Bijlagen bij Conceptrichtlijnmodules Cluster Oog

2e cyclus modulair onderhoud

INITIATIEF
Cluster Oog

IN SAMENWERKING MET
Nederlands Oogheelkundig Gezelschap (NOG)
Nederlandse Internisten Vereniging (NIV)
Nederlandse Vereniging voor Reumatologie (NVR)
De Oogvereniging

MET ONDERSTEUNING VAN
Het Kennisinstituut van de Federatie Medisch Specialisten.

FINANCIERING
De richtlijnontwikkeling werd gefinancierd uit de Stichting Kwaliteitsgelden Medisch Specialisten (SKMS).

Sommige onderdelen (inleiding, literatuursamenvatting) van de onderstaande tekst staan in het Engels, andere in het Nederlands. Dit is om internationale uitwisseling te bevorderen conform afspraken in Richtlijnen 3.0.

Colofon
Conceptrichtlijnmodules cluster oog

Inhoudsopgave

Dit document bevat de achtergrondinformatie behorende bij de moduleteksten uit het cluster oog. Het staat u vrij om commentaar op deze bijlagen te geven; dit is niet noodzakelijk.

Bijlage 1 Verantwoording module 1 – Keuze van anti-VEGF middel

Verantwoording

Voor meer details over de gebruikte richtlijnmethodologie verwijzen wij u naar de Werkwijze. Relevante informatie voor de ontwikkeling/herziening van deze richtlijnmodule is hieronder weergegeven.

Initiatief

Initiatief: cluster oog

Samenstelling van de werkgroep

Voor het ontwikkelen van de richtlijnmodule is in 2022 een multidisciplinair cluster ingesteld. Het cluster oog bestaat uit meerdere richltijnen, zie hier voor de actuele clusterindeling. De stuurgroep bewaakt het proces van modulair onderhoud binnen het cluster. De expertisegroepsleden geven hun expertise in, indien nodig. De volgende personen uit het cluster zijn betrokken geweest bij de herziening van deze module.

Clusterstuurgroepleden

- Dr. N.C. (Nicole) Naus, voorzitter cluster oog, oogarts, NOG, Erasmus MC
- Dr. M.C. (Marjolijn) Bartels, Voorzitter Cluster Oog, oogarts, NOG, Deventer Ziekenhuis
- Dr. A.J. (Arlette) van Sorge, oogarts, NOG, Koninklijke Visio,
- Drs. L.J. (Leo) Noordzij, oogarts, NOG, Oog op Zuid Oogkliniek
- Dr. R. (Redmer) van Leeuwen, oogarts, NOG, UMC Utrecht
- Dr. Ir M. (Marleen) van Aartrijk, Klinisch Fysicus NVKF, Koninklijke Visio
- C. (Caroline) Osterholt-Bel, Adviseur oogzorg Oogvereniging

Betrokken clusterexpertisegroepleden

Module 1: keuze anti-VEGF middel

- Drs. L.J. (Leo) Noordzij, oogarts, NOG, Oog op Zuid Oogkliniek
- Dr. S. (Suzanne) Yzer, oogarts, NOG, Radboud UMC
- P. (Pauline) de Heer, afgevaardigd op persoonlijke titel

Met ondersteuning van

- Dr. A.C.J. (Astrid) Balemans, senior-adviseur, Kennisinstituut van Medisch Specialisten
- MSc. D.G. (Dian) Ossendrijver, adviseur, Kennisinstituut van Medisch Specialisten
- A. (Alies) Oost, informatiespecialist, Kennisinstituut van de Federatie Medisch Specialisten

Belangenverklaringen

Een overzicht van de belangen van de clusterleden en het oordeel over het omgaan met eventuele belangen vindt u in onderstaande tabel. De ondertekende belangenverklaringen zijn op te vragen bij het secretariaat van het Kennisinstituut van de Federatie Medisch Specialisten via secretariaat@kennisinstituut.nl.

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Cluster stuurgroepleden

Tabel 1 Gemelde (neven)functies en belangen stuurgroep

Naam	Hoofdfunctie	Nevenwerkzaamheden	Persoonlijke financiële belangen	Persoonlijke relaties	Extern gefinancierd onderzoek	Intellectuele belangen en reputatie	Overige belangen	Datum	Restrictie
Dr. N.C. (Nicole) Naus,	Oogarts Erasmus MC Rotterdam	Geen	Geen	Geen	Geen	Geen	Geen	1-08-2025	Geen restricties
Dr. M.C. (Marjolijn) Bartels	Oogarts Deventer ziekenhuis	Lid van Concilium, lid van commissie kwaliteit en voorzitter van cornea werkgroep (NOG).	Geen	Geen	ja, 1. PHIC (PIONEERS IN HEALTH CARE INNOVATIEFONDS) voucher voor onderzoek in samenwerking Universiteit Twente ZonMWstudies: 2. BICAT-NL studie 3. EPICAT studie	persoonlijk belang van goed op de hoogte zijn van alles, hetgeen gebruikt wordt in de dagelijkse praktijk en als opleider, lid van Concilium, lid van commissie kwaliteit en voorzitter van cornea werkgroep.	Geen	1-08-2025	Geen restricties

Dr. A.J. (Arlette) van Sorge	Oogarts koninklijke Visio	Voorzitter VRS (vereniging voor revalidatie bij slechtziendheid, onbetaald). Stuurgroeplid bij cluster OOG (NOG). Visitator visitatiecommissie NOG. Bestuurslid Oogcontact (onbetaald).	Geen	Geen	Geen	Geen	Geen	6-05-2025	Geen restricties
Drs. L.J. (Leo) Noordzij	Oogarts bij Cooperatie Oogheelkunde op Zuid voor 3.5 dag in de week. Voor 1.5 dag in de week bestuurslid van de Cooperatie Oogheelkunde op Zuid, de Stichting Oogheelkunde op Zuid en medisch directeur het zelfstandig behandel centrum Oog op Zuid oogkliniek.	Lid richtlijn werkgroep FMS/ NOG betreffende leeftijdsgebonden macula degeneratie (tm juli 2023). Vaste programma commissie InSights symposium, Novartis (gestopt juni 2022). Lid medical innovation academy, Novartis (gestopt augustus 2022).	Geen	Geen	Geen	Geen	Geen	20-04-2025	Geen restricties ('advieswerk' neergelegd per juni/augustus 2022)

Dr. R. (Redmer) van Leeuwen	Oogarts UMC Utrecht	Geen	Geen	Geen	ESCH-R 1. NWO - Circulaire zorg (Projectleider NEE)	Geen	Geen	02-02-2025	Geen restricties
Dr. Ir M. (Marleen) van Aartrijk	Klinisch Fysicus bij Koninklijke Visio (Revalidatie & Advies): betaald, - beheer Oogheelkundige apparatuur - ondersteuning zorgprofessionals bij individuele patienttrajecten (bijv. op gebied van verlichting, autorijden) - producteigenaar elektronisch patientendossier	Geen	Geen persoonlijk financieel belang. Indien een richtlijn verwijzing naar revalidatiezorg stimuleert kan dat impact hebben op mijn werkgever (en dan indirect op mijzelf	Geen	Binnen de revalidatiezorg zijn er fondsen (oa Novum, ZonMW) die exptertiseprojecten ondersteunen. Aan een aantal van deze projecten draag ik bij, maar dat gaat om een zeer beperkt deel van mijn tijd (ben geen hoofdonderzoeker oid)	Verduidelijking van rol revalidatiezorg in de zorgketen	Geen	22-04-2025	Geen restricties
C. (Caroline) Osterholt-Bel	TOA Ikazia	Geen	Geen	Geen	Geen	Geen	Geen	29-04-2025	Geen restricties

Betrokken clusterexpertisegroepleden

Tabel 2 Gemelde (neven)functies en belangen expertisegroep

Naam	Hoofdfunctie	Nevenwerkzaamheden	Persoonlijke financiële belangen	Persoonlijke relaties	Extern gefinancierd onderzoek	Intellectuele belangen en reputatie	Overige belangen	Datum	Restrictie
Dr. S. (Suzanne) Yzer	Oogarts, Radboudumc	Penningmeester werkgroep medische retina	Geen	Geen	Geen	Geen	Mogelijk in de toekomst optreden als expert in een patentzaak rondom een geregistreerd anti-VEGF	04-06-2025	Geen restricties
P. (Pauline) de Heer	Strategisch adviseur bij Zorginstituut Nederland Adviseren over passende zorg, duurzaamheid, maatschappelijke opgaven, signalering en agendering.	Geen	Geen	Geen	Geen	Geen	Geen	08-04-2025	Geen resticties

Kwalitatieve raming van mogelijke financiële gevolgen in het kader van de Wkkgz

Bij de richtlijnmodule voerden de clusterleden conform de Wet kwaliteit, klachten en geschillen zorg (Wkkgz) een kwalitatieve raming uit om te beoordelen of de aanbevelingen mogelijk leiden tot substantiële financiële gevolgen. Bij het uitvoeren van deze beoordeling is de richtlijnmodule op verschillende domeinen getoetst (zie het stroomschema bij Werkwijze).

Module	Uitkomst raming	Toelichting
Module keuze van anti-VEGF middel	Geen financiële gevolgen	Hoewel uit de toetsing volgt dat de aanbeveling(en) breed toepasbaar zijn (>40.000 patiënten), volgt uit de toetsing dat het overgrote deel (±90%) van de zorgaanbieders en zorgverleners al aan de norm voldoet. Er worden daarom geen financiële gevolgen verwacht.

Bijlage 2 Literatuursamenvatting module 1 – Keuze anti-VEGF middel

Leeswijzer: de voorliggende herziene tekst vervangt de bestaande module over keuze van anti-VEGF middel. De tekst in blauw is afkomstig uit de huidige module en ongewijzigd overgenomen.

Introduction (English)

Patients with neovascular age-related macular degeneration (nAMD) are treated with intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections. An increasing number of anti-VEGF agents are becoming available, including biosimilars.

Currently, bevacizumab (Avastin®) is recommended as the first-choice agent based on its efficacy, cost differences "non-inferiority" compared to other anti-VEGFs and current insights into (systemic) side effects even though bevacizumab is not registered for nAMD. Anti-VEGF agents that are registered for this indication include aflibercept (2 mg, 8 mg) (Eylea®), ranibizumab (Lucentis®), brolucizumab (Beovu®), and faricimab (Vabysmo®). The anti-VEGF agents faricimab and aflibercept 8 mg were published after the previous search and subsequently were not included in the earlier comparison. The question is what role these two agents should play in the treatment of nAMD? The Dutch Ophthalmological Society (NOG) wrote a position paper on the use of biosimilars in ophthalmology on this matter.

Search and select

A systematic review of the literature was performed to answer the following questions:

- What is the effect of bevacizumab compared to any other anti-VEGF in patients with exudative age-related macular degeneration on vision maintenance/improvement, retinal thickness and safety (PICO 1)?
- What is the effect of aflibercept 2 mg compared to any other anti-VEGF in patients with exudative age-related macular degeneration on vision maintenance/improvement, retinal thickness and safety (PICO 2)?
- What is the effect of faricimab compared to any other anti-VEGF in patients with exudative age-related macular degeneration on vision maintenance/improvement, retinal thickness and safety (PICO 3)?
- What is the effect of aflibercept 8mg compared to any other anti-VEGF in patients with exudative age-related macular degeneration on vision maintenance/improvement, retinal thickness and safety (PICO 4)?

