Aanbevelingen voor het gebruik van vijf oftalmologische testen in de klinische praktijk

KCE reports 71A

Federaal Kenniscentrum voor de Gezondheidszorg
Centre fédéral d'expertise des soins de santé
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Belangenconflicten :	Prof Rakic verklaart te hebben deelgenomen aan klinische studies over de behandeling van leeftijdsgebonden macula degeneratie. Andere conflicten werden niet gemeld.
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VOORWOORD

Oftalmologie of oogheelkunde heeft een geschiedenis die terug gaat tot de oudheid. Al omstreeks 1600 voor Christus werden verscheidene oogaandoeningen, zoals cataract en trachoma, beschreven. Maar hoewel er al cataract operaties plaats vonden in India meer dan 2000 jaar geleden, was het toch pas in het West-Europa van de 19e eeuw dat de oftalmologie een stevige wetenschappelijke basis kreeg.

De snelle opmars van testen en behandelingen in de oftalmologie ging evenwel niet altijd gepaard met een systematische reflectie over de werkzaamheid en doelmatigheid ervan in de praktijk. Evidence-based medicine begint langzaam zijn intrede te doen in de Belgische oftalmologie.

Dit rapport ontwikkelt aanbevelingen voor de goede praktijk voor vijf oftalmologische testen, op basis van een systematisch overzicht van de literatuur. Het gaat hierbij niet om een kookboek dat de vrijheid van artsen inperkt, maar wel om het in vraag stellen van dogma's of tradities op basis van wetenschappelijke bewijzen.

Deze oefening werd maar mogelijk dankzij de gewaardeerde medewerking van een panel van klinische experten, die de evidence gewogen hebben in functie van de dagelijkse, Belgische oftalmologische praktijk. Dit om uiteindelijk te komen tot goed gefundeerde aanbevelingen die hopelijk als een nuttig instrument zullen worden ervaren door de Belgische oftalmologen. De beroepsgroep wacht nu de uitdaging om deze richtlijnen verder te ontwikkelen en te implementeren.

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SAMENVATTING

INLEIDING

De diagnostische en therapeutische mogelijkheden in oftalmologie zijn de laatste decennia enorm toegenomen. Anderzijds verwacht men op korte termijn een verdere stijging van de prevalentie van oogaandoeningen zoals diabetische retinopathie, cataract, leeftijdsgebonden macula degeneratie en glaucoom.

Er bestaan diverse methoden en procedures voor de diagnose en monitoring van oog- en gezichtsstoornissen. In België worden 24 oftalmologische diagnostische tests (ODTs) terugbetaald. Tot dusver bestaan er geen richtlijnen die specifiek rekening houden met de Belgische context.

Het doel van dit rapport was aanbevelingen voor de praktijk op te stellen voor een selectie van tests, gebaseerd op de huidige evidence en rekening houdend met de Belgische context.

GEBRUIK VAN ODT IN BELGIË

Het gebruik van alle ODTs werd geanalyseerd op basis van gegevens van het Rijksinstituut voor Ziekte en Invaliditeitsverzekering (RIZIV) en de ziekenfondsen over de periode van 1995 tot 2005.

De meest gebruikte ODTs waren binoculaire biomicroscopie van het voorste oogsegment, dynamometrie/tonometrie, en binoculaire oftalmoscopie.

Het gebruik van de meeste ODTs is stabiel gebleven tussen 1995 en 2005. Terugbetaling voor binoculaire biomicroscopie van het voorste oogsegment werd in juli 1999 van kracht; dat verklaart een onmiddellijke stijging gevolgd door een stabieler gebruik. Gelijkaardige effecten werden gevonden voor biometrie van het oog (ingevoerd in 2001) en computer perimetrie (geïntroduceerd in 1999). Binoculaire oftalmoscopie verviervoudigde bijna tussen 1995 en 2005. Het gebruik van andere tests daalde aanzienlijk: biomicroscopie van het achterste oogsegment, humero-retinale circulatietijd, perimetrie, drukcurve, en één- en tweedimensionele echografie van het oog.

In bijna 75% van de gevallen werd in de periode 2002-2005 één van de volgende drie combinaties uitgevoerd:

- dynamometrie/tonometrie + binoculaire biomicroscopie voorste oogsegment,
- binoculaire oftalmoscopie + binoculaire biomicroscopie voorste oogsegment,
- dynamometrie/tonometrie + binoculaire biomicroscopie voorste oogsegment + kwantitatieve computer perimetrie.

De invoering van de terugbetaling van binoculaire biomicroscopie van het voorste oogsegment en computer perimetrie had een belangrijk effect op de totale kosten van alle ODTs voor de ziekteverzekering. Tussen 1995 en 2005 zijn deze verdrievoudigd van 16,3 miljoen euro tot 49,3 miljoen euro. Ter vergelijking, de totale uitgaven voor alle gezondheidskosten stegen met 64,4% van 10,2 miljard euro in 1995 tot 16,8 miljard euro in 2005.

SYNTHESE VAN DE EVIDENCE

Voor elk onderdeel werd de literatuur doorzocht in Medline en Embase. Artikels werden geselecteerd volgens vooraf gespecificeerde criteria, en op kwaliteit beoordeeld met behulp van gestandaardiseerde checklists.

TELLING VAN ENDOTHEELCELLEN VOOR CATARACTCHIRURGIE

Het cornea-endotheel is een enkele cellaag die het binnenoppervlak van de cornea bedekt. Elk direct trauma of letsel van de endotheelcellaag resulteert in een daling van het aantal cellen. Aangezien de endotheelcellaag slecht regenereert, heeft elke vermindering van de endotheelcelvoorraad een invloed op het vermogen van het endotheel om verder trauma te weerstaan.

De endotheelceldensiteit (ECD) van de cornea wordt gemeten in cellen/mm², welke kan worden vergeleken met een vroeger gedocumenteerde densiteit voor die persoon of met een gemiddelde waarde van een populatie met dezelfde leeftijd. Ook bij een lage densiteit kunnen de resterende endotheelcellen voorkomen dat de cornea gaat zwellen tot er een kritische drempel wordt bereikt die geschat wordt op 500-1000 cellen/mm².

Het RIZIV betaalt de ECD meting terug voor de pre-operatieve voorbereiding van chirurgische ingrepen op het voorste oogsegment. In 2005 werden 46.915 tests terugbetaald. Ongeveer de helft van de patiënten met één of twee cataractingrepen tussen 2002 en 2005 ondergingen een ECD meting in de zes maanden voor of na de eerste cataractinterventie, waarbij die met één cataractinterventie meestal één meting hadden en het gros van de patiënten met twee interventies twee metingen ondergingen.

TECHNISCHE PRECISIE

De technische precisie is waarschijnlijk voldoende. De reproduceerbaarheid van de microscopen, zowel intra- als interobservator, is het meeste bestudeerd, met limits of agreement van ±250 cellen/mm².

DIAGNOSTISCHE PRECISIE

Er was slechts één studie die twee soorten spiegelmicroscopen vergeleek, deze vond geen significant verschil tussen de twee.

IMPACT OP DE PATIËNT

Er was geen directe evidence voor de evaluatie van de impact van een ECD meting bij patiënten voor cataractchirurgie. Er is indirecte evidence dat een lage preoperatieve ECD niet als uitsluitings criterium wordt gebruikt in klinische studies van cataractchirurgie. Bovendien zijn er tussen de verschillende cataractingrepen geen significante verschillen op postoperatief endotheliaal celverlies vastgesteld. Cornea decompensatie is uiterst zeldzaam in moderne cataractchirurgie. In alle studies die in de Cochrane review van cataractchirurgie zijn opgenomen zijn slechts drie gevallen geïdentificeerd. Maar de follow-up in deze studies is misschien onvoldoende om alle gevallen op lange termijn te identificeren. Er zijn geen studies over de prognostische waarde van de ECD meting voor gevolgen op lange termijn geïdentificeerd.

Een lage preoperatieve densiteit kan een reden zijn om een andere oftalmische visco-elastische substantie te kiezen, omdat aangenomen wordt dat sommige substanties een hoger beschermend effect hebben op de cornea. Dit werd geëvalueerd in een afzonderlijk literatuur overzicht. In totaal werden 34 artikels in het overzicht opgenomen, welke 22 verschillende viscoelastische substanties evalueren. Dertig studies vonden geen significant verschil in bescherming tegen endotheelcelverlies. De andere vier studies vonden een significant verschil tussen twee of meer substanties. Deze verschillen waren klinisch heterogeen en zelfs tegenstrijdig. Een meta-analyse van

directe en indirecte vergelijkingen toont aan dat het verschil tussen de substanties in celverlies kleiner is dan 100 cellen/mm², wat erop wijst dat het beschermend effect van de verschillende substanties ongeveer gelijk is.

HET SCHEIMPFLUG IMAGING SYSTEEM VOOR SUBKLINISCHE KERATOCONUS

Het Scheimpflug imaging systeem is een methode die 3D-beelden van het voorste oogsegment maakt, zonder rechtstreeks contact met het oog. Het systeem kan topografische analyses maken van de voor- en achterzijde van de cornea, analyse en kwantificatie van de dikte van de cornea en van de lensopacificatie, en het kan veranderingen van de cornea voor en na refractieve chirurgie vergelijken. De Scheimpflug wordt momenteel niet terugbetaald door de Belgische ziekteverzekering. Ons rapport focust op het gebruik van de Scheimpflug voor de screening van keratoconus bij patiënten die gepland staan voor refractieve chirurgie, zoals voorgesteld door de klinische experten betrokken bij dit rapport.

Keratoconus is een niet-inflammatoire ectatische dystrofie gekenmerkt door een progressief verdunnende, steiler wordende en apicale protrusie van de cornea wat resulteert in onregelmatig astigmatisme en myopie. Patiënten met keratoconus zijn ontevreden over hun visuscorrectie wat leidt tot zelfselectie voor refractieve chirurgie (1 tot 6% van chirurgiekandidaten). Maar keratoconus is een contraindicatie voor refractieve chirurgie omdat deze patiënten een slecht resultaat hebben en na corneachirurgie een progressieve cornea-ectasie kunnen ontwikkelen.

De meeste gevallen van keratoconus worden gediagnosticeerd of gedetecteerd met bestaande tests. *Matige tot ernstige* keratoconus wordt gewoonlijk gediagnosticeerd door klassiek visueel onderzoek met keratometrie en spleetlamp biomicroscopie. *Beginnende en milde* keratoconus is met deze tests soms moeilijk te detecteren, maar zelfs zeer milde gevallen worden gevonden door corneale computertopografie of pachymetrie via ofwel een direct-contact echografisch onderzoek, of een non-contact methode zoals een 'scanning optical slit device'. Een *subklinische* keratoconus is met deze bestaande instrumenten niet te detecteren; de vraag voor deze review was of de Scheimpflug wel in staat is om een subklinische keratoconus te detecteren.

TECHNISCHE PRECISIE

De intra- en interobservator variabiliteit is bevredigend en er is een goede correlatie tussen de Scheimpflug en de echo-pachymetrie voor meting van de centrale dikte van de cornea.

DIAGNOSTISCHE PRECISIE

Er werd één klinische studie gevonden over de detectie van keratoconus bij kandidaten voor refractieve chirurgie. Deze case-control studie toonde aan dat de Scheimpflug in staat is patiënten met milde of matige keratoconus te onderscheiden van normale patiënten. Er zijn tot dusver geen publicaties over subklinische keratoconus met de Scheimpflug. De rol van deze recente technologie moet opnieuw worden geëvalueerd als er nieuwe evidence verschijnt.

IMPACT OP DE PATIËNT

Er zijn geen studies gevonden die de impact van de Scheimpflug op de uitkomst van de patiënt direct evalueren. Bovendien is er geen indirect bewijs dat de Scheimpflug wordt gebruikt om patiënten uit te sluiten van refractieve corneachirurgie.

TESTS VOOR LEEFTIJDSGEBONDEN MACULADEGENERATIE

Leeftijdsgebonden macula degeneratie (AMD) is de meest voorkomende oorzaak van blindheid en ernstige gezichtsstoornis in geïndustrialiseerde landen. AMD is een ziekte van de retina gekenmerkt door opstapeling van metabole producten in de macula. Het veroorzaakt gezichtsstoornissen zoals een vertroebeling van het centrale deel van het gezichtsveld, wat uiteindelijk leidt tot een donkere vlek. Leeftijd, familiale antecedenten en roken zijn bekende risicofactoren.

Men onderscheidt vroegtijdig AMD, intermediair AMD en gevorderd AMD. De laatste categorie is onderverdeeld in geografische atrofie en neovasculaire maculopathie. De neovasculaire vorm is verantwoordelijk voor 80-90% van gevallen van ernstig visusverlies en wordt verder geclassificeerd volgens type en locatie van de lekkage zoals gevisualiseerd met fluoresceïne-angiografie.

FLUORESCEÏNE-ANGIOGRAFIE

Bij fluoresceïne-angiografie wordt een fluorescente kleurstof intraveneus ingespoten waarna de distributie in de bloedvaten van het oog wordt gevolgd. Een groot risico zijn anafylactische reacties die in ongeveer 1 op 200.000 patiënten fataal aflopen.

Technische precisie

De interobservator overeenkomst is matig gebleken en daalt naarmate het lekkagepatroon complexer wordt. Expertisecentra hebben een betere intra- en interobservator overeenkomst.

Diagnostische precisie

Er zijn geen diagnostische precisiestudies geïdentificeerd. Maar de fluoresceïne-angiografie wordt beschouwd als de gouden standaard voor choroïdale neovascularisatie.

Impact op de patiënt

Er zijn geen studies gevonden die de impact op de patiënt direct evalueren. Er is indirect bewijs dat fluoresceïne-angiografie wordt gebruikt als een selectiemiddel voor behandeling met bewezen effectiviteit, namelijk fotodynamische therapie en anti-angiogenese therapie met pegaptanib en ranibizumab, aangezien type en locatie van de door fluoresceïne-angiografie gedocumenteerde lekkage de therapeutische mogelijkheden bepalen. Fotodynamische therapie wordt direct geleid door de resultaten van de fluoresceïne-angiografie. Bovendien hebben het patroon en de locatie van de lekkage een prognostische waarde.

INDOCYANINE GROEN-ANGIOGRAFIE

Net als fluoresceïne-angiografie wordt indocyanine groen-angiografie uitgevoerd met een intraveneuze kleurstof, met dezelfde risico's op anafylactische reacties. De grotere ICG molecule visualiseert de choroïdale circulatie. Ze absorbeert en emitteert infrarood licht meer dan fluoresceïne-angiografie en kan dus nog door tamelijk dik bloed beelden vormen. ICGA wordt momenteel niet terugbetaald.

Technische precisie

Er is een goede interobservator overeenkomst voor indocyanine groen videoangiografie. Voor occulte neovascularisatie is de interobservator overeenkomst beter voor indocyanine dan voor fluoresceïne-angiografie. De interobservator overeenkomst is matig voor detectie van sereus-pigment-epitheelloslating met choroïdale neovasculaire membranen.

Diagnostische precisie

Studies hebben aangetoond dat indocyanine groen bijkomende informatie kan detecteren bij patiënten met occulte neovascularisatie zoals gedocumenteerd door fluoresceïne-angiografie. Deze bijkomende informatie omvat angiomateuze netvliesproliferatie ('retinal angiomatous proliferation') en polypoïdale choroïdale vasculopathie ('polypoidal choroidal vasculopathy').

Impact op de patiënt

Er zijn geen studies geïdentificeerd die de impact van indocyanine groen-angiografie op het patiëntresultaat direct evalueren. Bovendien is er geen indirecte evidence over het gebruik van indocyanine groen-angiografie voor de selectie van patiënten in therapeutische studies voor AMD.

ICGA kan prognostische informatie leveren. Patiënten gediagnosticeerd met neovascularisatie van pigmentepitheelloslating hebben een slechtere visuele prognose dan patiënten met klassieke neovascularisatie. De neovascularisatie van pigmentepitheelloslating wordt zichtbaar gemaakt door indocyanine groen-angiografie.

OPTISCHE COHERENTIE TOMOGRAFIE

Optische coherentie tomografie (OCT) is een niet-invasieve techniek om intraoculaire weefsels te visualiseren door meting van de echolatentie en intensiteit van gereflecteerd licht. Het resulterende beeld is een hoge-resolutie doorsnede van de structuur met bijna histologisch detail. Het is makkelijk uit te voeren en zonder risico voor de patiënt, en vormt hierdoor een aantrekkelijk alternatief voor fluoresceïne-angiografie. De OCT is momenteel niet terugbetaald.

Technische precisie

Onze literatuurzoektocht heeft geen studies gevonden over de interobservator overeenkomst.

Diagnostische precisie

De OCT kan een cystoïd maculair oedeem detecteren, wat moeilijk te detecteren is met fluoresceïne-angiografie. Bovendien heeft de OCT een sensitiviteit van 96% en een specificiteit van 66% om choroïdale neovascularisatie te ontdekken.

Een recente studie vond dat intraretinaal en subretinaal vocht op OCT een gevoeligheid heeft van 97% voor detectie van CNV activiteit, vergeleken met lekken op fluoresceïne-angiografie.

Impact op de patiënt

Er is geen direct bewijs voor de invloed van OCT op de uitkomst van de patiënt. Er is dan gezocht naar indirect bewijs: geen enkele van de grote studies over fotodynamische therapie en anti-angiogenese therapie gebruikten de OCT als selectiecriterium voor opname in de studie. Bovendien wordt de OCT niet vermeld in de methoden als een follow-up test om de behandeling te sturen. Er werd een zwakke correlatie gevonden tussen lekken op de fluoresceïne-angiografie en subretinaal vocht op OCT. Het is niet duidelijk wat het effect op de patiënt is als de OCT wordt gebruikt om te beslissen of de patiënt al dan niet behandeld wordt.

AANBEVELINGEN VOOR DE KLINISCHE PRAKTIJK

METHODOLOGIE

Op basis van de evidence die in de formele evaluatie van de geselecteerde tests is verzameld heeft een monodisciplinair klinisch expertisepanel klinische praktijkrichtlijnen geformuleerd.

Elke aanbeveling werd een graad toegekend, gebaseerd op de richtlijnen van de GRADE werkgroep[227]. De GRADE richtlijnen zijn opgebouwd rond 2 assen: het niveau van evidence dat verkregen is voor een bepaalde klinische vraag, en het evenwicht tussen het voor de patiënt verwachte voordeel of schade. Aanbevelingen worden verdeeld in twee categorieën, een sterke aanbeveling of een zwakke aanbeveling, het niveau van evidence waarop de aanbeveling gebaseerd is, kan hoog zijn, matig of laag.

Er werd daarbij ook rekening gehouden met bijkomende verklaringen door de experts over de tests, vermeld als 'expert verklaring'.

CATARACT

Endotheelceldensiteit bij patiënten gepland voor cataract chirurgie

Populatie	Patiënten met cataract en gepland voor een chirurgische cataractingreep.
Doel	Door het meten van de endotheelceldensiteit wil men cornea complicaties na de cataractchirurgie vermijden of voorspellen.
Sterke aanbeveling, Lage kwaliteit evidence	Meting van de endotheelceldensiteit is aanbevolen bij patiënten met oculaire comorbiditeit.
Expert verklaring	De mogelijkheid om een meting van de endotheelceldensiteit uit te voeren moet bij elke patiënt voor de cataractchirurgie overwogen worden.

REFRACTIEVE CHIRURGIE

Scheimpflug imaging systeem

Populatie	Patiënten die voor cornearefractieve chirurgie gepland zijn.
Doel	Een *subklinische* keratoconus detecteren.
Zwakke aanbeveling, Lage kwaliteit evidence	De Scheimpflug is een recente non-contact techniek die kan worden gebruikt om een *matige en ernstige* keratoconus uit te sluiten.
Expert verklaring	Maar het is wachten op verdere bewijzen om de veelbelovende eerste bevindingen over *subklinische* keratoconus te ondersteunen.
Expert verklaring	Non-contact methoden zijn om redenen van infectiecontrole te verkiezen boven contactmethoden.
Expert verklaring	Er bestaan andere diagnostische instrumenten dan het Scheimpflug imaging systeem voor de diagnose van *niet-subklinische* keratoconus, incl. non-contact methoden.

LEEFTIJDSGEBONDEN MACULADEGENERATIE

Fluoresceïne-angiografie

Populatie	Patiënten met leeftijdsgebonden maculadegeneratie.
Doel	Evaluatie van de uitgebreidheid en het type van choroïdale neovascularisatie, en selectie voor behandeling.
Sterke aanbeveling, Matige kwaliteit evidence	Fluoresceïne-angiografie blijft de gouden standaard voor de diagnose van patiënten met neovasculaire leeftijdsgebonden maculadegeneratie, om de locatie en het type van de lesies te documenteren.
Sterke aanbeveling, Hoge kwaliteit evidence	Fluoresceïne-angiografie leidt de behandeling met fotodynamische therapie.
Sterke aanbeveling, Matige kwaliteit evidence	Fluoresceïne-angiografie moet worden gebruikt in de follow-up van patiënten met neovasculaire leeftijdsgebonden maculadegeneratie, om het even hoe die wordt behandeld.

Indocyanine groen-angiografie

Populatie	Patiënten met leeftijdsgebonden maculadegeneratie
Doel	Evaluatie van twijfelgevallen na fluoresceïne-angiografie.
Sterke aanbeveling, Matige kwaliteit evidence	ICG is aanbevolen voor evaluatie van uitgebreidheid en aard van subretinale membranen, in het bijzonder retinale angiomateuze proliferatie en polypoïdale choroïdale vasculopathie.

Optische coherentie tomografie

Populatie	Patiënten met leeftijdsgebonden maculadegeneratie.
Doel	Evaluatie van de activiteit van neovascularisatie.
Sterke aanbeveling, Matige kwaliteit evidence	De OCT wordt aanbevolen voor detectie van maculair oedeem.
Expert verklaring	Retinaal oedeem gedocumenteerd door OCT is een van de voorwaarden voor terugbetaling van pegaptanib en ranibizumab.
Expert verklaring	De OCT wordt aanbevolen om de effecten van de behandeling te monitoren.

BELEIDSAANBEVELINGEN

1. Teneinde de variabiliteit in de praktijk te verminderen, evidence-based praktijk aan te moedigen en middelen effectief toe te wijzen, moesten er klinische praktijkrichtlijnen worden ontwikkeld, specifiek voor de Belgische context. Deze richtlijnen werden opgesteld door klinische experts, op basis van de laatst beschikbare evidence. Financiering voor verdere ontwikkeling en implementatie moet aan de wetenschappelijke verenigingen voor oftalmologie worden beschikbaar gesteld; samenwerking is gewenst met andere instellingen die ervaring hebben in het ontwikkelen van richtlijnen. Richtlijnen over frequente aandoeningen of procedures moeten voorrang krijgen.
2. Oftalmologen moeten worden aangemoedigd om evidence in hun klinische praktijk te evalueren en te integreren. De opleiding van jonge oftalmologen zou de principes van evidence-based geneeskunde moeten omvatten.
3. Evidence-hiaten die in dit rapport zijn geïdentificeerd moeten worden gevuld met goed opgezette studies zoals de waarde van de Scheimpflug in het voorspellen van een slecht resultaat of complicaties na refractieve corneachirurgie, of de waarde van de OCT om de behandeling van leeftijdsgebonden maculadegeneratie te monitoren en te sturen.
4. Fluoresceïne-angiografie en indocyanine groen-angiografie moeten worden uitgevoerd in klinische expertise centra wegens hun risico's op b.v. anafylactische shock, complexiteit in interpretatie en onmiddellijke gevolgen voor de behandeling, die reeds is voorbehouden aan oftalmologen met specifieke expertise.
5. De beslissing om therapieën terug te betalen is gebaseerd op de efficiëntie van de therapie zoals aangetoond door goede studies. Sommige terugbetalingsvoorwaarden van therapieën zijn echter niet evidence-based, bijvoorbeeld de terugbetaling van anti-angiogenese therapie in geval van een maculair oedeem gedocumenteerd door OCT. Er is geen evidence dat het effect van anti-angiogenese therapie evalueert bij patiënten die voor deze behandeling met OCT werden geselecteerd. Als de terugbetaling van een therapie afhangt van diagnostische criteria, moet het criterium in kwestie goed gevalideerd zijn.

Scientific summary

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1 INTRODUCTION

The diagnostic and therapeutic possibilities in ophthalmology have expanded rapidly over the last decades. Major progress has been made in for example cataract surgery, treatment of age related macular degeneration, or follow-up of diabetic retinopathy. On the other hand, the prevalence of certain eye conditions is likely to continue to increase in the near future, for example diabetic retinopathy and age-related conditions, i.e. cataract, age related macular degeneration and glaucoma.

Various methods and procedures exist for the diagnosis and monitoring of diseases of the eye and vision disorders. In Belgian health care, 24 diagnostic tests are reimbursed. At present, guidelines specific to the Belgian context are not available.

The objective for this report was to derive practice recommendations on a selection of tests, based on the current evidence and taking the Belgian context into account.

Tests were selected for this report in consensus with a group of external experts. Elements on which this selection was based were frequency of use, promising tests for the near future, costs, variation between physicians, etcetera. The following tests were chosen, each for a specific indication:

- Endothelial cell count in patients scheduled for cataract surgery: this indication is estimated to be responsible for approximately 80% of all endothelial cel counts in Belgium.
- Scheimpflug imaging system in patients scheduled for corneal refractive surgery: refractive surgery is responsible for approximately 30% of all tests with the Scheimpflug imaging system
- Fluorescein angiography in patients with age related macular degeneration: fluorescein angiography is one of the ten most common performed tests in Belgium, likely to increase in the near future.
- Indocyanine green angiography in patients with age related macular degeneration: might serve as an adjunct to fluorescein angiography.
- Optical coherence tomography in patients with age related macular degeneration: test frequently used in practice for this indication (among other indications), currently not reimbursed.

2 SELECTED TOPICS ON THE USE OF OPHTHALMIC TESTS IN BELGIUM

2.1 INTRODUCTION

At present, the health care insurance in Belgium reimburses 24 diagnostic ophthalmic acts. A patient receiving a diagnostic test during his or her visit to an ophthalmologist is reimbursed between 82% and 100% by the health care insurance depending on the test and the patient's preferentiality status[1]. Not all diagnostic tests currently used in ophthalmic practice are reimbursed as such. These analyses evaluate reimbursed tests only, including two imaging tests used in ophthalmology as listed in table 2.1 in the methodology section.

The analyses were not intended to provide a comprehensive account of the use of ophthalmic diagnostic tests (ODT) in Belgium. We chose three research questions relevant to the aim of the current study:

1. What was the evolution of use and expenditure for the health care insurance of ODT in Belgium?
2. What combinations of ODT are performed most frequently on the same day in the same patient?
3. How many patients undergoing cataract surgery have an endothelial cell count 6 months before or after the procedure?

2.2 METHODOLOGY

2.2.1 Ophthalmic diagnostic tests

All ODT (see table 2.1) were part of the nomenclature used by the Belgian health insurance and where retrieved from the RIZIV/INAMI (National Institute for Health and Disability Insurance).

[1] Patients belonging to a family with an income below certain limits (OMNIO status), or entitled to an "enlarged reimbursement", receive a higher reimbursement of their health care expenses (http://www.riziv.be/secure/nl/medical_cost/index.htm).

Table 2.1. ODT considered in the study with their associated cost for health insurance and patient in function of preferential patient status.

		Preferential patient status		Non-preferential patient status	
Nomenclature number	Description	Health insurance cost	Patient contribution	Health insurance cost	Patient contribution
249233	Binocular biomicroscopy anterior eye segment	€ 6.48	€ 0.00	€ 6.48	€ 0.00
248636	Dynamometry / tonometry	€ 6.48	€ 0.00	€ 5.51	€ 0.97
248975	Binocular oftalmoscopy	€ 6.48	€ 0.00	€ 5.51	€ 0.97
249211	Computerised perimetry	€ 22.68	€ 0.00	€ 22.68	€ 0.00
248835	Refractometry	€ 5.18	€ 0.00	€ 4.41	€ 0.77
249255	Biometry of the eye	€ 80.98	€ 0.00	€ 80.98	€ 0.00
248813	Perimetry	€ 12.96	€ 0.00	€ 11.02	€ 1.94
248791	Angiograph of the retina	€ 48.59	€ 0.00	€ 41.31	€ 7.28
248953	Endothelial cell count	€ 48.59	€ 0.00	€ 41.31	€ 7.28
248673	Biomicroscopy posterior eye segment	€ 9.72	€ 0.00	€ 8.27	€ 1.45
248710	Eye motility concomitant strabismus	€ 16.20	€ 0.00	€ 13.77	€ 2.43
248732	Eye motility paralytic strabismus	€ 16.20	€ 0.00	€ 13.77	€ 2.43
248850	Exploration of lachrymal duct	€ 6.48	€ 0.00	€ 5.51	€ 0.97
248872	Visual evoked potentials	€ 80.98	€ 0.00	€ 72.30	€ 8.68
248555	Tonography	€ 32.39	€ 0.00	€ 27.54	€ 4.85
248592	Measurement of scleral rigidity	€ 9.72	€ 0.00	€ 8.27	€ 1.45
248776	Topographical keratometry	€ 9.72	€ 0.00	€ 8.27	€ 1.45
248533	Electroretinography	€ 48.59	€ 0.00	€ 41.31	€ 7.28
248754	Diagnosis of dyschromatopsia	€ 9.72	€ 0.00	€ 8.27	€ 1.45
248511	Retinal adaptation curve	€ 29.15	€ 0.00	€ 24.78	€ 4.37
460014	Unidimensional echography of the eye	€ 9.46	€ 0.00	€ 8.33	€ 1.13
248570	Glaucoma provocation test	€ 19.44	€ 0.00	€ 16.53	€ 2.91
460073	Two-dimensional echography of the eye	€ 18.96	€ 0.00	€ 16.45	€ 2.51
248614	Pressure curve	€ 32.39	€ 0.00	€ 27.54	€ 4.85
248916	Measurement of humeral-retinal circulation time	€ 42.11	€ 0.00	€ 35.80	€ 6.31
248894	Brachial arterial and ophtalmic arterial pressure	€ 48.59	€ 0.00	€ 41.31	€ 7.28

2.2.2 First research question: general use

Number of ODT and expenditure in euro were extracted from the "N documents" of RIZIV/INAMI. We had the data on performed tests between 1995 and 2005 to our disposal. The data were analysed using descriptive statistics.

