED, HTA) and via the hand search were used.

3.2 Results

A0001 – For which health conditions, and for what purposes are intrastromal corneal implants used?

intrakorneale Ringe für Behandlung Myopie und ektatische Hornhauterkrankungen

Originally, intrastromal corneal rings were developed for the treatment of myopia. Later, intrastromal corneal implants were also considered for the correction of ectatic corneal disorders such as keratoconus and post-LASIK corneal ectasia [3, 7].

A0002 – What is the disease or health condition in the scope of this assessment?

Fokus auf Keratokonus und Keratektasie nach LASIK

Based on the information given in the VAEV (see also Chapter2.2), this systematic review will exclusively focus on the treatment of keratoconus and post-LASIK corneal ectasia.

Keratokonus: Krümmung und Ausdünnung Hornhaut

Keratoconus is a non-inflammatory corneal ectasia, characterised by a progressive increase in corneal curvature and thinning of the cornea. Eventually, an obvious cone-shaped protrusion of the corneal surface may develop [12].

Keratektasie nach LASIK: ähnlich wie Keratokonus

Post-LASIK corneal ectasia is a rare, but serious complication of LASIK. The condition is similar to keratoconus where the cornea starts to bulge forwards at a variable time after LASIK. The disease is mainly manifested by progressive corneal steepening, an increase in myopia (short-sightedness), corneal aberrations, plus astigmatism and the loss of visual acuity [3].

A0003 – What are the known risk factors for keratoconus or post-LASIK corneal ectasia?

Entstehung Keratokonus unklar

The pathophysiology of *keratoconus* is not well known. Genetic factors appear to be multifactorial and are considered fundamental to the aetiology and progression of keratoconus. However, the underlying molecular and/or genetic abnormalities are unknown [9, 12].

Zusammenhang mit systemischen Erkrankungen wahrscheinlich

Keratoconus has been linked with systemic conditions such as atopic disease, genetic conditions such as trisomy 21 and Turner's syndrome, and various connective tissue disorders, as well as with eye rubbing, rigid contact lens wear and ocular trauma [12].

oxidativer Stress könnte Keratokonus unterstützen

In addition, keratoconic corneas also have an accumulation of cytotoxic by-products, abnormal antioxidant enzymes and increased levels of mitochondrial DNA damage. This suggests that ongoing oxidative stress contributes to keratoconus [12].

mehrere Risikofaktoren für Keratektasie nach LASIK

Risk factors of *post-LASIK corneal ectasia* can be abnormal preoperative topography, low residual stromal bed (RSB) thickness, young age, low preoperative corneal thickness and/or high myopia [3, 13].

A0004 – What is the natural course of keratoconus or post-LASIK corneal ectasia?

Keratokonus oftmals bereits im Jugendalter

Keratoconus often occurs during teenage years and classically progresses until the 30th or 40th year of life. Many affected individuals experience an arrest of the disease's progression or probably a reduction in the rate of progression [12].

Einteilung Keratokonus in vier Stadien

Keratoconus has four stages, based on Amsler-Krumeich's classification system (see table below).

Table 3.2-1: Amsler-Krumeich's classification system

Grade	Characteristics
1	Eccentric corneal steepening Induced myopia and/or astigmatism <5 D (dioptre) Mean central K readings ≤48 D Vogt's striae, no scars
2	Induced myopia and/or astigmatism >5 D ≤8 D Mean central K readings ≤53 D Absence of scarring Corneal thickness ≥400 µm
3	Induced myopia and/or astigmatism >8 D <10 D Mean central K readings >53 D Absence of scarring Corneal thickness 200 to 400 µm
4	Refraction not measurable Mean central K readings >55 D Central corneal scarring perforation Corneal thickness ≤200 µm

References: [8, 9]

Keratektasie nach LASIK eine erhebliche Komplikation

Corneal ectasia is one of the most devastating complications after LASIK. The disease is defined in patients who developed increasing myopia, with or without increasing astigmatism, loss of uncorrected visual acuity, often loss of best-corrected visual acuity, with keratometric steepening, with or without central and paracentral corneal thinning, and topographic evidence of asymmetric inferior corneal steepening after LASIK procedure. Ectatic changes can occur as early as one week or can be delayed up to several years after LASIK [3, 13].

Effects of the disease or health condition on the individual and society

A0005 – What is the burden of keratoconus or post-LASIK corneal ectasia?

Keratokonus führt zu erheblichen Seheinschränkungen

Due to the thinning of the cornea, *keratoconus* can lead to irregular astigmatism and decrease in visual acuity [12]. Furthermore, keratoconus is unique among chronic eye diseases as it has an early age of onset (median age of 25 years) [9].

LASIK schwächt Hornhaut, was zu Ektasie führen kann

In addition, LASIK permanently thins and weakens the cornea, which may lead to progressive steepening or bulging (ectasia) of the cornea with associated deterioration of vision [6, 13].

Einschränkungen in Lebensqualität

Hence, both diseases implicate limitations in the quality of life up to disability [12, 14].

A0006 – What are the consequences of keratoconus or post-LASIK corneal ectasia for society?

Inzidenz Keratokonus: 2 pro 100.000

Keratoconus is associated with a low incidence of 2 per 100,000 people per year and a prevalence of approx. 1 per 2,000 people (or 5 per 10,000) [4, 9, 14]. Thus, keratoconus is defined as a rare disease[13].

Inzidenz Keratektasie nach LASIK: unbekannt

The actual incidence of *post-LASIK corneal ectasia* is unknown, although the reported incidence rate is less than 1% of patients who underwent LASIK [13].

Konsequenzen für Gesellschaft weniger relevant

Due to low prevalence rates of both indications, the estimated consequences for society do not seem considerable, but are so for the affected patients [9, 15].

Current clinical management of the disease or health condition

A0024 – How is keratoconus or post-LASIK corneal ectasia currently diagnosed according to published guidelines[14] and in practice?

in frühem Stadium Diagnose durch korneale Topographie und verschiedene Algorithmen

In early stages of *keratoconus* and *post-LASIK corneal ectasia*, computerised corneal topography (CCT) techniques using curvature-based analysis and newer forms of elevation-based tomography appear to be the most sensitive methods for detecting early keratoconus [9, 13]. Furthermore, a variety of diagnostic algorithms can help diagnose early keratoconus and corneal ectasia. However, there seems to be no universally diagnostic criterion to diagnose early forms of the disease [13].

mittleres Stadium: Diagnose mit Topo- und Tomographie

In patients with intermediately progressed keratoconus or post-LASIK corneal ectasia, computerised corneal topography and elevation-based tomography are probably the most widely used diagnosing methods [13].

in späteren Stadien Diagnose mit Spaltlampe

In more advanced cases, the diseases can be diagnosed by characteristic slit-lamp findings [9, 13].

A0025 – How is keratoconus or post-LASIK corneal ectasia currently managed according to published guidelines[14] and in practice?

gleiche Behandlung Keratokonus und Keratektasie nach LASIK

Treatment options for *post-LASIK corneal ectasia* are the same as for *keratoconus*. Therefore, only the treatments for keratoconus are explained – representative for both indications.

keine medikamentöse Behandlung verfügbar

There are no drugs known to reverse or prevent keratoconus. However, patients may slow the disease progression by refraining from rubbing their eyes [12, 13].

in frühem Stadium: weiche Kontaktlinsen oder Brille

Early in the process of keratoconus, the visual impairment is usually correctable with soft contact lenses or spectacles. As the disease progresses, it is more difficult to refract the patient to a clear visual acuity with soft contact lenses or spectacles [12].

mittleres Stadium: formstabile Kontaktlinsen

At the intermediate stage, patients usually experience vision loss that is no longer correctable with soft contact lenses or spectacles. The increasing irregularity of the astigmatism may call for rigid, gas-permeable contacts in order to achieve clear vision. Some patients require a scleral lens or a piggyback configuration consisting of hard contact lenses worn over soft lenses to achieve adequate fit, comfort and vision [4, 5, 12].

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[13] See: http://www.orpha.net/.../...Disease_Search_Simple

[14] No Austrian or German guidelines were identified.

spätes Stadium: korneale Transplantation ...

For patients who progress to more advanced stages (stage 2 and more) of the disease, contact lens wear may become increasingly difficult and often uncomfortable due to the steepness of the cornea and difficulty in fitting the lenses. Contact lens intolerance is a common indication for corneal transplantation at this stage [4, 12]:

... wie penetrierende oder lamelläre Keratoplastik ...