Table 1. PICO 1 bevacizumab compared to other anti-VEGFs

Patients	Patients with treatment naive neovascular age-related macular degeneration
Intervention	Bevacizumab
Control	Other ant-VEGFs: ranibizumab, aflibercept 2 mg, brolucizumab, biosimilars for anti-VEGF
Outcomes	Vision maintenance/improvement, retinal thickness, safety
Other selection criteria	Study design: systematic reviews and randomized controlled trials

Table 2. PICO 2 aflibercept 2 mg compared to other anti-VEGFs

Patients	Patients with treatment naive neovascular age-related macular degeneration
Intervention	Aflibercept 2mg
Control	Other anti-VEGFs: bevacizumab, ranibizumab, brolucizumab, biosimilars for anti-VEGF

Outcomes	Vision maintenance/improvement, retinal thickness, safety
Other selection criteria	Study design: systematic reviews and randomized controlled trials

Table 3. PICO 3 faricimab compared to other anti-VEGFs

Patients	Patients with treatment naive neovascular age-related macular degeneration
Intervention	Faricimab
Control	Other anti-VEGFs: Bevacizumab, ranibizumab, aflibercept 2mg, Aflibercept 8mg, brolucizumab, biosimilars for anti-VEGF
Outcomes	Vision maintenance/improvement, retinal thickness, safety, injection frequency
Other selection criteria	Study design: systematic reviews and randomized controlled trials

Table 4. PICO 4 aflibercept 8 mg compared to other anti-VEGFs

Patients	Patients with treatment naive neovascular age-related macular degeneration
Intervention	Aflibercept 8mg
Control	Other anti-VEGFs: Bevacizumab, ranibizumab, aflibercept 2 mg, Faricimab, brolucizumab, biosimilars for anti-VEGF
Outcomes	Vision maintenance/improvement, retinal thickness, safety, injection frequency
Other selection criteria	Study design: systematic reviews and randomized controlled trials

Relevant outcome measures

The guideline panel considered vision maintenance/improvement as a **critical** outcome measure for decision making; and retinal thickness, safety and injection frequency as **important** outcome measures for decision making.

The guideline panel defined the outcome measures as follows:

- Vision improvement: improvement of 15 letters or more from baseline
- Vision maintenance: no loss of letters from baseline
- Retinal thickness: change in central foveal/subfoveal thickness on OCT

The guideline panel defined 25% for dichotomous outcomes and 10% for continuous outcomes as a minimal clinically (patient) important difference.

Search and select (Methods)

In 2021 a search was performed for PICO 1 and PICO 2. The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until June 21st, 2021, for the comparison bevacizumab versus other anti-VEGFs. An additional search was performed until August 2nd, 2021, for the comparison between aflibercept 2mg and other anti-VEGFs. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 287 hits. Studies were selected based on the following criteria: study design was a systematic review or randomized controlled trial, included patients with neovascular AMD, compared bevacizumab with other anti-VEGFs or aflibercept 2mg vs. other anti-VEGFs, and reported at least one outcome of interest. Twenty-five studies were initially selected based on title and abstract screening. After

reading the full text, 21 studies were excluded (see the table with reasons for exclusion under the tab Methods), and three studies were included.

In 2025 a systematic literature search was performed for PICO 3 and 4. The systematic literature search was performed by a medical information specialist using the following bibliographic databases: Embase.com and Ovid/Medline all. Both databases were searched from 2021 to May 23th, 2025 for systematic reviews and RCTs. Systematic searches were completed using a combination of controlled vocabulary and natural language keywords. The overall search strategy was derived from the following primary search concepts: (1) age-related macular degeneration; (2) faricimab OR aflibercept. Duplicates were removed using EndNote software. After deduplication a total of 554 records were imported for title/abstract screening. Initially, for PICO 3, thirteen studies were selected based on title and abstract screening. After reading the full text, twelve studies were excluded (see the exclusion table under the tab 'Evidence tabellen'), and one study was included. For PICO 4, five studies were selected based on title and abstract screening. After reading the full text, three studies were excluded (see the exclusion table under the tab 'Evidence tabellen'), and two studies were included.

Summary of literature

Description of studies

A total of six studies were included in the analysis of the literature:

- One systematic review for PICO 1: Bevacizumab compared to other anti-VEGFs
- One systematic review and one randomized controlled trial for PICO 2: aflibercept 2 mg compared to other anti-VEGFs.
- One systematic review for PICO 3: faricimab compared to other anti-VEGFs
- Two randomized controlled trials for PICO 4: aflibercept 8 mg compared to other anti-VEGFs

Important study characteristics and results are summarized in table 5. The assessment of the risk of bias is summarized in the risk of bias tables (under the tab 'Evidence tabellen').

PICO 1 Bevacizumab compared to other anti-VEGFs

Solomon (2019), on behalf of the Cochrane Library, performed a systematic review to compare the relative effects of one of three anti-VEGF agents (pegaptanib, ranibizumab, and bevacizumab) versus another when administered in comparable dosages and regimen. Randomized controlled trials (RCTs) were included that evaluated pegaptanib, ranibizumab, or bevacizumab versus each other or versus a control treatment (e.g., sham treatment, photodynamic therapy), in which participants were followed for at least one year. A search was performed in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE Ovid, Embase Ovid, the Latin American and Caribbean Health Sciences Literature Database (LILACS), the
International Standard Randomized Controlled Trials Number (ISRCTN) Registry and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) until January 31, 2018. A total of 16 RCTs were included that enrolled 6347 participants with neovascular AMD and one potentially relevant ongoing trial. Of the included trials, 10 trials compared bevacizumab versus ranibizumab, which we included in our analysis. A meta-analysis was performed. The 16 trials were similar in that all enrolled both men and women 50 years of age or older who had subfoveal CNV secondary to AMD.

Study characteristics are summarized under the tab 'evidence tables'.

PICO 2 Aflibercept 2 mg compared to other anti-VEGFs

Aflibercept 2 mg versus ranibizumab

Sarwar (2016) performed a systematic review to assess and compare the effectiveness and safety of intravitreal injections of aflibercept 2 mg versus ranibizumab, bevacizumab, or sham for treatment of patients with neovascular AMD. Randomized controlled trials (RCTs) in which aflibercept 2mg monotherapy was compared with ranibizumab, bevacizumab, or sham for participants with neovascular AMD who were treatment-naive were included. A search was performed in the Cochrane Central Register of Controlled Trials (CENTRAL), Ovid MEDLINE, EMBASE, PubMed, Latin American and Caribbean Health Sciences Literature Database (LILACS), the metaRegister of Controlled Trials (mRCT) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) until November 30, 2015. A total of two RCTs were included (VIEW1 and VIEW2), which enrolled 2457 participants with neovascular AMD with active subfoveal choroidal neovascular lesions. Both trials followed the same protocol and compared aflibercept 2 mg at various doses versus ranibizumab. A meta-analysis was performed. The included studies enrolled both men and women 50 years of age or older who had subfoveal neovascular AMD in the study eye.

Study characteristics are summarized under the tab 'evidence tables'.

Aflibercept 2 mg versus brolucizumab

Dugel (2021) performed a randomized controlled trial to compare the efficacy and safety of brolucizumab in eyes with neovascular age-related macular degeneration (nAMD). Patients were randomized 1:1:1 to receive brolucizumab 3 mg or 6 mg or aflibercept 2 mg (HAWK) or 1:1 to receive brolucizumab 6 mg or aflibercept 2 mg (HARRIER). HAWK and HARRIER are phase 3, prospective, randomized, double-masked, multicenter studies designed to compare the efficacy and safety of brolucizumab 3 mg (HAWK only) and 6 mg with aflibercept 2 mg in patients with nAMD. Eligible patients were aged ≥50 years and had untreated, active choroidal neovascularization lesions secondary to AMD affecting the central subfield (the circular area within 1 mm diameter around the foveal center on imaging); choroidal neovascularization lesions (including classic and occult), as assessed by fluorescein angiography, comprising >50% of total lesion area; IRF and/or SRF affecting the central subfield as assessed on spectral-domain OCT; BCVA between 78 and 23 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (inclusive; Snellen equivalents, approximately 20/32 to 20/400); and no fibrosis or geographic atrophy affecting the central subfield. Patients could not have received any approved or investigational nAMD treatment at any time (study eye). Overall, 1082 patients were randomized in HAWK between December 2014 and May 2016, and 743 patients were randomized in HARRIER between June 2015 and April 2016. Mean baseline BCVA was 60.6 (HAWK) and 61.2 (HARRIER) letters, and approximately 25% of study eyes had BCVA ≥71 letters at baseline, which is reflective of current clinical practice and in line with BCVA inclusion criteria.

Study characteristics are summarized under 'evidence tables'.

PICO 3 faricimab compared to other anti-VEGFs

Yen (2024) performed a systematic review to assess the visual, anatomical, and safety outcomes of intravitreal faricimab in patients with nAMD. EMBASE, Ovid-Medline, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, Scopus, WHO ICTRP, ClinicalTrials.gov, the EU Clinical Trials Register, and the Chinese Clinical Trial Registry (ChiCTR) were searched on 17 August 2023. Inclusion criteria were randomized controlled trials about adults with nAMD who received **faricimab** compared to other anti-VEGF agents and reported at least one clinical outcome such as BCVA, central subfoveal retinal thickness or adverse events. Phase I clinical trials and studies that examined CNV arising from conditions other than AMD were excluded. Three studies, including four RCTs were included (Heier 2022 performed two phase III trials).

PICO 4 aflibercept 8 mg compared to other anti-VEGFs

Lanzetta (2024) performed a randomized phase III trial to determine the safety and efficacy of **aflibercept 8 mg** versus aflibercept 2 mg in patients with treatment-naive nAMD. The study was conducted in 223 sites across 27 countries. Adults aged 50 years or older were eligible for the study, with one eye per patient designated as the study eye. Inclusion criteria were active subfoveal choroidal neovascularisation (CNV) secondary to nAMD (including juxtafoveal lesions involving the fovea), best-corrected visual acuity (BCVA) with an Early Treatment Diabetic Retinopathy Study (ETDRS) letter score of 78–24 (approximately Snellen 20/32 to 20/320), and a total area of choroidal neovascularisation (classic and/or occult) comprising more than 50% of the total lesion area in the study eye. Patients with a total lesion size greater than 12 disc areas (30.5 mm^2) were excluded. In total, 335 patients received aflibercept 8 mg every 12 weeks and 336 patients received aflibercept 2 mg every 8 weeks. Outcomes of interest were vision maintenance/improvement, retinal thickness and safety.

The phase II randomized clinical trial of **Wykoff (2023)** aimed to evaluate the safety and efficacy of **8 mg aflibercept** in patients with nAMD. The study was conducted across 45 sites in the United States from November 2019 to November 2021. Patients aged 50 years or older were included if they had treatment-naive, active CNV due to nAMD—including juxtafoveal lesions involving the fovea in the study eye—with a BCVA of 78 to 24 on the Early Treatment Diabetic Retinopathy Study letter score (equivalent to a Snellen range of 20/32 to 20/320). Exclusion criteria were evidence of CNV from causes other than nAMD, presence of diabetic retinopathy or diabetic macular edema in either eye, or subretinal hemorrhage involving ≥50% of the total lesion area in the study eye. In total, 53 eyes received 3 monthly doses aflibercept 8 mg (70 μL) and 53 eyes received aflibercept 2 mg (50 μL), followed by doses at weeks 20 and 32. Eyes could receive additional treatment at 16 weeks if the disease persisted or showed signs of worsening. At weeks 24, 28, 36, and 40, eyes were eligible for as-needed treatment at the randomized dose if they met one of the following criteria: (1) a loss of 5 or more letters from week 20 attributable to disease progression, or (2) vision-threatening anatomic features as determined by the investigator, including worsening or persistent retinal fluid, new or worsening retinal pigment epithelial detachment, or new/persistent hemorrhage. Groups were comparable at baseline. Outcomes of interest were vision maintenance/improvement, retinal thickness and safety.