2.2.3 Second and third research question: ODT combinations

The data to answer our second and third research question were obtained from IMA-AIM (Common Sickness Funds Agency) which allows more detailed analyses. IMA-AIM has drawn a sample from the entire sickness funds' database: 1 out of 40 (2.5%) of the Belgian population younger than 64 years and 1 out of 20 (5%) of the Belgian population over 65 (for a detailed description of the sampling procedure see [1]). Of this sample of the Belgian population, all patients with at least one of the selected ODTs were included.

For the second research question on the occurrence of ODT combinations, the frequencies of all combinations were obtained for 2002 through 2005. A combination was defined as all ODTs performed on the same day in a given patient. These frequencies were analysed using descriptive statistics.

For the third research question on the relation between endothelial cell count and cataract interventions, we used the criteria defined in table A.2 to identify a cataract intervention (see appendix). Thus, 9327 patients were identified in the IMA sample. Except for 24 patients, all had one or two cataract interventions between 2002 and 2005.

We excluded the 23 patients receiving three cataract interventions and the one patient receiving four interventions as they probably were not representative of the normal cataract patient. For each cataract intervention, the number and performance date of all ODT performed in the six months prior to and following the intervention were analysed using descriptive statistics.

2.2.4 Software

All analyses were performed in SAS 9.1.3 [2] and R 2.5.1 [3].

2.3 RESULTS

2.3.1 General use and expenditure of ODT

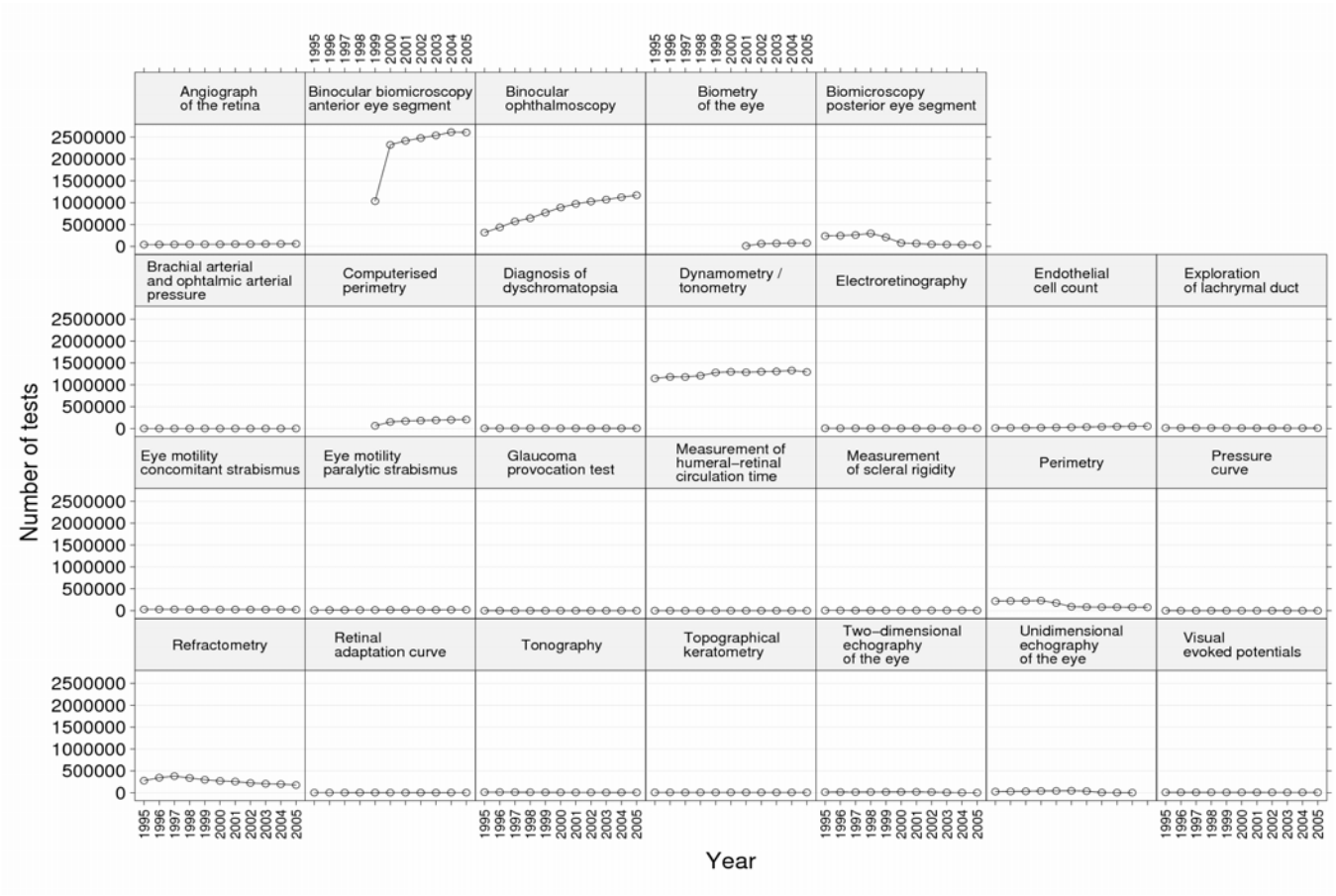
The ODTs most used between 1995 and 2005 were binocular biomicroscopy of the anterior eye segment, dynamometry/tonometry, and binocular ophthalmoscopy (see figure 1.1, and table A1 in the appendix to this chapter). Compared to these ODTs, the other ODTs were relatively rare.

The use of most ODTs has remained stable between 1995 and 2005 (see figure A2 in appendix). Reimbursement for binocular biomicroscopy of the anterior eye segment was introduced in July 1999 and explains the large increase in its reimbursement between 1999 and 2001 followed by a more or less stable use. Similar effects were found for biometry of the eye (introduced in 2001) and computerised perimetry (introduced in 1999).

Binocular ophthalmoscopy showed a steady increase between 1995 and 2005, the number of tests almost quadrupling in this period, but showing a less sharp increase over the last two years.

Biomicroscopy of the posterior eye segment showed a sudden drop in use in 2000: down to 37% of the 1999 volume. This decrease is probably due to the introduction of fundoscopy with a non contact method which is more comfortable for the patient. Similar effects were found for measurement of humeral-retinal circulation time, perimetry, pressure curve, and uni- and twodimensional echography of the eye (use dropped suddenly for both in 2002).

Figure 2.1: Number of ODT between 1995 and 2005 in function of ODT



Between 1995-2005, the health insurance cost for the ODTs has tripled from 16.3 million euro to 49.3 million euro (see table 2.2). In the same period, the total expenditure for all RIZIV/INAMI nomenclature has increased by 64.4% (from 10.2 billion euro in 1995 to 16.8 billion euro in 2005).

Table 2.2: Health insurance cost for all considered ODT between 1995 and 2005

Year	Health insurance cost	Percent increase	Cumulative increase
1995	€ 16 345 750		1.00
1996	€ 18 026 607	10.3%	1.10
1997	€ 18 351 067	1.8%	1.12
1998	€ 20 147 044	9.8%	1.23
1999	€ 27 640 911	37.2%	1.69
2000	€ 36 105 978	30.6%	2.21
2001	€ 39 093 949	8.3%	2.39
2002	€ 43 928 362	12.4%	2.69
2003	€ 46 614 237	6.1%	2.85
2004	€ 49 032 873	5.2%	3.00
2005	€ 49 356 527	0.7%	3.02

Due to the fact that each ODT has an associated fixed reimbursement amount, the expenditures per ODT showed the same effects as the number of ODT tests. Therefore these results are not shown here, but are available in the appendix (appendix 2).

2.3.2 Combinations of ODTs

The data from the IMA-AIM sample showed that almost three quarters of all ODT combinations in the period 2002-2005 were on account of three combinations:

- dynamometry/tonometry + binocular biomicroscopy anterior eye segment,
- binocular ophthalmoscopy + binocular biomicroscopy anterior eye segment,
- dynamometry/tonometry + binocular biomicroscopy anterior eye segment + computerised perimetry.

Table 2.3: Combinations of ODTs between 2002 and 2005.

ODT	Percentage	Cumulative percentage
Dynamometry / tonometry + Binocular biomicroscopy anterior eye segment	40.3%	40.3%
Binocular ophthalmoscopy + Binocular biomicroscopy anterior eye segment	28.8%	69.1%
Dynamometry / tonometry + Binocular biomicroscopy anterior eye segment + Computerised perimetry	4.2%	73.3%
Binocular biomicroscopy anterior eye segment	4.0%	77.3%
Binocular biomicroscopy anterior eye segment + Refractometry	3.7%	81.0%
Binocular ophthalmoscopy + Binocular biomicroscopy anterior eye segment + Computerised perimetry	1.8%	82.8%
Dynamometry / tonometry	1.6%	84.4%
Dynamometry / tonometry + Binocular biomicroscopy anterior eye segment + Perimetry	1.3%	85.7%
Binocular ophthalmoscopy + Binocular biomicroscopy anterior eye segment + Angiograph of the retina	1.2%	86.8%
Biomicroscopy posterior eye segment	1.03%	87.9%
Binocular ophthalmoscopy	0.88%	88.8%
Refractometry	0.62%	89.4%
Binocular ophthalmoscopy + Binocular biomicroscopy anterior eye segment + Dynamometry / tonometry	0.57%	90.0%
Binocular ophthalmoscopy + Binocular biomicroscopy anterior eye segment + Perimetry	0.56%	90.5%

2.3.3 Relationship of endothelial cell count and cataract interventions

The results on this research question are presented in the chapter on endothelial cell count.

2.4 DISCUSSION

The Belgian health insurance reimburses 24 ophthalmic diagnostic tests, but three tests are responsible for 87% of the use: binocular biomicroscopy of the anterior eye segment, dynamometry/tonometry, and binocular ophthalmoscopy. These tests also represent three quarters of all combinations.

These tests are considered as basic tests for the ophthalmic practice, as they evaluate the three basic parameters of the eye, i.e. the integrity of the anterior eye segment, the intraocular pressure and the integrity of the posterior eye segment.

The use of most ophthalmologic diagnostic tests remained stable in the period 1995 to 2005, with some notable exceptions. E.g. the three most frequently used tests, binocular biomicroscopy of the anterior eye segment, dynamometry/tonometry, and binocular ophthalmoscopy showed a steady increase over time. We could not verify whether this was in part due to an increasing number of patients in the same period of time. It can be hypothesised however, that due to the ageing of the population, more patients need ophthalmic care as various eye disorders are age-related. In addition, surgical solutions have increased, by which more disorders are treatable and taken in follow-up.

For some tests, a clear drop in use was found since 2000 or 2002. E.g. the use of biomicroscopy of the posterior eye segment dropped in the year 2000 to approximately one third of the 1999 volume. Most likely, this is due to the prohibition introduced in April 1999[2] to combine this test in the same session with biomicroscopy of the anterior eye segment. For pressure curve, and uni- and twodimensional echography of the eye in which the drop in use occurred in 2002, the most likely explanation is the enactment of the rule of application in January 2002 limiting reimbursement of these tests to only one act per session. The measurement of humeral-retinal circulation time is an outdated technique and its use had decreased accordingly.

The expenditure for the ODTs tripled between 1995 and 2005 whereas the overall expenditure for RIZIV/INAMI nomenclature increased by 65%. The data available do not allow explaining this higher increase. However, one plausible explanation is that for three common ODTs (binocular biomicroscopy of the anterior eye segment, biometry of the eye, and computerised perimetry) reimbursment was provided only from 1999 or later. This is evidenced by an increase of about 30% for both 1999 and 2000 in the expenditure of ODTs, compared to between 2% and 12.5% for the other years (see table 2.2). The total cost of these three tests represents approximately half of the total budget for ODTs in 2005.

2 Royal Decree of 29 April 1999. Royal decree to change the royal decree of 14 September 1984 of enactment of the nomenclature concerning the compulsory insurance of medical care and benifits (Koninklijk besluit tot wijziging van koninklijk besluit van 14 september 1984 tot vaststelling van de nomenclatuur van de geneeskundige verstrekkingen inzake verplichte verzekering voor geneeskundige verzorging en uitkeringen). Belgisch Staatsblad. 27 May 1999.

3 EVIDENCE REVIEW

3.1 INTRODUCTION

For the evidence review, a staged approach was chosen.

In a first step, evidence synthesis was searched by identifying guidelines, health technology assessment reports and systematic reviews for the selected eye disorders and ophthalmic tests.

In a second step, a formal evaluation was made for each specific test for that specific indication, in terms of technical accuracy, intended role in the clinical pathway, diagnostic accuracy and impact on patient outcome.

3.2 METHODS

3.2.1 Evidence synthesis

Guidelines were identified using the following databases or sites: the American Academy of Ophthalmology, the International Council of Ophthalmology, the Royal College of Ophthalmologists, Société Française d'Ophtalmologie, Scottish Intercollegiate Guidelines Network, the National Institute for Health and Clinical Excellence (NICE) and the National Guideline Clearinghouse (NGC). Where possible, all guidelines were hand searched. NICE and NGC were searched using the terms 'Ophthalmologic test OR eye'.

Health technology assessment (HTA) reports and systematic reviews were searched in the Centre for Reviews and Dissemination (CRD) database and the International Network of Agencies of HTA (INAHTA) database, equally using the terms 'eye OR ophthalmology OR ophthalmologist'. In addition, Medline was searched using the following search terms: ("Diagnostic Techniques, Ophthalmological"[MeSH]) AND systematic[sb]).

All output was sifted based on title and abstract using the following criteria: one of the selected eye disorders, containing information on diagnosis, monitoring or screening. Articles on telemedicine technology, narrative reviews, letters and editorials were excluded. Guidelines older than 5 years were excluded as well.

Documents were subsequently assessed in full text, applying the same in and exclusion criteria. Those fulfilling criteria were assessed for quality using standardised checklists, i.e. the AGREE checklist for guidelines, the INAHTA checklist for HTA reports and the checklist of the Dutch Cochrane Centre for systematic reviews.

3.2.1.1 Results

From the American Academy of Ophthalmology, 3 guidelines were identified, and 4 at the Royal College of Ophthalmologists' website. The site of the International Council of Ophthalmology contained only guidelines that were already available from other developers. No guideline was available from SIGN or NICE on the research questions. At the National Guideline Clearinghouse database, the search strategy yielded 275 results, of which 22 were possibly eligible, discarding duplicates already identified in any of the other sources. Two guidelines were in the scope of the report: one on AMD and one on cataract.

The critical appraisal of the eligible guidelines is summarized in appendix 2. As the guidelines from the American Academy of Ophthalmology (AAO) all had an identical methodology, assessment was made only once for all 3 guidelines. The quality of these guidelines was found to be fair, as very few to no details were available on evidence search, selection and appraisal. But, on the other hand, an explicit link between the recommendations and the evidence was provided and the balance between benefit and risks was considered when formulating the recommendations. Guidelines developed by the American Optometric Association were all found to be of poor quality.

No details were provided on evidence search or synthesis, on the methods used for formulating the recommendations and on the link between evidence and recommendations. Guidelines made by the Royal College of Ophthalmologists (RCO) varied in methods and quality

Ultimately, four guidelines were included in the report: two on cataract [4, 5], one on age related macular degeneration[6], and one on refractive errors[7].

The search in the CRD database for systematic reviews and HTA reports yielded 433 articles, in Medline 258. After discarding duplicates, 27 articles were selected for assessment on full text based on in and exclusion criteria. Two references were summaries of a systematic review also included in the search, one was a guideline. Of the remaining 24 articles, two were within the scope of the report: one on pachymetry examination pre-LASIK[8] and one on partial coherence interferometry prior to cataract surgery[9]. The articles were assessed on quality using the checklist for systematic reviews available from the Dutch Cochrane Centre. The quality appraisal is summarized in appendix 2.

3.2.2 Formal evaluation

Next to the global search for evidence synthesis, a formal evaluation was made for test-indication pairs, in other words, the clinical value of a given test was evaluated for a specific indication. The methodology used for this formal evaluation is that described by Van den Bruel et al.[10]. In short, tests are first evaluated on their technical accuracy. Secondly, the place of the test in the clinical pathway of the specific indication is determined. Then, the diagnostic accuracy of the test is evaluated and assessed whether this suffices for the intended place in the clinical pathway. Finally, the effect of the test on patient outcome is assessed by searching for direct and indirect evidence. Direct evidence relates to studies that evaluate the independent contribution of the test on the ultimate patient outcome, for example by performing an RCT in which patients undergoing the test+treatment strategy are compared to patients undergoing usual care without the test under evaluation. Indirect evidence relates to studies that show that by using the test under evaluation, patients can benefit. For example, the test has been used as a selection criterion for patients to enter a trial that shows the efficacy of a treatment. For each of these steps, different types of information are needed. The exact method used, including search terms, databases, selection criteria and critical appraisal will be presented in each chapter.

In the following chapters, details on the use of these selected ophthalmic tests are summarised for the selected indications. It is by no means the intention to describe the complete clinical management of these patients, as this might include other tests than those considered in this report.

4 ENDOTHELIAL CELL COUNT IN PATIENTS SCHEDULED FOR CATARACT SURGERY

The corneal endothelium is a single cell layer lining the inner surface of the cornea[11]. It acts as a barrier to the influx of aqueous humor into the stroma and pumps excess fluid out of the stroma. The endothelial lining of the cornea is important in maintaining corneal clarity, but has poor regenerative ability. Corneal epithelial swelling reduces epithelial clarity. A cloudy cornea misdirects or blurs light rays that pass through it.

The term endothelial cell count refers to the density of the endothelial cells lining the posterior surface of the cornea. The endothelial cell count or cell density of the cornea is measured in cells per square millimetre. The cell density of an individual can be compared to a previously documented cell density for that individual or to an average value of an age-matched population. Any direct trauma or injury to the endothelial cell layer results in a decrease in the number of cells and a decrease in endothelial cell reserve or the ability of the endothelium to withstand further insult. Even though the cell count may be low, the remaining endothelial cells are often capable of preventing corneal swelling until a critical threshold is reached.

The earliest method of evaluating corneal endothelium dates back to 1920 when Vogt first reported the method of examining the endothelial mosaic by specular reflection using the slit-lamp biomicroscope[11]. In 1968, Maurice first reported the use of a specifically designed corneal microscope to observe the endothelium at x400 magnification and coined the term specular microscope[12]. Brown described a noncontact specular microscope in 1970[13]. In 1975, Laing demonstrated a clinically useful microscope that could photograph the endothelium at x200[14]. Shortly thereafter, Bourne and Kaufman reported results with a photographic flash attachment that allowed clearer pictures[15].

4.1 CURRENT USE IN BELGIUM

Here, the results of the data analysis of chapter 2 on endothelial cell count are presented. The Belgian Health Insurance reimburses the endothelial cell count (ECC) as part of the preoperative work-up for surgical procedures of the anterior eye segment. In the year 2005, 46,915 tests were reimbursed. About half of the patients with either one or two cataract procedures between 2002 and 2005 did not have an ECC in the six months prior to or after the first cataract intervention (see table 4.1). Of those patients undergoing one or more ECC, most patients with one cataract intervention had only one ECC, whereas the majority of the patients with two cataract interventions had one or two ECC. In patients with one cataract intervention, three or more ECC was very rare. Approximately 12% of the patients with two cataract procedures had more than three EEC. Less than 0.8% of the patients in our sample had more than five ECC and is not shown in the table.

Table 4.1: Number of patients with zero or more ECC in function of cataract procedures

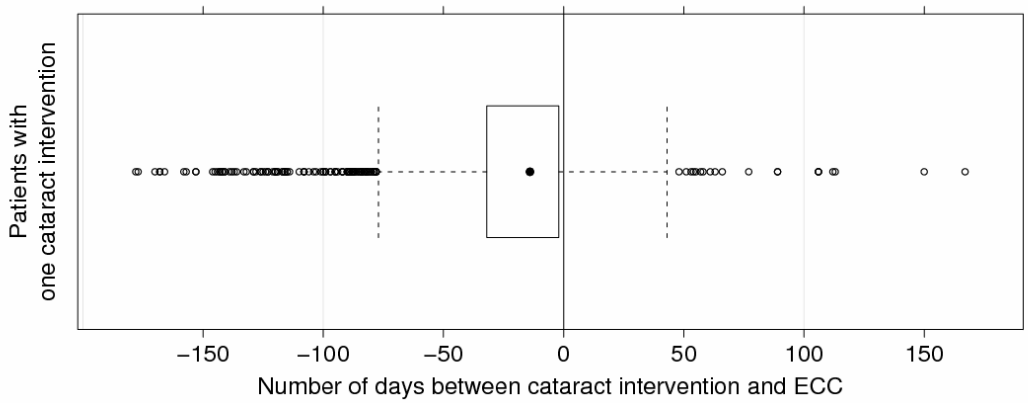
Number of ECC	one cataract		two cataracts	
	f	%	f	%
0	2637	56.8%	2155	46.0
1	1808	39.0%	893	19.1
2	144	3.1%	979	20.9
3			73	1.6
4	44	0.9%	457	9.8
5	5	0.1%	54	1.2

Of those patients having at least one ECC, those undergoing only one cataract procedure had the ECC before the intervention (see table 4.2), in 50% less than two weeks before the cataract procedure (see figure 4.1). Only 25% of the ECC were performed more than a month before the cataract procedure. The majority of the patients with two cataract procedures had two ECC, mostly one before each cataract intervention.

Table 4.2: Number of patients with one or two ECC prior to, between, or after the cataract procedures

Number of ECC	Prior	Between	After	one cataract f	one cataract % of patients relative to number of ECC	one cataract % relative to number of patients with one cataract	two cataracts f	two cataracts % of patients relative to number of ECC	two cataracts % relative to number of patients with two cataracts
1	1			1507	83.35%	32.48%	732	81.97%	15.62%
		1					157	17.58%	3.35%
			1	301	16.65%	6.49%	4	0.45%	0.09%
2	1	1					954	66.43%	20.35%
	1		1	144	76.60%	3.10%	9	0.63%	0.19%
		1	1				16	1.11%	0.34%
	2			19	13.30%	0.41%	42	2.92%	0.90%
		2					415	28.90%	8.85%
			2	25	10.11%	0.54%			

Figure 4.1: Distribution of the interval in days of ECC compared to the cataract intervention in patients with only one intervention.



In patients with two cataract procedures, again half of all ECC performed before the first procedure took place within two weeks prior to the procedure and only 25% more than one month prior to the procedure. Of the ECC performed after the first procedure, a distinction can be made between ECC after the first but before the second

procedure ("between") and ECC after the second procedure ("after"). Half of the "between" ECC are done within 11 days after the first cataract procedure, and three quarters within one month. Half of the "after" ECC are done within three weeks after the first procedure, while three quarters is performed within 1.5 month. Three quarters of all second cataract procedures in our sample were performed within approximately 2.5 months after the first procedure, and 50% of all second interventions within one month.

Key points

- **Half of all patients undergoing cataract surgery do not have a preoperative ECC.**
- **ECC are performed before the cataract procedure, in 50% within one month.**
- **Patients undergoing two cataract procedures mostly have an ECC before each procedure.**

4.2 EVIDENCE SYNTHESIS

Two guidelines were available, by the AAO and the RCO. No HTA report or systematic review on the endothelial cell count was identified.

According to the AAO guideline[5], the evaluation of a patient whose chief complaint might be related to a cataract should include, next to history taking and other tests of the physical examination:

- Visual acuity
- Intraocular pressure
- Slit-lamp biomicroscopy
- Dilated examination of the lens, macula, peripheral retina, optic nerve, and vitreous.
- Biometry

Additional tests may be indicated in selected cases

- Glare testing
- Contrast sensitivity testing
- Specular microscopy
- Pachymetry
- Corneal topography
- Fluorescein angiography
- Optical coherence tomography
- B-scan ultrasonography

According to the Royal College of Ophthalmologists[4], a patient scheduled for cataract surgery should have

- Visual acuity
- Intraocular pressure
- Slit lamp examination
- Dilated examination of the cataract and fundus
- Biometry

Special investigations may include B-scan ultrasonography and electrodiagnostic tests. According to the RCO, tests for contrast sensitivity, glare, laser interferometry and specular photography are not of proven value.

4.3 FORMAL EVALUATION-METHODS

The following research questions were formulated:

1. What is the technical accuracy of the endothelial cell count?
2. What is the place of the endothelial cell count in the clinical pathway?
3. What is the diagnostic value of the endothelial cell count in a patient scheduled for cataract surgery?
4. What is the benefit of the endothelial cell count in a patient scheduled for cataract surgery?
5. What is the cost-effectiveness of the the endothelial cell count in patients scheduled for cataract surgery?

Questions 1, 3, 4 and 5 were answered using a systematic literature search in Medline and Embase. Question 2 was answered based on expert opinion.

Endothelial cell density or cell count is neither a MeSH term nor an Emtree term. Therefore, MeSH and Emtree terms referring to the corneal endothelium in general were combined with free text words on the cell count. Subsequently, a diagnostic filter was applied to direct the search towards technical and diagnostic accuracy studies.

Medline, search date 23/04/2007. Search terms:

("Endothelium, Corneal"[MeSH] OR endothelial cell* count) AND (sensitiv*[Title/Abstract] OR sensitivity and specificity[MeSH Terms] OR diagnos*[Title/Abstract] OR diagnosis[MeSH:noexp] OR diagnostic *[MeSH:noexp] OR diagnosis,differential[MeSH:noexp] OR diagnosis[Subheading:noexp])

Embase, search date 23/04/2007. Search terms:

('cornea endothelium'/exp) AND (sensitiv* OR detect* OR accurac* OR specific* OR reliab* OR positiv* OR negativ* AND [embase]/lim AND [1966-2007]/py)

(search filter according to Bachmann et al. J Libr Med Assoc 2003)

The output was then sifted, based on the following inclusion and exclusion criteria:

Research question 1:

- Inclusion criteria: diagnostic accuracy studies, on research material, endothelial corneal cell count techniques
- Exclusion criteria: letters, editorials

Research question 3:

- Inclusion criteria: diagnostic accuracy studies, on patients scheduled for cataract surgery; endothelial corneal cell count
- Exclusion criteria: patients with another target condition than scheduled cataract surgery, e.g. cornea transplant; case reports, letters, editorials, narrative reviews

Those articles remaining were then evaluated in full text, and assessed for quality. Similar inclusion and exclusion criteria were used, with the addition of a language restriction: articles in languages other than English, French, German or Dutch were excluded. The quality assessment was based on QUADAS[16], a checklist for accuracy

studies on diagnostic tests. This checklist was constructed using empirical evidence on bias and variation of diagnostic studies, and is currently endorsed by the Cochrane Collaboration in their new handbook on diagnostic systematic reviews. Articles were not excluded based on quality assessment.

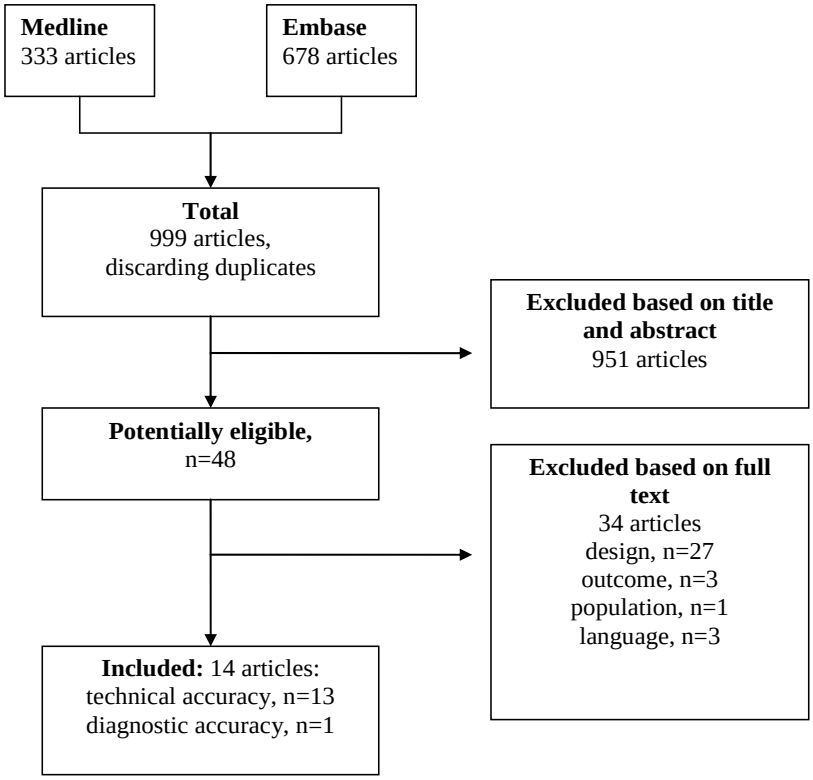
Data were extracted from the studies, on the following items:

- Patient population
- Study design: prospective/retrospective, case-control or cohort, blinding, consecutive inclusion, independent verification.
- Results: sensitivity, specificity, predictive values, likelihood ratios, odds ratio, ROC curve and AUC

4.4 SEARCH RESULTS

In figure 4.2, a flow chart of the literature search is presented.

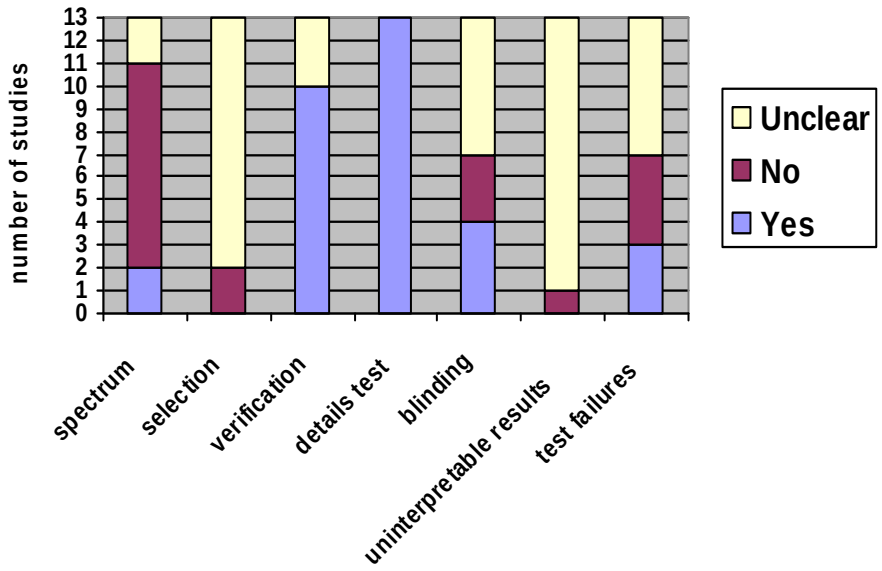
Figure 4.2: flow chart of the literature search



4.5 QUALITY ASSESSMENT

In total, 13 articles were included on technical accuracy[15, 17-28]. An overview of the quality assessment is provided in figure 4.3.