Penetrating keratoplasty (PK) – a corneal transplantation – is the mainstay of treatment for keratoconus. The procedure applies to be effective with a low rejection rate. In spite of successful surgery, residual corneal astigmatism and refractive error usually require additional correction with a contact lens. In addition, complications after PK can include allograft rejection, a fixed, dilated pupil and, on occasion, recurrence of keratoconus [4, 8]. For patients who have moderate keratoconus without significant scarring, there is renewed interest in *deep anterior lamellar keratoplasty* (DALK), especially with the precision, predictability and convenience of the femtosecond laser for these cases. The DALK technique aims to remove nearly all corneal stroma [4, 5].

... aber auch korneale Ringimplantate ...

Furthermore, *intrastromal corneal rings* or ring segments are also an option, particularly if the patient demonstrates disease progression with apical displacement. However, several products are not indicated anymore for keratoconus with a certain keratometry (e.g. >70 D for Keraring) [4, 14].

... und sogenannte Vernetzungsbehandlung

Besides, *collagen cross-linking* (CXL) is a relatively new treatment option. CXL involves a one-time application of riboflavin solution to the eye that is activated by illumination with UV light. The riboflavin causes new bonds to form across adjacent collagen strands in the stromal layer of the cornea, which recovers and preserves some of the cornea's mechanical strength, possibly slowing the progression of the disease [4, 5].

Target population

A0007 – What is the target population in this assessment?

PatientInnen mit Keratokonus oder Keratektasie nach LASIK mit Kontaktlinsenintoleranz

The target population are patients with keratoconus (mainly stages 1-3) or post-LASIK corneal ectasia that are contact lens intolerant (patients with keratoconus), have an adequate corneal thickness, particularly around the area of the implant incision site, and are without central corneal scarring [7, 9].

A0023 – How many people belong to the target population?

Frage nicht relevant

This question has been defined as not relevant for this report.

A0011 – How much are intrastromal corneal implants utilised?

geschätzte jährliche Erbringung in Österreich: 200

Based on the information given in the VAEV, the estimated annual utilisation of the intrastromal corneal rings technology in Austria is around 200.

In 2013, a total of 110,210 inpatient surgical interventions were performed in Austria on the cornea, iris or lens [16].

4 Clinical effectiveness

4.1 Methods

Research questions

Element ID	Research question	Importance 2 = critical 1 = optional
D0001	What is the expected beneficial effect of intrastromal corneal implants on mortality?	1
D0003	What is the effect of intrastromal corneal implants on the mortality due to causes other than keratoconus or post-LASIK corneal ectasia?	1
D0005	How do intrastromal corneal implants affect symptoms and findings (severity, frequency) of keratoconus or post-LASIK corneal ectasia?	2
D0006	How do intrastromal corneal implants affect progression (or recurrence) of keratoconus or post-LASIK corneal ectasia?	2
D0011	What is the effect of intrastromal corneal implants on patients' body functions?	1
D0016	How does the use of intrastromal corneal implants affect activities of daily living?	2
D0012	What is the effect of intrastromal corneal implants on generic health-related quality of life?	2
D0013	What is the effect of intrastromal corneal implants on disease-specific quality of life?	2
D0017	Was the use of intrastromal corneal implants worthwhile	2

Entscheidende Endpunkte für Wirksamkeit:

The following *crucial* outcomes were used as evidence to derive a recommendation:

- Length of hospital stay (or time to resume work/normal activities)
- Re-operation rate
- Change of visual acuity (change of two or more Snellen lines)

KH-Aufenthalt/ Wiedererlangung Arbeitsfähigkeit,

The implantation of intrastromal corneal implants is supposed to be less invasive than corneal transplantation (see Chapter 2.2). Therefore, the length of hospital stay, 3(or time to resume work or normal activities) after the intervention, was chosen as a crucial outcome.

Reoperationsrate

The re-operation rate (including explantations) is the rate of how frequently patients had to be operated again, e.g., due to complications. This outcome is an indicator of the "life-expectancy" of the implants and transplants.

lediglich Änderung Sehstärke (≥2 Linien) für Empfehlung herangezogen

The change of visual acuity can be measured, for example, by uncorrected visual acuity (UCVA) or best-corrected visual acuity (BCVA) on the Snellen chart. An improvement or worsening of two and more Snellen lines can be considered as clinically relevant. Furthermore, the percentage of patients or eyes with improved (or worsened) visual acuity (two or more Snellen lines) has been defined as more relevant than the mean increase in visual acuity [17, 18]. Therefore, only those studies where it was possible to cull this information from were considered.

zusätzlich Lebensqualität und PatientInnen-zufriedenheit

Besides the three crucial outcomes, two additional outcomes were used to answer efficacy-related outcomes in Chapter 4.2: quality of life and patient satisfaction. These two outcomes are also presented in Table A1-1 in the Appendix.

Sources

Quellen aus systematischer Literatursuche und Anfrage bei Herstellern

The assessment of the research questions regarding efficacy-related outcomes was based on a systematic literature search from the following sources:

- Medline via Ovid,
- Embase,
- the Cochrane Library,
- CRD (DARE, NHS-EED, HTA).

detaillierte Suchstrategie in Anhang

Details of the search strategy can be found in the Appendix (Chapter "Search strategies"). Additionally, literature provided by the manufacturers was also checked for eligible studies that were not found within the systematic literature search.

Erstautor extrahierte Studiendaten, Zweitautor kontrollierte

One author extracted the data (SF) of the included studies and a second author controlled the extracted data (IZ). If the same data were duplicated in multiple articles, only results from the most comprehensive or most recent article were included. Consensus on the inclusion and exclusion of individual studies was found in all cases.

Ergebnisse getrennt nach Indikation und Produkt

The extracted results of the identified studies are classified by indication (keratoconus and post-LASIK corneal ectasia) and by the individual products (Ferrara Ring™, Intacs®, etc.). The studies in the extraction table (Appendix Table A1-1) are sorted by publication date, starting with the oldest study.

Analysis

Bias-Risiko je Endpunkt

The relevant information from the feasible studies was retrieved without any further analysis. For ***all*** studies the methodological quality was assessed using the a checklist for case series [19] by two review authors (SF, IZ), independently from each other. The risk of bias analysis for each individual study is shown in the Appendix (Chapter "Risk of bias tables").

Synthesis

Beantwortung Forschungsfragen vorrangig als Text

Most of the research questions will be answered in plain text format. In addition, evidence tables are used to show relevant information on the individual studies. Based on the evidence tables, data on each selected outcome category were synthesised across studies according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) [20].

qualitative Analyse

The analysis is qualitative and not quantitative due to a lack of comparison groups and heterogeneity of the data.

4.2 Results

Included studies

For evaluating efficacy-related outcomes we accepted RCTs, prospective non-randomised controlled trials and – in case we were unable to identify relevant controlled studies – single-arm studies (see Chapter 1.2).

(un)kontrollierte Studien für Wirksamkeitsendpunkte

We could not identify any controlled trials comparing intrastromal corneal implants with either corneal transplantation or no intervention for the treatment of keratoconus or post-LASIK corneal ectasia. Therefore, we included uncontrolled studies (single-arm studies).

keine kontrollierte, nur unkontrollierte Studien identifiziert

The only studies that met our inclusion criteria are five single-arm studies with a total of 627 eyes [21-25] assessing the efficacy of intrastromal corneal implants for the treatment of keratoconus.

5 Fallserien mit 627 Augen bei Behandlung Keratokonus

The mean age of patients differed between 26 and 37 years [23, 25]. The minority of patients were females (30-50%) [22-25] with grade I to IV of keratoconus [21, 23, 24]. The follow-up of the studies was 12 months [21-23], 24 months and up to 96 months (8 years). The loss to follow-up rate differed between 18 and 76% [21-25].

PatientInnen: Ø 26-37 Jahre, 30-50 % Frauen, Stadium I-IV, Nachbetrachtungszeit 12-96 Monate

Intacs® were implanted in all studies [21-25]. Furthermore, Keraring intracorneal ring segments were implanted in two studies [23, 25].

Produkte: Intacs® und Keraring

There were no studies assessing the clinical effectiveness of other products, like Ferrara Ring™, MyoRing® or probably Bisantis Segment (see Chapter 2.2) for the treatment of keratoconus. In addition, there were no studies assessing the clinical effectiveness of intrastromal corneal implants for the treatment of post-LASIK corneal ectasia.

keine Studien zu anderen Produkten oder Keratektasie nach LASIK

The detailed study characteristics and results of the included studies are displayed in Table A1-1 in Appendix Capter "Evidence tables of individual studies included for clinical effectiveness and safety".

Extraktionstabelle in Anhang

Length of hospital stay (or time to resume work/normal activities) and re-operation rate were not considered for recommendation: Only a direct comparison with corneal transplantation would have been allowed to assess the clinical effectiveness of intrastromal corneal implants for a treatment of keratoconus and post-LASIK corneal ectasia.