Table 5. Characteristics of included studies (PICO 3 and PICO 4)

Study	Participants	Comparison	Follow-up	Outcome measures	Comments	Risk of bias (per outcome measure)*
Included in systematic review Yen, 2024 - FARICIMAB						
Heier, 2022 LUCERNE	N at baseline Intervention: 331 Control: 327	Intervention: Faricimab 6.0 mg up to every 16 weeks, based on activity assessments Control: Aflibercept 2.0 mg every 4 weeks up to week 8, followed by fixed 8-week dosing to study end	48 weeks	Mean BCVA (ETDRS) change	Phase 3 RCT Funding received from pharmaceutical companies, suggesting a potential conflict of interest.	Low
Heier, 2022 TENAYA	N at baseline Intervention: 334 Control: 337	Intervention: Faricimab 6.0 mg up to every 16 weeks, based	48 weeks	Mean BCVA (ETDRS) change	Phase 3 RCT Funding received from	Low

		on activity assessments Control: Aflibercept 2.0 mg every 4 weeks up to week 8, followed by fixed 8-week dosing to study end			pharmaceutical companies, suggesting a potential conflict of interest.	
Khanani, 2020 STAIRWAY	N at baseline Intervention: Arm B: 29 Arm C: 31 Control: 16	Intervention: Arm B: Faricimab, 6.0 mg every 12 weeks Arm C: Faricimab, 6.0 mg every 16 weeks Control: 0.5 mg Ranibizumab every 4 weeks	52 weeks	Mean BCVA (ETDRS) change	Phase 2 RCT Funding received from pharmaceutical companies, suggesting a potential conflict of interest.	Low
Sahni, 2020 AVENUE	N at baseline Intervention: Arm B: 47 Arm C: 42 Arm D: 47 Arm E: 69 Control: 68	Intervention: Arm B: Faricimab, 1.5 mg every 4 weeks Arm C: Faricimab, 6.0 mg every 4 weeks Arm D: Faricimab, 6.0 mg every 4 weeks up to week 12, followed by 6 mg every 8 weeks Arm E: Ranibizumab 0.5 mg + Faricimab 6.0 mg every 4 weeks Control: Ranibizumab, 0.5 mg every 4 weeks	36 weeks	Mean BCVA (ETDRS) change	Phase 2 RCT Funding received from pharmaceutical companies, suggesting a potential conflict of interest.	Low
Individual studies - AFLIBERCEPT						
Lanzetta, 2024 PULSAR	N at baseline Intervention: 335 Control: 336 Age (mean, SD) Intervention: 74.7 (7.9) years Control: 74.2 (8.8) Sex (% male)	Intervention: aflibercept 8 mg (every 12 weeks or every 16 weeks) Control: aflibercept 2 mg	48 weeks	Safety, change from baseline in BCVA, retinal thickness	This study was funded by Bayer AG and Regeneron Pharmaceuticals. Bayer AG and Regeneron Pharmaceuticals participated in the study design; the collection, analysis, and	Low

	Intervention: 45.7% Control: 44.0%				interpretation of data; the writing of the report; and the decision to submit the paper for publication.	
Wykoff, 2023 CANDELA	N at baseline Intervention: 53 Control: 53 Age (mean, SD) Intervention: 77.0 (7.7) years Control: 77.7 (8.3) years Sex (% male) Intervention: 43.4% Control: 32.1%	Intervention: aflibercept 8 mg (3 monthly) Control: aflibercept 2 mg (3 monthly)	44 weeks	Safety, retinal thickness, BCVA score	This study was funded by Regeneron Pharmaceuticals, Inc, and by Bayer AG (Leverkusen, Germany). The CANDELA study was sponsored by Regeneron Pharmaceuticals, Inc, and cofunded by Bayer AG (Leverkusen, Germany). The sponsors participated in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication	Some concerns

*For further details, see risk of bias table in the appendix

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Results

PICO 1 Bevacizumab compared to other anti-VEGFs

1. Vision maintenance / improvement

Bevacizumab versus ranibizumab

Solomon (2019) described vision maintenance/improvement, which was reported in eight RCTs, as the gain of 15 more letters visual acuity at 1 year (Biswas, 2011; BRAMD, 2016; CATT, 2011; GEFAL, 2013; IVAN, 2013; LUCAS, 2015; MANTA, 2013, Subramanian, 2010). In total, 3144 patients were analyzed, with 1542 in the bevacizumab group and 1602 in the ranibizumab group. The pooled risk ratio (RR) was 0.95 (95% confidence interval (CI): 0.81 to 1.12), towards ranibizumab was reported, which is not clinically relevant.

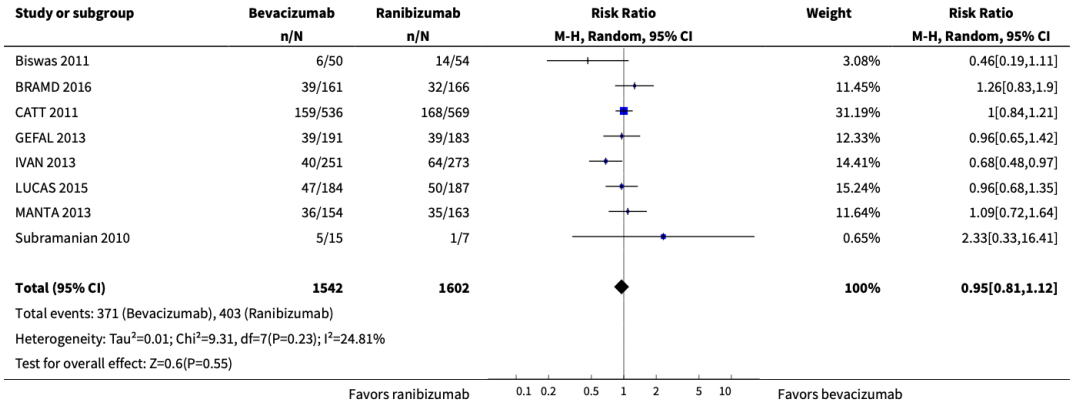

Figure 1. forest plot showing the comparison bevacizumab versus ranizumab for the outcome vision maintenance (at 1 year).

In addition, Solomon described the vision maintenance/improvement at 2 years, which was reported in two studies (CATT, 2011; IVAN, 2013). In total, 1547 patients were analyzed, with 751 in the bevacizumab group and 796 in the ranibizumab group. The pooled RR was 0.84 (95% CI 0.64 to 1.11) towards ranibizumab, which is not statistically significant or clinically relevant.

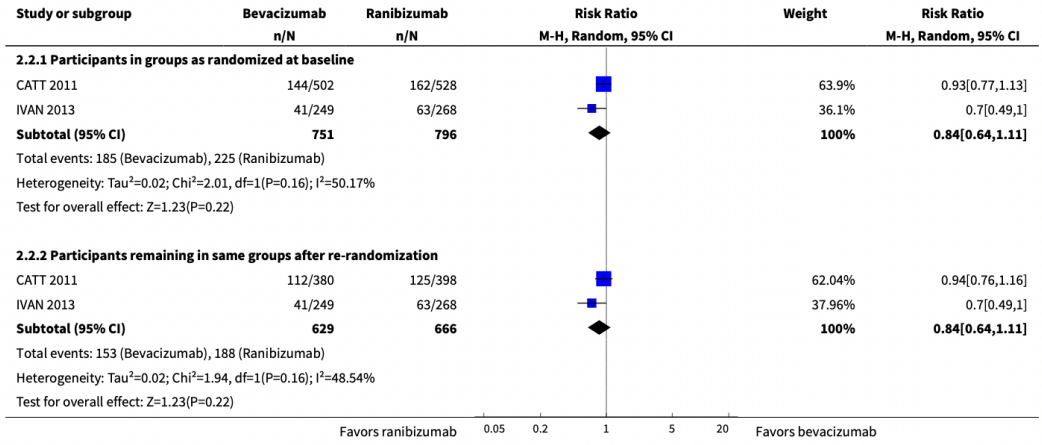

Figure 2. forest plot showing the comparison bevacizumab versus ranizumab for the outcome vision maintenance (at 2 years).

2. Retinal thickness

Bevacizumab versus ranibizumab

Solomon (2019) described retinal thickness, which was reported in six RCTs (Biswas, 2011; BRAMD, 2016; CATT, 2011; GEFAL, 2013; IVAN, 2013; LUCAS, 2015). In total 2693 patients were analyzed, with 1317 in the bevacizumab group and 1376 in the ranibizumab group. A pooled mean difference of 11.6 µm, 95% CI -21.6 to -1.7), towards ranibizumab was reported, which is not clinically relevant.

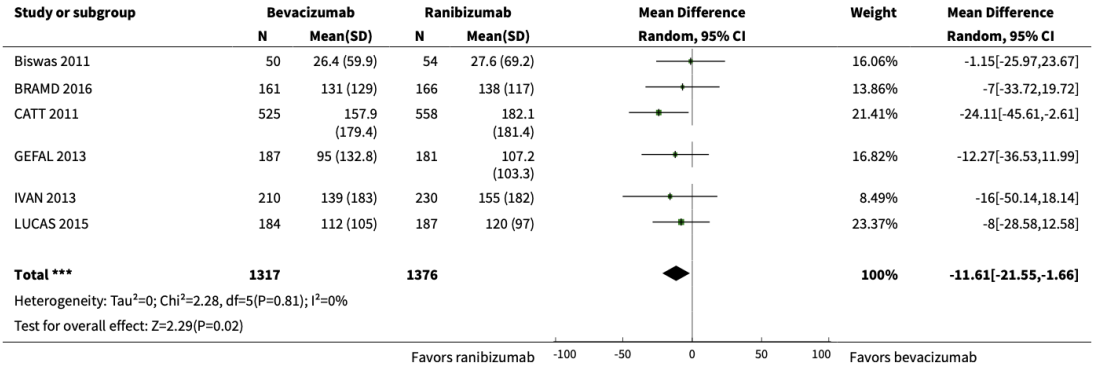

Figure 3. forest plot showing the comparison bevacizumab versus ranizumab for the outcome retinal thickness

In addition, two studies (CATT, 2011; IVAN, 2013) reported the outcome reduction in central retinal thickness at 2 years follow-up. In total 1199 patients were analyzed, with 592 in the bevacizumab group and 607 in the ranibizumab group. The pooled mean difference was -12.4 µm, (95% CI -33.83 to 9.04) towards ranibizumab, which is not clinically relevant.

3. Safety

Bevacizumab versus ranibizumab

Solomon (2019) described that in ten RCTs information about adverse events were provided, but the follow-up, and the types and specificity of the reported adverse events varied between studies.
At one year follow-up, no serious ocular events were reported by four trials (Biswas, 2011; MANTA, 2013; SAVE-AMD, 2017; Subramanian, 2010). Minor adverse events were reported in three of the four trials, including subconjunctival hemorrhage, increased intraocular pressure, transient post injection pain, and mild ocular inflammation. The numbers of participants who experienced these adverse events were not reported.
The occurrence of serious systemic adverse events was comparable across anti-VEGF-treated groups and control groups.