Figure 4.3: quality assessment for articles on technical accuracy



For the quality assessment of the diagnostic accuracy studies, no figure is presented as only one study was included[29]. The quality assessment of this study showed that the spectrum of included patients was not representative for the clinical population in which the test will be used and that selection criteria were not described sufficiently. On the other hand, the verification was done with a valid reference standard, within a short period of time and independent of the index test result. Sufficient details on the index and reference test were given to allow its replication in clinical practice. It was unclear to what extent the index and reference test results were read blinded from the other result and it was unclear whether clinical data were available or whether withdrawals or uninterpretable results were reported.

4.6 RESULTS FOR THE TECHNICAL ACCURACY

A description of each study and its results is summarised in the evidence tables (see appendix 3). From the studies included in the review, it is shown that the technical accuracy of specular microscopes used for determining endothelial cell density is probably sufficient. But, the number of studies that included participants with eye disorders is very low, as most studies used healthy volunteers. The reproducibility of the microscopes, both within and between observers has been studied most, with limits of agreement of ±250 cells/mm², although for one device, limits of agreement were larger than 400 cells/mm². This should be taken into account when evaluating the diagnostic accuracy and impact on patient outcome.

4.7 PLACE IN THE CLINICAL PATHWAY

According to expert opinion, the endothelial cell density is measured in patients prior to cataract surgery, for several reasons.

First, experts state that patients with a low endothelial cell count will undergo a different surgical procedure than patients that have not. Surgery may be postponed or even cancelled.

Secondly, viscoelastic substances are used during the surgical procedure. In patients with a low endothelial cell count, other substances are used as the protective effect of the substances would vary.

Thirdly, the postoperative recovery in patients with a low endothelial cell count may be prolonged due to corneal oedema postoperatively. The endothelial cell count is used to estimate the risk of this postoperative complication and inform the patient accordingly.

Finally, the operation of the fellow eye may be postponed until the outcome of the first eye has been established.

4.8 RESULTS FOR THE DIAGNOSTIC ACCURACY

For diagnostic accuracy, only one study was included, which compared two types of specular microscopy and found no significant difference between the two. The characteristics of the study are summarised in the evidence table in appendix 3.

4.9 IMPACT ON PATIENT OUTCOME

4.9.1 Direct evidence for a change in management

The effect of measuring endothelial cell density before cataract surgery and subsequently adapting the surgery procedure or excluding the patient from surgery, should be evaluated in a randomized controlled trial.

The literature search for this type of direct evidence is outlined below:

PubMed 08/06/07

(("Cataract Extraction"[Mesh]) AND ("Endothelium, Corneal"[MeSH] OR endothelial cell* count)) AND ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading])

Embase 08/06/07

('cornea endothelium'/exp) AND (random* AND [embase]/lim AND [1966-2007]/py)

Discarding duplicates, the search in Medline and Embase yielded 318 articles. The articles were subsequently selected according to the following inclusion criteria: randomized trials, pre-cataract surgery, endothelial cell count. Letters, editorials, comments, prognostic studies without comparison, studies using an outcome other than corneal oedema/decompensation were excluded.

No trials were identified in this literature search.

4.9.2 Indirect evidence on change in management

In the absence of direct evidence on the benefit of pre-operative endothelial cell count, indirect evidence may provide some of the answers. Several questions can be asked:

Is the measurement of endothelial cell density preoperative a reason for not performing the cataract surgery? Is the endothelial cell density a reason for choosing a specific type of surgery, in other words: is there a difference in endothelial cell loss between the various types of surgery? How often does endothelial cell loss result in corneal decompensation? Is there a difference in efficacy of viscoelastic substances in protecting the cornea from endothelial cell loss?

For this indirect evidence, a systematic review was available from the Cochrane Collaboration: Surgical interventions for age-related cataract[30]. In this high quality review, the evidence on surgical interventions for age-related cataract has been synthesized. A systematic literature search was performed using a sensitive search strategy in several databases. Quality assessment and data-extraction were done by two

authors independently. Meta-analyses and sensitivity analyses were performed on clinically relevant outcomes. The last update of this review was done in July 2006.

4.9.2.1 Is endothelial cell count preoperatively a reason for not performing the cataract surgery?

None of the nine included studies used a low pre-operative endothelial cell count as an exclusion criterion.

4.9.2.2 Is there a difference in endothelial cell loss between the different types of surgery?

This review does not provide any evidence from controlled trials as to the rates of corneal complications with anterior chamber lenses more than seven or eight years after surgery. However, observational data from developed country settings indicate that this is not likely to be a problem.

Three studies have shown no difference in mean percentage endothelial cell loss between the ECCE and phaco at respective follow up times (George 2005[31] (4.72% ECCE v 5.41% PHACO), Ravalico 1997[32] (10.1% ECCE v 8.5% PHACO), and MEHOX[33] (9.1% ECCE v 10.5% PHACO). In the MEHOX study however PHACO was associated with a higher risk of severe cell loss in patients with hard cataract (P = 0.04 RR 3.7, 95% CI 1.03 to 13.34). In addition, George[31] showed no statistically significant difference in endothelial cell loss between phaco and manual small incision cataract surgery (MSICS). There was a mean 5.41% (N = 60, SD10.99) induced cell loss in PHACO at 6 weeks follow-up compared with 4.21% (N = 53, SD 10.29) for MSICS and no statistically significant difference in endothelial cell loss between ECCE and MSICS. There was a mean 4.72% (N = 52, SD 13.07) induced cell loss in ECCE at 6 weeks follow-up compared to 4.21% (N = 53, SD 10.29) for MSICS. The sample size was adequate to detect a 7% difference in endothelial cell count between the groups, giving a power of 80%. In the SACMS trial comparing surgery with the placement of an intraocular lens or not found the corneal endothelial cell loss after six week follow-up was 17% in the IOL group and 14.4% in the aphakic group (P < 0.05)[34]. After six weeks there was no significant difference in the continuing cell loss between eyes having no lens compared to eyes with lens (12 months: IOL 5.3%, AG 4.1%, P = 0.06; 24 months: IOL 3.1%, AG 2.9% P = 0.71).

4.9.2.3 How often does endothelial cell loss caused by cataract surgery result in corneal decompensation?

There were three cases of corneal decompensation identified 12 to 24 months after surgery in 2867 participants, in 2 large trials in South East Asia comparing intracapsular extraction with anterior chamber IOL versus intracapsular extraction with glasses[35, 34]. Two of these cases occurred in the aphakic glasses group, one case occurred in a person with an anterior chamber IOL. None of the other trials in the systematic review reported cases of corneal decompensation. But, the experts indicate that the follow-up in these studies (1-2 years) might be insufficient to capture all long term events.

4.9.2.4 Do some viscoelastic substances or ophthalmic viscoelastic devices (OVD) protect the cornea more than others?

In order to answer this question, a separate evidence search was done.

Search for systematic reviews:

Medline, 11/06/07

(("Viscoat "[Substance Name]) OR ("Hyaluronic Acid"[Mesh]) AND (("Cataract Extraction"[Mesh]) AND ("Endothelium, Corneal"[MeSH] OR endothelial cell* count))) AND systematic[sb]:

This search identified one Cochrane review: "Viscoelastics for preventing endothelial cell loss in people who have undergone cataract extraction": title has been registered in 2004, by Agahan A., results are pending. No other systematic reviews were found.

Search for original studies:

Medline, 19/06/07

("Viscoat"[Substance Name]) OR ("Hyaluronic Acid"[Mesh] OR (hydroxypropyl methylcellulose)) AND (("Cataract Extraction"[Mesh]) AND ("Endothelium, Corneal"[MeSH] OR endothelial cell* count))

Embase, 19/06/07

'cataract extraction'/exp AND 'glycosaminoglycan'/exp AND ('cornea endothelium'/exp) AND [embase]/lim AND [1966-2007]/py

The search strategy yielded 126 articles, discarding duplicates. These articles were included according to the following criteria: randomized controlled trials, visco-elastic substances, cataract surgery, corneal decompensation/corneal oedema; surrogate outcome: endothelial cell count. Comments, letters, editorials, case series; all studies other than an RCT, studies in a language other than English, French, German were excluded. In case of any doubt, the articles were left in the selection for further evaluation in full text.

Applying these criteria, 48 articles were ordered in full text. The articles were subsequently again submitted to the same inclusion and exclusion criteria.

After appraisal in full text, 34 articles were included in the review[36-69]. Six articles were excluded based on language[70-75], four because they were not a randomised trial[76-79] and three because they studied animals instead of patients[80-82]. One article was not available from any of the collaborating libraries[83].

Following, a critical appraisal was performed of the remaining articles. This critical appraisal was based on the checklist of the Dutch Cochrane Centre (see tables in appendix 4). By and large, the quality of the studies was very low. Not one study reported adequate concealment of allocation. Blinding of the outcome assessors was not stated in 16 of the 34 studies, although this was easily feasible. In addition, sample sizes were too small to detect any difference between the various interventions in several studies. Moreover, in 8 studies patients were excluded from the analyses because of intra-operative and postoperative complications, and 5 studies excluded patients based on low preoperative endothelial cell count. In addition, one study excluded patient in which the endothelial cell count varied with more than 10% between both eyes, and one study excluded patients in which the endothelial cell count not be accurately read preoperatively.

In total, 22 different OVD or combinations of OVD were used in the various studies. A list of all OVD is provided in table 4.3. Some of the commercial products listed consist of the same active substance, for example Healon and Hyal-2000 both consist of 1% sodium hyaluronate. However, their properties are not completely identical. This explains why some studies have compared the efficacy of two OVD with the same active substance. Some studies only mentioned the active substance without specifying the commercial product. Healon was the most commonly used OVD, followed by Viscoat. All OVD were classified according to the Arshinoff classification[84], which distinguishes two main properties, viscosity and cohesion. Categories were as follows: no viscoelastic, Viscoadaptives, Super viscosity cohesives, Viscous cohesives, Medium viscosity dispersives, Very low viscosity dispersives, combination of viscous cohesives and medium viscosity dispersives (soft shell technique), sodium hyaluronate 1% not otherwise specified, collagen type 4.

Of the 34 studies included in the review, 25 compared two interventions, either OVD and placebo, or two OVDs. Five studies compared three interventions, three compared

four interventions and one study compared five interventions. The characteristics and results of all studies are shown in appendix 4.

Table 4.3: list of OVD and their classification

Commercial name	Active substance	Arshinoff classification	Number of studies
Amvisc	1.2% sodium hyaluronate	Viscous cohesive	2
Amvisc Plus	1.6% sodium hyaluronate	Viscous cohesive	1
Biolon	1% sodium hyaluronate	Viscous cohesive	1
Biovisc	1% sodium hyaluronate	Medium viscosity dispersive	1
Celoftal	2% hydroxypropyl methylcellulose	Very low viscosity dispersive	2
Collagel	1.4% collagen type IV	-	1
Healon	1% sodium hyaluronate	Viscous cohesive	18
Healon GV	1.4% sodium hyaluronate	Super viscosity cohesive	6
Healon5	2.3% sodium hyaluronate	Viscoadaptive	5
Healonid	1% sodium hyaluronate	Viscous cohesive	2
2% HPMC, not otherwise specified	2% hydroxypropyl methylcellulose	Very low viscosity dispersive	3
HPMC-Ophtal	2% hydroxypropyl methylcellulose	Very low viscosity dispersive	1
Hyal-2000	1% sodium hyaluronate	Viscous cohesive	1
Hymecel	2% hydroxypropyl methylcellulose	Very low viscosity dispersive	1
Occucoat	2% hydroxypropyl methylcellulose	Very low viscosity dispersive	4
Opegan	1% sodium hyaluronate	Viscous cohesive	2
Opthalin	1% sodium hyaluronate	Viscous cohesive	1
Provisc	1% sodium hyaluronate	Viscous cohesive	2
1% sodium hyaluronate, not otherwise specified	1% sodium hyaluronate	-	4
Viscoat	3% sodium hyaluronate + 4% sodium chondroitin	Medium viscosity dispersive	12
Vitrax	3% sodium hyaluronate	Medium viscosity dispersives	2
Soft shell = Healon + Viscoat	1% sodium hyaluronate and 3% sodium hyaluronate + 4% sodium chondroitin	-	4
No OVD	Air; serum; BSS	-	6
Total			82

RESULTS

In all, 30 studies did not find a significant difference in terms of preventing endothelial cell loss. The other four studies of the 34 included in the review found a significant difference between OVDs.

Kim et al. found that in patients with grade 4 nuclear opacity, the soft-shell technique resulted in significantly less cell loss as compared to Viscoat (medium viscosity dispersive), Hyal-2000 (viscous cohesive) and Provisc (viscous cohesive), being a loss of 12.2% (SD 6.6) for the soft-shell technique versus 18.6% (SD 15.2) for Provisc, 19.6% (SD 14.9) for Hyal-2000 and 17.4% (SD 9.8) for Viscoat.

Storr-Paulsen found Vitrax (medium viscosity dispersive) to be superior to Celoftal (very low viscosity dispersive) and Healon (viscous cohesive). Vitrax resulted in 7.0% cell loss, whereas Celoftal resulted in 18.0% and Healon in 18.5%.

Remarkably, the rates of endothelial cell loss in the Celoftal and Healon group are substantially higher than those in similar studies.

In the study by Holzer et al., Healon5 (viscoadaptive) was found to result in significantly less cell loss (6.2%; SD 6.5) than Occucoat: 16.7% (SD 10.8) and Celoftal: 12.9% (SD 6.2), both very low viscosity dispersives, and Healon GV: 10.9% (SD 7.5) (super viscosity cohesive), Viscoat: 15.4% (SD 9.1) (medium viscosity dispersive).

Finally, Ray-Chaudhuri found HPMC (very low viscosity dispersives) to be better than Ophtalin (viscous cohesive), as HPMS resulted in 4.3% loss in cell density and Ophthalin in 11.8%.

These significant differences are clinically very heterogeneous and even contradictory. They do not offer solid evidence for the superiority of one OVD over another. In addition, many more studies found no significant differences.

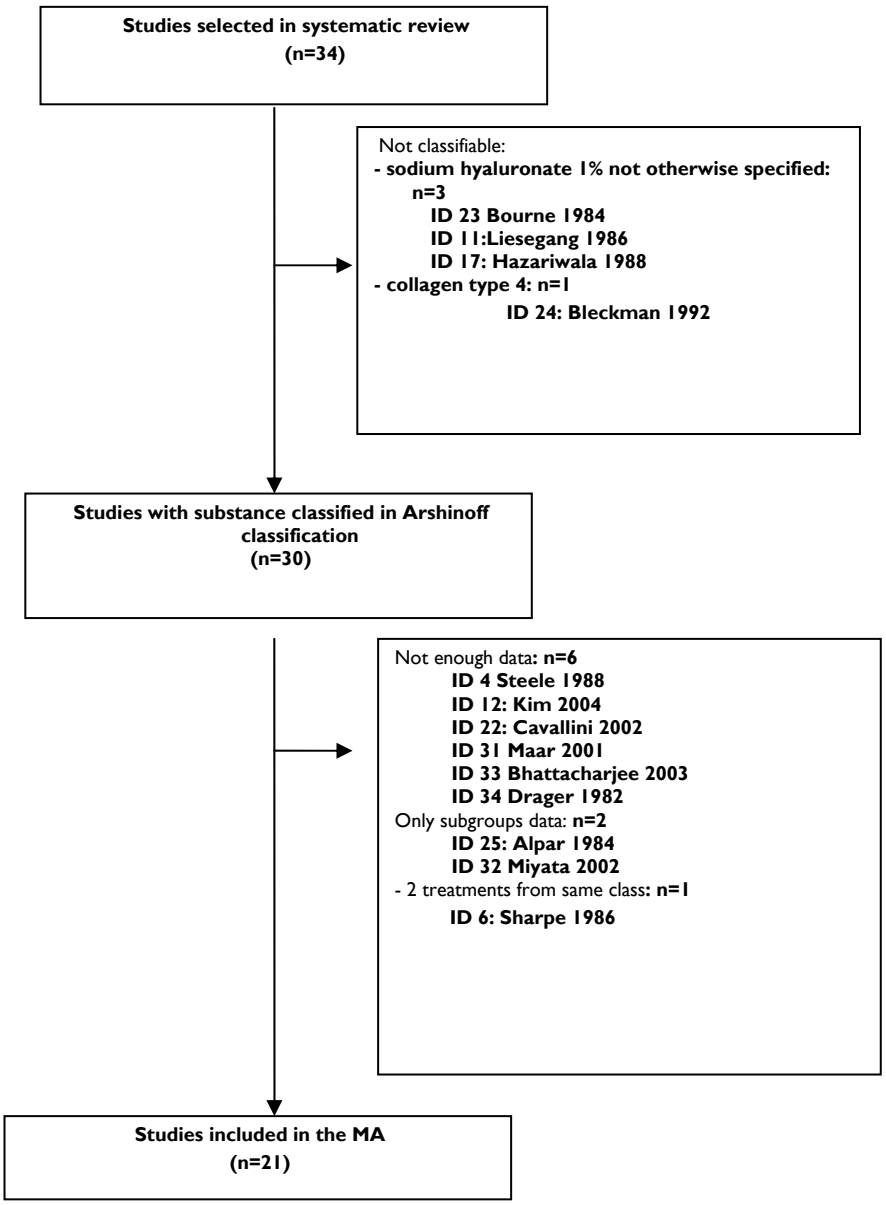
META-ANALYSIS

Due to the large number of studies that were identified using a very small sample size, a meta-analytical approach could provide additional information. It allows a more precise quantification of the difference between the OVDs in their protective effect on endothelial cells.

A total of 34 studies were selected in the systematic review. Four studies using a substance not classifiable in the Arshinoff classification were excluded, e.g. sodium hyaluronate 1% not otherwise specified (study ID 23 Bourne 1984, study ID 11 Liesegang 1986 and study ID 17 Hazariwala 1988) and collagen type 4 (study ID 24 Belckman 1992). Of the remaining 30 studies, 6 studies were excluded because poor availability of published data prevented their inclusion in the MA, 2 studies because only subgroups data were presented, and 1 study was excluded because two treatments from the same therapeutical class (but different commercial products) were compared to each other. A total of 21 studies were thus included in the meta-analysis.

The primary endpoint of the meta-analysis was the absolute change in cell density after surgery.

Figure 4.4: flow chart of study inclusion



In general, the reporting of the results was extremely poor. For example, variability measures of pre treatment values and post treatment values of endothelial cell density was presented, but the variance of the primary endpoint, the change from baseline, was often not presented.

To avoid the exclusion of the studies with poor reporting (and thus to avoid the potential introduction of bias in the analysis), we defined a set of 4 rules that were applied uniformly on all studies, when needed. It is important to note that these rules have no impact on the estimation of the treatment effects (i.e. do not introduce bias in the analysis), but only on the precision of that estimation (i.e. might have an implication on the significance of the effects).

1. Compute Variance of the Change from Baseline (Affected 13 studies) As explained above, the primary endpoint for all studies was the change from baseline, but very few studies reported the variance of that variable, only the SD of the baseline and of the post treatment values. A small set of studies reported all SD, and therefore the within patient correlations could be estimated. In this set of studies, within variances were 2.5 smaller than the within variance calculated under the hypotheses of independence. From that information, the missing variances for change from baseline were calculated under the hypothesis of independence, and reduced by a factor 2.5 to account for the within patient correlations.
2. Impute number of patients postoperative (Affected 11 studies). Some studies reported post treatment results but not the number of patients concerned. In that case, the number of patients at baseline was used instead, assuming that there was no loss–to-follow up.
3. Pooling of active arms (Affected 3 studies) Three studies (ID 13 Lane 1991, ID 16 Henry 1996, ID 27 Holzer 2001) had 2 treatment arms comparing the same active treatment, and were therefore pooled per active treatment group.
4. Impute baseline to estimate absolute effect (Affected 2 studies) Two studies (ID 5 Smith 1991 and ID 30 Oshika 2004) presented results on a relative scale (percent change from baseline) and no baseline data were available. The average baseline values of all other studies were thus used as imputed baseline values for these two studies, and the absolute treatment effect was then computed based on the published percent change from baseline.

The results of the systematic review led to the identification of 21 studies that could be analyzed in a meta-analysis. These studies compared 7 different treatment options (1 control and 6 active treatments.). The majority of these studies were 2 arms, but there were also three 3 arms studies and two 4 arms studies.

The coding of the different treatment options is:

treatment 0	Control treatment: no viscoelastic
treatment 1	Viscoadaptives
treatment 2	Super viscosity cohesives
treatment 3	Viscous cohesives
treatment 4	Medium viscosity dispersives
treatment 5	Very low viscosity dispersives
treatment 6	combination of Viscous cohesives (3) + Medium viscosity dispersives (4)

Not all treatment options have been equally studied: while treatment 0 (control treatment: no viscoelastic) appears only once in the structure, treatment 3 (Viscous cohesives) and treatment 4 (Medium viscosity dispersives) appear respectively 16 and 12 times.

Results from Direct Comparisons

All observed comparisons are presented in the upper triangle of table 4.4 (with the number of studies included in the meta-analyses). Of the 21 possible pair wise comparisons, 12 are observed. We pooled the data using standard pair wise meta-analysis for the 9 pair wise comparisons that had been observed in at least two studies. The remaining 3 pair wise comparisons were only directly compared in single studies, and so no pooling of results is possible.

Because some comparisons showed heterogeneity in the study results, we chose to perform random effects meta-analyses.

a. Viscoadaptives showed a treatment effect when compared to very low viscosity dispersives, and no effect compared to super viscosity cohesives, viscous cohesives and medium viscosity dispersives.

b. Super viscosity cohesives showed no treatment effect compared to viscoadaptives, viscous cohesives, medium viscosity dispersives, and very low viscosity dispersives.

c. Viscous cohesives showed no difference compared to viscoadaptives, super viscosity cohesives, medium viscosity dispersives, and very low viscosity dispersives. It was inferior to the soft-shell technique, but the effect was below the threshold of clinical relevance. Viscous cohesives also showed a clinical and statistically significant effect when compared to control treatment in one study.

d. Medium viscosity dispersives showed no difference compared to viscoadaptives, to super viscosity cohesives when pooled over 4 studies, to viscous cohesives when pooled over 7 studies, and to very low viscosity dispersives when pooled over 5 studies

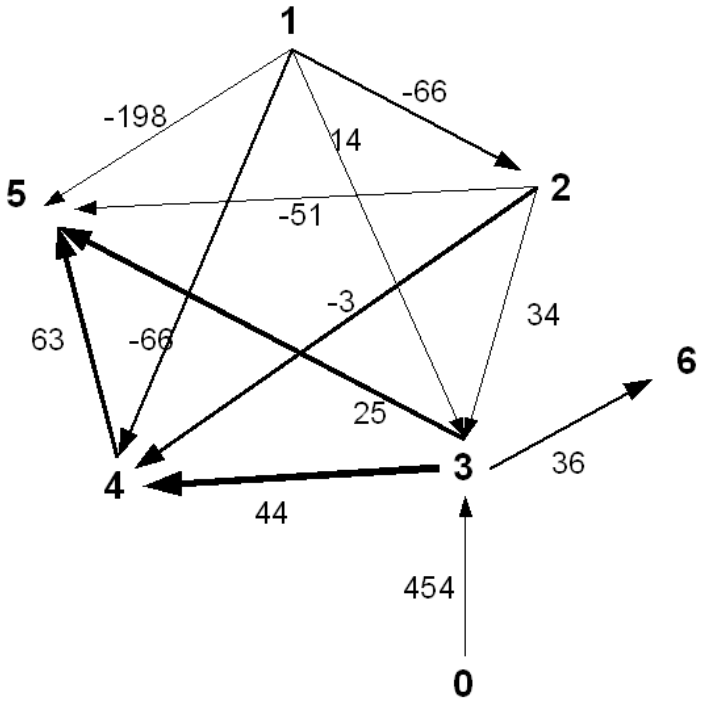
e. Very low viscosity dispersives has been compared to viscoadaptives in one study and proved to be inferior. It showed no effect compared to super viscosity cohesives, viscous cohesives and medium viscosity dispersives.

f. The soft-shell technique, a combination of viscous cohesives + medium viscosity dispersives has been compared in 3 studies to viscous cohesives. These three studies pooled together showed a statistically significant treatment effect in favour of the combination treatment, however, below the threshold of clinical relevance.

The forest plots showing the various meta-analyses used to construct this table are in appendix 4.

In the figure below, the data network of the mixed treatments comparison is shown. The width of the lines is proportional to the number of studies involved in the pair wise comparison.

Figure 4.5: the graphical presentation of the data network.



Results of the indirect comparisons

The one study comparing treatment 3 to control treatment (study ID 15 Holmberg in 1984) was excluded because drawing conclusions on the relative efficacy of all treatments compared to control treatment via one study only would be too hazardous.

The lower triangle of table 4.4 shows the results of the MTC analysis, together with the results of the direct comparisons (in the upper triangle). The "column treatment" represents the first treatment in the comparison (A), and the "row treatment" represents the treatment to which it is compared (B). The information within the cell provides the number of studies concerned (N), the estimate of the treatment effect and 95% CI. The treatment effect is the number of cells/mm² that was lost after the cataract surgery. The less cells are lost the better. Negative values of treatment effect indicate that treatment A is better than treatment B, i.e. with treatment A less cells were lost than with treatment B, while positive values of treatment effect indicate that treatment B is better than A.

It shows that the estimates of the MTC are generally in accordance with the results from the direct comparisons (with a few exceptions). In addition, the MTC method "fills the blanks" for the comparison of treatment 6 compared to the other treatments. Importantly, all treatment effects are below the level of clinical relevance (100 cells). Consequently, there might be no interest to further differentiate the treatments. The exercise is nevertheless done to illustrate the method (see appendix 4 for methodological details). Results from the MTC indicate that treatment 1 has 70% chance to be the best treatment option (among treatments 1 to 6), followed by treatment 6, which has 25%. The other treatments are almost never the best strategy.

In conclusion, the meta-analyses both direct and indirect show that the protective effect of the various visco-elastic substances is similar.

Table 4.4: direct and indirect comparisons

		Upper Triangle (Direct comparisons only): First Treatment in the Comparison (A) Lower Triangle (MTC analysis): Second Treatment in the Comparison (B)						
		0	1	2	3	4	5	6
Upper Triangle (Direct comparisons only): First Treatment in the Comparison (B) Lower Triangle (MTC analysis): Second Treatment in the Comparison (A)	0				(N=1) -454 (-690, -218)			
	1			(N=2) 66 (-22, 154)	(N=1) -14 (-84, 55)	(N=3) 66 (-112, 245)	(N=1) 198 (99, 298)	
	2		69 (1, 136)		(N=3) -34 (-120, 52)	(N=4) 3 (-70, 77)	(N=2) 51 (-14, 117)	
	3		54 (-8, 114)	-15 (-75, 43)		(N=7) -44 (-115, 27)	(N=5) -25 (-115, 65)	(N=3) -36 (-69, -3)
	4		56 (-8, 118)	-13 (-76, 48)	2 (-50, 54)		(N=5) -63 (-16, 141)	
	5		88 (18, 156)	19 (-51, 87)	34 (-23, 93)	33 (-31, 96)		
	6		27 (-62, 112)	-42 (-132, 46)	-27 (-97, 43)	-29 (-114, 58)	-61 (-150, 27)	

4.9.2.5 *What is the prognostic value of endothelial cell count in predicting postoperative outcome in patients undergoing cataract surgery?*

Medline, 28/08/2007

("Cornea"[Mesh] AND (endothelial cell density OR endothelial cell count)) AND (prognos*[Title/Abstract] OR (first[Title/Abstract] AND episode[Title/Abstract]) OR cohort[Title/Abstract])

28 articles were identified. Of these 28 articles, not one article was relevant for the research question.

4.10 COST-EFFECTIVENESS

As the review on technical and diagnostic accuracy and impact on patient outcome did not show benefit for patients scheduled for cataract surgery, a review on the cost-effectiveness was not performed.

Key message

- **The aim of measuring endothelial cell density is to avoid or predict corneal complications after cataract surgery.**
- **Corneal decompensation is an extremely uncommon, but serious adverse event.**
- **The technical accuracy using contact or non-contact specular microscopy is probably sufficient. Few data on patients suffering from ocular conditions are available. Limits of agreement are ±250 cells/mm².**
- **The diagnostic accuracy was described in only one study, comparing two different types of specular microscopes. No significant difference between the two types was found. Paucity of diagnostic evidence is less of a problem in this respect, because endothelial cell density does not refer to a specific target condition, but is the measurement of a physical parameter.**
- **Direct evidence on the impact of endothelial cell count on patient outcome is not available.**
- **Indirect evidence does not show clear benefit from measuring endothelial cell density in every patient scheduled for cataract surgery.**

5 SCHEIMPFLUG IMAGING SYSTEM

5.1 INTRODUCTION

The Scheimpflug imaging system provides pictures in three dimensions of the anterior segment of the eye. The Scheimpflug camera provides 2D cross sections of the anterior segment along a series of meridians, which can be used for modelling purposes. The view is limited to those areas where light can reach under an illumination angle of 45°, the iridocorneal angle and the ciliary body can not be visualised. Topographic analysis can be made in axial (sagittal), tangential or elevation representation modes. The measurement process lasts less than two seconds and minute eye movement are captured and corrected simultaneously. Pentacam®, Nidek EAS-1000® and Ziemer Galileo® are trademarks for this technique.

The potential capacities of the Scheimpflug imaging system are (such as described by Oculus USA Ophtalmic diagnostic devices)

- Topographic analysis of the corneal front and back surfaces
- Analysis and quantification of the corneal thickness (pachymetry)
- Analysis and quantification of lens opacification (pre and post operative cataract monitoring)
- Consideration of the influence of the posterior corneal surface (true net power, keratometric power deviation) for calculating IOL's for post LASIK (laser assisted in situ keratomileusis) patients, post PRK (photorefractive keratectomy) and RK (refractive keratectomy) interventions
- Comparison of changes of the cornea before and after refractive surgery (maps and numerical values)
- 3D analysis of the anterior segment of the eye: angle and volume of the anterior segment (monitoring of glaucoma)

5.2 RESEARCH QUESTIONS

In consultation with the ophthalmology experts, the main clinical indication chosen for this review is the preoperative exclusion of subclinical keratoconus in patients scheduled for corneal refractive surgery.