Wiedererlangung Arbeitsfähigkeit und Reoperationsrate nicht für Empfehlung herangezogen

Mortality

D0001 – What is the expected beneficial effect of intrastromal corneal implants on mortality?

D0003 – What is the effect of intrastromal corneal implants on the mortality due to causes other than keratoconus or post-LASIK corneal ectasia?

Mortality is not a relevant outcome for assessing the clinical effectiveness of intrastromal corneal implants, since neither the disease nor the intervention is life-threatening.

Mortalität nicht relevant

Morbidity

D0005 – How do intrastromal corneal implants affect symptoms and findings (severity, frequency) of keratoconus or post-LASIK corneal ectasia?

Änderung Sehschärfe als Grundlage

Answering this research question was based on the outcome "change of visual acuity". Due to a lack of controlled trials, the effect on visual acuity of intrastromal corneal implants for a treatment of keratoconus cannot be compared with corneal transplantation, but will be based on uncontrolled data.

in mehr Augen Verbesserung Sehstärke, als Verschlechterung

The change of visual acuity of *one and more Snellen lines* was reported in four single-arm studies. After 12 months, UCVA was improved in around 70-80% of eyes and worsened in less than 10% of eyes after 12 months [23, 24]. After 24 months, UCVA improved in 81% and worsened in 5% of treated eyes [24]. Similarly, BCVA improved in approx. 60-85% and worsened in 4-12% of the treated eyes (after 24 months: 68% improved, 15% worsened) [23, 24]. Moreover, the improvement of UCVA and BCVA was considered statistically significant after six 6 and 12 months of implantation in one study [24].

Änderung ≥2 Snellen-Linien in zwei Fallserien berichtet

The change of visual acuity of *two or more Snellen* lines after treatment, which has been defined as clinically relevant, has been reported in one single-arm study for UCVA [21] and in two single-arm studies for BCVA [21, 22]:

in mehr Augen *klinisch* relevante Verbesserung Sehstärke, als Verschlechterung

Six months after implantation, UCVA improved in 79% and worsened in none of the treated eyes [21]. In addition, BCVA rather improved in more eyes than worsened [21, 22]: For example, after 6 months of implantation BCVA improved in 39-62% and worsened in 6-12% of eyes [21, 22]. After 12 months of implantation, BCVA improved in 42% and worsened in 8% of the eyes that received an implant [22]. The improvement of UCVA and BCVA after six months of implantation compared to baseline was considered as statistically significant in one study [21].

D0006 – How do intrastromal corneal implants affect progression (or recurrence) of keratoconus or post-LASIK corneal ectasia?

Reoperationsrate als Grundlage

To answer this research question the outcome "re-operation rate" was used to (indirectly) measure the progression (or recurrence) of the disease. Thus, the higher the re-operation rate, the lower the chance of stopping or slowing the progression.

keine kontrollierten Studien

However, due to a lack of controlled trials, the effect on the re-operation rate of intrastromal corneal implants for a treatment of keratoconus cannot be compared with corneal transplantation, but will be based on uncontrolled data

in Fallserien: 4-23 % Reoperationsrate

According to the available data, between 4 and 23% of the eyes with an implanted intrastromal corneal ring had to be re-operated [21, 22, 24, 25].

Function

D0011 – What is the effect of intrastromal corneal implants on patients' body functions?

Frage nicht relevant

Keratoconus and the treatment with intrastromal corneal implants exclusively affect the eyes and not the whole body. Thus, answering this research questions has been defined as not relevant.

aber abgedeckt mit vorigen Abschnitt (D0005)

The effect on visual acuity (the only affected body function) has already been addressed in the previous section (question D0005).

D0016 – How does the use of intrastromal corneal implants affect activities of daily living?

KH-Aufenthalt nicht berichtet

Answering this research question was based on the outcome "length of hospital stay (or time to resume work/normal activities)". The outcome was not reported in any of the identified single-arm studies.

Health-related quality of life

D0012 – What is the effect of intrastromal corneal implants on generic health-related quality of life?

keine Evidenz

No evidence was found to answer this research question (no identified study reported generic health-related quality of life).

D0013 – What is the effect of intrastromal corneal implants on disease-specific quality of life?

sehkraftbezogene Lebensqualität als Grundlage

To answer this research question the outcome "vision-related quality of life" was used. Due to a lack of controlled trials, the effect on quality of health of intrastromal corneal implants for a treatment of keratoconus cannot be compared with corneal transplantation, but will be based on uncontrolled data.

sehkraftbezogene Lebensqualität großteils gestiegen

Vision-related quality of life was reported in two single-arm studies [21, 22]. In one study, vision-related quality of life improved in 88.5% and worsened in 11.5% of patients, measured with the Visual Function-7 score (no information on this questionnaire was presented) [22]. In another study, the quality of vision was measured with the characteristics "poor", "fair", "good" and "excellent" by asking the patients [21]. Before implantation, 70% of patients had a "poor", and none had an "excellent" quality of vision. At 6 months after implantation, 24% of patients had "poor" and 9% of patients had "excellent" quality of vision [21].

Patient satisfaction

D0017 – Was the use of intrastromal corneal implants worthwhile?

PatientInnenzufriedenheit als Grundlage

To answer this research question the outcome "patient satisfaction" was used. Due to a lack of controlled trials, the effect on patient satisfaction of intrastromal corneal implants for a treatment of keratoconus cannot be compared with corneal transplantation, but will be based on uncontrolled data.

mehr PatientInnen Verbesserung Zufriedenheit, als Verschlechterung

The outcome was reported in one of the identified single-arm studies as the change of self-reported satisfaction with vision [22]. According to that study, 73% of patients reported an improvement in satisfaction and 8% reported a worsening of satisfaction with their vision [22].

5 Safety

5.1 Methods

Research questions

Element ID	Research question	Importance 2 = critical 1 = optional
C0008	How safe are intrastromal corneal implants in comparison to corneal transplantation or no intervention?	2
C0002	Are the harms related to dosage or frequency of applying intrastromal corneal implants?	1
C0004	How does the frequency or severity of harms change over time or in different settings?	2
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of the intrastromal corneal implants?	2
C0007	Are intrastromal corneal implants and corneal transplantation (or no intervention) associated with user-dependent harms?	2
B0010	What kind of data/records and/or registry are needed to monitor the use of intrastromal corneal implants and corneal transplantation (or no intervention)?	2

entscheidende Endpunkte für Sicherheit:

The following *crucial* outcomes were used as evidence to derive a recommendation:

- intra-operative adverse events
- post-operative adverse events.

intra- und postoperative unerwünschte Ereignisse

Intra-operative adverse events are those complications that occur during the surgical procedure: during the ring implantation or during the corneal transplantation. Post-operative adverse events are those complications that occur after the surgical intervention: e.g., ring movement or infections after corneal transplantation.

Sources

Quellen aus systematischer Literatursuche und Anfrage bei Herstellern

The assessment of the research questions regarding safety-related outcomes was based on a systematic literature search from the following sources:

- Medline via Ovid,
- Embase,
- the Cochrane Library,
- CRD (DARE, NHS-EED, HTA).

detaillierte Suchstrategie in Anhang

Details of the search strategy can be found in the Appendix (Chapter "Search strategies"). Additionally, literature provided by the manufacturers was also checked for eligible studies that were not found within the systematic literature search.

Erstautor extrahierte Studiendaten, Zweitautor kontrollierte

One author extracted the data (SF) of the included studies and a second author controlled the extracted data (IZ). If the same data were duplicated in multiple articles, only results from the most comprehensive or most recent article were included. Consensus was found in all cases about the inclusion and exclusion of individual studies.

Ergebnisse getrennt nach Indikation und Produkt

The extracted results of the identified studies are classified by indication (keratoconus and post-LASIK corneal ectasia) and by the individual products (Ferrara Ring™, Intacs®, etc.). The studies in the extraction tables are sorted by publication date, starting with the oldest study.

Analysis

Bias-Risiko nach checkliste

The relevant information from the feasible studies was retrieved without any further analysis. For ***all*** studies the methodological quality was assessed using a checklist for case series [19], by two review authors (SF, IZ), independently from each other. The risk of bias analysis for each individual study is shown in the Appendix (Chapter "Risk of bias tables").

Vergleichende Analyse nicht möglich

Incidentally, a comparative analysis was not applicable, since we could not identify studies for every product and indication. Moreover, the quality of evidence did not allow any comparative analysis.

Synthesis

Beantwortung Forschungsfragen vorrangig in Text

Most of the research questions will be answered in plain text format. In addition, evidence tables are used to show relevant information on the individual studies. Based on the evidence tables, data on each selected outcome category were synthesised across studies according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) [20].

qualitative Analyse

The analysis is qualitative and not quantitative due to a lack of comparison groups and heterogeneity of the data.