Level of evidence of the literature

Bevacizumab versus ranibizumab

The level of evidence regarding the outcome measure "**Vision maintenance/improvement**" comes from randomized controlled trials and therefore starts at high. The level of evidence was not downgraded, resulting in a level of evidence of high.

The level of evidence regarding the outcome measure "**Retinal thickness**" comes from randomized controlled trials and therefore starts at high. The level of evidence was not downgraded, resulting in a level of evidence of high.

The level of evidence regarding the outcome measure "**safety**" comes from a randomized controlled trial and therefore starts at high. The level of evidence was downgraded by two levels due to low numbers of events and participants (imprecision), resulting in a level of evidence of low.

Conclusions

Bevacizumab versus ranibizumab

High GRADE	Ranibizumab results in little to no difference in **vision maintenance/improvement** when compared with bevacizumab in patients with neovascular age-related macular degeneration. *Sources: Solomon, 2019*

High GRADE	Ranibizumab results in little to no difference in **retinal thickness** on OCT macular when compared with bevacizumab in patients with neovascular age-related macular degeneration. *Sources: Solomon, 2019*

Low GRADE	Ranibizumab may result in little to no difference in **serious systemic adverse events** when compared with bevacizumab in patient with neovascular age-related macular degeneration. *Sources: Solomon, 2019*

PICO 2 Aflibercept 2 mg compared to other anti-VEGFs

1. Vision maintenance / improvement

Aflibercept 2 mg versus ranibizumab

Two studies reported on vision maintenance/improvement. **Sarwar (2016)** described vision maintenance/improvement, which was reported in two RCTs, as the proportion of participants who gained 15 or more letters of BCVA at one-year follow-up (VIEW1; VIEW2).

In total, 2412 patients were analyzed, with 1817 in the aflibercept 2 mg group and 595 in de ranibizumab group. The pooled RR was 0.97 (95% CI 0.85 to 1.11), towards ranibizumab. This result was not clinically relevant.

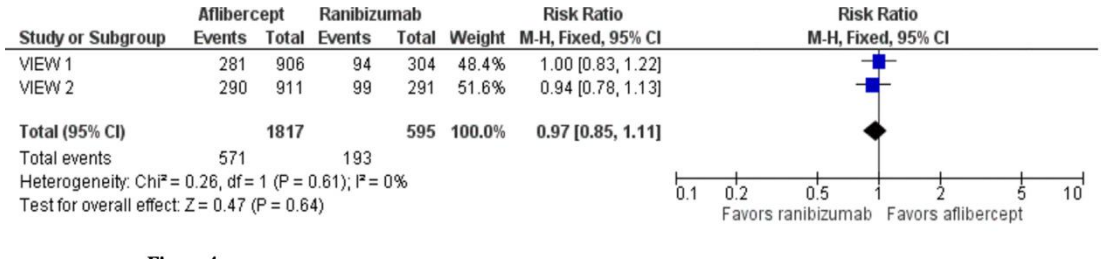

Figure 4. forest plot showing the comparison bevacizumab versus ranizumab for the outcome vision maintenance (at 2 years).

At two-year follow-up, 562 (30.9%) of 1817 participants in the aflibercept groups and 188 (31.6%) of 595 participants in the ranibizumab groups gained 15 or more letters from baseline. The pooled RR was 0.98 (95% CI 0.85 to 1.12), towards ranibizumab. This result was not clinically relevant.

Brolucizumab versus aflibercept 2 mg

One study reported on vision maintenance/improvement. **Dugel (2021)** reported the mean change in BCVA from baseline to week 48. Brolucizumab-treated eyes were noninferior to aflibercept 2 mg-treated eyes, and these visual gains were maintained to week 96.

HAWK: mean change (least squares [LS] mean ± standard error) in BCVA from baseline to 96w was 5.6 ± 0.79 ETDRS letters for brolucizumab 3 mg, 5.90 ± 0.78 letters for brolucizumab 6 mg, and 5.3 ± 0.78 letters for aflibercept 2 mg.

HARRIER: mean change was 6.1 ± 0.73 letters for brolucizumab 6 mg and 6.6 ± 0.73 letters for aflibercept 2 mg. These results were not clinically relevant.

2. retinal thickness

Aflibercept 2 mg versus ranibizumab

Two studies reported on retinal thickness. **Sarwar (2016)** described retinal thickness in two studies (VIEW1; VIEW2). In total, 2412 patients were analyzed, with 1817 in the aflibercept 2 mg group and 595 in de ranibizumab group. The pooled mean difference was −4.94 µm (95% CI −15.48 to 5.61) towards aflibercept 2 mg, which is not clinically relevant.

Aflibercept 2 mg versus brolucizumab

Dugel (2021) reported central subfield thickness for the comparison brolucizumab versus aflibercept 2 mg.
HAWK reported a mean change of -174.8 µm vs. -148.7 µm (95% CI for treatment difference, -46.2 to -5.9 µm; P = 0.0115) in the brolucizumab 6 mg group and aflibercept 2 mg group, respectively. The difference is not clinically relevant.
HARRIER reported a mean change of -197.7 µm vs. -155.1 µm; 95% CI for treatment difference, -62.0 to -23.3 µm; P < 0.0001) in the brolucizumab 6 mg group and aflibercept 2 mg group, respectively. The difference is clinically relevant.

3. Safety

Aflibercept 2 mg versus ranibizumab

Sarwar (2016) described safety in two studies (VIEW1; VIEW2). In total, 2412 patients were analyzed, with 1817 in the aflibercept 2 mg group and 595 in de ranibizumab group. The pooled RR for serious systemic adverse events was 0.99 (95%CI 0.79 to 1.25), towards aflibercept 2 mg. This result is not clinically relevant.
In the aflibercept 2 mg group, 36/1824 (1.9%) experienced serious ocular adverse events, compared to 19/595 (3.2%) in the ranibizumab group. The pooled RR for serious ocular adverse events was 0.62 (95%CI 0.36 to 1.07), towards aflibercept 2 mg. This result is clinically relevant.

Aflibercept 2 mg versus brolucizumab

Dugel (2021) reported that conjunctival hemorrhage was the most frequently reported ocular adverse event across all treatment groups in HAWK, occurring in 39 (10.9%), 29 (8.1%), and 32 (8.9%) patients in the brolucizumab 3 mg, brolucizumab 6 mg, and aflibercept 2 mg groups, respectively. The incidence of ocular adverse events (AEs) was similar across all treatment groups in both HAWK and HARRIER up to week 96 (see Table 1 in original paper), with the exception of combined intraocular inflammation (IOI) (iritis and uveitis), which was higher in the brolucizumab 6 mg group of HAWK compared with the aflibercept 2 mg group (4.7% vs. 0.6%). This result is clinically relevant.
In HARRIER, the most frequently reported ocular adverse events were reduced visual acuity in the brolucizumab 6 mg group (32 patients [8.6%]) and cataract in the aflibercept 2 mg group (43 patients [11.7%]). A RR of 0.73 (95%CI 0.48 to 1.13) towards brolucizumab for safety was calculated. This result is clinically relevant.

Level of evidence

Aflibercept 2 mg versus ranibizumab

The level of evidence regarding the outcome measure "**Vision maintenance/improvement**" comes from randomized controlled trials and therefore starts at high. The level of evidence was downgraded by one level because exceeding the limits of clinical relevance (imprecision), resulting in a level of moderate.

The level of evidence regarding the outcome measure "**Retinal thickness**" comes from randomized controlled trials and therefore starts at high. The level of evidence was downgraded by one level

because exceeding the limits of clinical relevance (imprecision), resulting in a level of evidence of moderate.

The level of evidence regarding the outcome measure "**safety**" comes from randomized controlled trials and therefore starts at high. The level of evidence was downgraded by one level due to low numbers of events (imprecision), resulting in a level of evidence of moderate.

Aflibercept 2 mg versus brolucizumab

The level of evidence regarding the outcome measure "**Vision maintenance/improvement**" comes from a randomized controlled trial and therefore starts at high. The level of evidence was not downgraded, resulting in a level of evidence of high.

The level of evidence regarding the outcome measure "**Retinal thickness on oct macular**" comes from a randomized controlled trial and therefore starts at high. The level of evidence was not downgraded, resulting in a level of evidence of high.

The level of evidence regarding the outcome measure "**safety**" comes from a randomized controlled trial and therefore starts at high. The level of evidence was downgraded by one level due to crossing the lower limit of clinical relevance (imprecision), resulting in a level of evidence of moderate.

Conclusions

Aflibercept 2 mg versus ranibizumab

Moderate GRADE	Ranibizumab likely results in little to no difference in vision maintenance/improvement when compared with Aflibercept 2 mg in patients with neovascular age-related macular degeneration *Sources: Sarwar, 2016*

Moderate GRADE	Ranibizumab likely results in little to no difference in retinal thickness on OCT macular when compared with Aflibercept 2 mg in patients with neovascular age-related macular degeneration. *Sources: Sarwar, 2016*

Moderate GRADE	Aflibercept 2 mg likely results in little to no difference in serious systemic adverse events when compared with ranibizumab in patients with neovascular age-related macular degeneration. Aflibercept 2 mg likely results in less serious ocular adverse events when compared with ranibizumab in patients with neovascular age-related macular degeneration. Note: The same authors conclude that current available information suggests that the safety profile of aflibercept 2 mg is comparable with that of ranibizumab. *Sources: Sarwar,2016*

Aflibercept 2 mg *versus brolucizumab*

High GRADE	Brolucizumab results in little to no difference in vision maintenance/improvement when compared with aflibercept 2 mg in patients with neovascular age-related macular degeneration.

	Sources: Dugel, 2021

High GRADE	Brolucizumab results in little to no difference in vision maintenance/improvement when compared with aflibercept 2 mg in patients with neovascular age-related macular degeneration. *Sources: Dugel, 2021*

Moderate GRADE	Brolucizumab likely results in a reduction of ocular adverse events when compared with aflibercept 2mg in patients with neovascular age-related macular degeneration.* *Sources: Dugel, 2021*

*Note: After the literature search, other important studies on the safety of brolucizumab were published, pointing towards an increased risk of ocular adverse events.

PICO 3 faricimab compared to other anti-VEGFs

Faricimab versus ranibizumab

1. Vision maintenance/improvement (critical)

Yen (2024) included two studies that reported vision improvement as gaining ≥15 ETDRS letters (Khanani, 2020; Sahni, 2020) (figure 1a). In total, 23 of the 72 patients (31.9%) who received faricimab gained ≥15 ETDRS letters as compared to 27 of the 83 patients (32.5%) who received ranibizumab (RR=0.92, 95%CI 0.54 to 1.54). This difference is not clinically relevant.