The research questions for this review were:

1. What is the place of the Scheimpflug imaging system in the clinical pathway?
2. What is the technical accuracy of the Scheimpflug imaging system?
3. What is the diagnostic value of the Scheimpflug imaging system for the preoperative detection of subclinical keratoconus in a patient scheduled for refractive surgery?
4. What is the impact on patient outcome of the Scheimpflug imaging system in refractive surgery?
5. What is the cost-effectiveness of the Scheimpflug imaging system in patients scheduled for refractive surgery?

5.3 PLACE IN THE CLINICAL PATHWAY

Keratoconus is a non-inflammatory ecstatic dystrophy characterized by a progressive thinning, steepening and apical protrusion of the cornea[85].

It results in irregular astigmatism and myopic shift, causing gradual impairment of vision. ECRI 2004 reported that prevalence varied considerably across studies, ranging from 1/25.000 to 1/200 people[8].

Patients with keratoconus feel dissatisfaction with vision correction provided by glasses or contact lenses and they expect a greater amelioration from surgery. Surgical refractive surgery procedures have been developed to permanently correct myopia such as photorefractive keratectomy (PRK) or laser-assisted in situ keratomileusis (LASIK). According to Ambrosio, there is a self-selection of these patients in surgery candidates, and 1 - 6% of myopic patients who have vision-correction surgery have keratoconus or are suspected of having keratoconus or other forms of corneal ectasia[85]. But, the patients with keratoconus often have a poor outcome and may have progressive ectasia after LASIK and photorefractive keratectomy. Additional thinning of the cornea in keratoconus may contribute to a progression of the disease and may lead to the need for a corneal transplant. The presence of a keratoconus is therefore a contra-indication for refractive surgery.

The diagnosis of keratoconus is currently realized by history of progressive decreased vision, slit lamp biomicroscopy, retinoscopy and refraction (irregular astigmatism and waterdrop or scissors red reflex) and computed corneal topography also called videokeratography (for central and inferior steepening) and keratometry (irregular mires and steepening)[86]. Moderate to severe keratoconus is usually diagnosed by classical visual examination with keratometry and slit-lamp biomicroscopy during adolescence or young adult age. A patient with a known keratoconus is not a potential candidate for refractive surgery. The goal of preoperative testing is to exclude the few patients who have an undiagnosed form (mild or subclinical forms) of keratoconus, not detected by classical examination and who are candidates for refractive surgery.

Several additional methods are available to screen surgery candidates: the computerized corneal topography (CCT) and the pachymetry that can be realized by several methods: ultrasound, Orbscan® or Scheimpflug imaging system.

The cornea of patients with early or mild keratoconus may appear normal by keratometry and slit-lamp biomicroscopy but in even very mild cases of keratoconus, corneal protrusion is detectable by computerized corneal topography[8]. CCT provides a color coded topographical image of the cornea by incandescent light, also known as videokeratography (based on Placido disk method), for mapping of the surface curvature of the cornea. A series of illuminated rings are projected on to the corneal surface. A video camera captures the reflected lights rings measurements, to create a computerised three dimensional map of the cornea: the corneal topography. CCT can also be realized by the Orbscan II system that combines a videokeratograph and a pachymeter in the same device.

To detect subclinical keratoconus, the measurement of corneal thickness by pachymetry may also be used. This is performed either by a direct contact ultrasound method, either by non contact methods such as the Orbscan® II system (a scanning optical slit device) or the Scheimpflug imaging system (rotating Scheimpflug camera measurement). The corneal topography provides only a view of the anterior face of the cornea. The pachymetry may investigate local variations of corneal thickness. Ultrasound pachymetry is fast, reproducible and requires little training. It is the least expensive method. However, the necessity of direct contact with the cornea introduces the risk of infection and corneal trauma[8].

The Obscan® II system is a hybrid device that includes a slit lamp and a Placido disk method. It can be used as videokeratograph for the corneal topography and for pachymetry of the complete corneal area and the depth of the anterior chamber of the eye.

Difficulties have been reported in patients with unsteady gaze, frequent blinking, poor tear films and excessive tearing. It provides reproducible measurements but commonly calculates a greater corneal thickness than either ultrasound or optical measurements of the same cornea[8].

The Scheimpflug imaging system consists of a rotating Scheimpflug camera (25 to 50 pictures in 1 to 2 seconds which allow the reconstruction of three dimensional structures). Our systematic search did not find an HTA report, guidelines or systematic reviews describing the potential limitations or adverse effects of the Scheimpflug imaging system. The Scheimpflug can only image areas where light can go (and reflect back to the camera). Strong reflection of light irises can give errors in the ACD mapping, the iridocorneal angle is not always reliable and patients need to hold still for a couple of seconds.

5.4 FORMAL EVALUATION - METHODS

5.4.1 Search methodology

There is not an existing MeSH term for Scheimpflug or Pentacam; thus the terms were used as a text word.

An additional search was done on refractive surgery in Medline and in the CRD database such as described below:

Database: Ovid MEDLINE(R) 1950 to Present with Daily Update (20/0507)

Search Strategy:

---

1 *Keratectomy, Photorefractive, Excimer Laser/ (1870)

2 *Keratomileusis, Laser In Situ/ (2204)

3 1 or 2 (3793)

4 Pentacam.mp. (35)

5 scheimpflug.mp. (342)

6 *Diagnostic Techniques, Ophthalmological/ (1368)

7 orbscan.mp. (239)

8 ultrasonic pachymetry.mp. (160)

9 4 or 5 or 6 or 7 or 8 (2035)

10 3 and 9 (127)

The search in Embase (11/05/07) using the terms “Pentacam AND [humans]/lim AND [2003-2007]/py” identified 42 articles. An additional search with the terms “'keratoconus'/exp AND scheimpflug” found 7 articles.

For the CRD database (10/05/07), the terms “Pentacam”and “Scheimpflug” have been used. Only one article (on cataract) was found.

We also searched (20/05/07) the Cochrane database of systematic reviews (1 relevant from 73 references found with the term “eye”) and HTA reports in the Centre for Reviews and Dissemination (CRD) databases with the terms “refractive surgery OR PRK OR LASIK”: 31 references were founded.

A search with (("Keratoconus"[Mesh])) AND (specificity[Title/Abstract]) in Medline (11/06/07) yielded 23 articles. Additional searches in clinical queries with (Scheimpflug) AND (specificity[Title/Abstract]) and with (pentacam) AND (specificity[Title/Abstract]) yielded no results.

Discarding duplicates, a total of 234 articles were identified. (Figure 5.1)

5.4.2 Selection of the references:

The articles were subsequently selected based on title and abstract:

Inclusion criteria:

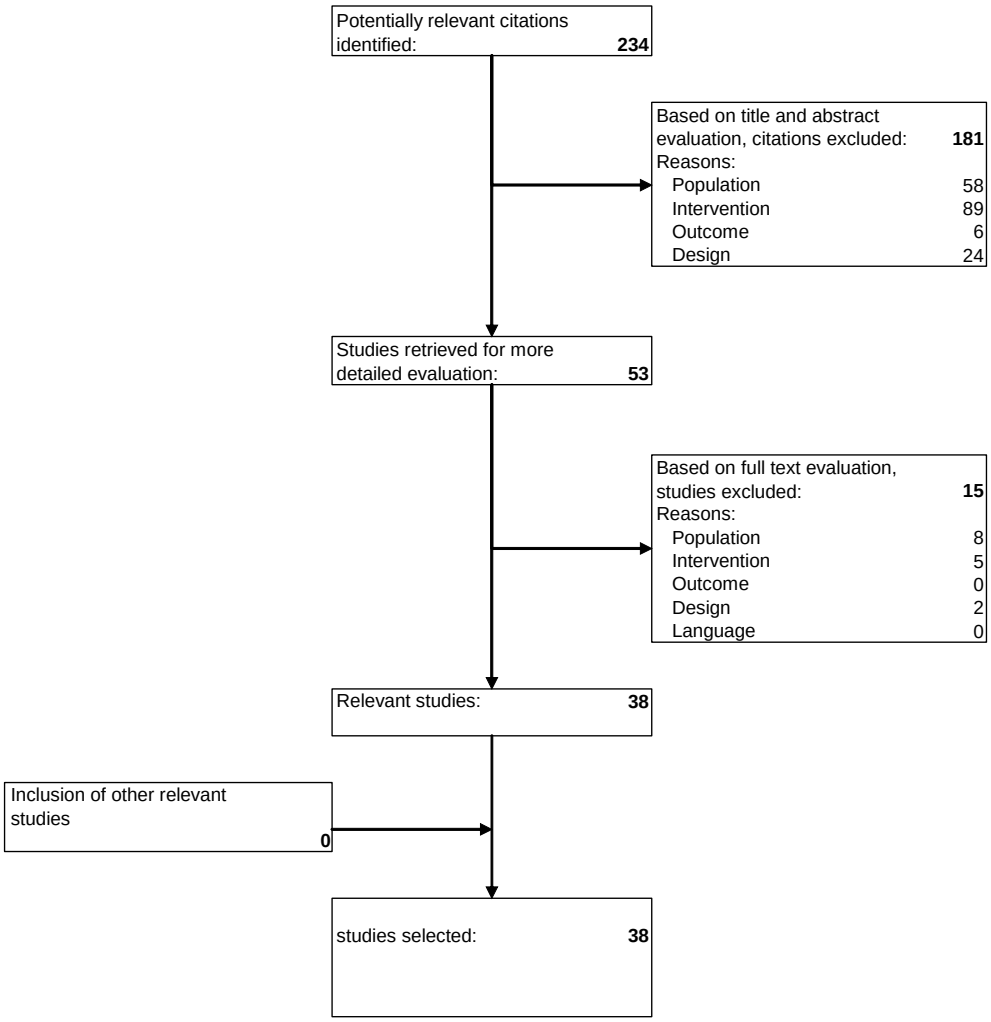
- Diagnostic accuracy studies
- Scheimpflug imaging system techniques or pachymetry or corneal topography
- Refractive surgery
- Keratoconus

Exclusion criteria:

- Patients, interventions or outcome out of our clinical question
- Design: retrospective data
- Language (Japanese, Chinese)
- Studies including < 10 eyes

Based on the full text 13 studies were excluded: 8 with a population[87-94] and 5 with an intervention[95-99] not in relation to our clinical question. Two studies[100, 101] have been excluded because they were not original studies but narrative reviews.

Figure 5.1: flow chart of literature search on Scheimpflug imaging system



5.4.3 Quality appraisal

For the quality appraisal, similar checklists were used as in the previous chapter, i.e. the INAHTA checklist for HTA reports, the checklists of the Dutch Cochrane Collaboration for systematic reviews and the QUADAS checklist for the diagnostic accuracy studies.

5.5 TECHNICAL ACCURACY

Our systematic review found 15 studies on this topic. Three studies[102-104] did not consider the Scheimpflug but other techniques such as Orbscan or ultrasound, and were subsequently excluded. One study was excluded because it was limited to one single eye[105]. Two others studies were excluded because they considered the measurement of the anterior chamber of the eye[106, 107]. Another study was excluded because of a retrospective design prone to bias[108]. Therefore 8 studies remained[109-111 112-114 115 116]. More details are given in the evidence tables (appendix 8).

All studies except one[111] compared Scheimpflug imaging system with ultrasound devices (US). Some studies dealt with more devices. The study of Elbaz[113] gave only comparative results with US for the measurement of the anterior chamber depth.

Ultrasound pachymetry is considered as the gold standard for this indication in most publications except one[112]. Ultrasound pachymetry has a high degree of intraoperator, interoperator and interinstrument reproducibility for the measurement of central corneal thickness:

The intra and inter operator reproducibility seems satisfactory for the Scheimpflug and there is a good correlation between the results of the Scheimpflug and US pachymetry for the measurement of the corneal central thickness. The different methods (Scheimpflug camera, ultrasonic pachymetry) have highly satisfactory repeatability[110]. In the study of Barkana, the coefficient of interoperator reproducibility for the Scheimpflug imaging system Scheimpflug system was 1.10% and the 95% limits of agreement were -10.2 µm to + 11.9 µm in healthy patients. Mean difference between Scheimpflug imaging system and US was 6.09 µm. The values were similar to those obtained with an US pachymeter. The study of Fujioka[114] confirmed that the corneal central thickness measured by Scheimpflug or US methods correlated well with one another. In some studies[112], the Scheimpflug imaging system was superior to US in healthy eyes with narrower limits of agreement within and between observers. In other studies[115] however, the results are better for US. In the study of O'Donnell on normal corneas, the repeatability 95% limits of agreement were -18.3 to + 17.7 µm for US and -24.1 to + 21.1 µm for Scheimpflug imaging system.

One study[116] compared the results of the Scheimpflug imaging system versus US pachymetry in a group of patients with myopia and in a group with keratoconus (mild, moderate or severe). In myopia and mild keratoconus, the results between Scheimpflug imaging system and US were not significantly different for the measurement of corneal thickness. In moderate and severe keratoconus, the Scheimpflug imaging system showed better reproducibility than US pachymetry.

5.6 DIAGNOSTIC ACCURACY

Our systematic review found 4 HTA reports. The HTA report of ECRI[8] relates to the detection of keratoconus by Pre-Lasik pachymetry examination specifically. It had a good score (9 Yes 3 Partly 5 No) on the INAHTA checklist: It is based on a systematic search, the criteria for the study selection are well described and the quality of the included studies is discussed. In the other HTA report, the part relating to the diagnosis[117] is based on expert opinion: there is no description of the search methods or scientific references cited for this part. Two HTA reports did not consider the diagnostic aspect[118, 119] and are thus not considered in this report. The systematic review of the Cochrane database[120] used the good quality methodology as a rule in the Cochrane database. One guideline treated refractive surgery[7]. The part relating to the diagnosis is also based on expert opinion, with no description of search methods or scientific references. The guideline provided grades of evidence and grades of recommendation.

The systematic review of the interventional procedure programme of NICE[117] recommends that in addition to standard ophthalmic examination (including refraction), corneal topography and measurement of corneal thickness are required to exclude keratoconus preoperatively and to evaluate the residual stromal thickness after surgery. The cited methods are US pachymetry and computerised topography (Orbscan). This is however not supported by references and levels of evidence are absent. The guideline on refractive surgery of the American Academy of ophthalmology recommends as preoperative evaluation the following elements: visual acuity without correction, computerized corneal topography, corneal pachymetry, measurement of pupil size in low-light conditions, evaluation of tear film and cycloplegic refraction. This is, in this guideline, an important

recommendation (A) based on a poor level of evidence (III) such as expert consensus. Not one study was cited on preoperative tests.

In addition, 14 original studies were identified. The QUADAS checklist has been used for the two diagnostic accuracy studies (Kalin 1996[121] 7Y, 5U, 2N and Maeda 1994[122] 6Y, 6U, 2N). There are 3 prospective case series with candidates for refractive surgery[123-125].Four studies are case control studies comparing a group of known keratoconus patients with another group of patients[126-128, 85]. One study has been excluded because of the retrospective design[129] and four other because it was not a clinical study but a physiological or technical study[130 131-133 134]. More details are given in the evidence tables in appendix 8.

The study of Klein[133] evaluated 27 eyes of 25 patients (from 1555 patients) who developed ectasia with no apparent preoperative risk factors and report the preoperative characteristics of those patients. Many of these eyes had topography that might have been considered suspicious for subclinical keratoconus. Eight eyes with ectasia post LASIK had no sign of apparent preoperative risk factors on topography or pachymetry (US or Orbscan).

5.6.1 Computerized Corneal Topography

According to ECRI, the primary reason for performing CCT in the LASIK clinic is to detect the few individuals who present with undiagnosed keratoconus or other corneal abnormalities[8]. CCT, also called videokeratography, is considered the "gold standard" technique for diagnosing keratoconus not detected by conventional clinical evaluation.

In a series of 91 candidates for refractive surgery, screening with videokeratography found definite keratoconus in 2 patients and suspected keratoconus in 3 others, missed by conventional clinical evaluation[124]. Wilson found 3/53 (5.7%) patients with definite keratoconus[123]. Ambrosio found 13 eyes (in 8 patients) with subclinical keratoconus and 6 eyes (in 4 patients) with definite keratoconus in a screening study of 1392 consecutive candidates for refractive surgery[125]. Only 4 of the 19 eyes with keratoconus had signs on corneal biomicroscopy.

In the study of Kalin[121], 5/5 keratoconus were diagnosed by videokeratography (expert system classifier) and 3 were false positives, versus keratoconus diagnosed by conventional findings. In another study[122], all 22 previously diagnosed keratoconus patients were diagnosed by videokeratography (expert system classifier) and there were 3 false positive. In a validation test, 25/28 keratoconus were diagnosed with one false positive. In these studies, the sensitivity for the videokeratograph ranged from 89 to 100%, the specificity from 96 to 100%, and the accuracy from 96 to 97%. The positive predictive value was 63 to 96% and the negative predictive value was from 96 to 100%. One study[126] compared three methods using videokeratography and found better results with the Expert system classifier.

5.6.2 Ultrasound pachymetry

Ultrasound pachymetry is considered as the reference test for pachymetry. The ECRI 2004 HTA report[8] studied the evidence for the detection of keratoconus by pre-LASIK pachymetry examination using ultrasound pachymetry and Orbscan II pachymetry. The report dealt on severe to mild keratoconus. Subclinical keratoconus is not considered. It included one screening study[125] and 6 case control studies. In patients with severe keratoconus, US pachymetry is able to distinguish between patients with overt keratoconus and control patients. For mild keratoconus, the data suggest but not prove, that ultrasound may be able to identify patients with mild keratoconus (based on 2 studies with conflicting results[135, 125]. For mild keratoconus in the favourable study by Ambrosio et al. sensitivity was 66.2% and specificity 80.9% at the threshold of 515 µm. With a disease prevalence of 0.7%, the positive predictive value was only 3.0%: most patients diagnosed with mild keratoconus were false positive. For a theoretical prevalence of 6%, the positive predictive value of US pachymetry would increase only to 18%. An important number of patients with false positive results would then be excluded for LASIK.

The negative predictive value however was close to 100% at every threshold. Patients with a negative diagnosis for keratoconus with US pachymetry are almost certain not to have it. Only one patient for every 300 with a negative result for keratoconus will mistakenly undergo LASIK. The ECRI report concludes that US pachymetry does not have sufficient positive predictive value to warrant its use as a stand-alone technology to screen for keratoconus. Ultrasound may however be useful as a primary screening tool. Patients testing positive could be referred for further screening by CCT.

Our systematic search did not find any study on the diagnosis of subclinical keratoconus with ultrasound pachymetry.

5.6.3 Orbscan pachymetry

The ECRI report cites 2 case control studies on the capacity of Orbscan II pachymetry to accurately detect cases of keratoconus[136, 128]. Our search found no more studies on this topic.

The Orbscan II system can realize both pachymetry and CCT but only pachymetry is studied in the ECRI report. The Orbscan II system can distinguish between control patients and patients with severe keratoconus (based on a single case control study with a retrospective design Pflugfelder 2002). For patients with mild keratoconus the data do not support the use of Orbscan II pachymetry (based on the study of Rao 2002). The strength of evidence to support this conclusion is weak.

Our systematic search did not find any study on the diagnosis of subclinical keratoconus with Orbscan II pachymetry.

5.6.4 Scheimpflug imaging system

Our systematic search found only one clinical study with Scheimpflug imaging system[85]. This case control study concludes that Scheimpflug imaging system can distinguish between patients with mild or moderate keratoconus (diagnosed with classical corneal topography findings) and normal patients.

Our search did not find studies on the use of Scheimpflug imaging system for the screening of subclinical keratoconus in candidates for refractive surgery.

5.7 IMPACT ON PATIENT OUTCOME

The impact on patient outcome is defined as the influence of the test on the ultimate outcome of the patient, i.e. visual acuity, or on intermediate outcomes such as management decisions. The actual impact of the test can be evaluated directly in randomized controlled trials, or indirectly by assessing whether the test is used as a selection criterion for the treatment that has proven efficient.

5.7.1 Direct evidence

An additional search was done (28/07/09) in Pubmed with ("Keratoconus"[Mesh] AND Scheimpflug) AND (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract])). No articles were found. Another search was done in EMBASE (28/09/07) with the terms 'keratoconus'/de AND Scheimpflug AND 'randomized controlled trial'/de. No study was found.

5.7.2 Indirect evidence

For indirect evidence we searched in the guideline[7] previously considered in this report, in the HTA reports and in systematic reviews if Scheimpflug has been used for the patient selection before refractive surgery. We searched in CRD databases (28/09/07) with the term 'refractive' and we found 38 references.

The search of systematic reviews has been done in the Cochrane library (28/09/07) with the terms 'refractive' and we found 7 references. Two were relevant recent publications: one Cochrane systematic review[120] and one NICE HTA report[117]. The Scheimpflug is not used in the guideline or in the original studies of the systematic review or the HTA report.

5.8 COST-EFFECTIVENESS

Our systematic search did not find evidence for the use of Scheimpflug in detecting subclinical keratoconus in patients scheduled for refractive surgery; the cost-effectiveness question has thus not been developed.

Key points

- **This report studied the place of Scheimpflug imaging system to exclude subclinical keratoconus in patients scheduled for corneal refractive surgery.**
- **The Scheimpflug has the advantage of being a non-contact device. Mapping of the corneal thickness is obtained after one single measurement procedure.**
- **The reproducibility intra and inter operator has been described as satisfactory for Scheimpflug imaging system and there is a good correlation between the results of Scheimpflug imaging system and US pachymetry for the measurement of the corneal central thickness.**
- **One study found better reproducibility with the Scheimpflug imaging system (than with US pachymetry) in moderate and severe keratoconus but not in mild keratoconus.**
- **Scheimpflug imaging system can distinguish between severe or mild cases of keratoconus and control patients.**
- **Further research is awaited to support the Scheimpflug imaging system for the screening of subclinical keratoconus in candidates for corneal refractive surgery.**

6 AGE RELATED MACULAR DEGENERATION

Age related macular degeneration (AMD) is the most common cause of blindness and severe visual impairment in industrialised nations. AMD is a disease of the retina characterised by the accumulation of metabolic products in the macula. AMD causes vision disorders such as blurred vision of the central part of the visual field, leading finally to a dark spot. A large population based study in Europe found the prevalence of any form of age related macular degeneration to be 3.32 (95% CI 2.52-4.13) in people over 65 years of age. Prevalence increases with increasing age, with a steep increase in people 80 years or older[137]. This European prevalence is similar to the prevalence found in the United States by the Eye Diseases Prevalence Research Group[138]. Age and a positive family history for AMD are well known risk factors. The impact of genetic factors has been established in recent years. Smoking is the most important life style factor increasing the risk of AMD.

The Age Related Eye Disease Study[139] used the following classification:

No AMD (AREDS category 1) the control group for the AREDS, has no or few small drusen (<63 microns in diameter).

Early AMD (AREDS category 2) consists of a combination of multiple small drusen, few intermediate drusen (63 to 124 microns in diameter), or RPE abnormalities.

Intermediate AMD (AREDS category 3) consists of extensive intermediate drusen, at least one large druse (≥125 microns in diameter), or geographic atrophy not involving the center of the fovea.

Advanced AMD (AREDS category 4) is characterized by one or more of the following (in the absence of other causes):

- Geographic atrophy of the retinal pigment epithelium (RPE) and choriocapillaris involving the center of the fovea
- Neovascular maculopathy such as:
    - Choroidal neovascularization (CNV)
    - Serous and/or hemorrhagic detachment of the sensory retina or RPE
    - Lipid exudates (a secondary phenomenon resulting from chronic leakage from any source)
    - Subretinal and sub-RPE fibrovascular proliferation
    - Disciform scar

The neovascular form is responsible for 80-90% of cases of severe vision loss due to AMD[140]. Neovascular AMD is classified on the basis of the type of leakage pattern observed on intravenous fluorescein angiography (diagnostic retinal photographic imaging), and the location of abnormal blood vessel growth (extrafoveal, juxtafoveal, subfoveal). Angiographic patterns of leakage for choroidal neovascularization, classic and occult, have prognostic and treatment implications.

Therapeutic options are limited for the treatment of the early stages of AMD, whereas several therapies are available for the exudative form. In the AREDS, the participants who benefited from antioxidant vitamin and mineral supplementation were those with either intermediate AMD, or advanced AMD in one eye.

For patients with neovascular ARMD, Clinical Evidence rates three interventions as beneficial to patients[141]: antiangionesis using pegaptanib and ranibizumab, and photodynamic treatment with verteporfin. Antiangiogenesis treatment using anecortave acetate is rated as likely to be beneficial. There is a trade off between benefit and harm for thermal laser

photocoagulation. External beam radiotherapy and transpupillary thermotherapy have unknown effectiveness and antiangiogenesis using interferon alfa-2a and submacular surgery are harmful rather than beneficial.

Three tests were evaluated for the clinical value in patients with age related macular degeneration: fluorescein angiography, indocyanin green angiography and optical coherence tomography.

6.1 FLUORESCEIN ANGIOGRAPHY

For fluorescein angiography, a fluorescent dye is applied intravenously after which its distribution is monitored in the blood vessels of the eye. The invasive character and possible allergic reactions are major disadvantages of this investigation.

A search for systematic reviews using the following search terms ("Fluorescein Angiography"[Mesh] AND "Macular Degeneration"[Mesh]) AND systematic[sb], yielded 20 articles, of which one was relevant to the report[142]: guidelines for the interpretation and coding findings in the SST trial. The content of this publication will be discussed in the section on technical accuracy.

6.1.1 Technical accuracy for age related macular degeneration

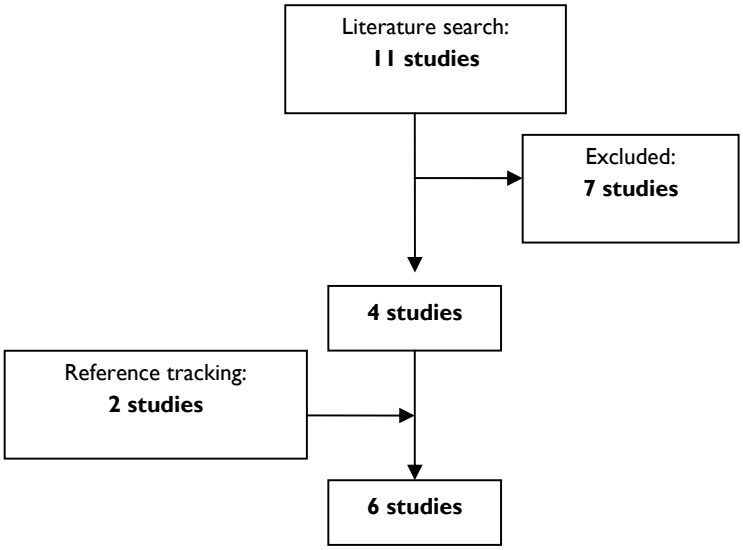
According to the guidelines by the AAO, fluorescein angiography should be performed and interpreted by an individual experienced in managing patients with neovascular AMD if CNV is suspected.76-78 [A:I]. In addition, the physician must be aware of potential risks associated with this procedure; severe medical complications may occur, including death (approximately 1 in 200,000 patients). Each angiographic facility should have in place a care plan or an emergency plan and a clear protocol to minimize the risks and to manage any complications.[A:III]

The review on technical accuracy was limited to interobserver and intraobserver variability.

Search terms were "Fluorescein Angiography"[Mesh] AND "Macular Degeneration"[Mesh] AND "Observer Variation"[Mesh].

The search yielded 11 articles of which four were relevant for the review. An additional 2 studies were found by reference tracking.

Figure 6.1: flow chart of study selection for fluorescein angiography



Van Velthoven et al. have shown that agreement between two observers for the presence of leakage on fluorescein angiography was moderate (kappa=0.51) before deciding on retreatment with photodynamic therapy[143].

Another study showed fluorescein angiograms in two random sequences to 16 different readers. The mean kappa for the classification in classic, occult or mixed was 0.64 +/- 0.11 for intraobserver variation, with a range from 0.44 to 0.89. For interobserver variation, the intraclass correlation coefficients were 0.66 (95% CI 0.56, 0.77) for series A and 0.55 (95% CI 0.43, 0.67) for series B[144].

The angiograms of 6 patients included in the TAP trial were read by 8 graders, including two TAP-certified ophthalmologists[145]. Each patient's baseline angiogram was evaluated to determine whether the CNV lesion was predominantly (≥50%) classic. For each follow-up angiogram, at 3, 6, 12, and 24 months, the grader was required to determine whether fluorescein leakage was present. Six months after the initial gradings, each reader was again presented with the baseline angiogram for each patient without knowledge of the previous grading or of the clinical course. In grading initial visit and follow-up visit angiograms, the overall concordance rates were 81% and 82%, respectively. Concordance rates were not statistically different between the groups as a whole when compared with the gradings of the two TAP-certified ophthalmologists. When initial visit angiograms were regraded, an intraobserver variability of 17% was noted. Overall, gradings were discordant with the majority opinion in approximately 19% of decisions.

Friedman et al. found the interobserver agreement of 21 retina specialists from perfect concordance for a small, classic membrane to near-random classification for a complex pattern. Interobserver agreement of membrane size was most variable for intermediate size lesions (mean kappa coefficient =.40)[146].

Barbazetto et al.[147] published fluorescein angiographic guidelines for evaluation and treatment in the context of the TAP and VIP report. Fluorescein angiography was performed on all patients at enrollment and at regular 3-month follow-up visits through 2 years. Photographic materials forwarded to the Wilmer Photograph Reading Center were reviewed by masked graders. Reliability (kappa values) of grading selected characteristics was based on a 10% regrading of baseline visits. The kappa statistics for agreement of identification of lesion characteristics by the Wilmer Photograph Reading Center for these trials ranged from 0.70 to 0.85.

Solomon[142] described the guidelines used in the SST trial. At baseline, two independent trained readers from the SST reading centre at Johns Hopkins assessed the photographs, and discussed any disagreement. A 5% random sample was reassessed and kappa statistics were derived: for the lesion (%) that was classic CNV (<50%, ≥50%): kappa was 0.90 (0.70–1.00), for occult CNV (absent, present) 0.47 (0.23–0.71), for lesion size (MPS disk area category) 0.78 (0.51–0.80) and for CNV subfoveal 1.0 (no confidence interval given).

6.1.2 Place in the clinical pathway

Fluorescein angiography is used to classify patients in having geographic atrophy or choroidal neovascularisation (CNV), and to describe lesions in terms of classic lesions or occult lesions and determine the size of the neovascular membrane.

In addition, fluorescein angiography is used to monitor disease progression and treatment effects.