5.2 Results

Included studies

(un)kontrollierte Studien für Sicherheitsendpunkte

For evaluating safety-related outcomes we accepted RCTs, prospective non-randomised controlled trials and – in case we were unable to identify relevant controlled studies – single-arm studies (see Chapter "Risk of bias tables").

keine passenden kontrollierten Studien identifiziert

However, we could not identify any controlled trials comparing intrastromal corneal implants with either corneal transplantation or no intervention for the treatment of keratoconus or post-LASIK ectasia.

5 Fallserien mit 168 Augen bei Behandlung Keratokonus

The only studies that met our inclusion criteria are five single-arm studies with a total of 627 eyes [21-25] assessing the safety of intrastromal corneal implants for the treatment of keratoconus.

The mean age of patients differed between 26 and 37 years [23, 25]. The minority of patients were females (30-50%) [22-25] with grades I to IV of keratoconus [21, 23, 24]. The follow-up of the studies was 12 months [21-23], 24 months up to 96 months (8 years). The loss to follow-up rate differed between 18 and 76% [21-25].

PatientInnen: Ø 26-37 Jahre, 30-50 % Frauen, Stadium I-IV, Nachbetrachtungszeit 12-96 Monate

Intacs® were implanted in all studies [21-25]. Furthermore, Keraring intracorneal ring segments were implanted in two studies [23, 25].

Produkte: Intacs® und Keraring

The detailed study characteristics and results of the included studies are displayed in Table A1-1 in Appendix Evidence tables of individual studies included for clinical effectiveness and safety.

Extraktionstabelle in Anhang

There were no studies assessing the safety of other products, like Ferrara Ring™, MyoRing® or probably Bisantis Segment (see Chapter 2.2) for the treatment of keratoconus. In addition, there were no studies assessing the safety of intrastromal corneal implants for the treatment of post-LASIK corneal ectasia.

keine Studien zu anderen Produkten oder Keratektasie nach LASIK

Patient safety

C0008 – How safe are intrastromal corneal implants in comparison to corneal transplantation or no intervention?

No studies were identified that are directly comparing the implantation of intrastromal corneal implants with corneal transplantation (e.g., keratoplasty) or no intervention for the treatment of keratoconus.

keine Studien für Vergleich

In the single-arm studies, general adverse events occurred in 7 to 16% of the eyes [21-24]. Intra-operative adverse events, like difficulties in forming the intrastromal tunnel to implant the rings or anterior perforation, occurred in 0-2% of the eyes [21-24]. Post-operative adverse events occurred in 2 to 23% of the treated eyes [21-25], e.g., extrusion or migration of a segment, external infection or corneal perforation.

Komplikationen während OP: in 0-2 % Augen Komplikationen nach OP: in 2-23 % Augen

C0002 – Are the harms related to dosage or frequency of applying intrastromal corneal implants?

Naturally, since the implantation of intracorneal rings is performed only once, the question is not relevant.

Frage für Bericht irrelevant

C0004 – How does the frequency or severity of harms change over time or in different settings?

No direct evidence was found to answer this research question in an appropriate way.

keine verlässliche Evidenz

However, it seems likely that the frequency and/or severity of harms slightly increase over time. The identified study with the longest duration and the most patients is the only one that shows the number of post-operative events per year of follow-up [25]. In Figure 5.2-1, the number and the percentage of post-operative events (per number of patients in the study) per year are shown.

scheinbar leichter Anstieg postoperativer Komplikationen über Jahre

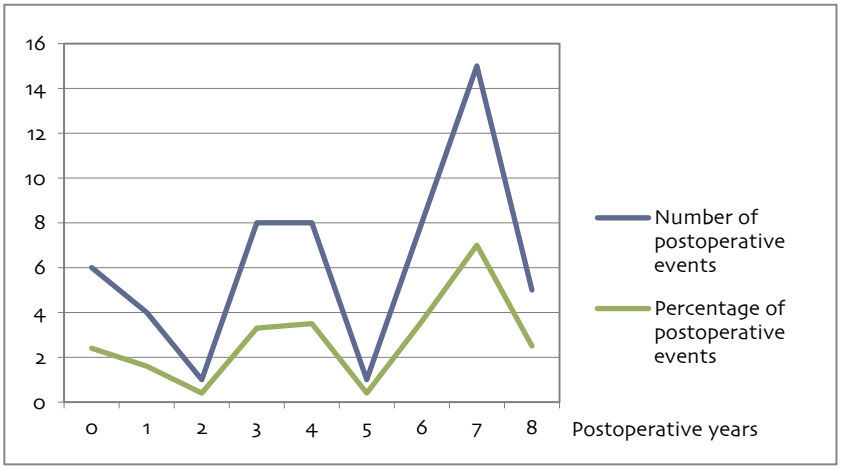

Figure 5.2-1: Number and percentage of post-operative events

C0005 – What are the susceptible patient groups that are more likely to be harmed through the use of the intrastromal corneal implants?

keine Evidenz

No direct evidence was found to answer this research question.

C0007 – Are intrastromal corneal implants and corneal transplantation (or no intervention) associated with user-dependent harms?

keine Evidenz

No direct evidence was found to answer this research question. However, in all included studies intrastromal corneal implants were implanted by experienced eye surgeons [21-25].

Investments and tools required

B0010 – What kind of data/records and/or registry are needed to monitor the use of intrastromal corneal implants and corneal transplantation (or no intervention)?

keine Literatur zu Beantwortung der Frage

No literature was retrieved that identified specific data or monitoring records of outcome for the treatment of keratoconus or post-LASIK corneal ectasia.

6 Quality of evidence

Bewertung Evidenzstärke von zwei AutorInnen nach GRADE

The strength of evidence was rated according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach [20] for every defined outcome parameter individually. Each study was rated by two independent researchers (SF, IZ). All relevant study results for each endpoint were thereby summarised and assessed regarding the strength of evidence. In case of disagreement, a third researcher was involved to solve the difference. A detailed description of the used criteria for assessing the strength of evidence is stated in the internal manual of the LBI-HTA [26] or in the recommendations of GRADE, respectively [20]. The ranking according to the GRADE scheme for the research question can be found in Table 6–1.

GRADE-Kategorien

GRADE uses four categories to rank the strength of evidence:

- High = We are very confident that the true effect lies close to that of the estimate of the effect[15];
- Moderate = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- Low = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect[16];
- *Very low:* Evidence either is unavailable or does not permit a conclusion.

Evidenzstärke gering bis sehr gering

Overall, the strength of evidence for clinical effectiveness and the safety of intrastromal corneal implants for the treatment of keratoconus is low to very low.

keine Evidenz zu Wirksamkeit bei Keratokonus oder zu Behandlung Keratektasie nach LASIK

There was neither any evidence available to assess the efficacy, nor to assess the safety of intrastromal corneal implants for the treatment of post-LASIK corneal ectasia (compared to corneal transplantation or no intervention) that matched our inclusion criteria.

[15] In case of RCTs: the strength of evidence starts with “high”.

[16] In case of observational studies (e.g., single-arm studies): the strength of evidence starts with “low”.

Table 6–1: Evidence profile: Efficacy and safety of intrastromal corneal implants for keratoconus (single-arm studies)

No of studies/ eyes	Study Design	Estimate of effect	Study limitations	Inconsistency	Indirectness	Other modifying factors	Strength of evidence
Clinical Effectiveness							
Change of visual acuity: UCVA (in % of improved/worsened eyes ≥2 Snellen lines)							
1/59	Single-arm study	6 mo: 79/0; p=S.S. from baseline	No serious limitations	n/a (only 1 trial)	Direct	None	Low
Change of visual acuity: BCVA (in % of improved/worsened eyes≥2 Snellen lines)							
1/50	Single-arm study	1 mo: 26/8	No serious limitations	n/a (only 1 trial)	Direct	None	Low
1/50	Single-arm study	3 mo: 41/8	No serious limitations	n/a (only 1 trial)	Direct	None	Low
2/109	Single-arm studies	6 mo: 39-62/6-12; p=S.S. from baseline, in one study	No serious limitations	Important inconsistency[17] (-1)	Direct	None	Very low
1/50	Single-arm study	12 mo: 42/8	No serious limitations	n/a (only 1 trial)	Direct	None	Low
Safety							
Adverse events: intraoperative (in % of eyes)							
4/377	Single-arm studies	0-2	No serious limitations	No important inconsistency	Direct	None	Low
Adverse events: post-operative (in % of eyes)							
5/627	Single-arm studies	2-23	No serious limitations	Important inconsistency[18] (-1)	Direct	None	Very low

Abbreviations: BCVA = best-corrected visual acuity; UCVA = uncorrected visual acuity; S.S. = statistically significant

[17] The difference between the lowest and the highest percentage of eyes with improved BCVA was more than 20%.