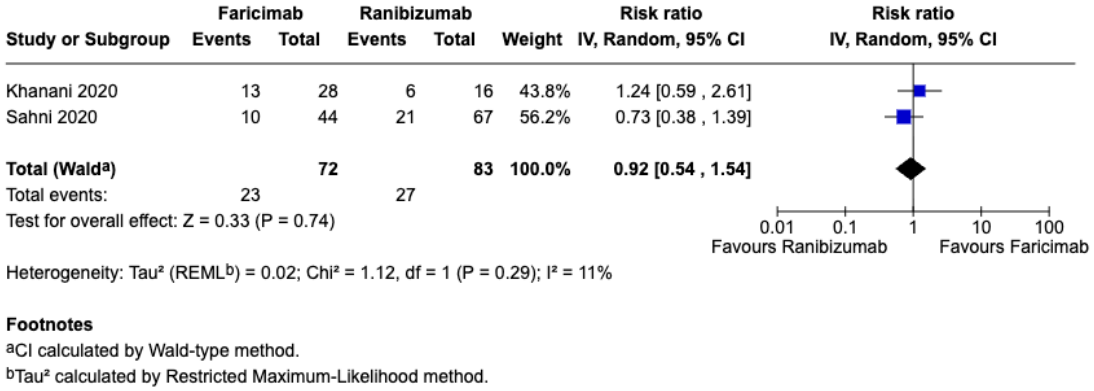

Figure 5a. Forest plot showing outcome vision maintenance: gaining ≥15 ETDRS letters for comparison faricimab versus ranibizumab.

Besides, **Yen (2024)** also included two studies that reported the mean difference in BCVA (Khanani, 2020; Sahni, 2020) (figure 1b). A mean difference of -1.03 ETDRS letters (95%CI -4.67 to 2.61) was found.

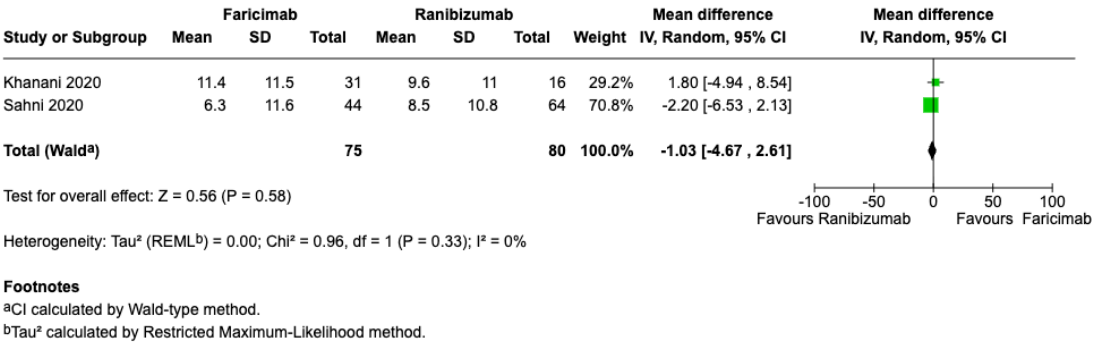

Figure 5b. Forestplot showing outcome vision maintenance: mean difference in BCVA (ETDRS letters) for comparison faricimab versus ranibizumab.

2. Retinal thickness (important)

Yen (2024) included two studies that reported the central subfield thickness (CST) change from baseline (Khanani, 2020; Sahni, 2020) (figure 2). A mean difference of 8.07 µm (95%CI -17.92 to 34.06) was found.

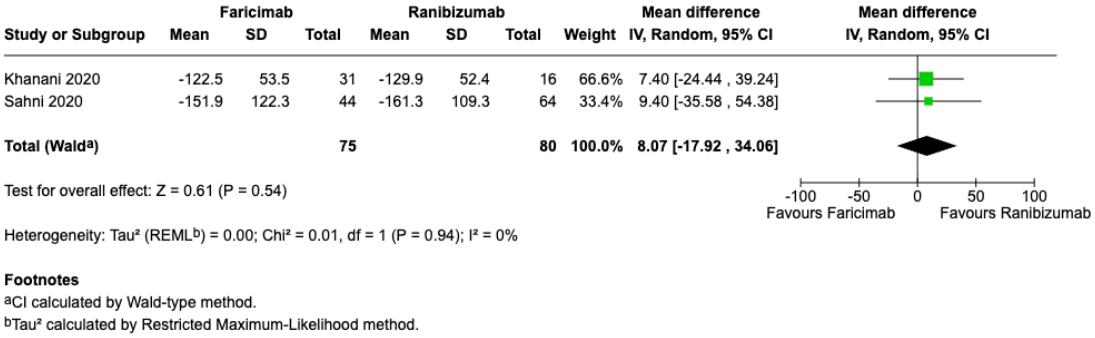

Figure 6. Forest plot showing outcome retinal thickness for comparison faricimab versus ranibizumab.

3. Safety (important)

3.1. Ocular adverse events

Yen (2024) included two studies that reported ocular adverse events (not specified) (Khanani, 2020; Sahni, 2020) (figure 3). In total, 38 of the 77 patients (49.4%) who received faricimab had ocular adverse events (not specified) as compared to 36 of the 83 patients (43.4%) who received ranibizumab (RR=1.06, 95%CI 0.55 to 2.05). This difference is not clinically relevant.

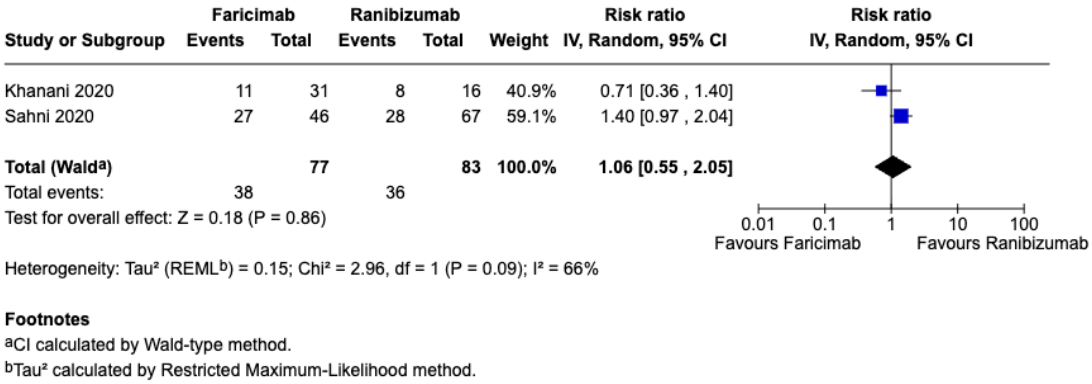

Figure 7. Forest plot showing outcome ocular adverse events for comparison faricimab versus ranibizumab.

3.2. Ocular serious adverse events

Yen (2024) included two studies that reported ocular serious adverse events (not specified) (Khanani, 2020; Sahni, 2020). *Khanani (2020)* and *Sahni (2020)* reported that no ocular serious adverse events occurred for eyes who either received faricimab or ranibizumab.

4. Injection frequency (important)

The outcome injection frequency was not reported for the outcome faricimab compared to other ranibizumab

Faricimab versus Aflibercept 2 mg

1. Vision maintenance/improvement (critical)

Yen (2024) included one study (Heier, 2022) with two trials (LUCERNE, 2022; TENAYA, 2022) that reported vision improvement as gaining ≥15 ETDRS letters (figure 4a). In total, 119 of the 594 patients (20.0%) who received faricimab gained ≥15 ETDRS letters as compared to 112 of the 591 patients (19.0%) who received 2 mg aflibercept (RR=1.06, 95%CI 0.76 to 1.48). This difference is not clinically relevant.

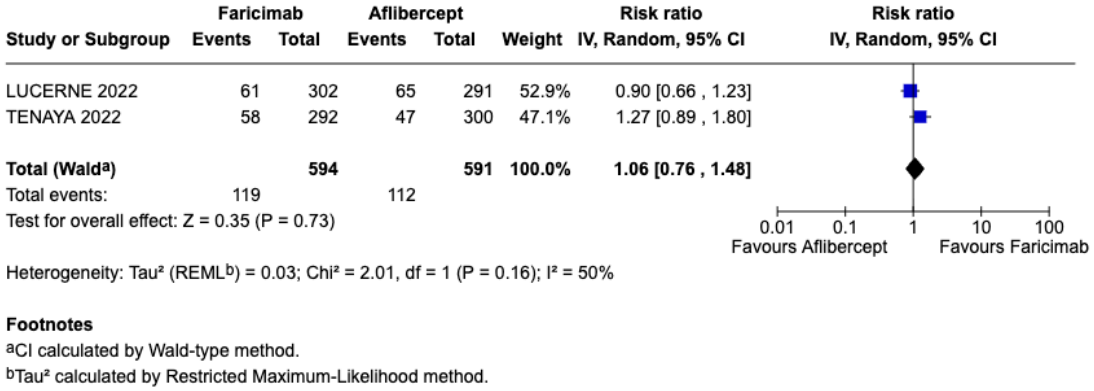

Figure 8a. forest plot showing outcome vision maintenance: gaining ≥15 ETDRS letters for comparison faricimab versus aflibercept 2 mg.

Besides, **Yen (2024)** also included one study (Heier, 2022) with two trials (LUCERNE, 2022; TENAYA, 2022) that reported the mean difference in BCVA (figure 4b). A mean difference of 0.35 ETDRS letters (95%CI -0.34 to 1.04) was found.

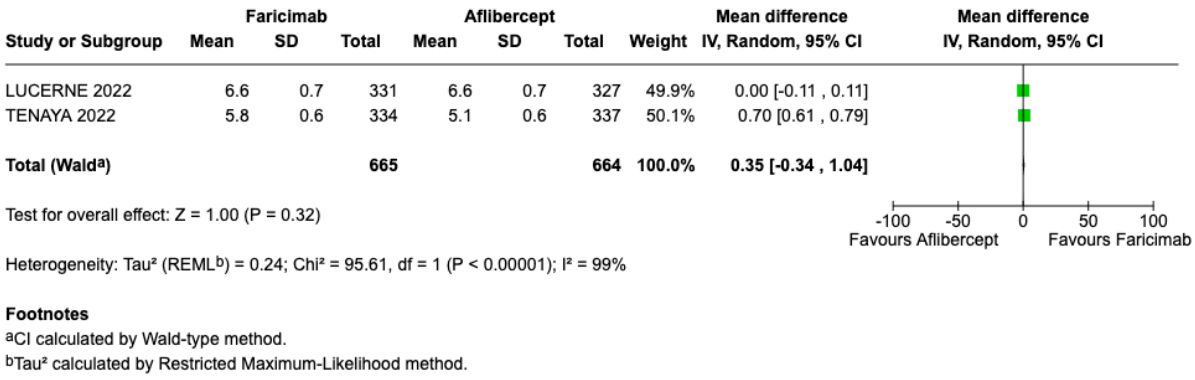

Figure 8b. forest plot showing outcome vision maintenance: mean difference in BCVA (ETDRS letters) for comparison faricimab versus aflibercept 2 mg.

2. Retinal thickness (important)

Yen (2024) included one study (Heier, 2022) with two trials (LUCERNE, 2022; TENAYA, 2022) that reported the central subfield thickness (CST) change from baseline (figure 5). A mean difference of -6.84 µm (95%CI -12.71 to -0.96) was reported.

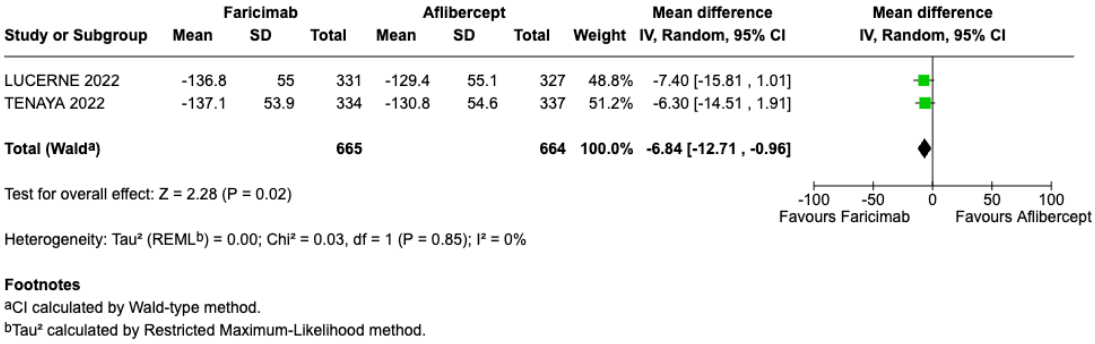

Figure 9. Retinal thickness for comparison faricimab versus aflibercept 2 mg.