The AAO guideline on the diagnosis and management of patients with AMD, recommends fluorescein angiography when the patient complains of new metamorphopsia or has unexplained blurred vision, and/or when clinical examination reveals elevation of the RPE or retina, subretinal blood, hard exudates, or subretinal fibrosis and in the following situations:

- To detect the presence of and determine the extent, type, size, and location of CNV and to calculate the percentage of the lesion composed of or consisting of classic CNV.
- If laser photocoagulation or verteporfin PDT is being considered, the angiogram is also used as a guide to direct treatment.
- To detect persistent or recurrent CNV following treatment.
- To assist in determining the cause of visual loss that is not explained by the clinical examination.

In the MPS, TAP, and VIP protocols, a 30-degree photographic field centered on the macula was used. Stereoscopic fluorescein angiography offers an advantage over nonstereoscopic studies for detecting the presence, extent, type, and location of the CNV.

6.1.3 Diagnostic accuracy for age related macular degeneration

The search for diagnostic accuracy of fluorescein angiography, using the following search terms ((("Fluorescein Angiography"[Mesh] AND "Macular Degeneration"[Mesh])) AND (specificity[Title/Abstract]) yielded 13 articles. None was found to be relevant to the research question. However, as fluorescein angiography is to be considered the gold standard for CNV, this is to be expected. Other reports have also found that evidence on the sensitivity and specificity of fluorescein angiography is not available.

6.1.4 Impact on patient outcome

The impact on patient outcome is defined as the influence of the test on the ultimate outcome of the patient, i.e. visual acuity, or on intermediate outcomes such as management decisions. The actual impact of the test can be evaluated directly in randomised controlled trials, or indirectly by assessing whether the test is used as a selection criterion for the treatments which have proven efficacy.

6.1.4.1 Direct evidence

A search for the identification of trials :((("Fluorescein Angiography"[Mesh] AND "Macular Degeneration"[Mesh])) AND (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract])) yielded 144 articles. Not one article was possibly relevant.

6.1.4.2 Indirect evidence

Indirect evidence for fluorescein angiography was evaluated by assessing whether FA was used as a selection criterion for effective therapies. Various therapies have been shown to be effective in patients with exudative AMD. Their effectiveness, however, depends on the location and type of the lesions.

A Cochrane review identified fifteen trials (2064 participants) on laser photocoagulation[148]. Data on the progression of visual loss could be extracted from five of the eight trials of direct photocoagulation of the CNV versus observation. The treatment effect was in the direction of harm in all studies at three months follow up (RR 1.41, 95% confidence intervals (CI) 1.08 to 1.82). After two years the treatment effect was in the direction of benefit (RR 0.67, 95% CI 0.53 to 0.83).

One study comparing perifoveal photocoagulation or observation of subfoveal CNV found benefits that were statistically significant only at two years (RR 0.36, 95% CI 0.18 to 0.72). Other comparisons did not demonstrate differences. In the medium to long term laser photocoagulation of CNV slows the progression of visual loss in people with neovascular AMD. This treatment has not been proven beneficial in patients with subfoveal AMD.

With the advent of modern pharmacological therapies, and concern for the impact of iatrogenic scotoma in subfoveal CNV, laser photocoagulation of subfoveal CNV is not recommended.

Until recently, the only proven treatment for central (subfoveal) neovascular AMD was photodynamic therapy (PDT) using verteporfin. The technique consists of injecting a photosensitive drug (verteporfin) that is selectively up-taken in the diseased area of the eye. When the drug is activated by light emitted by a non-thermal laser, it selectively destroys neovascularisation areas. The procedure is costly, basically due to the cost of the drug (the price of 1 vial of verteporfin was € 1,150 in 2006) and to the fact that several treatment sessions are required (with an average 5.5 sessions for two years). Treatments are administered every three months with retreatment typically recommended if there is ongoing leakage on fluorescein angiography. Two pivotal trials are available (TAP and VIP studies) showing a combined relative risk (RR) of losing 3 or more lines of visual acuity of 0.80 [95% CI 0.70-0.91] after one year of treatment and 0.77 (95% CI 0.69-0.87) after 2 years, according to the meta-analysis conducted by the Cochrane Collaboration. Patients with evidence of occult choroidal neovascularisation (CNV) are found to have a RR of losing 3 or more lines of visual acuity per year of 0.90 (95% CI 0.73-1.11) and 0.34 (95% CI 0.22-0.51) if occult CNV was absent. These differences are maintained at 2 years[149]. These subgroups analyses have to be treated with caution, as they were defined post-hoc. The lesions that responded most favourably to treatment were: the predominantly classic lesion [RR of losing 3 or more lines of visual acuity was 0.54 (95% CI 0.41-0.79) at 1 year and 0.60 (95% CI 0.48-0.75) at 2 years] and the occult lesion with no classic component at 2 years [RR of losing 3 or more lines of vision was 0.77 (95% CI 0.64-0.92)]. In the USA, the cost per quality adjusted life year (QALY)[150] has been estimated at 31,103 US dollars, and according to NICE[151] this treatment is at the limit of what is considered an effective use of healthcare resources. Early treatment of predominantly classic subfoveal CNV appears to increase efficacy. The aim should be to try and reduce as much as possible the time between diagnosis and patient treatment, to apply photodynamic therapy by ophthalmologists experienced in the diagnosis and treatment of macular disease, and to create units specialising in macular disease with a fast patient referral. Verteporfin is currently reimbursed by the Belgian Health Insurance in case of active neovascularisation - leakage documented by fluorescence angiography, retinal oedema documented by stereoscopic fluorescence angiography or optical coherence tomography or a similar device and visual acuity of 1/10 or more.

A recent systematic review synthesised the available evidence on pegaptanib and ranibizumab for neovascualr age-related macular degeneration[152]. Two concurrent randomized controlled clinical trials were performed to evaluate pegaptanib as a treatment for neovascular AMD, the VISION trial[153-155]. For 0.3 mg of pegaptanib, an 18% absolute reduction in legal blindness, compared to sham treatment, translates into a number needed to treat of 5.6. Three RCTs evaluated the efficacy of ranibizumab, the MARINA trial[156], the FOCUS trial[157] and the ANCHOR trial[158]. In these trials, the absolute reduction in legal blindness ranged from 17% to 44%. However, it should be noted that differences in baseline proportions of patients with visual acuity less than 6/60 could have affected outcomes at 12 and 24 months, with a markedly higher proportion of patients in the control group (32%) than in the ranibizumab group (23%) in the ANCHOR trial for example.

In the context of this report on ophthalmic tests, it is relevant to note that treatment is not titrated to the disease status of the eye, but is administered continuously for at least one year and will likely be used for all angiographic lesion types of AMD, particularly for large minimally classic and occult lesions where verteporfin may be less effective. Currently, both drugs are reimbursed for that indication in Belgium. The reimbursement is granted in case of active leakage documented with fluorescein angiography, retinal oedema documented by stereoscopic fluorescence angiography, optical coherence tomography or similar devices and limited fibrosis.

6.1.4.3 Prognostic value

(("Fluorescein Angiography"[Mesh] AND "Macular Degeneration"[Mesh])) AND (prognos*[Title/Abstract] OR (first[Title/Abstract] AND episode[Title/Abstract]) OR cohort[Title/Abstract])

Of the 141 articles identified, 5 were selected as potentially relevant for the research question. One article was in Chinese, and therefore not included.

In the untreated arm of the Macular Photocoagulation Study group, patients with extrafoveal lesions showed a mean visual acuity loss of 7.1 lines compared to baseline at 5 years follow-up, and 60% of untreated eyes had visual acuity of 20/200 or worse. In patients with juxtafoveal lesions, visual acuity deteriorates rapidly, with >80% losing at least 2 lines within 2 years, and almost 90% losing 2 lines in 5 years. In addition, there is a high risk (>90%) that untreated lesions progress to subfoveal lesions. In patients with classic subfoveal lesions, the percentage with visual acuity of 20/200 or worse increased from 36% at baseline to 89% after 4 years[159]. Data from the VIP trial show that in patients with occult with no classic CNV, the number of eyes with visual acuity of 20/200 or worse increased from 0 at baseline to 41 (45%) at 2 years[160].

In the MPS, 26% of fellow eyes initially free of CNV developed photographically documented CNV after 5 years of follow-up. Patients with bilateral CNV at baseline were legally blind in 49% of cases after 5 years, compared to 12% of patients with unilateral CNV at baseline[159].

The risk of developing CNV in patients diagnosed with geographic atrophy has been reported to be 18% (95% CI 4-30) after two years and 34% (95% CI 12-51) after four years if CNV was already present in the fellow eye[161]. Similar findings were reported by the MPS, in which 45% of patients went on to develop CNV in the eye with geographic atrophy during 5 years of follow-up[159]. If no CNV was present, the risk was 2% (95% CI 0-5) at two years and 11% (95% CI 0-21) at four years[161]. Patients with unilateral occult CNV have a significant risk of occult CNV developing in the second eye, and the type of occult disease in the first eye is highly predictive of the type of neovascularized disease in the second eye[162].

Key points

- **Fluorescein angiography is the gold standard for the classification of AMD in geographic atrophy or neovascularisation.**
- **The agreement between and within observers is only fair. Agreement is good in expert reading centres.**
- **The location and type (classic or occult) of the neovascular lesions as documented with fluorescein angiography determines the therapeutic possibilities.**
- **In addition, the location and type of the neovascular lesions has prognostic value.**
- **Photodynamic therapy is guided by the results of the angiogram used in follow-up.**

6.2 INDOCYANINE GREEN ANGIOGRAPHY

6.2.1 Introduction

Fluorescein Angiography (FA) is currently the gold standard to diagnose CNV in patients with Age Related Macular Degeneration (ARMD). FA is however unable to image through hemorrhage or retinal pigment epithelial (RPE) abnormalities and does not image the choroidal vascularization well. In some eyes, FA can only reveal poorly defined or so-called occult CNV.

Indocyanine green angiography (ICGA) is used to diagnose CNV in patients with ARMD since 1990. It is currently used to guide laser treatment of occult CNV associated with ARMD. ICGA is realized by intravenous injection. It should be used with caution, anaphylactic deaths having been reported. The AAO guideline states that an emergency plan and a protocol to minimize risks and manage complications are necessary equal to FA and that a qualified physician should supervise the dye injection[163].

The large ICG molecule is almost completely protein–bound in blood, rendering it relatively permeable to the choriocapillaris. As a result, the dye does not leak extensively through its fenestrations to obscure the deep layers of the choroidal circulation [164]. Moreover, ICG absorbs and emits infrared light to a greater degree than fluorescein and is thus able to image through mildly thick blood. Several forms of CNV have been described: focal CNV, plaque CNV, multifocal CNV or mixed forms (focal and plaque CNV). Finally, areas of late hyperfluorescence (hot spots) may be seen 20 minutes or longer after ICG injections. A hot spot is defined as any area of abnormal hyperfluorescence, in the mid to late stages of ICGA, measuring less than 1 disk area in size. Among 190 newly diagnosed patients (220 eyes) with neovascular ARMD, 16% (30 patients, 34 eyes) were found to have a hot spot[164], with three distinct patterns: polypoidal choroidal neovascularisation (PCV) in 21 eyes (62%), retinal angiomatous proliferation in 11 eyes (30%) and focal occult CNV in 2 eyes (8%). The series included both classic and occult CNV. In 2000, a consecutive series of 374 eyes with characteristics of occult CNV on FA in Caucasian patients of at least 58 years old were retrospectively studied to define the type of lesion found by ICGA. Polypoïdal lesion was considered when one or more focal vascular dilatations in the inner choroid were already visualized in the early phase of ICGA. Fourteen eyes (4%) were diagnosed as PCV in patients with occult CNV[165].

6.2.2 Research questions

1. What is the technical accuracy of indocyanine green angiography?
2. What is the place of indocyanine green angiography in the clinical pathway?
3. What is the diagnostic value of indocyanine green angiography in a patient suspected of or with age macular related degeneration?
4. What is the impact on patient outcome using indocyanine green angiography?
5. What is the prognosis value of indocyanine green angiography in a patient with ARMD?

6.2.3 Technical accuracy

The search was done in PubMed (01/10/07) with the terms "Indocyanine Green"[Mesh] AND "Observer Variation"[Mesh] AND "Macular Degeneration"[Mesh]. Two studies were found [166] [167] One study [167] was not a study on technical accuracy. In Embase, the search was done with the terms 'retina macula age related degeneration'/de AND 'observer variation'/de AND 'indocyanine green angiography'/de and found no study. An additional study[168] has been found during the selection of studies for the diagnosis question.

Watzke et al. [166] compared the results of 3 independent interpreters of stereoscopic fluorescein angiography and late indocyanine green videoangiography in 104 patients with age-related macular degeneration. The kappa between the two methods in identifying serous pigment epithelial detachments (SPEDs), fibrovascular- serous pigment epithelial detachments (FV-SPEDS) and classic choroïdal neovascular membranes (CCNVs) was more than 0.8, which is almost perfect. The agreement for eyes with only late leakage of undetermined source (LLUs) was substantial (0.644). The agreement between the two methods for SPEDs associated with choroïdal neovascular membranes (CNV) was 0.477 which is moderate. The ICG videoangiography agreement between two observers was substantial (K=0.754).

In a recent study[168], 79 eyes with occult CNV previously diagnosed with FA were evaluated independently by two skilled physicians at first with FA alone and then with FA combined with ICGA by fundus camera. Lesions were classified as plaque, focal, multifocal, plaque+focal, no CNV and not evaluable.

By FA alone, 43/79 (54%) eyes were classified equally (K=0.291) by the two physicians. For the ICGA classification of CNV, 57/79 eyes (72%) (K=0.621) were concordant for both physicians. For the classification according to FA and ICGA, the first physician correctly classified 58/79 (73%) eyes (K=0.585) and the second one 54/79 (68%) eyes (K=0.512). K value lower than 0;4 have a low agreement; K between 0.4 and 0.75 agreement is fair to good; K values larger than 0.75 indicate a close agreement.

6.2.4 Clinical pathway

ICGA does not replace fluorescein angiography. The test is performed in addition to FA either separately (the most often) either simultaneously (experimental). ICGA shows some anatomical details not seen with FA and allows a better view of the choroidal circulation.

The test is thus proposed to be used in case of[86]

- occult CNV
- recurrent CNV after treatment (follow-up)
- CNV with retinal pigment epithelial detachment
- polypoïdal chroïdal vasculopathy

The ophthalmologic experts added "retinal angiomatous proliferation" as an indication.

6.2.5 Diagnostic accuracy

6.2.5.1 Evidence search

For this question, we considered the guidelines, systematic reviews selected previously for the report. An additional search was done in Pubmed and Embase.

Indocyanine green angiography is not a MeSH term. Therefore, a global search for angiography was done in pubmed (06/08/07) first: (("Macular Degeneration"[Mesh]) AND ("Fluorescein Angiography"[Mesh])) AND (sensitiv*[Title/Abstract] OR sensitivity and specificity[MeSH Terms] OR diagnos*[Title/Abstract] OR diagnosis[MeSH:noexp] OR diagnostic *[MeSH:noexp] OR diagnosis,differential[MeSH:noexp] OR diagnosis[Subheading:noexp]): 1140 references were found with 76 on indocyanine green angiography diagnosis.

A second Pubmed search was done (04/09/07) with the terms "Macular Degeneration"[Mesh] AND "indocyanine green angiography" AND (sensitiv*[Title/Abstract] OR sensitivity and specificity[MeSH Terms] OR diagnos*[Title/Abstract] OR diagnosis[MeSH:noexp] OR diagnostic *[MeSH:noexp] OR diagnosis,differential[MeSH:noexp] OR diagnosis[Subheading:noexp]): 136 articles were found. 72 were on ICGA diagnosis (duplicates excluded).

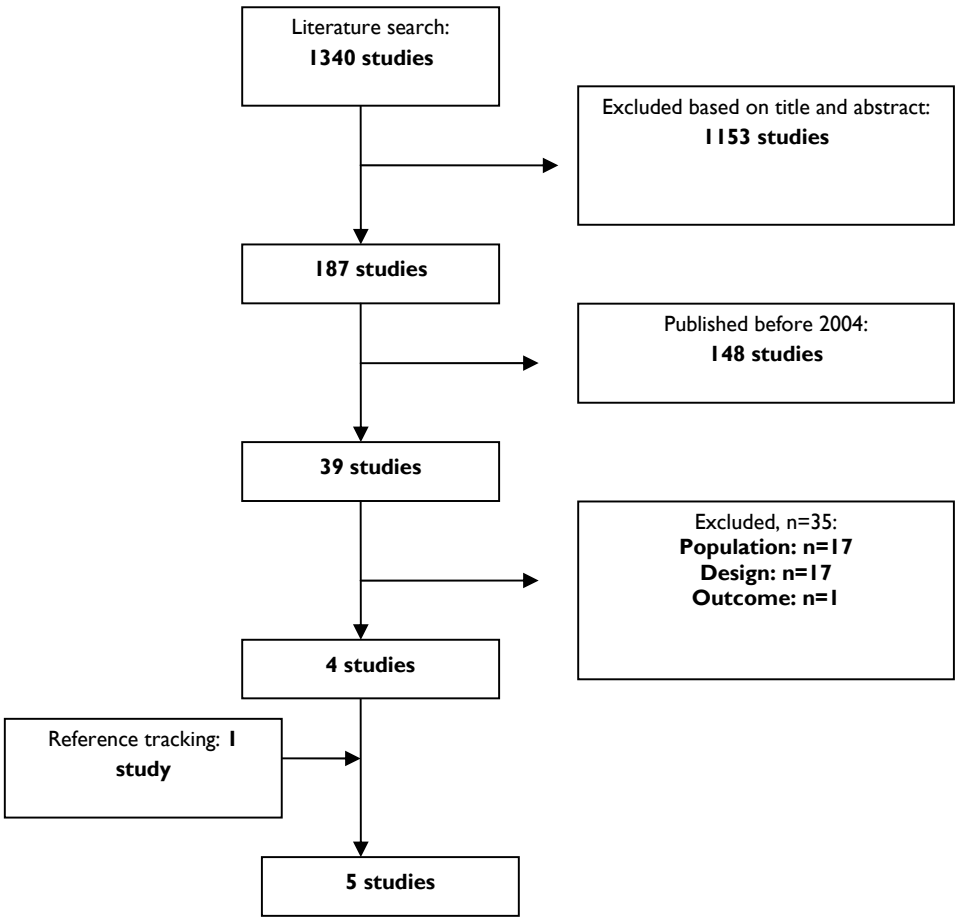
An additional search was done in Embase (03/09/07) using the following search strategy: 'retina macula age related degeneration'/exp AND 'indocyanine green angiography'/exp AND sensitiv* OR detect* OR accurac* OR specific* OR reliab* OR positiv* OR negativ*: 64 references of which 39 on indocyanine green angiography (duplicates excluded).

As the good quality guideline of the American Academy of Ophtalmologogy [6] on ARMD was published in 2006, we limited our additional search to studies published in 2004 or after: 39 articles. Based on the titles and abstracts, we excluded 7 studies for sample size < 10 patients[169-172 173-175] and 6 for design (letter[176], narrative review[177-181]). One study on submacular hemorrhage in Korean patients[182] was also excluded.

The 25 remaining studies were assessed in full text. Ten studies used ICGA and FA as follow-up of treatment effects[183-192]. Two studies used the angiography as an intervention [193, 194]. Nine studies are not diagnostic accuracy studies on ICGA[195] Battaglia Parodi, 2004 #716; Cohen, 2007 #736} [196-201].

Thus four studies remained, including a comparison between angiography and Indocyanine green angiography[168, 202-204]. A systematic review not included in the AAO guideline [6] was found by reference tracking[205].

Figure 6.2: flow ch art of study selection for indocyanine green angiography



Inclusion criteria

- Population: ≥ 10 patients with ARMD (diagnosis or follow up)
- Indocyanine green angiography used for the diagnosis
- Outcome: drusen, occult choroidal neovascular membranes (CNVMs), PCV choroïdal vasculopathy, PED (pigment epithelial detachment), RAP (retinal angiomatous proliferation)
- Design: randomized control trial, diagnosis accuracy study, comparative series, cohort

Exclusion criteria

- Population: < 10 patients, other ocular diseases than ARMD, patients after intervention or treatment
- Oral indocyanine green angiography, fluorescein angiography guided indocyanine green angiography, indocyanine green angiography as part of a treatment procedure
- Design: editorial, letter, narrative review
- Language: Japanese, Chinese

The QUADAS tool was used for the critical appraisal of the four remaining studies with the following scores: 7Y, 6U, 1N for the study of Iranmanesh 2007[203], 6Y, 7U, 1N for the study of Pece 2005[168], 5Y, 7U, 2N for the study of Schneider 2005[202] and 5Y, 5U, 4N for the study of Talks 2007[204]. The two last studies have however a retrospective design.

6.2.5.2 *Results*

GUIDELINES

The guideline of the American Academy of Ophtalmology (AAO) on ARMD cites the indocyanine green angiography as an ancillary test for the diagnosis. It states that indocyanine green angiography may prove useful in evaluating certain types of ARMD such as pigment epithelial detachment, poorly defined CNV, and lesions such as retinal angiomatous proliferation"206, 6.

The guideline refers to a previous report of the AAO focusing on indocyanine green angiography[163]. It specified that ICGA is a technique that can provide images through mildly thick blood, serous fluid and hypertrophied retinal pigment epithelial (RPE) cells. This report concludes however that current literature on ICGA is poor to document the value of ICGA and its absolute and relative indications in the management of retinal disease.

The AAO guideline's conclusions referred also to the retrospective study of Yannuzzi 2001 who analyzed retinal angiomatous proliferation (stage I: intraretinal neovascularization, stage II: subretinal neovascularization and stage III: choroidal neovascularization) in 143 eyes. They found the ICG angiogram not essential for the diagnosis in stage I. However, the ICGA is helpful in making an accurate diagnosis of stage II and stage III.[206]

A prospective analyze of 167 consecutive newly diagnosed patients aged 55 years or older with presumed neovascularized AMD (diagnosed with FA) was performed by Yannuzzi in a mixed racial population[207]. In this series, 13 patients (7.8%) were diagnosed with polypoidal choroidal vasculopathy using ICGA.

ADDITIONAL STUDIES

Our systematic search found 4 recent studies and one systematic review not included in the AAO guideline. Evidence tables are in appendix 9.

The systematic review[205] concluded that ICGA is recommended for identification of polypoidal chroroidal vasculopathy, occult choroidal neovascularization, neovascularization associated with pigment epithelial detachments, and recurrent choroidal neovascular membranes. This recommendation is based on published peer-reviewed articles. The methodology of the systematic review is however poorly described.

One prospective diagnostic study[203] considered 100 eyes of 93 consecutive newly diagnoses of neovascular ARMD. With FA, the diagnoses were classic choroïdal vascularization (CNV) in 15 eyes, minimally classic CNV in 15 eyes and occult CNV in 70 eyes. For the classic CNV diagnoses, there were no additional findings with ICGA.

In patients with minimally classic CNV, ICGA found 4 Retinal Angiomatous Proliferation (RAP) and 1 Polypoidal Choroidal Vasculopathy (PCV). And amongst the patients with occult CNV, 12 were diagnosed with RAP and 13 with PCV.

One study[204] found also that ICGA identifies additional diagnoses in 14.2% of the cases in patients with occult CNV (10 RAP and 9 PCV amongst 111 occult CNV). One study[202] considered patients with pigment epithelial detachment and found that ICGA diagnosed more Retinal Vascular Anomalous Complex than FA. These two studies are however of fair quality with a retrospective design. One study was on technical accuracy[168] and is discussed in that specific section.

6.2.6 What is the impact of ICGA on patient outcome

As described in the previous chapter, the impact on patient outcome is defined as the influence of the test on the ultimate outcome of the patient, i.e. visual acuity, or on intermediate outcomes such as management decisions. The actual impact of the test can be evaluated directly in randomized controlled trials, or indirectly by assessing whether the test is used as a selection criterion for the treatment with proven efficacy.

6.2.6.1 Direct evidence

EVIDENCE SEARCH

Two searches were done (14/09/07) in Pubmed with ("Macular Degeneration"[Mesh] AND "Indocyanine green angiography" AND "Randomized Controlled Trial "[Publication Type]) and with ("Choroidal Neovascularization"[Mesh] AND Indocyanine green angiography AND "Randomized Controlled Trial "[Publication Type]). Another search was done in Embase (14/09/07) with the terms 'subretinal neovascularization'/de AND 'indocyanine green angiography'/de AND 'randomized controlled trial'/de. These searches yielded 13 articles. Considering the small number of articles found, an additional search was done (17/09/07) with the terms: (("Diagnostic Techniques, Ophthalmological"[Mesh] AND "Indocyanine Green"[Mesh]) AND "Macular Degeneration"[Mesh]) AND ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]), which yielded 94 articles. After discarding duplicates, 87 articles were identified altogether.

Not one article was relevant to our research question.

INDIRECT EVIDENCE

Is IGCA used a selection tool for treatment? Do the diagnoses of RAP and PCV made by ICGA have an impact on management?

For these questions we considered the same systematic reviews, HTA reports and guidelines than previously selected in this report.

An additional search for randomized controlled trial has been made in pubmed (17/09/07) with the terms: (Retinal angiomatous proliferation OR polypoidal choroidal vasculopathy) AND (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract])) and in Embase with the terms retinal AND angiomatous AND proliferation OR polypoidal AND choroidal AND neovascularization OR polypoidal AND choroidal AND vasculopathy AND 'randomized controlled trial'/de. Only one reference was found[208].

The available treatments for CNV in ARMD have been described previously in the paragraph on indirect evidence for fluorescein angiography. The classification of patients and the decision to treat is based on the results of the fluorescein angiography in most publications. Only the HTA report on photodynamic therapy with verteporfin[209] cited that

"The final diagnostic process involves clinical evaluation of the macula with stereoscopic biomicroscopy, fluorescein angiography, and rarely, indocyanin green angiography."

There is however no reference in the report to support this statement. The Cochrane systematic review[149] on photodynamic therapy included three studies. Indocyanine green angiography was not mentioned as a test to select the patients for treatment in those studies.

Our additional search found one randomized trial[208] comparing three different doses of anecorvate acetate in patients with retinal angiomatous proliferation (RAP) diagnosed with fluorescein angiography and indocyanine green angiography. In this study, anecorvate acetate alone does not appear to benefit those patients, independent of the concentration administered.

6.2.6.2 Prognosis

EVIDENCE SEARCH

A search was done (18/09/07) in Pubmed with the strategy ("Indocyanine Green"[Mesh] AND "Diagnostic Techniques, Ophthalmological"[Mesh] AND "Macular Degeneration"[Mesh]) AND (prognos*[Title/Abstract] OR (first[Title/Abstract] AND episode[Title/Abstract]) OR cohort[Title/Abstract]) and 23 articles were found. A search in Embase (18/09/07) with the terms '"indocyanine green angiography'/de AND 'retina macula age related degeneration'/de AND 'prognosis'/de" identified 14 articles. An additional search in Pubmed (09/10/07) with the terms ("Choroidal Neovascularization"[Mesh]OR "retinal angiomatous proliferation" OR "polypoidal choroidal neovascularization") AND (prognos*[Title/Abstract] OR (first[Title/Abstract] AND episode[Title/Abstract]) OR cohort[Title/Abstract]) found 117 articles. A similar search in Embase with the terms 'subretinal neovascularization'/de OR 'retinal angiomatous proliferation' OR 'polypoidal choroidal neovascularization' AND 'prognosis'/de found 169 articles. After discarding duplicates, this totaled 239 references.

Inclusion criteria were on population (> 20 patients ARMD with retinal angiomatous proliferation or polypoidal chroroidal vascularization) and on design (cohort study). Nine studies were selected based on title and abstracts. Four studies were excluded because of a retrospective design [198] [210] [211] [196]. One study was not on prognosis [212]. The review of Pauleikhoff 2005 [213] was a narrative review. Finally, we selected three original studies[214] [215] [162].

RESULTS

The AAO guideline([6] discusses the natural history of ARMD according to AREDS categories. Neovascularization diagnosed by ICGA is not considered in this guideline.

The three studies selected in our search considered patients with pigment epithelial detachment (PED). The study of Brumm[215] showed that the classification of PED in 3 groups with ICGA (1=no vascularization, 2=associated choroidal vascularization, 3=associated polypoidal vasculopathy) showed best correlation with associated neovascular membranes, area, volume and height, and showed statistically significant correlation with visual acuity (p=0.0004). The study of Chang[162] showed that the type of occult disease in one eye is highly predictive of the type of neovascularized disease in the fellow eye. The study of Pauleikhoff [214] showed a significant difference in risk of visual acuity loss in the second eye (EDTRS ≥ 3 lines) according to the type of late exudative AMD (both FA and ICGA were used). In classic CNV, the risk was 6-7% per year and in PED, it was 15 -16 % per year ($p < 0.001$).

Key points

- **Interobserver agreement with ICGA is good in patients with ARMD. The interobserver agreement is moderate in case of serous pigment epithelial detachment with choroïdal neovascular membranes.**
- **Anaphylactic reactions are described. An emergency plan and a protocol to minimize the risks have to be developed.**
- **ICGA can not replace FA, but may provide additional information. One diagnostic accuracy study showed that polypoidal choroidal vasculopathy and retinal angiomatous proliferation are better diagnosed with ICGA than with FA in patients with newly diagnosed neovascular ARMD.**

6.3 OPTICAL COHERENCE TOMOGRAPHY

6.3.1 Introduction

Optical coherence tomography is a non-invasive technique to image intraocular tissues by measuring the echo time delay and intensity of back-reflected light. Interference patterns produced by low coherence light (wavelength 820 mm) are reflected from the retinal tissues and a two-dimensional image of the retina can be produced. The resulting image provides high resolution, cross-sectional representation of structure with near-histological detail.

The main advantages of the OCT are its objective, reproducible and quantifiable results of the retina. It is easy to perform and free of risks to the patient, which makes it an attractive alternative for fluorescein angiography. The technique is limited in patients with high-grade cataract or vitreous flare. In addition, the quality of the results depends on the operation of the machine. The costs of the machine are high. The test is currently not reimbursed by the Belgian Health Care Insurance.

6.3.2 Methods

In accordance with the previous sections, the following research questions were formulated:

- What is the technical accuracy of the OCT?
- What is the place of the OCT in the clinical pathway?
- What is the diagnostic accuracy of the OCT?
- What is the impact of the OCT on patient outcome?

The literature search started with a search for good quality evidence synthesis, being systematic reviews and HTA reports.