[18] The difference between the lowest and the highest rate of postoperative events was more than 20%.

7 Discussion

Keratokonus und Keratektasie nach LASIK seltene Erkrankungen

Keratoconus and post-LASIK corneal ectasia are rare diseases, affecting 1 per 2,000 people in case of keratoconus and probably less in case of post-LASIK ectasia. Even if both diseases are not common and the impact for society is minor, the diseases severely reduce the quality of life of the persons affected, due to low visual acuity. Furthermore, the diagnosis of the diseases can result in occupational disability in several professions (e.g., police, military and aviation).

Ziel: Wirksamkeit und Sicherheit intrakornealer Ringe

The aim of this report was to assess the clinical effectiveness and safety of a treatment of keratoconus or post-LASIK ectasia with intrastromal corneal rings (or ring segments) compared to corneal transplantations (or no intervention).

5 Fallserien für Datensynthese eingeschlossen, keine kontrollierten Studien

Overall, there were no controlled trials available to assess the clinical effectiveness or safety of intrastromal corneal implants in comparison to corneal transplantations (or no intervention). In total, we selected 5 single-arm studies with 627 eyes that met our inclusion criteria [21-25]. Two of these studies [21, 22] were considered for recommendation based on efficacy-related outcomes.

vorrangig PatientInnen mit Keratokonus

All identified studies included patients with keratoconus, with one exception where a few patients had myopia or post-LASIK corneal ectasia [25]. However, since keratoconus and post-LASIK corneal ectasia are very similar, the studies for keratoconus are more or less transferable. All studies implanted either Intacs® or Keraring.

Studienpopulationen realistisch

All studies (when stated) included young (mean age: 26-37) [23, 25] and predominantly male patients (50-70%) [22-25]. The stage of keratoconus was grades I-IV [21, 23, 24] and patients had (mostly) contact lens intolerance. All these factors seem to reflect the "ordinary" population of keratoconus that is feasible for implantation of intrastromal corneal implants.

Evidenzstärke gering bis sehr gering, bedingt durch Studiendesigns

Overall, the strength of evidence for efficacy and safety is low to very low. Naturally, this is mainly due to the study design of the identified single-arm studies: the strength of evidence of observational studies generally starts with "low". In addition, for change of visual acuity (BCVA) after 6 months and post-operative adverse events, the quality of evidence was downgraded to very low due to an important inconsistency (the differences between the lowest and highest rates were enormous).

kurze Nachbeobachtungs-zeiträume

The majority of studies had a relatively short follow-up of one year [21-23] or two years [24] and a high rate of drop outs during the follow-up phase of 18 to 76%. Only one study had a longer follow-up (or better: study duration) of 8 years [25]. Therefore, reliable data of long-term efficacy and safety-related outcomes are missing.

einige nicht berichtete Eigenschaften der PatientInnen

Moreover, several studies had a lack of reporting information of the included study population. For example, two studies did not report the number of patients (only eyes) [21, 25], the age of patients [21, 24] and the clinical classification of keratoconus [22, 25]; one study did not mention the sex ratio of patients [21].

Wiedererlangung Arbeitsfähigkeit in Studien nicht berichtet

One outcome that was defined as crucial – the length of hospital stay (or time to resume work or normal activities) – was not reported in any of the identified single-arm studies. Anyway, due to the lack of controlled trials, this outcome was not considered for recommendation.

nur zwei Studien zu Verbesserung Sehstärke von 2+ Snellen-Linien

Four studies reported the change of visual acuity [21-24]. However, only two studies [21, 22] allowed culling information on improvement or worsening of two or more Snellen lines, which can be considered as clinically relevant.

eine Studie nur Gründe für Explantationen

Furthermore, in one paper only the reasons for explantations were studied [25]. Thus, the real number of post-operative complications is unknown in this study, since there were probably complications that did not implicate any explantation.

andere Studie erwähnte eventuell nicht alle Komplikationen

In another study, it seems very likely that not all post-operative complications were reported: "Ocular observations at all postoperative examinations were minor and were not considered clinically significant by the investigators" [21].

zwei Studien mit inkorrekten Angaben

Besides, two studies declared that no author had a financial interest in the used products [21, 24]. However, the first author of these studies is a consultant of the investigated product, as well as the editor of the journal the articles were published in.

Ein-Arm-Studien: durchaus Verbesserung Sehschärfe

Considering the findings of the included single-arm studies regarding clinical effectiveness, it seems that the implantation of intrastromal corneal implants can improve visual acuity in a clinically relevant manner (two or more Snellen lines). The uncorrected visual acuity improved two or more Snellen lines in approx. 80% of the eyes and the best-corrected visual acuity improved two or more Snellen lines in approx. 40-60% of the eyes during 6 to 12 months of follow-up [21, 22].

aber auch Fälle mit Sehverschlechterung

However, there were also several cases with worsened visual acuity after a treatment with intrastromal corneal implants: worsened best-corrected visual acuity (two and more Snellen lines) in 6-12% of the eyes during follow-up [21, 22].

Reoperationen wenig und ohne Schäden

Only 4-23% of the patients had to be operated again [21, 22, 24, 25]. Furthermore, the re-operations were performed without any injuries. A restriction is the relatively short follow-up of the studies.

kein Vergleich Wirksamkeit Transplantation

Nevertheless, due to a lack of controlled trials we are not able to draw any conclusions on the clinical effectiveness of intrastromal corneal implants for a treatment of keratoconus or post-LASIK ectasia compared to corneal transplantation or even no intervention.

kein Vergleich Zeit bis Wiedererlangung Arbeitsfähigkeit

In particular, the direct comparison of the length of the hospital stay or the time the patients return to their normal activities or work after a treatment with intrastromal rings or corneal transplantation is missing.

nur leichte Komplikationen

Although the strength of evidence for safety was low to very low, a treatment of keratoconus (and post-LASIK ectasia) with intrastromal corneal implants does not seem to be related with major adverse events. The rate of intra-operative adverse events seems to be low. However, the rate of post-operative adverse events was high in several studies.

intrakorneale Ringe, zumindest kurzfristig, relativ sicher

Finally, a treatment of keratoconus as well as post-LASIK corneal ectasia with intrastromal corneal implants seems relatively safe – at least within a short time horizon. Additionally, all explantations or adjustments of intrastromal corneal implants due to adverse events were without any complications.

Naturally, our systematic review has several weaknesses:

Schwächen Review:

First of all, we excluded case series with less than 50 eyes. There were probably studies with less than 50 eyes with a longer follow-up or studies implanting other products (e.g., Ferrara Ring™ or MyoRing®).

Ausschluss Studien <50 Augen

Furthermore, we excluded retrospective studies – even controlled studies with a retrospective control group where patients received a corneal transplantation – because sources of error due to confounding and bias are more common in retrospective studies than in prospective ones.

Ausschluss retrospektive Studien

There were two studies included without precise information on whether they were conducted pro- or retrospectively [23, 25].

zwei Studien eventuell nicht prospektiv

One of the studies also included patients who had other diseases than keratoconus or post-LASIK corneal ectasia (e.g., myopia) [25]. Hence, we had to exclude this study although it included a large number of patients and had a long follow-up.

einige PatientInnen einer Studie mit anderen Indikationen

A major issue is that keratoconus and post-LASIK corneal ectasia are rare diseases with a low incidence, resulting in low patient numbers. There are even fewer patients who are contact lens intolerant and/or need a corneal transplantation (and are therefore eligible for implantation of intrastromal corneal rings). Therefore, it is difficult to conduct prospective controlled trials or randomised controlled trials for assessing the clinical effectiveness of intrastromal corneal implants compared to corneal transplantation (or no intervention). An additional issue for conducting controlled trials is that one study group needs an adequate donor for the corneal transplant and patients must wait for the transplantation.

Problem: Durchführung prospektive kontrollierte Studien bei seltenen Erkrankungen

Thus, the FDA approved one device (Intacs® and supplying products) under the Humanitarian Device Exemption (HDE) program, by only assessing the safety. That means the product may only be used in facilities that have an institutional review board to supervise clinical testing. The device must be for humanitarian use and the effectiveness of the device for the specific indication does not have to be demonstrated.