3. Safety (important)

3.1. Ocular adverse events

Yen (2024) included one study (Heier, 2022) with two trials (LUCERNE, 2022; TENAYA, 2022) that reported ocular adverse events (not specified) (figure 6). In total, 234 of the 664 patients (35.2%) who received faricimab had ocular adverse events as compared to 246 of the 662 patients (37.2%) who received 2 mg aflibercept (RR=0.95, 95%CI 0.82 to 1.09). This difference is not clinically relevant.

3.2. Ocular serious adverse events

Yen (2024) included one study (Heier, 2022) with two trials (LUCERNE, 2022; TENAYA, 2022) that reported ocular serious adverse events (not specified) (figure 6). In total, 11 of the 664 patients (1.7%) who received faricimab had ocular serious adverse events as compared to 13 of the 662 patients (2.0%) who received 2 mg aflibercept (RR=0.84, 95%CI 0.38 to 1.88). This difference is not clinically relevant.

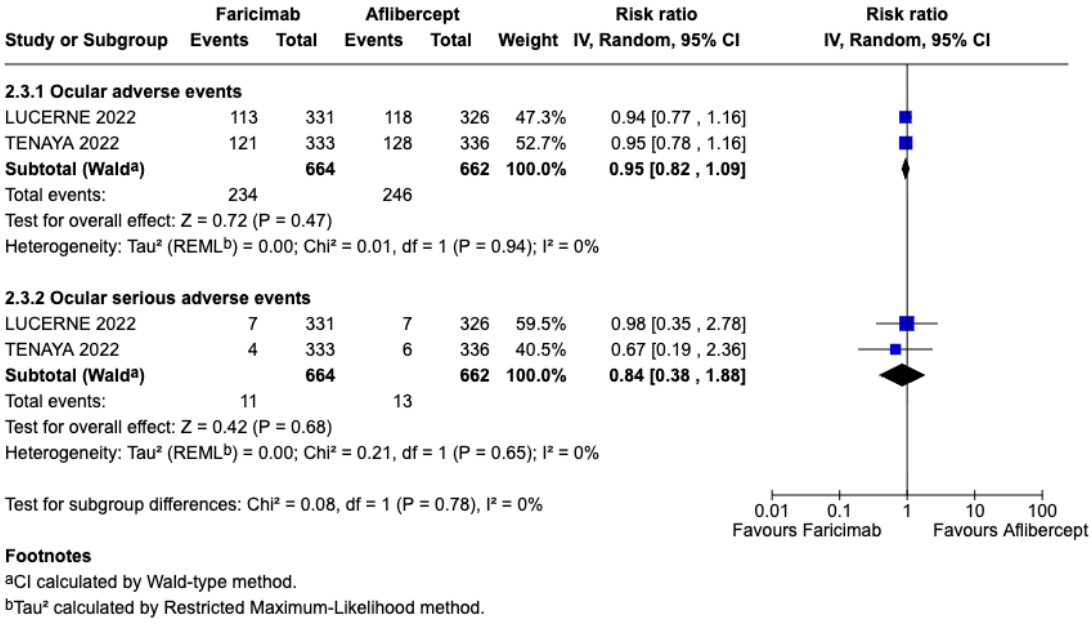

Figure 10. Forest plot showing outcome ocular adverse events and serious adverse events for comparison faricimab versus 2 mg aflibercept.

4. Injection frequency (important)

The outcome injection frequency was not reported for the outcome faricimab compared to other aflibercept 2 mg.

PICO 3 faricimab compared to other anti-VEGFs

Table 6. Summary of Findings faricimab compared to ranibizumab

Population: Patients with treatment naive neovascular age-related macular degeneration
Intervention: Faricimab
Comparator: Ranibizumab

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence** (Quality of evidence)	**Conclusions**
		Ranibizumab	Faricimab		
Vision maintenance/improvement					
Vision maintenance/improvement - gaining ≥15 ETDRS letters (critical)	Relative risk: 0.92 (CI 95% 0.54 — 1.54) Based on data from 155 participants in 2 studies	**344** per 1000	**316** Per 100 Difference: **28 fewer per 1000** (CI 95% 158 fewer – 186 more)	**Very low GRADE** Due to serious risk of bias and very serious imprecision[1]	The evidence is very uncertain about the effect of faricimab on vision maintenance/improvement when compared with ranibizumab in patients with treatment naive neovascular age-related macular degeneration. *(Khanani, 2020; Sahni, 2020)*
Vision maintenance/improvement - Mean difference in BCVA (critical)	Based on data from 155 participants in 2 studies	Difference: **1.03 ETDRS letters lower (MD)** (CI 95% 4.67 lower to 2.61 higher)		**Very low GRADE** Due to serious risk of bias and very serious imprecision[2]	
Retinal thickness (important)	Based on data from 155 participants in 2 studies	Difference: **8.07 µm higher (MD)** (CI 95% 17.92 lower – 34.06 higher)		**Very low GRADE** Due to serious risk of bias and very serious imprecision[2]	The evidence is very uncertain about the effect of faricimab on retinal thickness when compared with ranibizumab in patients with treatment naive neovascular age-related macular degeneration. *(Khanani, 2020; Sahni, 2020)*
Safety (important)					
Ocular adverse events	Relative risk: 1.06 (CI 95% 0.55 — 2.05) Based on data	**459** per 1000	**487** per 1000	**Very low GRADE**	The evidence is very uncertain about the effect of faricimab on ocular adverse events when compared with ranibizumab

	from 160 participants in 2 studies	Difference: **28 more per 1000** (CI 95% 207 fewer – 482 more)	Due to serious risk of bias, serious inconsistency and very serious imprecision[3]	in patients with treatment naive neovascular age-related macular degeneration. *(Khanani, 2020; Sahni, 2020)*
Ocular serious adverse events	Based on data from 160 participants in 2 studies	No ocular serious adverse events occurred	**Very low GRADE** Due to serious risk of bias and very serious imprecision[4]	The evidence is very uncertain about the effect of faricimab on ocular serious adverse events when compared with ranibizumab in patients with treatment naive neovascular age-related macular degeneration. *(Khanani, 2020; Sahni, 2020)*
Injection frequency (important)	-	-	**No GRADE** (no evidence was found)	No evidence was found regarding the effect of faricimab on injection frequency when compared with ranibizumab in patients with treatment naive neovascular age-related macular degeneration.

1. ***Risk of bias: serious***. *Due to concerns about conflicts of interest (pharmaceutical sponsoring).*
   Imprecision: very serious. *Due to overlap of the lower and upper limit of the 95% confidence interval with the minimal clinically important difference.*
2. ***Risk of bias: serious***. *Due to concerns about conflicts of interest (pharmaceutical sponsoring).*
   Imprecision: very serious. *The optimal information size was not achieved.*
3. ***Risk of bias: serious***. *Due to concerns about conflicts of interest (pharmaceutical sponsoring).*
   Inconsistency: serious. *Due to serious heterogeneity.*
   Imprecision: very serious. *Due to overlap of the lower and upper limit of the 95% confidence interval with the minimal clinically important difference.*
4. ***Risk of bias: serious***. *Due to concerns about conflicts of interest (pharmaceutical sponsoring).*
   Imprecision: very serious. *Because the optimal information size was not achieved and no events occurred.*

Table 7. Summary of Findings faricimab compared to aflibercept 2 mg

Population: Patients with treatment naive neovascular age-related macular degeneration
Intervention: Faricimab
Comparator: Aflibercept 2 mg

5

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence** (Quality of evidence)	**Conclusions**
		Aflibercept 2mg	Faricimab		
Vision maintenance/improvement					
Vision maintenance/improvement - gaining ≥15 ETDRS letters (critical)	Relative risk: 1.06 (CI 95% 0.76 — 1.48) Based on data from 1185 participants in 2 studies	**190** per 1000	**201** per 1000 Difference: **11 more per 1000** (CI 95% 46 fewer – 91 more)	**Very low GRADE** Due to serious risk of bias, serious inconsistency and very serious imprecision[1]	The evidence is very uncertain about the effect of faricimab on gaining ≥15 ETDRS letters when compared with aflibercept 2 mg in patients with treatment naive neovascular age-related macular degeneration. *(Heier 2022: trials LUCERNE 2022 and TENAYA 2022)*
Vision maintenance/improvement - Mean difference in BCVA (critical)	Based on data from 1329 participants in 2 studies	Difference: **0.35 ETDRS letters higher (MD)** (CI 95% 0.34 lower to 1.04 higher)		**Moderate** Due to serious risk of bias[2]	Faricimab likely results in little to no difference in mean difference in BCVA when compared with aflibercept 2 mg in patients with treatment naive neovascular age-related macular degeneration. *(Heier 2022: trials LUCERNE 2022 and TENAYA 2022)*
Retinal thickness (important)	Based on data from 1329 participants in 2 studies	Difference: **6.84 µm lower (MD)** (CI 95% 12.71 lower – 0.96 lower)		**Moderate** Due to serious risk of bias[2]	Faricimab likely results in little to no difference in retinal thickness when compared with aflibercept 2 mg in patients with treatment naive neovascular age-related macular degeneration. *(Heier 2022: trials LUCERNE 2022 and TENAYA 2022)*
Safety (important)					

Ocular adverse events	Relative risk: 0.95 (CI 95% 0.82— 1.09) Based on data from 1326 participants in 2 studies	**372** per 1000 **353** per 1000 Difference: **19 fewer per 1000** (CI 95% 67 fewer – 33 more)	**Moderate** Due to serious risk of bias[2]	Faricimab likely results in little to no difference in ocular adverse events when compared with aflibercept 2 mg in patients with treatment naive neovascular age-related macular degeneration. *(Heier 2022: trials LUCERNE 2022 and TENAYA 2022)*
Ocular serious adverse events	Relative risk: 0.84 (CI 95% 0.38 – 1.88) Based on data from 1326 participants in 2 studies	**20** per 1000 **17** per 1000 Difference: **3 fewer per 1000** (CI 95% 12 fewer – 18 more)	**Very low GRADE** Due to risk of bias and very serious imprecision[3]	The evidence is very uncertain about the effect of faricimab on ocular serious adverse events when compared with aflibercept 2 mg in patients with treatment naive neovascular age-related macular degeneration. *(Heier 2022: trials LUCERNE 2022 and TENAYA 2022)*
Injection frequency (important)	-	-	**No GRADE** (no evidence was found)	No evidence was found regarding the effect of faricimab on injection frequency when compared with aflibercept 2 mg in patients with treatment naive neovascular age-related macular degeneration.