6.3.3 Technical accuracy

The literature search on technical accuracy was limited to an evaluation of the observer variation. Search terms: "Observer Variation"[Mesh] AND "Tomography, Optical Coherence"[Mesh] AND "Macular Degeneration"[Mesh]. The inclusion criteria were: OCT, 20 patients or more, assessment of observer variation. Articles were excluded in case of a retrospective design, narrative review or case series of less than 20 patients. Five articles were identified, of which one was possibly relevant to the research question[216]. However, on appraisal in full text, the study did not apply to the inclusion criteria and was subsequently excluded.

6.3.4 Place in the clinical pathway

The OCT can be used for various indications. The indication for which the literature was searched and collated was the diagnosis of age related macular degeneration.

6.3.5 Diagnostic accuracy

Embase, search date 12/07/07

'optical coherence tomography'/exp AND 'retina macula age related degeneration'/exp AND (sensitiv* OR detect* OR accurac* OR specific* OR reliab* OR positiv* OR negativ* AND [embase]/lim AND [1966-2007]/py)

Medline, search date 12/07/07

(("Tomography, Optical Coherence"[Mesh]) AND ("Macular Degeneration"[Mesh])) AND (sensitiv*[Title/Abstract] OR sensitivity and specificity[MeSH Terms] OR diagnos*[Title/Abstract] OR diagnosis[MeSH:noexp] OR diagnostic *[MeSH:noexp] OR diagnosis,differential[MeSH:noexp] OR diagnosis[Subheading:noexp])

These were selected using title and abstract according to the following criteria: studies on OCT, age related macular degeneration, diagnostic or technical accuracy study. Studies on any other illness than age related macular degeneration, narrative reviews, case reports, case series of less than 20 patients and studies using a retrospective design were excluded.

The search in Medline yielded 279 articles, the search in Embase 47. Discarding duplicates, 318 articles were identified. After applying in and exclusion criteria, 25 articles were selected for appraisal in full text.

The selected articles contained one HTA report, published by the German HTA agency[217] on July 5th 2007, comparing the value of OCT with fluorescein angiography for age related macular degeneration.

The methods of this report are of high quality. The literature was searched in 34 international databases, using a very sensitive search strategy. This search yielded 2324 articles of which eight publications remained after a two-stage selection. Studies were included in case they were a primary study, systematic review or HTA report on the early detection or diagnosis of AMD in adults, comparing OCT and FA. Letters, comments, congress abstracts, articles in another language than English or German were excluded, in addition to in vitro studies, animal experiments or case series (up until 10 persons). Quality assessment and data extraction was performed according to predefined criteria and procedures.

According to the selection criteria eight publications comparing OCT results with fluorescein angiographic results in patients with AMD were identified for medical assessment. Both the patients evaluated as well as the aims of the studies were quite heterogeneous. In most of the articles, highly selected patient groups were studied. According to the defined criteria, quality of the studies was low except for one study.

The number of investigated patients is below 35 in four publications, between 35 and 61 in three studies, and above 100 in only one publication.

In one study 26 patients (36 eyes) with drusen were investigated[218]. In the majority of the cases drusen could not be detected by OCT. These cases include small hard drusen, extrafoveal serous drusen or very small soft drusen. In another publication of the same group of authors[219] less than half of the patients with geographic atrophy (37 patients, 55 eyes) could be diagnosed reliably. However, in one case an angiographically suspected

choroidal neovascularisation could be confirmed by OCT. In addition, certain changes can be shown by OCT, which are not documented by FA, such as cystoid maculopathia and macular holes.

In another study OCT identified retinal pigment epithelial detachment in all 16 patients with retinal pigment epithelial tears and in 14 of these patients one or more focal interruptions of the retinal pigment epithelium were detected[220].

One study investigated patients with choroidal neovascularisation, 13 of which were diagnosed as AMD[221]. Neither by FA nor by OCT the boundary of the lesions could be determined in all cases, but OCT added relevant information to the angiographic diagnosis.

The prevalence of cystoid macular oedema was determined in 61 patients with subfoveal neovascular AMD[222]. The results show that the OCT is a useful test to detect the presence of cystoid macular oedema because the latter may be difficult to identify with FA.

OCT findings are correlated with angiographic signs of choroidal neovascularisation in retinal pigment epithelial detachment associated with AMD in 35 patients[197]. In patients with choroidal neovascularisation at the margin of the pigment epithelial detachment the correlations between OCT and FA were better than in patients with choroidal neovascularisation beneath the detached retinal pigment.

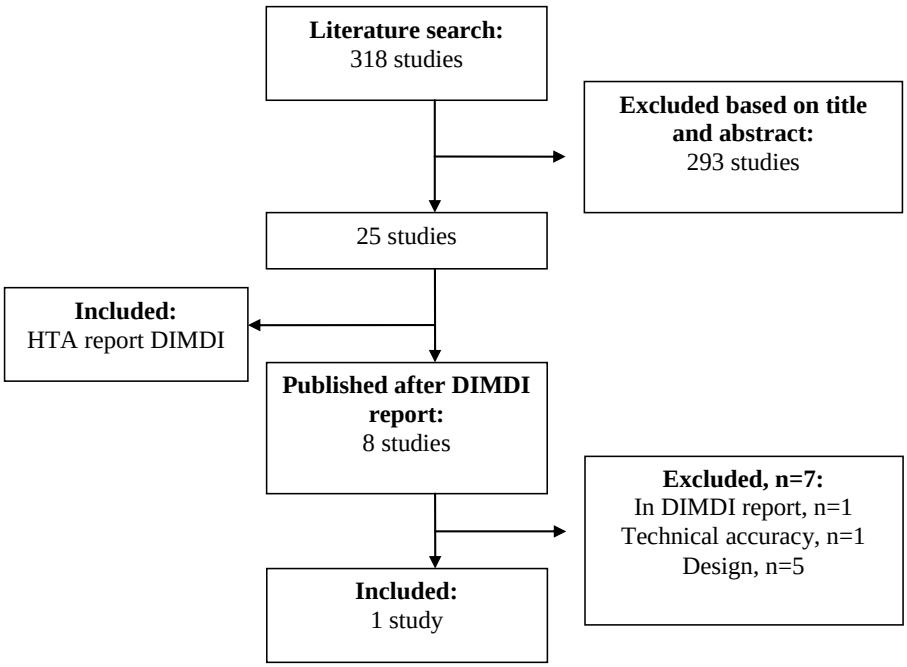
The study with the highest quality evaluated the diagnostic accuracy of OCT compared to FA in 131 eyes of 118 patients suspected of having choroidal neovascularisation[223]. For OCT the sensitivity in detecting new potentially treatable lesions was 96% and the specificity was 66%. Including stereo colour images lead to a sensitivity of 94% and a specificity of 89%. This is the only study included in the report that used a newer model of OCT (OCT 3). Based on the results of this study, OCT has been recommended for the screening of potentially treatable neovascularisations prior to FA.

An update of this report was made starting from the date of the literature search, being November 2005. These were subsequently selected based on title and abstract using the following criteria: Inclusion criteria: OCT, age related macular degeneration and diagnostic accuracy studies. Exclusion criteria: narrative review, case series including less than 20 patients, comments, letters, conditions not related to age related macular degeneration.

Eight articles were potentially relevant based on title and abstract. Of these, one was already in the DIMDI report[223], and one was identified in the technical accuracy section[216]. Two articles evaluated OCT in monitoring patients during PDT treatment. These will be discussed in the section on impact on patient outcome. This leaves four articles potentially relevant on diagnostic accuracy, and these were subsequently assessed for quality. The case-control study by Ahlers et al. on the diagnosis of fibrovascular PED and serous PED describes the findings of various tests including OCT, but does not compare them; the article was subsequently excluded[224]. The study by Talks used a retrospective design, and was therefore excluded[204]. Finally, the study by Iranmanesh was excluded because of insufficient reporting of results [203]. Only one study was of sufficient quality to be included: Salinas-Alaman found that intraretinal and subretinal fluid on OCT has a sensitivity of 96.8% in detecting CNV activity as compared to leakage on fluorescein angiography, once the diagnosis of ARMD was made. This study was of good quality, including 53 consecutive patients with signs of exudative ARMD with predominantly classic CNV.

Results of OCT and fluorescein angiograhy were assessed by independent observers, blinded to the other result[225].

Figure 6.3: flow chart of study selection for OCT



6.3.6 Impact on patient outcome

6.3.6.1 Direct evidence

Impact on patient outcome is measured directly using randomised trials in which the strategy with OCT is compared to a strategy without OCT. The following search terms were used: ("Macular Degeneration"[Mesh] AND "Tomography, Optical Coherence"[Mesh]) AND (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract])), which yielded 37 articles. Studies were eligible if they were RCTs, evaluating the independent contribution of OCT to patient outcome. However, none of these 37 articles was potentially eligible.

6.3.6.2 Indirect evidence

None of the large pivotal trials on the treatment of ARMD used OCT as a selection for treatment. However, the external experts state that the OCT is increasingly used in the follow-up of patients after treatment. Reviewing the methods of the various trials, TAP, VIP, VISION, MARINA and ANCHOR, the OCT is not mentioned as follow-up test.

A separate search was performed using the following terms: "Follow-Up Studies"[Mesh] AND "Macular Degeneration"[Mesh] AND "Tomography, Optical Coherence"[Mesh].

Using these terms, 75 studies were identified of which none was eligible for further review using the inclusion criteria of studies in which OCT was used as a follow-up tool to guide treatment of ARMD patients. Studies were excluded if they were narrative reviews, case series of less than 20 patients, retrospective design, target condition other than ARMD.

From the search for diagnostic accuracy studies, a few studies were identified that used OCT in the follow-up of mainly PDT. Eter et al. compared fluorescein angiography and OCT three months after PDT treatment[226]. They found that leakage on fluorescein angiography is correlated with cystoid spaces in the macula as detected by OCT, but not correlated with subretinal fluid on OCT. Van Velthoven et al. found that in patients after treatment with PDT, the correlation between fluorescein angiography and OCT on the presence of leakage was poor (kappa=0.16)[143]. It is not clear what the effect on patient outcome would be if the decision to retreat patients was made on the basis of OCT instead of on fluorescein angiography.

Key points

- **Only a small number of clinical studies of low quality are currently available.**
- **OCT can not replace FA, but may provide additional information and may verify unclear findings on the activity and treatment of AMD.**

7 CLINICAL RECOMMENDATIONS

Disclaimer:

It is by no means the intention that the recommendations of this report would be strictly adhered to in every individual patient. Recommendations are based on the available evidence and can change as new evidence comes forward. Therefore, the recommendations should be considered as guidance. Adhering to the recommendations does not guarantee success in every patient. In addition, they can not be considered the only appropriate clinical approach and thereby exclude other approaches that strive for the same result. The ultimate decision to use a certain clinical procedure or treatment is the responsibility of the treating physician, taking all clinical information of the patient and the available diagnostic and therapeutic measures into account. It is to be expected that these recommendations are adapted to the local context after discussion in peer groups.

7.1 METHODOLOGY

Based on the evidence gathered in the formal evaluation of the selected tests, a panel of physicians working in the field has formulated clinical practice guidelines. The panel consisted of several ophthalmologists with extensive clinical expertise.

Each recommendation has been assigned a grade of recommendation, based on the guidelines of the GRADE working group[227]. The GRADE guidelines are centred on 2 axes: the level of evidence obtained for a certain clinical question, and the balance between benefit or harm that is expected for the patient.

Additional statements were made by the experts related to the tests were considered.

Table 7.1: GRADE CLASSIFICATION

Grade of Recommendation/ Description	Benefit vs. Risk and Burdens	Methodological Quality of Supporting Evidence	Implications
1A/ Strong recommendation, high quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B/ Strong recommendation, moderate quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C/ Strong recommendation, low quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation, but may change when higher quality evidence becomes available
2A/ Weak recommendation, high quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2B/ Weak recommendation, moderate quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2C/ Weak recommendation, low quality evidence	Benefits closely balanced with risks and burden	Observational studies or case series	Very weak recommendation, other alternatives may be equally reasonable

7.2 CATARACT

7.2.1 Endothelial cell density in patients scheduled for cataract surgery

Population	Patients diagnosed with cataract and scheduled for a surgical cataract procedure.
Aim	The measurement of endothelial cell density aims at avoiding or predicting corneal complications after cataract surgery.
Strong recommendation, Low quality evidence	Measuring endothelial cell density is recommended in patients with ocular co-morbidity.
Expert statement	The possibility of performing an endothelial cell density measurement should be considered in every patient prior to cataract surgery

7.3 REFRACTIVE SURGERY

7.3.1 Scheimpflug imaging system

Population	Patients scheduled for corneal refractive surgery.
Aim	Detecting *subclinical* keratoconus.
Very weak recommendation, Low quality evidence	The Scheimpflug is a recent, non-contact technique which can be used to exclude moderate and severe keratoconus.
Expert statement	Further evidence is awaited to support the promising early findings available now on *subclinical* keratoconus.
Expert statement	Non-contact methods are preferable over contact methods for reasons of infection control.
Expert statement	Other diagnostic instruments than the Scheimpflug imaging system exist for the diagnosis of *non-subclinical* keratoconus, including non-contact methods.

7.4 AGE RELATED MACULAR DEGENERATION

7.4.1 Fluorescein angiography

Population	Patients diagnosed with age related macular degeneration.
Aim	To evaluate the extent and type of choroidal neovascularisation, and assess eligibility for treatment.
Strong recommendation, Moderate quality evidence	Fluorescein angiography remains the gold standard for the diagnosis of patients with neovascular age related macular degeneration, to document the location and type of the lesions.
Strong recommendation, High quality evidence	Fluorescein angiography should be used to guide treatment with photodynamic therapy.
Strong recommendation, Moderate quality evidence	Fluorescein angiography should be used in the follow-up of patients with neovascular age related macular degeneration, treated with any intervention.

7.4.2 Indocyanine green angiography

Population	Patients diagnosed with age related macular degeneration
Aim	To evaluate patients in case of doubt after fluorescein angiography.
Strong recommendation, Moderate quality evidence	ICG is recommended to assess the extent and nature of subretinal membranes, in particular retinal angiomatous proliferation and polypoidal choroidal vasculopathy.

7.4.3 Optical coherence tomography

Population	Patients diagnosed with age related macular degeneration.
Aim	To evaluate the activity of the neovascular process.
Strong recommendation, Moderate quality evidence	The OCT is recommended for the detection of macular oedema.
Expert statement	Retinal oedema documented by OCT is one of the conditions by which pegaptanib and ranibizumab are reimbursed.
Very weak recommendation, Low quality evidence	The OCT is recommended to monitor the effects of treatment.

8 POLICY RECOMMENDATIONS

- In order to decrease the variability in practice, increase evidence based practice and allocating resources effectively, the development of clinical practice guidelines specific to the Belgian context was needed. These guidelines were drawn up by clinical experts, based on the best available evidence. Funding for further development and implementation should be made available to the scientific ophthalmology associations; collaboration may be sought with other institutions with experience in guideline development. Guidelines on frequent disorders or procedures should be prioritised.
- Ophthalmologists should be encouraged to appraise and incorporate evidence in their clinical practice. The formation of young ophthalmologists should include the principles of evidence based medicine.
- Evidence gaps that were identified in this report should be filled by well designed studies, such as the value of Scheimpflug in predicting poor outcome or complications after refractive corneal surgery, or the value of the OCT in monitoring and guiding treatment for age related macular degeneration.
- Fluorescein angiography and indocyanine green angiography should be performed in centres of clinical excellence because of their risks like anaphylactic shock, degree of complexity in interpretation and immediate consequences for treatment that is already reserved to a limited number of ophthalmologists with specific expertise.
- The decision to reimburse therapies is based on the efficacy of the therapy, as shown by good evidence. In contrast, some of the conditions by which therapies are reimbursed are not based on evidence, for example the reimbursement of anti-angiogenesis therapy in case of macular oedema documented by OCT. There is no evidence that assesses the effect of anti-angiogenesis therapy in patients selected for treatment by OCT. If the reimbursement of a therapy is dependent on diagnostic criteria, this diagnostic criterion should be well validated.

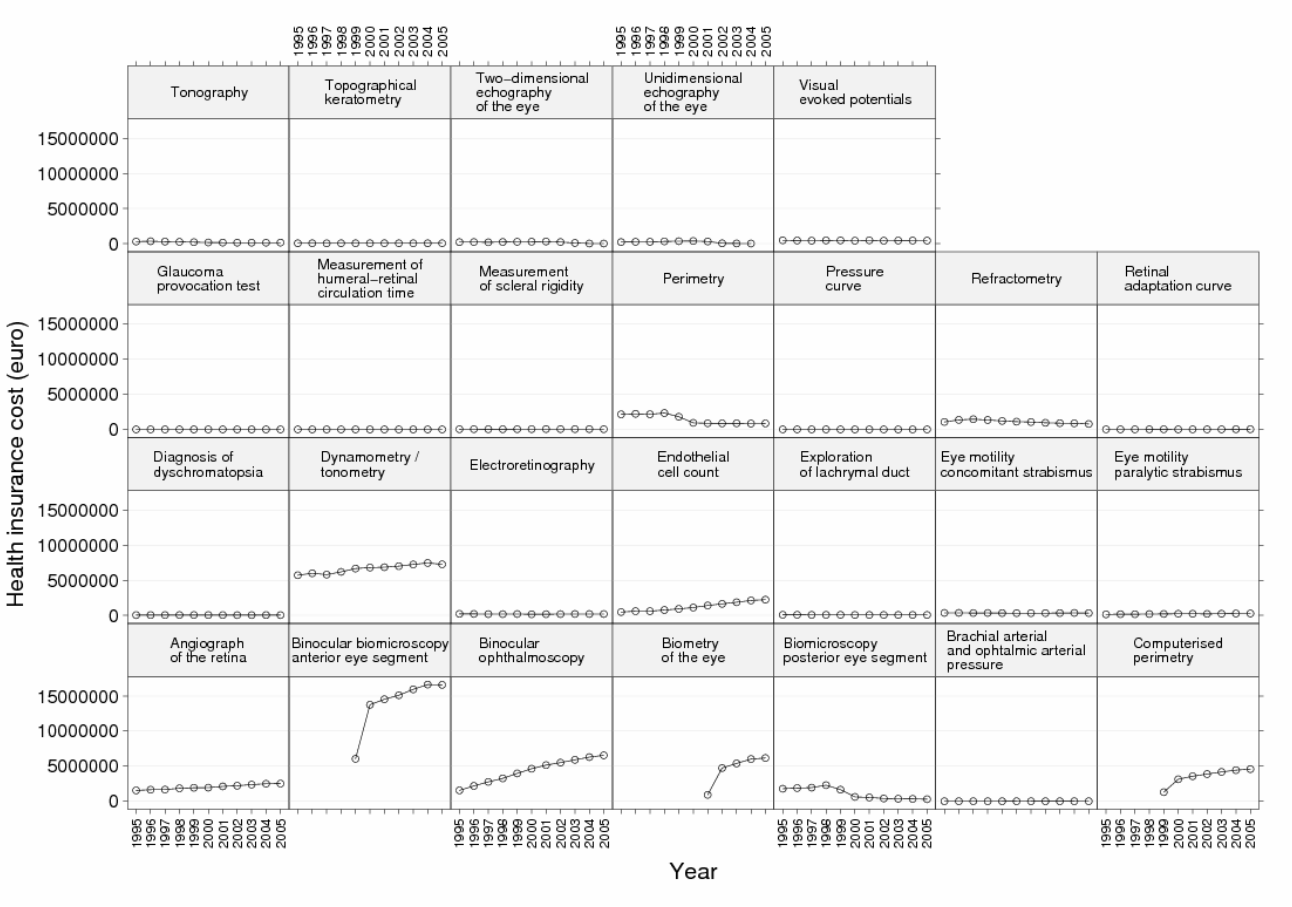
9 APPENDIX

APPENDIX 1: DATA ANALYSIS

Table A1. Number of ODT between 1995 and 2005 in function of ODT

ODT	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
Angiograph of the retina	41 018	42 826	44 741	47 594	48 759	48 730	52 303	53 867	56 269	58 263	58 870
Binocular biomicroscopy anterior eye segment					1 034 568	2 322 664	2 415 578	2 477 585	2 537 244	2 612 431	2 605 841
Binocular ophthalmoscopy	316 676	436 984	570 393	645 273	770 864	889 965	972 424	1 025 943	1 069 473	1 124 601	1 169 854
Biometry of the eye							12 116	62 379	68 674	75 558	77 413
Biomicroscopy posterior eye segment	237 732	245 931	261 349	297 254	209 807	77 744	66 640	48 765	42 388	39 340	33 953
Brachial arterial and ophtalmic arterial pressure	21	28	28	16	17	8	5	11	4	11	10
Computerised perimetry					63 047	151 015	169 404	181 444	189 876	198 772	205 321
Diagnosis of dyschromatopsia	4 445	4 845	5 494	5 853	5 944	5 220	4 503	3 594	3 935	4 309	3 595
Dynamometry / tonometry	1 144 406	1 179 652	1 177 533	1 207 135	1 279 471	1 294 637	1 283 802	1 297 730	1 304 483	1 325 485	1 291 560
Electroretinography	5 583	5 225	4 677	4 473	4 747	3 844	4 126	4 295	4 562	4 429	4 446
Endothelial cell count	12 236	15 222	15 802	19 437	23 168	27 738	34 519	39 680	44 090	49 581	52 180
Exploration of lachrymal duct	14 926	14 280	13 258	13 291	12 376	10 251	9 995	9 760	10 005	9 946	9 539
Eye motility concomitant strabismus	28 774	28 682	27 897	27 333	25 423	24 418	24 323	23 865	23 867	24 810	23 366
Eye motility paralytic strabismus	11 462	13 257	13 515	14 952	15 522	17 231	16 956	15 428	16 574	18 620	18 916
Glaucoma provocation test	149	540	144	146	352	353	271	235	192	115	143
Measurement of humeral-retinal circulation time	73	74	71	31	33	37	43	55	70	73	61
Measurement of scleral rigidity	4 731	4 947	4 128	3 758	4 763	5 132	6 089	5 853	5 415	5 258	4 514
Perimetry	216 371	220 321	220 781	228 601	173 982	88 629	81 704	79 144	77 958	73 895	75 494
Pressure curve	451	376	354	294	213	105	103	96	53	56	73
Refractometry	274 238	341 701	378 551	335 135	294 537	268 030	254 215	221 803	204 386	195 039	174 687
Retinal adaptation curve	649	630	561	817	1 155	473	536	350	568	1 138	1 312
Tonography	11 294	12 705	11 080	9 100	7 403	5 617	4 848	4 474	4 361	4 225	4 618
Topographical keratometry	5 067	5 539	4 207	5 357	5 198	5 186	5 546	4 615	4 799	4 450	4 634
Two-dimensional echography of the eye	12 519	13 048	12 256	14 674	16 209	16 887	18 368	13 292	5 139	136	105
Unidimensional echography of the eye	24 239	27 784	31 303	37 951	40 925	43 750	34 938	3 725	1 090	3	
Visual evoked potentials	7 192	6 616	6 433	6 671	6 673	5 964	6 608	5 738	5 960	5 771	5 742

Figure A1. Health insurance cost per ODT between 1995 and 2005



APPENDIX 2: CRITICAL APPRAISAL OF THE GUIDELINES AND SYSTEMATIC REVIEWS

	Evidence search	Evidence selection	Methods recommendations	Balance benefit/risk	Explicit link recommendations and evidence	External review	Updating procedure	Overall quality
AAO Preferred Practice Patterns® Including on cataract[5], on AMD[6] and on refractive errors[7]	Disagree	Disagree	Disagree	Agree	Agree	Disagree	Agree	Fair
RCO AMD interim guidelines[228]	Strongly disagree	Strongly disagree	Strongly disagree	Disagree	Strongly disagree	Disagree	Disagree	Low
RCO Cataract surgery[4]	Agree	Agree	Agree	Agree	Agree	Agree	Agree	Good
AOA AMD	Strongly disagree	Strongly disagree	Strongly disagree	Disagree	Strongly disagree	Agree	Disagree	Low
AOA Cataract	Strongly disagree	Strongly disagree	Strongly disagree	Disagree	Strongly disagree	Agree	Disagree	Low

	Well formulated question	Evidence search	Evidence selection	Quality appraisal	Data extraction	Study characteristics	Statistical methods	Conclusion
Ecri 2004[8]	Good	Fair	Good	Fair	Fair	Good	NA	Good
MSAC 2003[9]	Good	Good	Good	Good	Good	Fair	NA	Good

APPENDIX 3: EVIDENCE TABLES ENDOTHELIAL CELL COUNT

TECHNICAL ACCURACY STUDIES

Study ID	Population	Design	Index test	Mean difference	Reproducibility
Benetz 1999[22]	Subjects visiting ophthalmology clinic, without history of surgery; normal intraocular pressure n=98; aged 4-87 years Both eyes	Prospective cross-sectional	Konan SP8000 noncontact specular microscope Konan versus Bio-optics Bambi fixed frame method Konan dot method versus Bio-optics Bambi corners method	Fixed frame methods: 157 cells/mm² Morphometric methods: 19 cells/mm²	Konan: ICC 0.79-0.97 Bio-optics Bambi 0.4-1.5% cv
Bourne 1976[15]	White persons without history of ocular abnormalities, normal slit-lamp examination n=40; aged 6-87 year 40 eyes	Prospective cross-sectional	Contact specular microscope	Decreasing density with age ($p<0.001$)	Intraperson variability: 161.4 cells/mm²
Doughty 2000[23]	White persons without history of ocular abnormalities or contact lens wear n=56; aged 6-83 years 56 eyes	Prospective cross-sectional	Topcon SP-1000 noncontact specular microscope	Decreasing density with age	Variance* when counting 70 cells: 0.8%
Hartmann 1984[20]	In vitro: human, rabbit and pig eyes In vivo: patients with various eye disease before and after surgery Number and age not stated	Possibly prospective, Further details on design unclear	Contact specular microscopes: Leitz Biopthal Pocklington Keeler-Konan	Feasibility study for the analysis using video registration; no clinical estimates available	
Hirst 1984[19]	9 different corneas: 3 normal, 2 graft rejection, 4 corneal oedema	Prospective cross-sectional	Wide-field contact specular microscope; rectangles from the photograph using an overlay grid are digitized		Inter and intra-observer error not significant (chi²) Significant difference between central and peripheral cell areas in 3 of 9 photographs
Imre 2001[25]	Healthy subjects n=12; aged 17-78 years Right eyes	Prospective cross-sectional	Tomey confoscan P4 slit-scanning type instrument	Mean difference between automatic and manual analysis: 90-175 cells/mm² ($p<<0.05$)	Intraobserver variability not significant Interobserver variability significant using manual analysis
Nichols 2003[26]	Healthy subjects without history of ocular surgery, trauma and	Prospective cross-sectional	Konan SP 9000LC, noncontact wide field specular microscope		Test-retest reliability ICC: 0.38-0.72 manual method; 0.58-0.69

Study ID	Population	Design	Index test	Mean difference	Reproducibility
	contact lens wear n=25; mean age 30 year right eyes				automatic Konan method Interobserver agreement ICC: 0.60-0.65 manual; 0.70-0.73 automatic
Olsen 1979[17]	Normal subjects without history of trauma or disease N=unclear; aged 27-53 years 24 eyes	Prospective cross-sectional	Preisler noncontact specular microscope	Decrease in density with age ($p<0.001$); variation in density larger in older age group High concordance between right and left eyes	Test-retest reliability SD 3.7%
Schutten 1980[18]	Not stated	Not stated	Contact specular microscope; minimum of 60 cells projected on paper, weight of the paper used for measuring cell density		Test-retest reliability SD 0.94% of the mean
Vecchi 1996[21]	n=38 63 eyes	Retrospective	Topcon SP 1000; cell density estimation using Image NET system automated, semi-automated and manual		Interobserver agreement (K statistic) medium to fair Test-retest reliability Mean difference between two readings 53-192 cells/mm², smallest difference for the manual method
Wirbelauer 2005[27]	Patients presenting for cataract surgery without prior ocular surgery n=62; aged 57-93 years 30 right + 33 left eyes	Prospective cohort	Konan Roboca SP 8000 noncontact specular microscopy; fixed frame method: manual and automatic center algorithm	Mean difference in central area -19.4 cells/mm² Limits of agreement (-234) – 195 cells/mm² Immediately postoperative accuracy decreased and relative error increased	
Sin Wan Cheung 2000[24]	Healthy male optometry students, non-contact or occasional contact lens wearers n=27; aged 20-27 years	Prospective cohort	SP-2000P with IMAGEnet system: comparison between automated and retraced method	Automated method overestimated cell density with at least 200 cells/mm²	95% limits of agreement intra-examiner: (-70) and 70 cells/mm² approximately inter-examiner: (-150) and 220 cells/mm² No statistically significant

Study ID	Population	Design	Index test	Mean difference	Reproducibility
					differences in ECD determined from images captured by the same examiner on different visits ($p > 0.05$) ECD obtained from the analysis of images captured by different examiners were not significantly different ($p > 0.05$)
De Sanctis 2006[28]	Normal individuals n=49; aged 19-60 years no contact lens wearing, no history of ocular disease, trauma or surgery, normal slit-lamp examination	Prospective cohort	Topcon 2000P IMAGEnet retraced method Konan CC7000 center method	Topcon versus Konan Examiner 1: -185 (SD 171) Examiner 2: -229 (SD 255) Both differences $p<0.0001$	Inter-examiner correlation Topcon: ICC>0.90; 95% limits of agreement (-203) and 219 cells/mm² Konan: ICC>0.85; 95% limits of agreement (-478) and 377 cells/mm²

ICC = intraclass coefficient
cv = coefficient of variation
*variance = ±1 SD, expressed as a percentage of the arithmetic mean of the first 75 cells in each micrograph

DIAGNOSTIC ACCURACY STUDIES

Study ID	Population	Design	Index test	Reference test	Results
Modis 2002[29]	Healthy subjects, n=39; aged 41-88 years; 65 eyes patients with penetrating corneal grafts n=41; aged 21-81 years; 50 eyes	Prospective case-control	Topcon SP 2000P Non-contact specular microscopy	Tomey EM-1000 Contact specular microscopy	Mean difference Normal eyes: 20 cells/mm² (p=0.52) Corneal graft eyes: 26 cells/mm² (p=0.88)