FDA hat daher ein Produkt unter Einschränkungen zugelassen

Nevertheless, we identified two abstracts of two RCTs that compared intrastromal corneal ring segments with keratoplasty for a treatment of keratoconus [27, 28], but were not able to find full texts of these RCTs. We directly contacted one study author and tried to reach another study author – without any reply (status: 18th March 2015).

dennoch: es wurden RCTs durchgeführt, aber nicht veröffentlicht

Although conducting RCTs of intrastromal corneal implants versus corneal transplantation for keratoconus is difficult, it does not seem impossible.

Durchführung RCTs nicht unmöglich

8 Recommendation

In Table 8–1, the scheme for recommendations is displayed and the according choice is highlighted.

Empfehlungsschema

Table 8–1: Evidence-based recommendations

	The **inclusion** in the catalogue of benefits is **recommended**.
X	The **inclusion** in the catalogue of benefits is **recommended with restrictions**.
	The inclusion in the catalogue of benefits is ***currently*** **not recommended.**
	The **inclusion** in the catalogue of benefits is **not recommended.**

Reasoning:

The current evidence is not sufficient to prove that intrastromal corneal implants are equally or more effective and safe than corneal transplantation or no intervention for a treatment of keratoconus or post-LASIK corneal ectasia.

kein Beweis, dass Ringe wirksamer und sicherer als Transplantation

However, the comparison before and after the ring implantations of the single-arm studies have shown that the visual acuity has improved after implanting intrastromal corneal rings/ring segments and that improvement has been clinically relevant in a large proportion of patients.

Vergleich vor und nach Implantation: Verbesserung Sehschärfe

Furthermore, the implantation of intrastromal corneal rings seems to be relatively safe and adverse events were minor. In cases where the implants had to be explanted or readjusted, this was performed without any complications or injuries.

Ringimplantate scheinen sicher

A major benefit of intrastromal corneal implants compared to corneal transplantation is their reversibility (the rings can be explanted relatively easily); the rings can be ordered when they are required (for corneal transplantation an adequate donor is needed) and after implantation no immunosuppressive drugs are needed. Moreover, corneal transplantation is a more invasive intervention with higher risks for complications than the implantation of intrastromal corneal rings. Due to the minor invasivity and the reversibility, intrastromal corneal implants should be considered before corneal transplantation.

Ringimplantate: reversibel, keine Immunsuppressiva nötig, weniger invasiv

The **inclusion** in the catalogue of benefits is recommended **with the following restrictions**:

Aufnahme in Leistungskatalog mit Einschränkungen empfohlen

- The patient has contact lens intolerance (or is not able to wear contact lenses anymore).
- The individual indications and contra-indications for the use of the several products must be considered (e.g. adequate thickness of cornea).
- The implantation of intrastromal corneal rings (or ring segments) should exclusively be offered in big centres, like medical universities.
- The safety of intrastromal corneal implants for a treatment of keratoconus or post-LASIK corneal ectasia should be monitored and recorded in a national database. The data can be used to further adapt the recommendations for the use of intrastromal corneal implants.

keine laufenden Studien mit Hornhaut-transplantation als Kontrollgruppe

Currently, there are no registered ongoing or planned controlled trials comparing intrastromal corneal implants with corneal transplantation for a treatment of keratoconus or post-LASIK ectasia (see Appendix Capter "Ongoing studies"). Additionally, two ongoing RCTs are comparing different intrastromal corneal implants for a treatment of keratoconus.

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A1-1: Results from single-arm studies of intrastromal corneal implants for keratoconus

Author, year, reference number	Hellstedt 2005 [22]	Colin 2006 [21]	Colin 2007 [24]	Ferrer 2010[25]	Kubaloglu2010 [23]
Country	Finland	France, Germany, UK	France	Spain	Turkey
Study design	Single-arm study, prospective	Single-arm study, prospective	Single-arm study, prospective	Single-arm study, prospective[19]	Single-arm study, prospective[19, 20]
Sponsor	Supported by Finnish government and Finnish Eye Foundation	Unclear[21]	Unclear[21]	Spanish Ministry of Health	None
Intervention/Product	ICRS (Intacs®), topical anaesthetics, manual tunnel creation	ICRS (Intacs®), topical or general anaesthetics, manual tunnel creation	ICRS (Intacs®), topical or general anaesthetics, manual tunnel creation	ICRS (Intacs® and Keraring), used anaesthetics not stated, manual or femtosecond laser tunnel creation	ICRS (Intacs® and Keraring), topical anaesthetics, manual or femtosecond laser tunnel creation
Comparator	None	None	None	None	None
Number of eyes/pts.	50/37	59/n/a	100/82	250/n/a[22]	Total: 168/119 Keraring: 100/77 Intacs®: 68/42
Age of patients (yrs.)	20-69[23]	n/a	n/a	Ø 37 (17-64)	Total: Ø 26 (18-57) Keraring: Ø 26 (18-57) Intacs®: Ø 26 (18-45)
Sex (% female)	30	n/a	35	49	Total: 48 Keraring: 47 Intacs®: 50

[19] It is not stated whether the study was conducted pro- or retrospectively. Contacting the authors did not bring a result. However, the study seems to be prospective.

[20] The study was conducted as a controlled trial comparing two products of intrastromal corneal ring implants (Intacs® and Keraring). However, for the purposes of this review each study group was analysed separately and therefore the study was considered a single-arm study.

[21] Authors declare no financial interest. However, the first author is a consultant of the manufacturer.

[22] The study evaluated ICRS that were explanted in several centres in Spain during 2000 and 2008. A total of 250 implantations were performed during this period. The rates regarding age and sex refer to the patients with ICRS explantations.

[23] Mean age was not stated.

Author, year, reference number	Hellstedt 2005 [22]	Colin 2006 [21]	Colin 2007 [24]	Ferrer 2010[25]	Kubaloglu2010 [23]
Clinical classification	n/a	Grade I-II	Grade I-III	n/a[24]	Grade I-IV
Primary endpoint(s)	n/a	Safety of the device, maintenance of BCVA, improvement in UCVA, reduction in manifest refraction spherical equivalent, reduction in asymmetric astigmatism	Adverse events, visual acuity outcome, determine the efficacy of the segments	n/a	n/a
Inclusion criteria	Patients with: keratoconus, clear central cornea and contact lens intolerance, BSCVA of ≥20/100 in the treatment eye, corneal thickness of ≥400 µm	n/a	Patients had been referred for a PKP procedure due to contact lens intolerance, with Amsler-Krumeich grades I, II, and III keratoconus + no central corneal opacities or scarring	n/a[25]	Patients with keratoconus, clear central cornea and contact lens intolerance
Follow-up (months)	12 (Ø 6.3)[26]	12[27]	24	96 (8 yrs.)	12[28]
Loss to follow-up, n (%) of eyes	38 (76)	25 (42)[29]	18 (18)	n/a[30]	53 (32)
Efficacy-related outcomes					
Length of hospital stay/time to work resumption in days	n/a	n/a	n/a	n/a	n/a
Re-operation rate in % (n) eyes	22 (11)[31]	12 (7)[32]	4 (4)[33]	23 (57)[34]	n/a

[24] The majority of patients had primary keratoconus (80%), post-LASIK ectasia (12%), marginal pellucid degeneration (5%), previous keratoplasty (1.5%) or myopia (1.5%).

[25] Since the study evaluated all patients with an explantation of intrastromal corneal ring segments, no inclusion criteria were needed.

[26] Follow-up was up to 12 months. However, 8 patients (10 eyes) were followed up for more than 12 months.

[27] Most outcomes (especially adverse events) were reported after 6 months.

[28] Follow-up was at least six months for all eyes/patients and up to 12 months for some eyes/patients.

[29] This contains only eyes that were lost to follow-up until the 6th month of follow-up. Reasons for drop-outs not stated.

[30] Actually, study duration (or follow-up) was 8 years to evaluate the reasons of explantations; therefore, a loss to follow-up is not applicable, plus the duration of follow-up does not apply for all patients.

[31] Segments/rings were removed in 4 eyes (8%) and adjusted in 7 eyes (14%).

[32] Segments/rings were partially or totally removed in 7 eyes (12%).

[33] Segments/rings were removed in 4 eyes (4%).

[34] Segments/rings were removed in 57 eyes (23%). However, the number of reoperations was not investigated in this study.