1. ***Risk of bias: serious****. Due to concerns about conflicts of interest (pharmaceutical sponsoring).*
   Inconsistency: serious. *Due to serious heterogeneity.*
   Imprecision: very serious. *Due to overlap of the lower and upper limit of the 95% confidence interval with the minimal clinically important difference.*
2. ***Risk of bias: serious****. Due to concerns about conflicts of interest (pharmaceutical sponsoring).*
3. ***Risk of bias: serious****. Due to concerns about conflicts of interest (pharmaceutical sponsoring).*
   Imprecision: very serious. *Due to overlap of the lower and upper limit of the 95% confidence interval with the minimal clinically important difference.*

PICO 4 aflibercept 8 mg compared to other anti-VEGFs

Aflibercept 8 mg versus Aflibercept 2 mg

1. Vision maintenance/improvement (critical)

Two studies reported the mean change from baseline in BVCA letters (Lanzetta, 2024; Wykoff, 2023) (figure 7). For the comparison between aflibercept 8 mg every 12 weeks compared to aflibercept 2 mg, a mean difference of 0.47 letters (95%CI -3.03 to 3.97) was reported. For the comparison between aflibercept 8 mg every 16 weeks compared to aflibercept 2 mg, a mean difference of -1.40 letters (95%CI -3.20 to 0.40) was found.

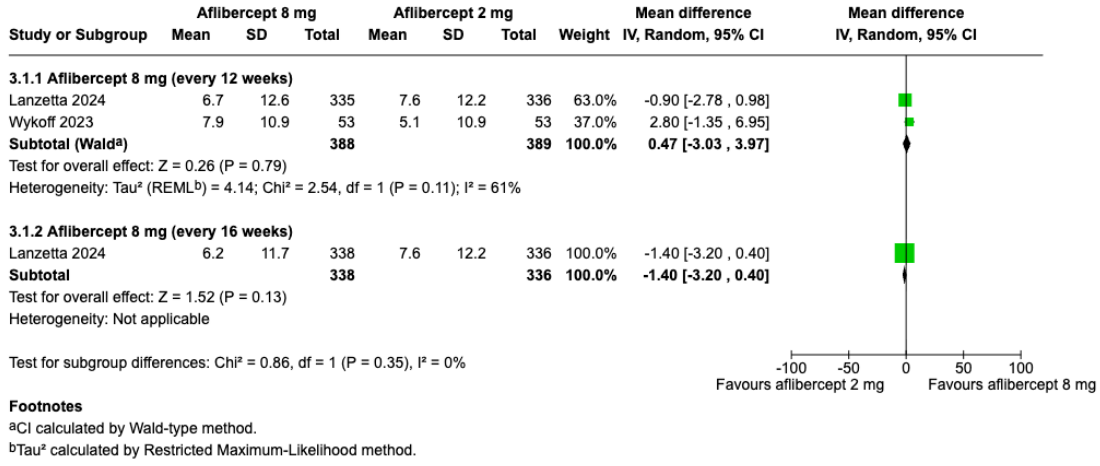

Figure 11. Forest plot showing outcome Vision improvement for comparison aflibercept 8 mg (every 12 weeks or every 16 weeks) versus aflibercept 2 mg.

2. Retinal thickness (important)

Two studies reported the mean change from baseline in retinal thickness (Lanzetta, 2024; Wykoff, 2023) (figure 8). For the comparison between aflibercept 8 mg every 12 weeks compared to aflibercept 2 mg, a mean difference of -16.27 µm (95%CI -33.80 to 1.26) was reported. For the comparison between aflibercept 8 mg every 16 weeks compared to aflibercept 2 mg, a mean difference of -20.80 µm (95%CI -40.09 to -1.51).

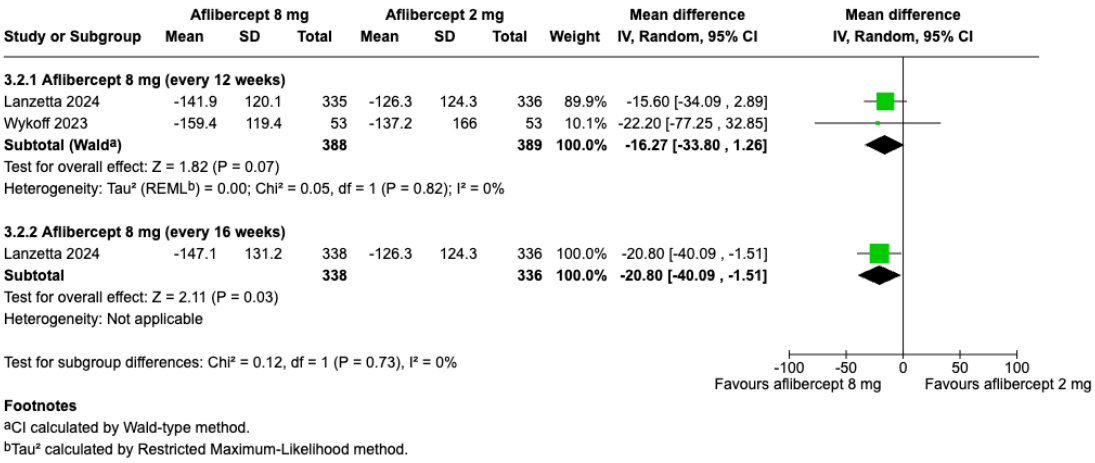

Figure 12. Forest plot showing the outcome Retinal thickness for comparison aflibercept 8 mg (every 12 weeks or every 16 weeks) versus aflibercept 2 mg.

3. Safety (important)

The studies of Lanzetta (2024) and Wykoff (2023) reported ocular treatment-emergent adverse events (TEAE) and ocular serious TEAE. In addition, adverse events such as retinal hemorrhage, inflammation and increased ocular pressure were reported. See description below.

3.1. Ocular treatment-emergent adverse event (TEAE)

Two studies reported ocular treatment-emergent adverse events (TEAEs) (Lanzetta, 2024; Wykoff, 2023) (figure 9). In total, 149 of the 388 patients (38.4%) who received 8 mg aflibercept every 12 weeks had ocular TEAEs as compared to 150 of the 389 patients (38.6%) who received 2 mg aflibercept (RR=1.00, 95%CI 0.83 to 1.19). This difference is not clinically relevant. In addition, 127 of the 338 patients (37.6%) who received 8 mg aflibercept every 16 weeks had ocular TEAEs as compared to 130 of the 336 patients (38.7%) who received 2 mg aflibercept (RR=0.97, 95%CI 0.80 to 1.18). This difference is not clinically relevant.

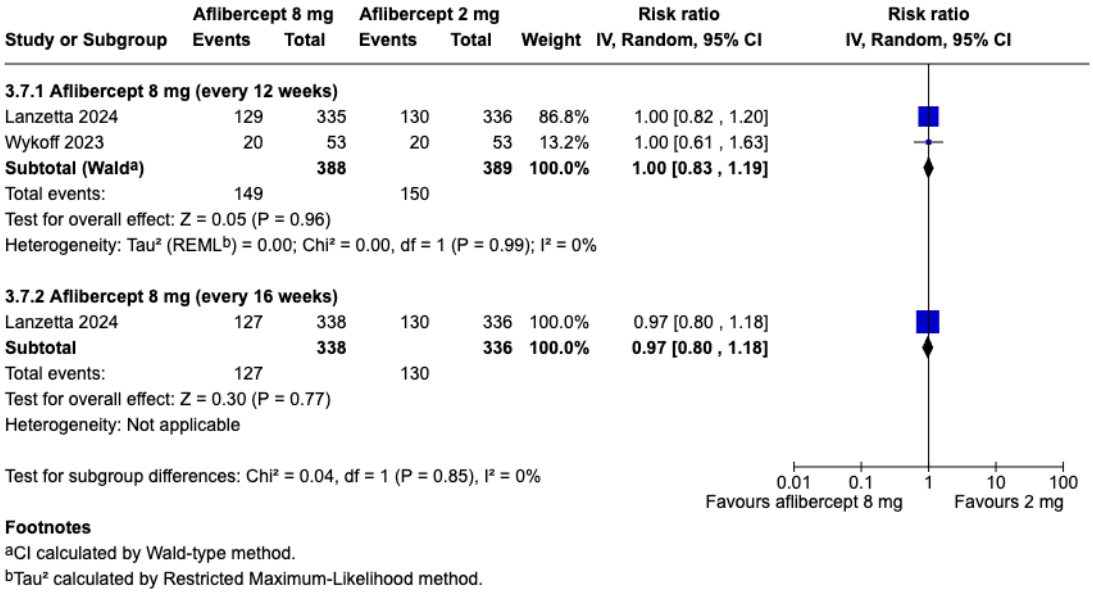

Figure 13. Forest plot showing the outcome ocular adverse events for comparison aflibercept 8 mg (every 12 weeks or every 16 weeks) versus aflibercept 2 mg.

3.2. Ocular serious TEAE

Two studies reported ocular serious treatment-emergent adverse events (TEAEs) (Lanzetta, 2024; Wykoff, 2023) (figure 9). In total, 8 of the 388 patients (2.1%) who received 8 mg aflibercept every 12 weeks had ocular serious TEAEs as compared to 3 of the 389 patients (0.8%) who received 2 mg aflibercept (RR=2.65, 95%CI 0.71 to 9.94). This difference is clinically relevant favoring 2 mg aflibercept. In addition, 5 of the 338 patients (1.5%) who received 8 mg aflibercept every 16 weeks had ocular serious TEAEs as compared to 3 of the 389 patients (0.8%) who received 2 mg aflibercept (RR=2.49, 95%CI 0.49 to 12.72). This difference is clinically relevant favoring 2 mg aflibercept.

Lanzetta (2024) reported that these ocular serious TEAEs consisted of retinal detachment, retinal hemorrhage, increased intraocular pressure, angleclosure glaucoma, cataract, vitreous haemorrhage and skin laceration. Wykoff (2023) reported that the two patients who received 8 mg aflibercept had retinal tear and visual impairment and the patient who received 2 mg aflibercept had reduced visual acuity.

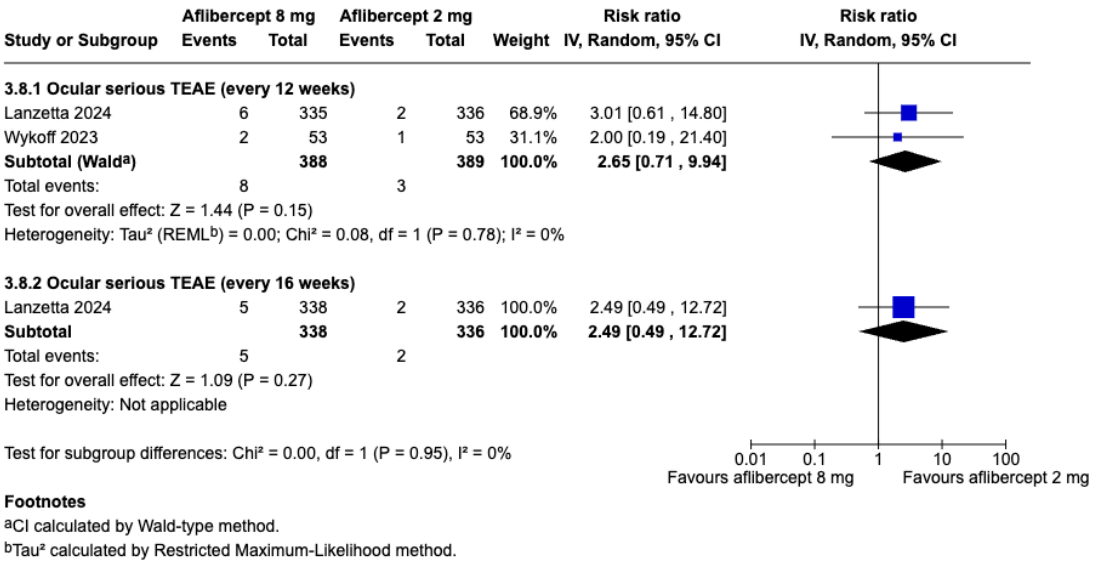

Figure 14. Forest plot showing the outcome ocular serious adverse events for comparison aflibercept 8 mg (every 12 weeks or every 16 weeks) versus aflibercept 2 mg.