APPENDIX 4: OPHTHALMIC VISCOELASTIC DEVICES

CRITICAL APPRAISAL

Quality appraisal	Yachimori 2004	Vajpayee 2005	Storr-Paulsen 2007	Steele 1988	Smith 1991	Sharpe 1986	Schwenn 2000	Schmidl 1999	Ray-Chaudhuri 2006
Were patients assigned to the intervention at random?	yes	yes	yes	yes	unclear	yes	yes	yes	yes
Was there concealment of allocation?	no	unclear	unclear	unclear	unclear	no	unclear	no	unclear
Were the patients blinded to the treatment?	yes	unclear	unclear	unclear	unclear	unclear	unclear	unclear	unclear
Were the treating physicians blinded to the treatment?	no	no	unclear	unclear	no	no	unclear	no	no
Were the outcome assessors blinded to the treatment?	yes	yes	yes	unclear	yes	unclear	yes	unclear	yes
Were the groups comparable at baseline?	yes	yes	yes	unclear	unclear	unclear	yes	yes	unclear
Is complete follow-up available for a sufficient number of included patients?	unclear	unclear	yes	no	no	no	unclear	yes	yes
Has an intention-to-treat analysis been performed?	unclear	no	no	no	no	unclear	unclear	no	no
Have the groups been treated equally, apart from the intervention?	no	no	unclear	unclear	no	yes	yes	unclear	unclear

Quality appraisal	Liesegang 1986	Kim 2004	Lane 1991	Koch 1993	Holmberg 1984	Henry 1996	Hazariwala 1988	Fry 1993	Cosemans 1999
Were patients assigned to the intervention at random?	yes	yes	yes	yes	yes	yes	yes	yes	yes
Was there concealment of allocation?	unclear	unclear	unclear	no	partly	no	unclear	yes	unclear
Were the patients blinded to the treatment?	no	unclear	unclear	unclear	unclear	unclear	unclear	yes	unclear
Were the treating physicians blinded to the treatment?	no	unclear	no	no	no	no	unclear	no	no
Were the outcome assessors blinded to the treatment?	no	unclear	yes	yes	no	no	unclear	yes	yes
Were the groups comparable at baseline?	unclear	yes	unclear	yes	unclear	unclear	unclear	yes	no
Is complete follow-up available for a sufficient number of included patients?	yes	unclear	unclear	yes	yes	no	unclear	yes	unclear
Has an intention-to-treat analysis been performed?	unclear	unclear	unclear	no	no	no	unclear	unclear	no
Have the groups been treated equally, apart from the intervention?	unclear	yes	unclear	no	no	unclear	yes	yes	yes

Quality appraisal	Colin 1995	Cavallini 2002	Bourne 1984	Bleckmann 1992	Alpar 1984	Ravalico 1997	Colin 1995	Kiss 2001	Holzer 2001
Were patients assigned to the intervention at random?	yes	unclear	yes	yes	yes	yes	yes	yes	yes
Was there concealment of allocation?	no	unclear	unclear	unclear	no	unclear	no	no	no
Were the patients blinded to the treatment?	unclear	unclear	unclear	unclear	unclear	unclear	no	yes	yes
Were the treating physicians blinded to the treatment?	no	no	no	no	no	unclear	no	no	no
Were the outcome assessors blinded to the treatment?	unclear	unclear	yes	yes	no	unclear	yes	yes	yes
Were the groups comparable at baseline?	yes	unclear	unclear	unclear	unclear	unclear	yes	unclear	unclear
Is complete follow-up available for a sufficient number of included patients?	yes	unclear	yes	no	unclear	yes	yes	yes	yes
Has an intention-to-treat analysis been performed?	no	unclear	no	unclear	unclear	no	no	no	no
Have the groups been treated equally, apart from the intervention?	no	yes	yes	yes	no	yes	yes	no	no

Quality appraisal	Miller 1999	Miyata 2002 a	Oshika 2004	Maar 2001	Miyata 2002 b	Bhattacharjee 2003	Draeger 1982
Were patients assigned to the intervention at random?	yes	unclear	yes	yes	yes	yes	yes
Was there concealment of allocation?	no	unclear	no	unclear	no	unclear	no
Were the patients blinded to the treatment?	unclear	unclear	unclear	unclear	unclear	unclear	no
Were the treating physicians blinded to the treatment?	no	unclear	no	no	no	no	no
Were the outcome assessors blinded to the treatment?	yes	unclear	unclear	unclear	yes	unclear	no
Were the groups comparable at baseline?	yes	yes	unclear	yes	unclear	unclear	unclear
Is complete follow-up available for a sufficient number of included patients?	yes	unclear	yes	unclear	unclear	unclear	unclear
Has an intention-to-treat analysis been performed?	yes	unclear	unclear	unclear	unclear	no	unclear
Have the groups been treated equally, apart from the intervention?	yes	no	unclear	unclear	unclear	unclear	unclear

EVIDENCE TABLES

	Population	Interventions	Absolute decrease density (cells/mm²; SD)	Relative decrease density (%; SD)
Alpar 1984[37]	Candidates for extra and intracapsular cataract extraction,	Healon, n=20 Serum, n=20 Air, n=20	NA NA NA	9.6/9.8 $ 15.0/15.1 13.5/13.9
Bhattacharjee 2003[62]	Consecutive patients scheduled for phaco Excluded: previous trauma, surgery or ocular disease other than cataract, ECC<2000 cells/mm², diabetes mellitus, intraoperative complications	Biolon, n=30 Viscoat, n=30	209.2 590.1	8.1 21.4
Bleckmann 1992[46]	Patients scheduled for ECCE (manual or phaco) Excluded: not stated	Healon, n=24 Collagel, n=24	440 259	16.9 10.0
Bourne 1984[38]	Patients undergoing ECCE Excluded: patients with abnormal cornea guttata; glaucoma; uveitis; disorders of the anterior ocular segment other than cataract	1% sodium hyaluronate nos, n=92, No OVD, n=89	182 219	6.1 (11.4) 7.6 (14.7) §
Cavallini 2002[59]	Patients age 40 or over; available for postoperative follow-up visits, undergoing phaco Excluded: IOP ≥25 mmHg; corneal pathology, previous uveitis; proliferative diabetic retinopathy, glaucoma or significant eye-threatening pathology in either eye, monocular; pupil <5 mm after preoperative dilatation	Healon, n=27 Healon5, n=27	NA NA	8 10
Colin a 1995[49]	Patients scheduled for ECCE Excluded: previous or evolving pathologies beyond cataract, ECC <1500 cells/mm²	Healon, n=47 Vitrax, n=48	137 (225) 116 (172)	6.3 (10.5) 4.9 (8.3)
Colin b 1995[50]	Patients >18 years, undergoing ECCE (manual or with phaco) Excluded: monocular; history of intolerance to a derivative of hyaluronic acid derivatives; concomitant ocular pathology (glaucoma, diabetic retinopathy, uveitis, cornea guttata, intraocular infection); bilateral extraction; intracapsular extraction	Healonid, n=50 Biovisc, n=53	219 240	7.8 8.6
Cosemans 1999	Patients scheduled for routine phaco Excluded: previous trauma, surgery or ocular disease other than cataract; <1650 cells/mm²; major intraoperative complications such as posterior capsule rupture or vitreous loss	Healon+Viscoat, n=10 Healon, n=10	227 (SEM 12.7) 254 (SEM 15.6)	9.7 (SEM 2.6) 10.2 (SEM 3.1)
Draeger 1982[36]	Patients undergoing intracapsular cataract extraction	1% sodium hyaluronate nos, n=25	481 1388	17.3 49.9

	Population	Interventions	Absolute decrease density (cells/mm²; SD)	Relative decrease density (%; SD)
		BSS, n=25		
Fry 1993[47]	Patients undergoing ECCE Excluded: diabetes; corneal scars or pathology; corneal endothelial guttata; glaucoma; IOP >22 mmHg; not able to return for follow-up visits	Healon, n=35 Healon GV, n=35	42,3 (180,1) increase 79,0 (313,1)	2,0 (7,8) increase 2,5 (11,7)
Hazariwala 1988[42]	Patients undergoing routine ECCE Excluded: glaucoma, diabetes mellitus, keratopathy, iritis, previous ocular surgery	1% sodium hyaluronate nos, n=44 2% HPMC, n=40	643 (125) 646 (115)	24.3 25.1
Henry 1996[51]	Patients scheduled for routine ECCE, 18 years or older, willing to cooperate and mentally competent Excluded: IOP >20 mmHg, preoperative use of ocular or systemic medication that could influence postoperatice IOP; pre-existing ocular pathologies (diabetic retinopathy, glaucoma); bilateral ophthalmic procedures on the same day or additional surgical procedures Only 35 of 69 patients available for postoperative endothelial cell density	Amvisc, n=18 Amvisc Plus, n=16 Healon, n=18 Viscoat, n=17	174.4 (282) 247.0 (391) 257.5 (291) 235.0 (262)	NA NA NA NA
Holmberg 1984[39]	Patients undergoing phaco. Excluded: signs of active or inactive eye disease (glaucoma, uveitis, pseudoexfoliation, high myopia), diabetes; malignancies	Healon, n=19 BSS, n=19	805 1259	26.6 (20.0) 41.1 (31.1)
Holzer 2001[57]	Patients undergoing phaco Excluded: not stated	Viscoat, n=20 Occucoat, n=15 Celoftal, n=15 Healon GV, n=12 Healon5, n=19	351.7 (176.3) 376.7 (248.8) 301.4 (198.2) 235.0 (157.7) 140.7 (132.5)	15.4 (9.1) 16.7 (10.8) 12.9 (6.2) 10.9 (7.5) 6.2 (6.5)*
Kim 2004[64]	Patients undergoing phaco Excluded: abnormal corneal layers Results expressed as % of change only and per grade of nuclear opacity	Hyal-2000, n=64 Provisc, n=55 Viscoat, n=64	NA NA NA NA NA NA NA NA NA NA	Grade 1: 6.4 (14.3) Grade 2: 9.6 (12.1) Grade 3: 15.4 (10.9) Grade 4: 19.6 (14.9) Grade 1: 7.4 (7.2) Grade 2: 13.7 (12.4) Grade 3: 13.4 (9.0) Grade 4: 18.6 (15.2) Grade 1: 7.0 (20.1) Grade 2: 10.5 (17.1)

	Population	Interventions	Absolute decrease density (cells/mm²; SD)	Relative decrease density (%; SD)
		Healon+Viscoat, n=69	NA NA NA NA NA NA	Grade 3: 16.1 (15.0) Grade 4: 17.4 (9.8)* Grade 1: 5.3 (12.5) Grade 2: 10.5 (13.1) Grade 3: 10.5 (9.9) Grade 4: 12.2 (6.6)*
Kiss 2003[63]	Consecutive patients undergoing ECCE Excluded: not stated	Viscoat, n=39 Occucoat, n=39	0 (188) 62 (233)	0.3 (8.5) 4.0 (12.6)
Koch 1993[48]	Patients scheduled for phaco Excluded: age <18; abnormal preoperative endothelial cell density or shape; inability to obtain high-quality endothelial photographs; systemic or ocular conditions that might affect the corneal endothelium; inability to return to follow-up visits; intraoperative and postoperative complications	Healon, n=29 Viscoat, n=30	NA NA	6.5 (16.4) 5.8 (14.2)
Lane 1991[44]	Consecutive patients undergoing ECCE Excluded: glaucoma; medication known to affect IOP; monocular patients; anterior or posterior segment disease that could be adversely affected by an acute IOP elevation	Healon, n=38 Viscoat, removed, n=16 Viscoat, retained, n=22 Occucoat removed, n=21 Occucoat, retained, n=17	185 216 139 269 97	5.4 8.1 5.8 9.3 5.1
Liesegang 1986[40]	Patients undergoing ECCE, 70 in total Excluded: no IOL, glaucoma, cornea guttata, history of iritis	1% sodium hyaluronate nos, n=? 2% HPMC, n=?	132 127	4.8 (7.3) 4.4 (9.8)
Maar 2001[58]	Patients undergoing phaco(total of 43 patients) Excluded: history of ophthalmic disease, diabetes mellitus, use of ophthalmic medication or a beta-blocker	Healon, n=? Viscoat, n=?	53 20	NA NA
Miller 1999[54]	Patients scheduled for phaco Excluded: <40 years; Fuchs' corneal endothelial dystrophy; ECC <1500 cells/mm²; ocular condition that might interfere with specular microscopy	Viscoat, n=70 Healon GV, n=70	26.5 (314.6) 74.1 (287.0)	1.2 3.2
Miyata a 2002	Patients with grade 3 or more of Emery-Little classification of lens nucleus, undergoing phaco Excluded: not stated	Healon+Viscoat, n=37 Healon, n=20	271 336	6.4 (9.6) 16.3 (9.8)*
Miyata b 2002[60]	Patients undergoing phaco Excluded: systemic or ocular complications preoperatively Results expressed according to < or ≥50% ultrasound time	Opegan, n=91 Healon, n=56	87/204 151/390	3.2 (4.1)/7.5 (10.6) 5.9 (5.3)/14.8 (9.0)

	Population	Interventions	Absolute decrease density (cells/mm²; SD)	Relative decrease density (%; SD)
Oshika 2004[65]	Patients 40 years or older and age related cataract, undergoing phaco Excluded: IOP>21 mmHg; glaucoma in either eye; proliferative diabetic retinopathy; corneal thickness <0,450 mm or >0,600 mm, cornea guttata; neovascularisation; history of uveitis	Healon, n=78 Healon5, n=79	NA NA	2.0 (10.4) 2.6 (9.7)
Ravalico 1997[52]	Patients undergoing phaco Excluded: other ocular pathologies; high refractive defects; diabetes mellitus; intraoperative and postoperative complications	Healon, n=16 Viscoat, n=14 Healon GV, n=15 Hymecel, n=13	178.5 (78.8) 164.6 (148.8) 166.7 (80.6) 196.7 (111.2)	8.0 7.6 7.6 8.9
Ray-Chaudhuri 2006[68]	Patients scheduled for routine phaco Excluded: history of ocular surgery, corneal disease, uveitis, ocular hypertension, glaucoma, any ocular medication or systemic steroids, systemic diseases likely to affect the eye (diabetes), peroperative complications, procedure converted to ECCE	Ophtalin, n=58 HPMC-Ophtal, n=52	260 96	11.8 4.3*
Schmidl 1999[55]	Patients, suffering from both sided cornea guttata, undergoing phaco; all patients received both interventions, one in each eye Excluded: deviation of the endothelial cell density between both eyes of >10%, intraoperative and postoperative complications, postoperative IOP >24 mmHg, extreme nucleus sclerosis	Provisc, n=30 Healon GV, n=30	103.4 130.9	5.5 7.0
Schwenn 2000[56]	Patients scheduled for routine phaco Excluded: age <25, pregnancy, diabetes mellitus or other endocrinological disease, serious general disease (heart, kidney), lung disease, neurological or psychiatric disease, rheumatic disease under systemic therapy, corneal disease, pseudoexfoliation, previous ophthalmologic trauma, ocular infections, iris disease, other serious ophthalmologic diseases, intraoperative exclusions	Healon5, n=20 Viscoat, n=28	122 139	4.3 6.2
Sharpe 1986[41]	Patients undergoing ECCE Exclusion criteria not stated	Amvisc, n=16 Healon, n=18	NA NA	6.9 1.6
Smith 1991[45]	Patients undergoing ECCE or phaco Excluded: glaucoma, cornea guttata, iritis, preoperative endothelial cell count that could not be accurately read	Healon, n=56 Occucoat, n=166		9.8 12.0
Steele 1988[43]	Patients undergoing extracapsular cataract extraction	Healonid, n=22 2% HPMC, n=25 Air, n=19	NA NA NA	NA NA NA
Storr-Paulsen 2007[69]	Consecutive patients undergoing phaco Excluded: corneal abnormalities, traumas or previous intraocular	Healon, n=19 Vitrax, n=16	523 186	18.5 7.0*

	Population	Interventions	Absolute decrease density (cells/mm²; SD)	Relative decrease density (%; SD)
	surgery, history of intraocular inflammation, diabetes; preoperative pupil dilatation <4mm, age <40, preoperative ECC <1500 cells/mm² and surgical complications	Celoftal, n=17	484	18.0
Vajpayee 2005[67]	Patients >40 years of age, senile cataract, nucleus hardness grade 3/4, undergoing phaco with IOL. Excluded: evidence of subluxation, pseudoexfoliation, any other ocular pathology, IOP>20mmHg or preoperative diagnosis of glaucoma and intra-operative events.	Viscoat, n=19 Healon GV, n=19 Healon5, n=18	338.7 400.8 394.6	14.7 17.0 15.6
Yachimori 2004	Patients undergoing phaco, only the first eye was included Excluded: ocular pathology other than senile cataract; history of prior ocular surgery or inflammation; pseudoexfoliation syndrome; diabetes	Healon+Viscoat, n=35 Opegan, n=34	121 175	4.9 (8.7) 5.5 (8.5)

$ Results expressed for extra and intracapsular cataract extraction respectively

§ All patients received sodium hyaluronate to expand the capsular bag before insertion of the IOL. Only the experimental group had sodium hyaluronate during anterior capsulotomy.

* Significant difference between the interventions at $p<0.05$

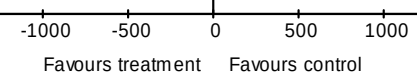
DIRECT COMPARISON META-ANALYSES

TRT 2 (Super viscosity cohesives)VS TRT 1 (Viscoadaptives)

Review: Ophthalmology
Comparison: 01 Trt 2 (Super viscosity cohesives) versus Trt 1 (Viscoadaptives)
Outcome: 01 endothelial cell density

Study or sub-category	N	Trt 2 Mean (SD)	N	Trt 1 Mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI	Year
27 Holzer	12	235.00(157.70)	19	140.70(132.50)		67.63	94.30 [-12.99, 201.59]	2001
02 Vajpayee	19	400.80(252.90)	18	394.60(228.20)		32.37	6.20 [-148.86, 161.26]	2005
Total (95% CI)	31		37			100.00	65.78 [-22.45, 154.01]	

Test for heterogeneity: Chi² = 0.84, df = 1 (P = 0.36), I² = 0%
Test for overall effect: Z = 1.46 (P = 0.14)

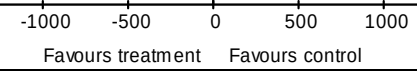


TRT 3 (Viscous cohesives) VS TRT 0 (Control)

Review: Ophthalmology
Comparison: 15 Trt 3(Viscous cohesives) vs Trt 0 (no viscoelastic)
Outcome: 01 endothelial cell density

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI	Year
15 Holmberg	19	805.00(310.60)	19	1259.00(423.10)		0.00	-454.00 [-690.00, -218.00]	1984
Total (95% CI)	19		19			0.00	-454.00 [-690.00, -218.00]	

Test for heterogeneity: not applicable
Test for overall effect: Z = 3.77 (P = 0.0002)

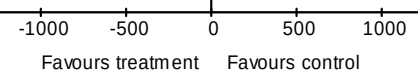


TRT 3 (Viscous cohesives) VS TRT 1 (Viscoadaptives)

Review: Ophthalmology
Comparison: 11 Trt 3 (Viscous cohesives) vs Trt 1 (Viscoadaptives)
Outcome: 01 endothelial cell density

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI	Year
30 Oshika	74	47.90(215.30)	74	62.20(215.30)		0.00	-14.30 [-83.67, 55.07]	2004
Total (95% CI)	74		74			0.00	-14.30 [-83.67, 55.07]	

Test for heterogeneity: not applicable
Test for overall effect: Z = 0.40 (P = 0.69)

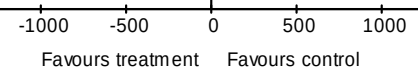


TRT 3 (Viscous cohesives)VS TRT 2 (Super viscosity cohesives)

Review: Ophthalmology
Comparison: 03 Trt 3 (Viscous cohesives) vs Trt 2 (Super viscosity cohesives)
Outcome: 01 endothelial cell density

Study or sub-category	N	Trt 3 Mean (SD)	N	Trt 2 Mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI	Year
18 Fry	34	-42.30(180.10)	35	79.00(313.10)		28.89	-121.30 [-241.40, -1.20]	1993
10 Ravalico	16	178.50(78.80)	15	166.70(80.60)		51.74	11.80 [-44.37, 67.97]	1997
08 Schmidl	30	103.40(346.90)	30	130.90(300.40)		19.37	-27.50 [-191.71, 136.71]	1999
Total (95% CI)	80		80			100.00	-34.26 [-120.12, 51.59]	

Test for heterogeneity: Chi² = 3.90, df = 2 (P = 0.14), I² = 48.7%
Test for overall effect: Z = 0.78 (P = 0.43)

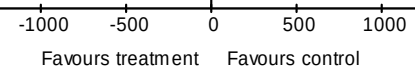


TRT 4 (Medium viscosity dispersives)VS TRT 1 (Viscoadaptives)

Review: Ophthalmology
Comparison: 02 Trt 4 (Medium viscosity dispersives) vs Trt 1 (No viscoelastic)
Outcome: 01 endothelial cell density

Study or sub-category	N	Trt 4 Mean (SD)	N	Trt 1 Mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI	Year
07 Schwenn	28	139.00(344.10)	20	122.00(285.00)		29.84	17.00 [-161.45, 195.45]	2000
27 Holzer	20	351.70(176.30)	19	140.70(132.50)		37.68	211.00 [113.43, 308.57]	2001
02 Vajpayee	19	338.70(243.70)	18	394.60(228.20)		32.48	-55.90 [-207.96, 96.16]	2005
Total (95% CI)	67		57			100.00	66.42 [-112.52, 245.36]	

Test for heterogeneity: Chi² = 9.73, df = 2 (P = 0.008), I² = 79.4%
Test for overall effect: Z = 0.73 (P = 0.47)

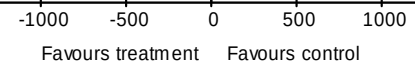


TRT 4 (Medium viscosity dispersives)VS TRT 2 (Super viscosity cohesives)

Review: Ophthalmology
Comparison: 04 Trt 4 (Medium viscosity dispersives) vs Trt 2 (Super viscosity cohesives)
Outcome: 01 endothelial cell density

Study or sub-category	N	Trt 4 Mean (SD)	N	Trt 2 Mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI	Year
10 Ravalico	14	164.60(148.80)	15	166.70(80.60)		32.15	-2.10 [-90.07, 85.87]	1997
28 Miller	70	26.50(314.60)	70	74.10(287.00)		28.42	-47.60 [-147.36, 52.16]	1999
27 Holzer	20	351.70(176.30)	12	235.00(157.70)		23.51	116.70 [-1.33, 234.73]	2001
02 Vajpayee	19	338.70(243.70)	19	400.80(252.90)		15.91	-62.10 [-220.02, 95.82]	2005
Total (95% CI)	123		116			100.00	3.35 [-70.26, 76.97]	

Test for heterogeneity: Chi² = 5.22, df = 3 (P = 0.16), I² = 42.5%
Test for overall effect: Z = 0.09 (P = 0.93)

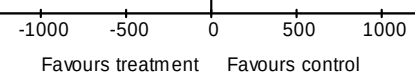


TRT 4 (Medium viscosity dispersives)VS TRT 3 (Viscous cohesives)

Review: Ophthalmology
Comparison: 05 Trt 4 (Medium viscosity dispersives) vs Trt 3 (Viscous cohesives)
Outcome: 01 endothelial cell density

Study or sub-category	N	Trt 4 Mean (SD)	N	Trt 3 Mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI	Year
13 Lane	38	171.40(218.60)	38	185.00(238.20)		16.76	-13.60 [-116.39, 89.19]	1991
14 Koch	30	175.70(289.10)	29	191.20(244.90)		13.21	-15.50 [-152.05, 121.05]	1993
20 Colin	46	116.00(172.00)	46	137.00(225.00)		19.24	-21.00 [-102.84, 60.84]	1995
21 Colin	49	240.00(343.40)	47	219.00(348.40)		13.03	21.00 [-117.44, 159.44]	1995
16 Henry	10	235.00(262.40)	25	221.30(315.20)		8.23	13.70 [-190.54, 217.94]	1996
10 Ravalico	14	164.60(148.80)	16	178.50(78.80)		18.62	-13.90 [-100.88, 73.08]	1997
03 Storr-Paulsen	16	186.00(208.00)	19	523.00(283.90)		10.91	-337.00 [-500.35, -173.65]	2007
Total (95% CI)	203		220			100.00	-43.85 [-114.79, 27.09]	

Test for heterogeneity: Chi² = 14.56, df = 6 (P = 0.02), I² = 58.8%
Test for overall effect: Z = 1.21 (P = 0.23)

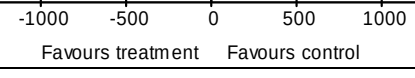


TRT 5 (Very low viscosity dispersives)VS TRT 1 (Viscoadaptives)

Review: Ophthalmology
Comparison: 12 Trt 5 (Very low viscosity dispersives) vs Trt 1 (Viscoadaptives)
Outcome: 01 endothelial cell density

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI	Year
27 Holzer	30	339.10(223.50)	19	140.70(132.50)		100.00	198.40 [98.67, 298.13]	2001
Total (95% CI)	30		19			100.00	198.40 [98.67, 298.13]	

Test for heterogeneity: not applicable
Test for overall effect: Z = 3.90 (P < 0.0001)

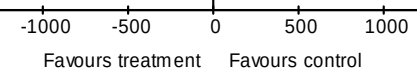


TRT 5 (Very low viscosity dispersives)VS TRT 2 (Super viscosity cohesives)

Review: Ophthalmology
Comparison: 06 Trt 5 (Very low viscosity dispersives) vs Trt 2 (Super viscosity cohesives)
Outcome: 01 endothelial cell density

Study or sub-category	N	Trt 5 Mean (SD)	N	Trt 2 Mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI	Year
10 Ravalico	13	196.70(111.20)	15	166.70(80.60)		71.43	30.00 [-42.92, 102.92]	1997
27 Holzer	30	339.10(223.50)	12	235.00(157.70)		28.57	104.10 [-15.72, 223.92]	2001
Total (95% CI)	43		27			100.00	51.17 [-14.44, 116.78]	

Test for heterogeneity: Chi² = 1.07, df = 1 (P = 0.30), I² = 6.7%
Test for overall effect: Z = 1.53 (P = 0.13)

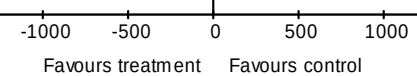


TRT 5 (Very low viscosity dispersives) vs TRT 3 (Viscous cohesives)

Review: Ophthalmology
Comparison: 07 Trt 5 (Very low viscosity dispersives) vs Trt 3 (Viscous cohesives)
Outcome: 01 endothelial cell density

Study or sub-category	N	Trt 5 Mean (SD)	N	Trt 3 Mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI	Year
05 Smith	109	287.30(215.30)	36	234.60(215.30)		22.16	52.70 [-28.42, 133.82]	1991
13 Lane	38	192.10(241.00)	38	185.00(238.20)		19.47	7.10 [-100.64, 114.84]	1991
10 Ravalico	13	196.70(111.20)	16	178.50(78.80)		23.08	18.20 [-53.53, 89.93]	1997
09 Ray-Chaudhuri	47	96.00(172.80)	52	260.00(210.00)		22.72	-164.00 [-239.49, -88.51]	2006
03 Storr-Paulsen	17	484.00(282.10)	19	523.00(283.90)		12.58	-39.00 [-224.14, 146.14]	2007
Total (95% CI)	224		161			100.00	-24.89 [-114.62, 64.83]	

Test for heterogeneity: Chi² = 18.29, df = 4 (P = 0.001), I² = 78.1%
Test for overall effect: Z = 0.54 (P = 0.59)

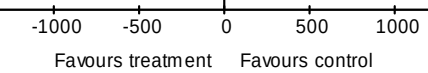


TRT 5 (Very low viscosity dispersives) vs TRT 4 (Medium viscosity dispersives)

Review: Opthalmology
Comparison: 08 Trt 5 (Very low viscosity dispersives) vs Trt 4 (Medium viscosity dispersives)
Outcome: 01 endothelial cell density

Study or sub-category	N	Trt 5 Mean (SD)	N	Trt 4 Mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI	Year
13 Lane	38	192.10(241.00)	38	171.40(218.60)		21.42	20.70 [-82.75, 124.15]	1991
10 Ravalico	13	196.70(111.20)	14	164.60(148.80)		22.17	32.10 [-66.54, 130.74]	1997
26 Kiss	39	62.00(233.00)	39	0.00(188.00)		22.91	62.00 [-31.96, 155.96]	2001
27 Holzer	30	339.10(223.50)	20	351.70(176.30)		20.25	-12.60 [-123.80, 98.60]	2001
03 Storr-Paulsen	17	484.00(282.10)	16	186.00(208.90)		13.26	298.00 [129.30, 466.70]	2007
Total (95% CI)	137		127			100.00	62.70 [-15.89, 141.29]	

Test for heterogeneity: Chi² = 10.01, df = 4 (P = 0.04), I² = 60.1%
Test for overall effect: Z = 1.56 (P = 0.12)

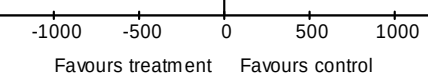


TRT 6 (combination of Viscous cohesives (3) + Medium viscosity dispersives (4)) vs TRT 3 (Viscous cohesives)

Review: Ophthalmology
Comparison: 09 Trt 6 (Viscous cohesives + Medium viscosity dispersives) vs Trt 3 (Viscous cohesives)
Outcome: 01 endothelial cell density

Study or sub-category	N	Trt 6 Mean (SD)	N	Trt 3 Mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI	Year
19 Cosemans	10	227.00(40.20)	10	254.00(49.30)		69.90	-27.00 [-66.43, 12.43]	1999
29 Miyata	37	271.00(206.10)	20	336.00(199.90)		8.99	-65.00 [-174.93, 44.93]	2002
01 Yachimori	35	121.00(127.80)	34	175.00(172.30)		21.11	-54.00 [-125.74, 17.74]	2004
Total (95% CI)	82		64			100.00	-36.12 [-69.08, -3.15]	

Test for heterogeneity: Chi² = 0.71, df = 2 (P = 0.70), I² = 0%
Test for overall effect: Z = 2.15 (P = 0.03)

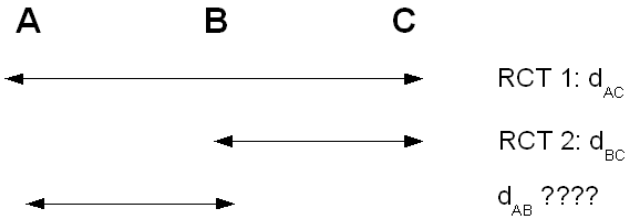


INDIRECT COMPARISONS

Introduction

RCTs with direct (head to head) treatment comparisons are usually referred to as level I evidence. But this level I evidence is not always available: placebo controlled trials are sufficient for regulatory approval of the drug, and even when active comparisons are made, such direct evidence is often limited. In that situation, indirect comparisons are usually accepted to supplement direct evidence. A simple model has first been presented by Bucher[229], and is usually referred to as the adjusted indirect comparison, as the model preserves the randomization of the originally assigned patient groups.