Author, year, reference number	Hellstedt 2005 [22]	Colin 2006 [21]	Colin 2007 [24]	Ferrer 2010[25]	Kubaloglu2010 [23]
Change of visual acuity	*UCVA (improved/ worsened % of eyes)*[35]: After 1, 3 months: n/a After 6 months: 73/7; p=n/a After 12, 24 months: n/a *BCVA (improved/ worsened % of eyes)*[36]: Baseline: - After 1 month: 26/8; p=n/a After 3 months: 41/8; p=n/a After 6 months: 39/12; p=n/a After 12 months: 42/8; p=n/a After 24 months: n/a	*UCVA(improved/ worsened % of eyes)*[36]: Baseline: - After 1, 3 months: n/a After 6 months: 79/0; p<0.001 from baseline After 12, 24 months: n/a *BCVA(improved/ worsened % of eyes)*[36]: Baseline: - After 1, 3 months: n/a After 6 months: 62/6; p<0.001 from baseline After 12, 24 months: n/a	*UCVA (improved/ worsened % of eyes)*[35]: Baseline: - After 1, 3, 6 months: n/a After 12 months: 69/9; p<0.001 from baseline After 24 months: 81/5; p<0.001 from baseline *BCVA(improved/ worsened % of eyes)*[35]: Baseline: - After 1, 3, 6 months: n/a After 12 months: 61/12; p<0.001 from baseline After 24 months: 68/15; p<0.001 from baseline	n/a	*UCVA (improved/ worsened % of eyes)*[35]: Baseline: - After 1, 3, 6 months: n/a After 12 months: Keraring: 83/7; p=n/a Intacs®: 82/7; p=n/a After 24 months: n/a *BCVA(improved/ worsened % of eyes)*[35]: Baseline: - After 1, 3, 6 months: n/a After 12 months: Keraring: 85/4; p=n/a Intacs®: 82/7; p=n/a After 24 months: n/a
Quality of life (health- or vision-related)	*Change of Visual Function-7 score*[37] *(improved/worsened % of pts.):* Baseline: - After 1, 3 months: n/a After 6 months: 88.5/11.5 After 12, 24 months: n/a	*Quality of vision (poor/fair/good/excellent in % of pts.):* Baseline: 70/20/10/0 After 1, 3 months: n/a After 6 months: 24/29/38/9; P<0.001 from baseline After 12, 24 months: n/a	n/a	n/a	n/a
Patient satisfaction	*Change of self-reported satisfaction with vision (improved/worsened % of pts.):* Baseline: - After 1, 3 months: n/a After 6 months: 73/8 After 12, 24 months: n/a	n/a	n/a	n/a	n/a

[35] Improvement/declining were considered as change of 1 Snellen line and more.

[36] Improvement/declining were considered as change of 2 Snellen lines and more.

[37] Questionnaire is based on 7 items (no further information found).

Author, year, reference number	Hellstedt 2005 [22]	Colin 2006 [21]	Colin 2007 [24]	Ferrer 2010[25]	Kubaloglu2010 [23]
Safety-related outcomes					
Adverse events, general in % (n) eyes	16 (8)	15 (9)[38]	2 (2)	n/a	Keraring: 7 (7) Intacs®: 10 (7)
Adverse events, intra-operative in % (n) eyes	2 (1) (difficulty in forming intrastromal tunnel)	0(0)	0 (0)	n/a	Keraring: 1 (1) Intacs®: 0 (0) (anterior perforation)
Adverse events, post-operative in % (n) eyes	14 (7) (external infection, segment migration, surgical aim not achieved)	15 (9) (discomfort, glare, itching, burning, photophobia, difficulty with night vision, fluctuating vision)	2 (2) (extrusion of a segment)	23 (57) (extrusion, refractive failure, corneal melting, corneal perforation)	Keraring: 6 (6) Intacs®: 10 (7) (extrusion, decentration, shallow placement)

Abbreviations: BCVA = best-corrected visual acuity; BSCVA = best spectacle-corrected visual acuity; ICRS = intrastromal corneal ring segments; PKP = penetrating keratoplasty; n = number; n/a = not applicable; pts. = patients; UCVA = uncorrected visual acuity; yrs. = year

Risk of bias tables

The internal validity of the included studies was judged by two independent researchers. In case of disagreement, a third researcher was involved to solve the differences. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in the Internal Manual of the LBI-HTA and in the Guidelines of EUnetHTA [26].

Table A2-1: Risk of bias – study level of single-arm studies

18 criteria checklist: critical appraisal single-arm studies	Hellstedt 2005	Colin 2006	Colin 2007	Ferrer 2010	Kubaloglu 2010
Study objective					
Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	Yes	Yes	Yes	Yes	Yes
Study population					
Are the characteristics of the participants included in the study described?	Yes	No[39]	No[40]	No[41]	Yes

[38] Complications were counted in patients and not in eyes. However, the rates were based on the number of eyes.

[39] The number, age and sex of patients were not stated.

[40] The age of patients was not stated.

[41] The number of patients was not stated.

18 criteria checklist: critical appraisal single-arm studies	Hellstedt 2005	Colin 2006	Colin 2007	Ferrer 2010	Kubaloglu 2010
Were the cases collected in more than one centre?	No	Yes	No	Yes	No
Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?	Yes	No[42]	Yes	n/a[43]	Yes
Were participants recruited consecutively?	Yes	Yes	Yes	Yes	Yes
Did participants enter the study at similar point in the disease?	Yes	Unclear	Yes	No[44]	Yes
Intervention and co-intervention					
Was the intervention clearly described in the study?	Yes	Yes	Yes	No	Yes
Were additional interventions (co-interventions) clearly reported in the study?	Yes	Yes	Yes	No	Yes
Are the outcome measures clearly defined in the introduction or methods section?	Yes	Yes	Yes	Yes	Yes
Were relevant outcomes appropriately measured with objective and/or subjective methods?	Yes	Yes	Yes	Yes	Yes
Were outcomes measured before and after intervention?	Yes	Yes	Yes	n/a[45]	Yes
Statistical analysis					
Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	n/a[46]	Yes	n/a[46]	Yes
Results and conclusions					
Was the length of follow-up reported?	Yes	Yes	Yes	Yes	Yes
Was the loss to follow-up reported?	No[47]	Yes	Yes	n/a[48]	No[47]
Does the study provide estimates of the random variability in the data analysis of relevant outcomes?[49]	n/a	n/a	n/a	n/a	n/a
Are adverse events reported?	Yes	Yes	Yes	Yes	Yes
Are the conclusions of the study supported by results?	Yes	Yes	Yes	Yes	Yes
Competing interests and sources of support					
Are both competing interests and sources of support for the study reported?	Yes	No[50]	No[50]	Yes	Yes

[42] The inclusion criteria were not stated.

[43] Since the study evaluated all patients with an explantation of intrastromal corneal ring segments, no inclusion criteria were needed.

[44] The majority of patients had keratoconus, whereas several patients had other diseases.

[45] Study investigated only explantations/removals of intrastromal corneal ring segments.

[46] There was no description whether a statistical test was performed or not.

[47] The loss to follow-up was not clearly mentioned.

[48] Study duration was 8 years to evaluate the reasons of explantations, therefore a loss to follow-up is not applicable, plus the duration of follow-up does not apply for all patients.

[49] This criterion was not applicable for the relevant outcomes that were used for recommendation.

[50] Authors declared no financial interest. However, first author is a consultant of the manufacturer and the editor of the journal.

Table A2-2: Risk of bias – outcome level of single-arm studies (crucial outcomes used for recommendation)

Outcome Trial	Risk of bias – study level	Blinding – outcome assessors	ITT principle adequately realised	Selective outcome reporting likely	Other aspects according to risk of bias	Risk of bias – outcome level
Change of visual acuity (UCVA/BCVA: improved/worsened % of eyes)						
Hellstedt 2005	Low	Not possible	High	Low	Low	Low
Colin 2006	Low	Not possible	High	Low	Low	Low
Adverse events (intra- and post-operative)						
Hellstedt 2005	Low	Not possible	High	Low	Low	Low
Colin 2006	Low	Not possible	High	High[51]	High[52]	High
Colin 2007	Low	Not possible	High	Low	High[52]	High
Ferrer 2010	Low	Not possible	High	Low	Low	Low
Kubaloglu 2010	Low	Not possible	High	Low	Low	Low

[51] Study says: "ocular observations at all postoperative examinations were minor and were not considered clinically significant by the investigators".

[52] The first author is the editor of the journal the study was published in.

Applicability table

Table A3-1: Summary table characterising the applicability of a body of studies (single-arm studies)

Domain	Description of applicability of evidence
Population	None of the studies distinguished between male and female or young or elderly patients when recruiting patients for the study. The majority of patients had keratoconus, with grades I-IV (stated in three studies). One study included also (a few) patients with other diseases than keratoconus (e.g., myopia). There was no study that exclusively included patients with post-LASIK corneal ectasia. The inclusion criteria and the population in the studies seem to be in accordance with the intended patient population for the technology.
Intervention	The implantation of intrastromal corneal implants was performed using commercially available devices. Patients in the included studies received either Intacs® or Keraring. The devices were either inserted under general or topical anaesthetics. In the majority of studies the tunnel creation for inserting the implants was performed manually or by using a femtosecond laser.
Comparators	To date, there are no published studies in which intrastromal corneal implants have been compared with corneal transplantation or no intervention.
Outcomes	A range of clinically relevant outcome criteria were applied in the studies and have shown objective and/or subjective benefits from intrastromal corneal implants for the treatment of keratoconus. However, due to limited data, especially lack of comparative data, it is not possible to evaluate the clinical effectiveness of intrastromal corneal implants for the treatment of keratoconus or post-LASIK corneal ectasia. For the assessment of safety, intra- and/or post-operative adverse events were recorded.
Setting	With one exception, the studies were carried out in Europe: in Finland, France, Germany and Spain. One study was carried out in Turkey. Patients were recruited from and the operations were performed at ophthalmologic centres in- or outpatiently. Study centres had experience in the technology used, as well as in clinical research in general. The settings of the studies reflects the clinical setting in which the technology is intended to be used in an appropriate way.

Search strategies

Medline via OVID

Database: Ovid MEDLINE(R) <1946 to November Week 3 2014>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <December 24, 2014>, Ovid MEDLINE(R) Daily Update <November 19, 2014>, Ovid OLDMEDLINE(R) <1946 to 1965>	
Search Strategy:	
1	exp Keratoconus/(3681)
2	keratoconu*.mp. (4770)
3	keratoconi*.mp. (517)
4	cornea* ectasia*.mp. (378)
5	iatrogenic cornea*.mp. (17)
6	exp Iatrogenic Disease/(13521)
7	exp Corneal Diseases/(41837)
8	6 and 7 (117)
9	keratectasia*.mp. (192)
10	1 or 2 or 3 or 4 or 5 or 8 or 9 (5150)
11	((intracornea* or intra-cornea* or intrastroma* or intra-stroma*) adj5 ring*).mp. (404)
12	ICRS.mp. (557)
13	ferrara ring*.mp. (16)
14	intacs.mp. (197)
15	(cornea* adj5 implant*).mp. (1154)
16	Addition Technolog*.mp. (93)
17	Keraring*.mp. (44)
18	Mediphacos.mp. (23)
19	Bisantis.mp. (0)
20	Optikon.mp. (32)
21	*Eye, Artificial/(961)
22	*"Prostheses and Implants"/(26657)
23	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 20 or 21 or 22 (29023)
24	10 and 23 (345)
25	exp Clinical Trial/or double-blind method/or (clinical trial* or randomized controlled trial or multicenter study).pt. or exp Clinical Trials as Topic/or ((randomi?ed adj7 trial*) or (controlled adj3 trial*) or (clinical adj2 trial*) or ((single or doubl* or tripl* or treb*) and (blind* or mask*))).ti,ab. (1246098)
26	((systematic adj3 literature) or systematic review* or meta-analy* or metaanaly* or "research synthesis" or ((information or data) adj3 synthesis) or (data adj2 extract*)).ti,ab. or (cinahl or (cochrane adj3 trial*) or embase or medline or psyclit or (psycinfo not "psycinfo database") or pubmed or scopus or "sociological abstracts" or "web of science").ab. or "cochrane database of systematic reviews".jn. or ((review adj5 (rationale or evidence)).ti,ab. and review.pt.) or meta-analysis as topic/or Meta-Analysis.pt. or review.pt. (2093955)
27	25 or 26 (3130953)
28	24 and 27 (77)
29	remove duplicates from 28 (73)
Search date: 29th December 2014	

EMBASE

No.	Query Results	Results	Date
#24	intracornea* OR 'intra-cornea' OR 'intra-corneal' OR intrastroma* OR 'intra-stroma' OR 'intra-stromal') NEAR/5 ring* OR (icrs NOT knee*) OR ferrara:dn OR intacs OR cornea* NEAR/5 implant* OR 'addition technology' OR 'addition technologies' OR keraring* OR mediphacos OR bisantis OR optikon OR 'visual prosthesis'/mj AND ([cochrane review]/lim OR [systematic review]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim OR [meta analysis]/lim)	111	29 Dec 2014
#22	(intracornea* OR 'intra-cornea' OR 'intra-corneal' OR intrastroma* OR 'intra-stroma' OR 'intra-stromal') NEAR/5 ring* OR (icrs NOT knee*) OR ferrara:dn OR intacs OR cornea* NEAR/5 implant* OR 'addition technology' OR 'addition technologies' OR keraring* OR mediphacos OR bisantis OR optikon OR 'visual prosthesis'/mj	3,484	29 Dec 2014
#21	'visual prosthesis'/mj	1,085	29 Dec 2014
#20	optikon	94	29 Dec 2014
#19	bisantis	45	29 Dec 2014
#18	mediphacos	54	29 Dec 2014
#17	keraring*	56	29 Dec 2014
#16	'addition technologies'	16	29 Dec 2014
#15	'addition technology'	121	29 Dec 2014
#14	cornea* NEAR/5 implant*	1,568	29 Dec 2014
#13	intacs	247	29 Dec 2014
#12	ferrara:dn	16	29 Dec 2014
#11	icrs NOT knee*	512	29 Dec 2014
#10	(intracornea* OR 'intra-cornea' OR 'intra-corneal' OR intrastroma* OR 'intra-stroma' OR 'intra-stromal') NEAR/5 ring*	464	29 Dec 2014
#5	iatrogenic NEAR/1 cornea*	27	29 Dec 2014
#4	cornea* NEAR/1 ectasia*	452	29 Dec 2014
#3	keratoconi*	522	29 Dec 2014
#2	keratoconu*	5,717	29 Dec 2014
#1	'keratoconus'/exp	5,227	29 Dec 2014

Cochrane Library

Search Name: ICRS for Keratoconus Last Saved: 29/12/2014 23:17:51.127	
ID	Search
#1	MeSH descriptor: [Keratoconus] explode all trees
#2	keratoconu* (Word variations have been searched)
#3	keratoconi* (Word variations have been searched)
#4	cornea* near ectasia* (Word variations have been searched)
#5	iatrogenic cornea* (Word variations have been searched)
#6	MeSH descriptor: [Iatrogenic Disease] explode all trees
#7	MeSH descriptor: [Corneal Diseases] explode all trees
#8	#6 and #7
#9	keratectasia* (Word variations have been searched)
#10	#1 or #2 or #3 or #4 or #5 or #8 or #9
#11	(intracornea* or intra-cornea* or intrastroma* or intra-stroma*) near ring* (Word variations have been searched)
#12	ICRS (Word variations have been searched)
#13	ferrara* near ring* (Word variations have been searched)
#14	intacs (Word variations have been searched)
#15	cornea* near implant* (Word variations have been searched)
#16	"Addition Technology" (Word variations have been searched)
#17	Keraring* (Word variations have been searched)
#18	Mediphacos (Word variations have been searched)
#19	Bisantis (Word variations have been searched)
#20	Optikon (Word variations have been searched)
#21	MeSH descriptor: [Eye, Artificial] explode all trees
#22	MeSH descriptor: [Prostheses and Implants] this term only
#23	#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22
#24	#10 and #23
33 Hits	

CRD (DARE-NHS EED-HTA)

#### ICRS for Keratoconus	
1	MeSH DESCRIPTOR Keratoconus EXPLODE ALL TREES
2	(keratocon*)
3	(cornea* NEAR ectasia*)
4	(iatrogeniccornea*)
5	(keratectasia*)
6	#1 OR #2
24 Hits	

Ongoing studies

Source	Trial ID	Title	Recruitment	Study Results	Start Date	Completion Date	Number of patients	Study design
ClinicalTrials.gov	NCT01869517	Myoring Versus Keraring Implantation for Keratoconus	Recruiting	No Results Available	May 2013	n/a	23	RCT
ClinicalTrials.gov	NCT00347230	Intacs for Keratoconus	Recruiting	No Results Available	October 2005	n/a	20	Single-arm study
ClinicalTrials.gov	NCT01261013	Intrastromal Corneal Ring Segment Implantation in 219 Keratoconic Eyes at Different Stages	Completed	No Results Available	January 2008	March 2010	219	Single-arm study
ClinicalTrials.gov	NCT00832897	Evaluation of Topical Riboflavin Exposed to UVA Radiation and Implantation of Corneal Ring	Completed	No Results Available	March 2008	October 2010	31	RCT
ClinicalTrials.gov	NCT01112072	Corneal Collagen Crosslinking and Intacs for Keratoconus and Ectasia	Recruiting	No Results Available	April 2010	December 2015	160	RCT
WHO-ICTRP	IRCT201402251 6738N1	Comparison of two types of rings in treatment of keratoconus	Recruiting	n/a	April 2014	n/a	76	RCT