This model is very simple. Let *d* be the appropriate measure of the treatment effect between 2 groups; (log odds ratio, difference between 2 means, etc…), and let A, B and C be the 3 treatments groups (C is the control treatment). If data from 2 RCTs are available, each comparing an active (A or B) to a control, then the question is how to compare A versus B.



An indirect comparison

The treatment effect of A versus B is given by:

$$d^{indirect}_{AB} = d^{direct}_{AC} - d^{direct}_{BC}$$

and the variance of this effect is given by:

$$var^{indirect}_{AB} = var^{direct}_{AC} + var^{direct}_{BC}$$

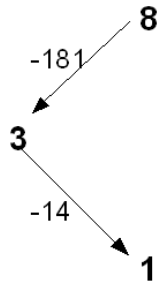
An extensive study of the use of indirect comparisons in systematic reviews, to evaluate the statistical methods used and to compare direct and indirect estimates of the same effect within reviews, has recently been published[230]. The authors conclude that "in the majority of the meta analyses reviewed, there was no statistically significant discrepancy between direct and indirect estimate. When direct evidence is not sufficient, the direct and indirect estimate could be combined to obtain a more precise estimate". This is exactly the purpose of the mixed treatment comparison.

In this section 2 studies are used to illustrate the concept of indirect comparison:
Study 24 compares treatment 8 versus treatment 3: -181 (-378, 16).
Study 3 compares 3 versus 1: -14 (-84, 55)

In order to derive an estimate of the effect of trt 8 vs trt 1, the formula above is used:
Estimate Treatment effect 8 versus 1: = -181 – 14 = -195
SE of trt effect : = $\sqrt{(100.51^2 + 35.71^2)}$= 106.66

Indirect Comparison: Estimate and 95% CI Trt 8 versus Trt 1= -195 (-304 , 14)

Lumley[231] proposed a graphical method to assess consistency in a network of treatments. We illustrate the method based on that simple example, and apply it in the next section on the whole set of studies.



A simple graphical presentation of indirect comparison of treatment 8 versus treatment 1

The points represent treatments and the arrows represent randomized comparisons. Numbers next to the lines represent treatment differences and the arrow indicates the direction of the comparison. A positive number indicates that the treatment at the head of the arrow has a higher outcome than at the tail. (In our case) a higher outcome is harmful. This is thus a simple graphical method which allows exploring consistency of direct and indirect comparisons.

What if both direct and indirect evidence are available? There is a simple pooling method, based on the inverse variance approach, which permits pooling the results[232]. Although this approach is very intuitive and straightforward to implement, it quickly becomes limited when the number of treatments starts to increase:

N treatments	2	3	4	5	6	7	8	9	10
N pairwise	1	2	6	10	15	21	28	36	45

With such a large number of treatments and comparisons, such an approach is meaningless. In a decision context, two questions might be of interest.

What's needed is a single statistical analysis combining all available evidence from all comparisons, between all treatments

Mixed treatments comparisons (MTC) are still a research area in statistics. It is currently part of the MRC from Bristol University current research program. This note is thus mainly based on their work, on a presentation of D. Cadwell[232] and on the notes from the course « Evidence Synthesis for decision making »[233], organized jointly by the MRC of Bristol and Leicester. A recent article also described the methods in more details.[234].

Methods for ophthalmic viscoelastic devices

The MTC method is briefly described below (for 6 treatments):
There are 6 treatments: A, B, C, D, E, F
Let A be the reference treatment
5 basic parameters (treatments effect) need to be defined: dBA, dCA, dDA, dEA, dFA.
All the remaining contrasts are called functional parameters, as they can be derived from the basic parameters. For example, the comparison F vs D can be written in terms of basic parameters dFD = dFA – dDA. This means that functional parameters are fully determined by basic parameters, and inversely, that information on functional parameters gives indirect info on basic parameters.
For each study, a model is fitted and the treatment effect is estimated. Then, the model makes the link between all the functional parameters and all basic parameters. As in regular meta-analysis, a fixed effect model will assume that all treatment effects are independent, while a random effect model will assume that there is a common random distribution for all the treatments effects, and allow for more heterogeneity between the different comparisons.

The software used to fit these models is WINBUGS (version 1.4.1)[235], and so non informative prior distributions need to be placed on the basic parameters. The software calculates the posterior distribution of the parameters by using simulations. Details on Bayesian analysis are beyond the scope of this note, but more information on Bayesian methods for health care evaluation can be found in the book of Abrams et al[236].

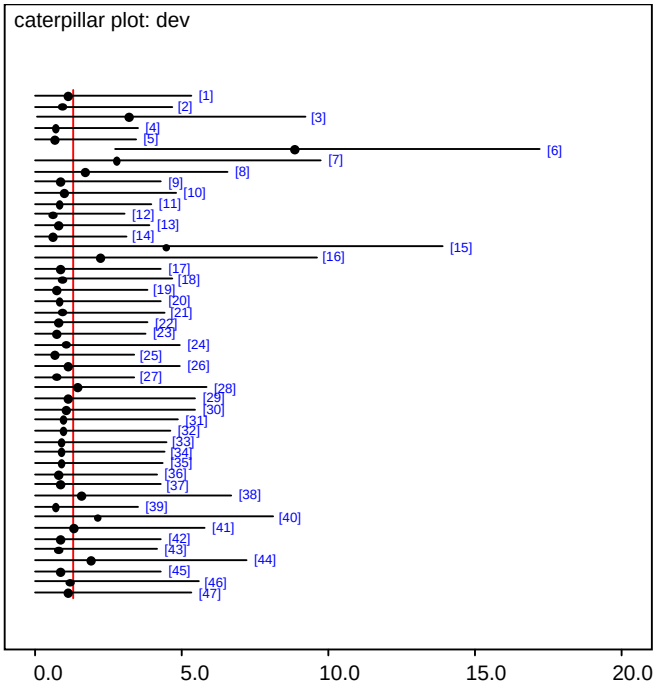
Below we illustrate the MTC methodology on **treatments 1 to 6**. The final structure for the MTC analysis involves 20 studies and 47 datapoints (number of treatment arms).

The table below presents summary of fit statistics. For a perfect fit, the residual deviance should be equal to the number of datapoints in the model (here 47). We see that the fixed effect model indicates lack of fit (residual deviance 97), and that the fit is improved by the choice of the random model (although there is still some indication of lack of fit, residual deviance of 63).

Model	Residual deviance	Dbar	pD	DIC
Fixed effect	97	525	23	548
Random effects	63	492	34	526

The residual deviance can be calculated for each individual datapoint (thus for each individual treatment arm). A result close to 1 indicates a good fit. The figure below shows the deviance for each of these datapoints. This graphic identifies one treatment arm which does not fit well in the model: datapoint 6 (study ID 3 Storr Paulsen, treatment 3). The treatment comparator (trt 4) of the same study shows also some problems of fit. Because datapoints 6 and 7 from study ID 3 show the largest deviance, it was investigated whether this particular study was influential on the results. All models were run with and without that study, and results were very robust (only the fit of the model was improved when the study was removed).

We thus choose to present the results with the inclusion of study 3.

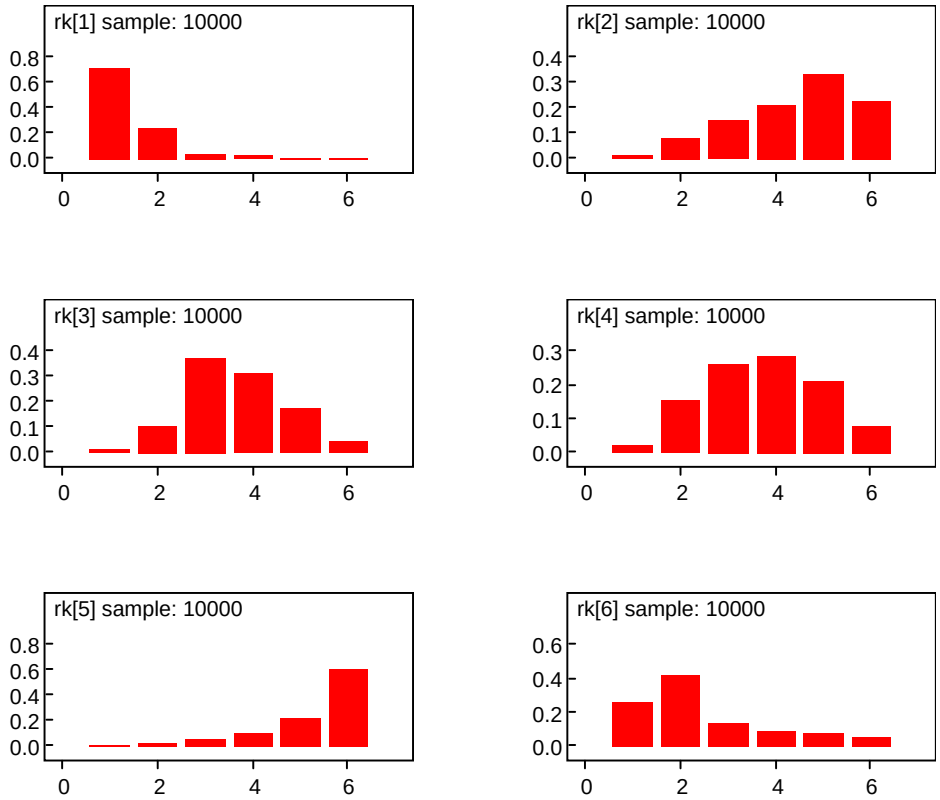


Estimation of basic parameters

Basic parameters are presented below. They compare all treatments versus the reference treatment, treatment 1. From these basic parameters, all treatments effects can be estimated.

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
d[2]	69.09	34.47	0.6627	0.7254	69.03	136.2	10001	10000
d[3]	53.83	30.87	0.5985	-7.996	54.05	113.0	10001	10000
d[4]	55.69	31.63	0.6212	-7.694	56.12	117.2	10001	10000
d[5]	88.25	34.91	0.5806	17.88	88.37	156.4	10001	10000
d[6]	26.8	44.41	0.7197	-62.45	27.37	112.4	10001	10000

The ranks of each treatment have been simulated:



node	mean	sd	MC error	2.5%	median	97.5%	start	sample
best[1]	0.7046	0.4562	0.00666	0.0	1.0	1.0	10001	10000
best[2]	0.0101	0.09999	0.001411	0.0	0.0	0.0	10001	10000
best[3]	0.011	0.1043	0.001283	0.0	0.0	0.0	10001	10000
best[4]	0.018	0.133	0.001456	0.0	0.0	0.0	10001	10000
best[5]	0.0023	0.0479	4.683E-4	0.0	0.0	0.0	10001	10000
best[6]	0.254	0.4353	0.005929	0.0	0.0	1.0	10001	10000

APPENDIX 5: EVIDENCE TABLES FOR SCHEIMPFLUG IMAGING SYSTEM

Reference	Population	Design	Index test	Ref test	Results
Technical accuracy					
Amano S 2005[110]	Eyes of subjects without ocular abnormalities other than cataract 54 eyes in 54 subjects Absolute difference of the first and second measurement by a single examiner; absolute difference of the 2 measurements by 2 examiners and relative amount of variation	Cross sectional study Prospective	Rotating Scheimpflug camera Orbscan scanning-slit corneal topography/pachymetry	Ultrasonic pachymetry	Central corneal thickness measurement No statistically significant differences in the measurement results among the 3 methods Ultrasonic pachymetry had the smallest intraexaminer variability, and scanning slit topography had the largest intraexaminer variability among the 3 methods. There were similar variations in interexaminer reproducibility among the 3 methods.
Barkana Y 2005[109]	Healthy patients Repeatability: 10 successive measurements in 2 eyes Reproducibility: 2 operators in 2 eyes of 24 patients for Scheimpflug imaging system versus US pachymetry 2 operators in 2 eyes of 16 patients for OLCR pachymeter versus Scheimpflug imaging system	Cross sectional study prospective	Scheimpflug imaging system (oculus) Optical low coherence reflectometer (OLCR) pachymeter (Haag-Streit)	Ultrasound (US) pachymetry	Central corneal thickness measurement For the Scheimpflug imaging system, mean coefficient of repeatability was 0.84%. (0.71% for US) The coefficient of interoperator reproducibility was 1.10% and the 95% limits of agreement were -10.2 µm to + 11.9 µm. Mean difference between Scheimpflug imaging system and US was 6.09 µm.
Buehl W 2006[111]	88 eyes of 44 healthy subjects		Scheimpflug imaging system (rotative Scheimpflug camera) AC-Master (partial coherence interferometry) Orbscan I (scanning slit topography system)	Not stated	Central corneal thickness (CT) and CT at four peripheral points and anterior chamber depth (ACD) measurement: Correlation was high between the three methods for central CT (r= 0.94 to 0.97) and central ACD (r= 0.96) between Orbscan and Scheimpflug imaging system Correlation was lower for the CT measurements at the four peripheral points.
Elbaz U 2007[113]	22 eyes in 11 healthy subjects	Cross sectional study Prospective	Scheimpflug imaging system	Ultra-sound (US) A-scan and IOLMaster (for ACD) And with automated keratometry (AK) and IOLMaster (for keratometry)	Measurements of anterior chamber depth (ACD) and corneal curvature (keratometry) Measurements of ACD by the Scheimpflug imaging system differed statistically significantly from those of US ($p< 0.05$) and IOLMaster ($p< 0.01$). Measurements of keratometry by the IOL Master differed statistically significantly from those of the Scheimpflug imaging system ($p< 0.01$) and AK ($p< 0.01$).
Fujioka M 2007[114]	Right eye of 135 patients without antiglaucoma drug use (100 F and 35 M): 32 primary open-angle glaucoma;	Cross sectional study Prospective	Scheimpflug imaging system (oculus) Non contact specular	Ultrasound (US) pachymetry	Central corneal thickness measurement Mean values: Scheimpflug imaging system: 559 ± 38 µm NCSM : 553 ± 40 µm

Reference	Population	Design	Index test	Ref test	Results
	14 ocular hypertension; 45 primary angle-closure glaucoma and 44 controls		microscopy (NCSM)		US: 552 ± 32 µm Mean difference between Scheimpflug imaging system and US was 6.47 µm ± 43 µm
Lackner B 2005[112]	30 healthy eyes 2 measures by 2 independent observers	Cross sectional study Prospective	Scheimpflug imaging system (oculus) Orbscan I (scanning slit topography system)	Ultrasound (US) pachymetry	Central corneal thickness measurement Mean values: Scheimpflug imaging system: 542 ± 29 µm Orbscan : 576 ± 37 µm (uncorrected) 530 ± 34 µm (corrected) US: 552 ± 32 µm Differences between Scheimpflug imaging system and US (95% limits of agreement) were -9.8 ± 31 µm And 33 ± 27 µm between orbscan and Scheimpflug imaging system And 24 ± 31.2 µm between Orbscan and US The coefficient of reproducibility for intra and interoperators was 2.2% for Scheimpflug imaging system and 4.2% for Orbscan and US
O'Donnell C 2005[115]	21 normal corneas measured on 2 separate occasions by the same examiner	Cross sectional study Prospective	Oculus Scheimpflug imaging system intrument	Allergan-Humphrey 850 ultrasonic pachymeter	measurement of CCT (corneal central thickness) mean values 534 ± 47 µm for US and 528 ± 45 µm for Scheimpflug imaging system Repeatability limits of agreement: -18.3 to + 17.7 µm for US and -24.1 to + 21.1 µm for Scheimpflug imaging system
Uçakhan O 2006[116]	1 eye /patient 45 consecutive patients with myopia (group A) 62 consecutive patients previously diagnosed with keratoconus (group B) divided in 3 subgroup: mild, moderate, and severe.	Case control study Prospective	Scheimpflug imaging comprehensive eye scanner Non contact specular microscopy	Ultrasound (US) pachymetry	Central corneal thickness measurement In normal eyes: reproducibility comparable between Scheimpflug imaging system (r= 0.994) and US (r= 0.993). In keratoconus eyes, the reproducibility of Scheimpflug imaging system (r= 0.998) is better than US (r= 0.969).
Keratoconus diagnosis					
Ambrosio R 2003[125]	1392 consecutive candidates for refractive surgery	prospective case series study screening of subclinical corneal abnormalities	videokeratography	ultrasonic pachymetry	Total 18/1392 patients (1.3%) eyes detected as poor refractive candidates with topographic analyses (videokeratography) 13 eyes of 8 patients with form subclinical of keratoconus (keratoconus suspected 6 eyes of 4 patients with definite keratoconus Only 4 of the 19 eyes with keratoconus had signs on corneal biomicroscopy
Ambrosio R 2006[85]	46 eyes (23 patients) diagnosed with mild to moderate keratoconus 364 normal eyes (196 patients)	case control study	Keratoconus diagnosed with "classic corneal topography findings"	Scheimpflug imaging system comprehensive eye scanner Measurements of Corneal thickness spatial profile: 22 imagery circles centered on the thinnest point with increased	Significant differences in all positions of the corneal-thickness spatial profile in normal eyes and keratoconic eyes ($p<0.01$) The calculated percentage increased in thickness was different between the groups ($p<0.001$) Significant differences were found in all positions of the corneal volume distribution ($p<0.05$)

Reference	Population	Design	Index test	Ref test	Results
				diameters at 0.4 steps Corneal volume distribution: diameters from 1.0 to 7.0 with 0.5mm steps centered on the thinnest point	
Chastang P 2000[130]	208 corneas (in 8 groups a groups of 23 keratoconus) a training set n= 104 and a validation set n=104	case control study	Eyesys system 2000 videokeratography	Keratometry	a tree combining 2 indices (with the videokeratograph) can detect clinical apparent keratoconus among normal corneas and irregular corneas
Fam HB 2006[129]	166 normal subjects 15 keratoconus 11 keratoconus suspects	retrospective study design	Orbscan corneal elevation maps	search of an index to distinguish normal of keratoconic eye	For an anterior elevation ratio (anterior elevation/ best fit sphere) of 5.122mm or <: sensitivity 99% specificity 95.2% For a ratio of 16.5µm or < sensitivity 80.1% specificity 80.8%
Gobbe M 2004[131]	a group (n=28 eyes) with suspected keratoconus a group (n=45)with diagnosed keratoconus a group (n=870) with regular cornea	case control study	videokeratoscope and software		to develop a keratoconus scheme detection based on Zernicke coefficient
Jonsson M 2005[132]	308 eyes of 156 healthy volunteers with various refractive errors	cross sectional study	Orbscan II	autorefractometer-keratometer	localization of the thinnest point of the cornea
Kalin N 1996[121]	Both eyes of 53 consecutive refractive surgery candidates (screening for keratoconus)	diagnosis accuracy study	Topographic pattern and objective biomicroscopy signs	videokeratoscopic data (expert system classifier incorporating 8 indices)	5/5 keratoconus diagnosed and 3 false positive sensitivity 100% specificity 97%
Klein S 2006[133]	27 eyes of patients with corneal ectasia after LASIK without apparent preoperative risk factors	Case series			ectasia may occur even in the absence of preoperative risk factors
Maeda N 1994[122]	100 corneas with a variety of diagnoses (mild to advance keratoconus, normal, keratoplasty…) for the training and 100 others corneas for a validation set	diagnosis accuracy study	Keratoconus al diagnosed by conventional clinical findings	computer assist (TMS1) videokeratoscope	training set: 22/22 diagnosed and 3 false positive sensitivity 100% specificity 96% accuracy 97% Validation test: 25/28 diagnosed and 1 false positive sensitivity 89% specificity 99% accuracy 96%
Maeda N 1995[126]	44 keratoconus 132 non keratoconus conditions	case control study	clinical diagnose	3 methods using videokeratography	Sensitivity (Se) Specificity (Sp) keratometry (sim K) Se 84% Sp 86% Rabinowitz –McDonnell Se 96% Sp 85% Expert system classifier Se 98% Sp 99%
Nesburn A 1995[124]	146 apparently normal myopic eyes (-1 to -7 diopters D with less than 1.5 D cylinder) of 91	prospective case series study screening of subclinical	conventional clinical evaluation	videokeratography	7/146 eyes detected: 2 definite keratoconus 3 suspected keratoconus

Reference	Population	Design	Index test	Ref test	Results
	consecutive patients who were candidates for refractive surgery	corneal abnormalities			1 early pellucid marginal degeneration
Rabinowitz Y 1998[127]	142 normal and 99 keratoconus patients	case control study	videokeratography	ultrasonic pachymetry	videokeratography indices: 97.5% correct classification rate (93/99 keratoconus) ultrasonic pachymetry: 86% rate (83/99 keratoconus) p<0.01
Rao S 2002[128]	6 consecutive eyes with suspicious videokeratography Control group of 50 consecutive eyes without suspicious features in videokeratography	case control study	orbscan II topography	videokeratography	difference in anterior elevation and posterior elevation between the groups but not difference for the thinnest pachymetry
Watters 1998[134]	41 patients with keratoconus al diagnosed	case series	videokeratoscope		comparison of measures in two disparate corneal locations
Wilson S 1994[123]	2 eyes of 53 patients before refractive surgery	prospective case series study		computer assist (TMS1) videokeratoscope	3 patients with definite keratoconus (5.7%) and 38% of the eyes with other corneal topographic abnormalities such irregular astigmatism, loss of radial symmetry…

APPENDIX 6: EVIDENCE TABLES INDOCYANINE GREEN ANGIOGRAPHY

Study	Population	Reference test	Index test	Results	Critical appraisal
Iranmanesh 2007[203]	100 eyes of 93 consecutive newly diagnoses of neovascularARMD	FA	ICGA	16 PCV and 14 RAP diagnosed by ICGA and not by FA	Prospective QUADAS: 7Y, 6U, 1N.
Pece 2005[168]	79 eyes of 77 consecutive patients with occult CNV in ARMD	FA	ICGA + FA	Occult CNV is correctly identified in 60% of cases by FA alone	Prospective QUADAS 6Y, 7U, 1N.
Schneider 2005[202]	180 patients with a vascularized PED (occult CNV) secondary to ARMD	FA	ICGA	12 RVAC (with retinal choroidal anastomosis identified with ICGA 6 RVAC identified with FA	Retrospective QUADAS: 5Y, 7U, 2N
Talks 2007[204]	111 wet ARMD diagnosed with OCT (/134 consecutive referred patients)	FA	ICGA	Additional diagnosis in 19 patients (14,17%): 10 RAP 9 PCV	Retrospective QUADAS: 5Y,5U,4N

APPENDIX 7: GLOSSARY

AMD or ARMD: Age Related Macular Degeneration
ARM: Age Related Maculopathy
CNV: Choroidal NeoVascular membranes
ECC: endothelial cell count
FA or FFA: Fundus Fluorescein Angiography
ICGA: Indocyanine Green Angiography
OCT: Optical Coherence Tomography
Nos: not otherwise specified
PCV: Polypoidal Choroidal Vasculopathy
PDT: PhotoDynamic Therapy
PED Pigment Epithelial Detachment
RAP: Retinal Angiomatous Proliferation
RPD: Reticular Pseudo Drusen
RPE: Retinal pigment epithelial
RVAC: Retinal Vascular Anomalous Complex

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Wettelijk depot : D/2008/10.273/04

KCE reports

1. Effectiviteit en kosten-effectiviteit van behandelingen voor rookstop. D/2004/10.273/1.
2. Studie naar de mogelijke kosten van een eventuele wijziging van de rechtsregels inzake medische aansprakelijkheid (fase 1). D/2004/10.273/2.
3. Antibioticagebruik in ziekenhuizen bij acute pyelonefritis. D/2004/10.273/5.
4. Leukoreductie. Een mogelijke maatregel in het kader van een nationaal beleid voor bloedtransfusieveiligheid. D/2004/10.273/7.
5. Het preoperatief onderzoek. D/2004/10.273/9.
6. Validatie van het rapport van de Onderzoekscommissie over de onderfinanciering van de ziekenhuizen. D/2004/10.273/11.
7. Nationale richtlijn prenatale zorg. Een basis voor een klinisch pad voor de opvolging van zwangerschappen. D/2004/10.273/13.
8. Financieringssystemen van ziekenhuisgeneesmiddelen: een beschrijvende studie van een aantal Europese landen en Canada. D/2004/10.273/15.
9. Feedback: onderzoek naar de impact en barrières bij implementatie – Onderzoeksrapport: deel 1. D/2005/10.273/01.
10. De kost van tandprothesen. D/2005/10.273/03.
11. Borstkankerscreening. D/2005/10.273/05.
12. Studie naar een alternatieve financiering van bloed en labiele bloedderivaten in de ziekenhuizen. D/2005/10.273/07.
13. Endovasculaire behandeling van Carotisstenose. D/2005/10.273/09.
14. Variaties in de ziekenhuispraktijk bij acuut myocardinfarct in België. D/2005/10.273/11.
15. Evolutie van de uitgaven voor gezondheidszorg. D/2005/10.273/13.
16. Studie naar de mogelijke kosten van een eventuele wijziging van de rechtsregels inzake medische aansprakelijkheid. Fase II : ontwikkeling van een actuarieel model en eerste schattingen. D/2005/10.273/15.
17. Evaluatie van de referentiebedragen. D/2005/10.273/17.
18. Prospectief bepalen van de honoraria van ziekenhuisartsen op basis van klinische paden en guidelines: makkelijker gezegd dan gedaan.. D/2005/10.273/19.
19. Evaluatie van forfaitaire persoonlijk bijdrage op het gebruik van spoedgevallendienst. D/2005/10.273/21.
20. HTA Moleculaire Diagnostiek in België. D/2005/10.273/23, D/2005/10.273/25.
21. HTA Stomamateriaal in België. D/2005/10.273/27.
22. HTA Positronen Emissie Tomografie in België. D/2005/10.273/29.
23. HTA De electieve endovasculaire behandeling van het abdominale aorta aneurysma (AAA). D/2005/10.273/32.
24. Het gebruik van natriuretische peptides in de diagnostische aanpak van patiënten met vermoeden van hartfalen. D/2005/10.273/34.
25. Capsule endoscopie. D/2006/10.273/01.
26. Medico–legale aspecten van klinische praktijkrichtlijnen. D2006/10.273/05.
27. De kwaliteit en de organisatie van type 2 diabeteszorg. D2006/10.273/07.
28. Voorlopige richtlijnen voor farmaco-economisch onderzoek in België. D2006/10.273/10.
29. Nationale Richtlijnen College voor Oncologie: A. algemeen kader oncologisch kwaliteitshandboek B. wetenschappelijke basis voor klinische paden voor diagnose en behandeling colorectale kanker en testiskanker. D2006/10.273/12.
30. Inventaris van databanken gezondheidszorg. D2006/10.273/14.
31. Health Technology Assessment prostate-specific-antigen (PSA) voor prostaatkankerscreening. D2006/10.273/17.
32. Feedback : onderzoek naar de impact en barrières bij implementatie – Onderzoeksrapport : deel II. D/2006/10.273/19.
33. Effecten en kosten van de vaccinatie van Belgische kinderen met geconjugeerd pneumokokkenvaccin. D/2006/10.273/21.
34. Trastuzumab bij vroegtijdige stadia van borstkanker. D/2006/10.273/23.
35. Studie naar de mogelijke kosten van een eventuele wijziging van de rechtsregels inzake medische aansprakelijkheid (fase III)- precisering van de kostenraming. D/2006/10.273/26.
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38. Baarmoederhalskankerscreening en testen op Human Papillomavirus (HPV). D/2006/10.273/35
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43. Herziening bestaande praktijkrichtlijnen. D/2006/10.273/48.
44. Een procedure voor de beoordeling van nieuwe medische hulpmiddelen. D/2006/10.273/50.
45. HTA Colorectale Kankerscreening: wetenschappelijke stand van zaken en budgetimpact voor België. D/2006/10.273/53.
46. Health Technology Assessment. Polysomnografie en thuismonitoring van zuigelingen voor de preventie van wiegendood. D/2006/10.273/59.
47. Geneesmiddelengebruik in de belgische rusthuizen en rust- en verzorgingstehuizen. D/2006/10.273/61
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49. Antivirale middelen bij seizoensgriep en grieppandemie. Literatuurstudie en ontwikkeling van praktijkrichtlijnen. D/2006/10.273/65.
50. Eigen betalingen in de Belgische gezondheidszorg. De impact van supplementen. D/2006/10.273/68.
51. Chronische zorgbehoeften bij personen met een niet- aangeboren hersenletsel (NAH) tussen 18 en 65 jaar. D/2007/10.273/01.
52. Rapid Assessment: Cardiovasculaire Primaire Preventie in de Belgische Huisartspraktijk. D/2007/10.273/03.
53. Financiering van verpleegkundige zorg in ziekenhuizen. D/2007/10 273/06
54. Kosten-effectiviteitsanalyse van rotavirus vaccinatie van zuigelingen in België
55. Evidence-based inhoud van geschreven informatie vanuit de farmaceutische industrie aan huisartsen. D/2007/10.273/12.
56. Orthopedisch Materiaal in België: Health Technology Assessment. D/2007/10.273/14.
57. Organisatie en Financiering van Musculoskeletale en Neurologische Revalidatie in België. D/2007/10.273/18.
58. De Implanteerbare Defibrillator: een Health Technology Assessment. D/2007/10.273/21.
59. Laboratoriumtesten in de huisartsgeneeskunde. D2007/10.273/24.
60. Longfunctie testen bij volwassenen. D/2007/10.273/27.
61. Vacuümgeassisteerde Wondbehandeling: een Rapid Assessment. D/2007/10.273/30
62. Intensiteitsgemoduleerde Radiotherapie (IMRT). D/2007/10.273/32.
63. Wetenschappelijke ondersteuning van het College voor Oncologie: een nationale praktijkrichtlijn voor de aanpak van borstkanker. D/2007/10.273/35.
64. HPV Vaccinatie ter Preventie van Baarmoederhalskanker in België: Health Technology Assessment. D/2007/10.273/41.
65. Organisatie en financiering van genetische diagnostiek in België. D/2007/10.273/44.
66. Health Technology Assessment: Drug-Eluting Stents in België. D/2007/10.273/47.
67. Hadrontherapie. D/2007/10.273/50.
68. Vergoeding van schade als gevolg van gezondheidszorg – Fase IV : Verdeelsleutel tussen het Fonds en de verzekeraars. D/2007/10.273/52.
69. Kwaliteit van rectale kankerzorg – Fase 1: een praktijkrichtlijn voor rectale kanker D/2007/10.273/54.
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71. Aanbevelingen voor het gebruik van vijf oftalmologische testen in de klinische praktijk .D/2008/10.273/04.