3.3. Retinal hemorrhage (ocular TEAE)

Two studies reported retinal hemorrhage (Lanzetta, 2024; Wykoff, 2023) (figure 11). In total, 12 of the 388 patients (3.1%) who received 8 mg aflibercept every 12 weeks had retinal hemorrhage as compared to 16 of the 389 patients (4.1%) who received 2 mg aflibercept (RR=0.75, 95%CI 0.36 to 1.58). This difference is clinically relevant favoring 8 mg aflibercept. In addition, 10 of the 338 patients (3.0%) who received 8 mg aflibercept every 16 weeks had retinal hemorrhage as compared to 16 of the 389 patients (4.1%) who received 2 mg aflibercept (RR=0.75, 95%CI 0.36 to 1.58). This difference is clinically relevant favoring 8 mg aflibercept.

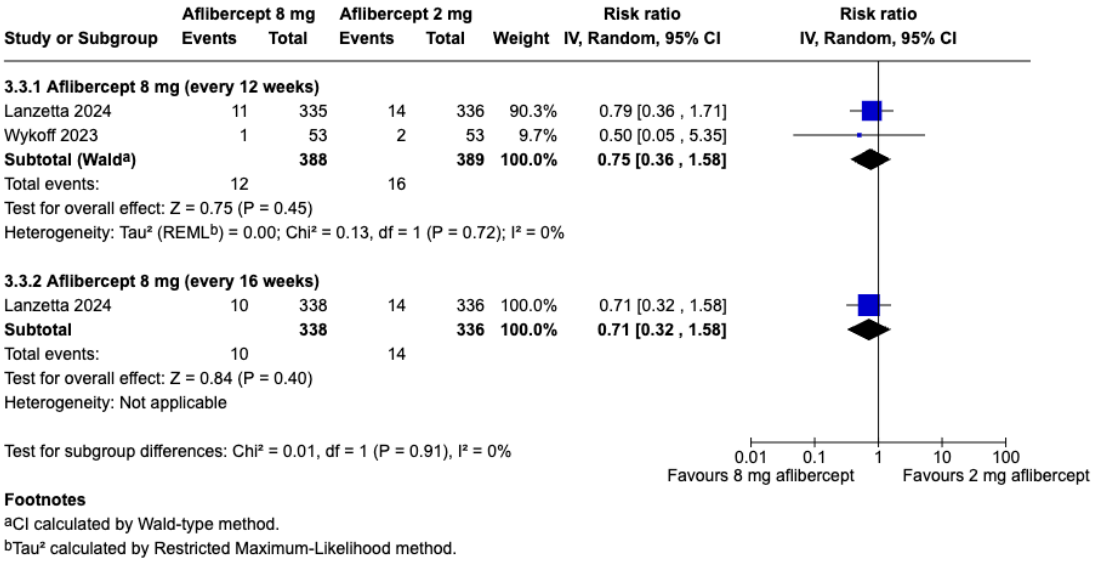

Figure 15. Retinal hemorrhage for comparison aflibercept 8 mg (every 12 weeks or every 16 weeks) versus aflibercept 2 mg.

3.4. Any TEAE of intraocular inflammation

Lanzetta (2024) reported that 4 of the 335 patients (1.2%) who received 8 mg aflibercept every 12 weeks had intraocular inflammation as compared to 2 of the 336 patients (0.6%) who received 2 mg aflibercept (RR=2.01, 95%CI 0.37 to 10.88). This difference is clinically relevant favoring 2 mg aflibercept. In addition, 1 of the 388 patients (0.3%) who received 8 mg aflibercept

every 16 weeks had intraocular inflammation as compared to 2 of the 336 patients (0.6%) who received 2 mg aflibercept (RR=0.50, 95%CI 0.05 to 5.46). This difference is clinically relevant favoring aflibercept 8 mg every 16 weeks.

3.5. Increased intraocular pressure

Lanzetta (2024) reported that 11 of the 335 patients (3%) who received 8 mg aflibercept had increased intraocular pressure as compared to 7 of the 336 patients (2%) who received 2 mg aflibercept (RR=1.58, 95%CI 0.62 to 4.02). This difference is clinically relevant favoring 2 mg aflibercept. In addition, 9 of the 338 patients (2.7%) who received 8 mg aflibercept every 16 weeks had increased intraocular pressure as compared to 7 of the 336 patients (2%) who received 2 mg aflibercept (RR=1.28, 95%CI 0.48 to 3.39). This difference is clinically relevant favoring 2 mg aflibercept.

4. Injection frequency (important)

Wykoff (2023) reported that patients who received aflibercept 8 mg (n = 53) had a mean of 5.8 (SD=1.2) injections as compared to 5.8 (SD=1.5) injections for patients who received 2 mg aflibercept (n = 53) (MD=0.00, 95%CI -0.52 to 0.52). _This was in week 44 from baseline.

PICO 4 aflibercept 8 mg compared to other anti-VEGFs

Table 8. Summary of findings aflibercept 8 mg compared to aflibercept 2 mg

Population: Patients with treatment neovascular age-related macular degeneration
Intervention: Aflibercept 8 mg (every 12 weeks or every 16 weeks)
Comparator: Aflibercept 2 mg

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence** (Quality of evidence)	**Conclusions**
		Aflibercept 2 mg	Aflibercept 8 mg		
Vision maintenance/improvement – 8 mg aflibercept every 12 weeks (critical)	Based on data from 777 participants in 2 studies	Difference: **0.47 letters higher (MD)** (CI 95% 3.03 lower – 3.97 higher)		**Low GRADE** Due to serious risk of bias and serious inconsistency[1]	Aflibercept 8 mg every 12 weeks may result in little to no difference in vision maintenance/improvement when compared with aflibercept 2 mg in patients with treatment naive neovascular age-related macular degeneration. *(Lanzetta, 2024; Wykoff, 2023)*
Vision maintenance/improvement – 8 mg aflibercept every 16 weeks (critical)	Based on data from 674 participants in 1 study	Difference **1.40 letters lower (MD)** (CI 95%CI 3.20 lower to 0.40 higher)		**Moderate GRADE** Due to serious risk of bias[2]	Aflibercept 8 mg every 16 weeks likely results in little to no difference in vision maintenance when compared with aflibercept 2 mg in patients with treatment naive neovascular age-related macular degeneration. *(Lanzetta, 2024)*
Retinal thickness – 8 mg aflibercept every 12 weeks (important)	Based on data from 777 participants in 2 studies	Difference: **16.27 µm lower (MD)** (CI 95%CI 33.80 lower to 1.26 higher)		**Moderate GRADE** Due to serious risk of bias[2]	Aflibercept 8 mg every 12 weeks likely results in little to no difference in retinal thickness when compared with aflibercept 2 mg in patients with treatment naive neovascular age-related macular degeneration. *(Lanzetta, 2024; Wykoff, 2023)*

Retinal thickness – 8 mg aflibercept every 16 weeks (important)	Based on data from 674 participants in 1 study	Difference: **20.80 µm lower (MD)** (CI 95% 40.09 lower to 1.51 lower)	**Moderate GRADE** Due to serious risk of bias[2]	Aflibercept 8 mg every 16 weeks likely results in little to no difference in retinal thickness when compared with aflibercept 2 mg in patients with treatment naive neovascular age-related macular degeneration. *(Lanzetta, 2024)*
Safety (important)				
Ocular treatment-emergent adverse event (TEAE) – 8 mg aflibercept every 12 weeks	Relative risk: 1.00 (CI 95% 0.83– 1.19) Based on data from 777 participants in 2 studies	**382** per 1000 — **382** per 1000 Difference: **0 fewer per 1000** (CI 95% 65 fewer – 73 more)	**Moderate GRADE** Due to serious risk of bias[2]	Aflibercept 8 mg every 12 weeks likely results in little to no difference in ocular treatment-emergent adverse events when compared with aflibercept 2 mg in patients with treatment naive neovascular age-related macular degeneration. *(Lanzetta, 2024; Wykoff, 2023)*
Ocular treatment-emergent adverse event (TEAE) - 8 mg aflibercept every 16 weeks	Relative risk: 0.97 (CI 95%CI 0.80 – 1.18) Based on data from 674 participants in 1 study	**387** per 1000 — **375** per 1000 Difference: **12 fewer per 1000** (CI 95%CI 77 fewer – 70 more)	**Moderate GRADE** Due to serious risk of bias[2]	Aflibercept 8 mg every 16 weeks likely results in little to no difference in ocular treatment-emergent adverse events when compared with aflibercept 2 mg in patients with treatment naive neovascular age-related macular degeneration. *(Lanzetta, 2024)*
Ocular serious TEAE - 8 mg aflibercept every 12 weeks	Relative risk: 2.65 (CI 95% 0.71 – 9.94) Based on data from 777 participants in 2 studies	**12** per 1000 — **32** per 1000 Difference: **20 more per 1000** (CI 95%CI 3 fewer – 107 more)	**Very low GRADE** Due to serious risk of bias and very serious imprecision[3]	The evidence is very uncertain about the effect of aflibercept 8 mg every 12 weeks on ocular serious treatment-emergent adverse events when compared with aflibercept 2 mg in patients with treatment naive neovascular age-related macular degeneration. *(Lanzetta, 2024; Wykoff, 2023)*
Ocular serious TEAE - 8 mg aflibercept every 16 weeks	Relative risk: 2.49 (CI 95% 0.49 – 12.72) Based on data from 674 participants in 1 study	**6** per 1000 — **15** per 1000 Difference: **9 more per 1000**	**Very low GRADE** Due to serious risk of bias and very serious imprecision[3]	The evidence is very uncertain about the effect of aflibercept 8 mg every 16 weeks on ocular serious treatment-emergent adverse events when compared with aflibercept 2 mg in patients with

		(CI 95% 3 fewer – 70 more)		treatment naive neovascular age-related macular degeneration. *(Lanzetta, 2024; Wykoff, 2023)*
Retinal hemorrhage - 8 mg aflibercept every 12 weeks	Relative risk: 0.75 (CI 95% 0.36 – 1.58) Based on data from 777 participants in 2 studies	**40** per 1000 **30** per 1000 Difference: **10 fewer per 1000** (CI 95%CI 26 fewer – 23 more)	**Very low GRADE** Due to risk of bias and very serious imprecision[3]	The evidence is very uncertain about the effect of aflibercept 8 mg every 12 weeks on retinal hemorrhage when compared with aflibercept 2 mg in patients with treatment naive neovascular age-related macular degeneration. *(Lanzetta, 2024; Wykoff, 2023)*
Retinal hemorrhage - 8 mg aflibercept every 16 weeks	Relative risk: 0.71 (CI 95% 0.32 – 1.58) Based on data from 674 participants in 1 study	**42** per 1000 **30** per 1000 Difference: **12 fewer per 1000** (CI 95% 29 fewer – 24 more)	**Very low GRADE** Due to risk of bias and very serious imprecision[3]	The evidence is very uncertain about the effect of aflibercept 8 mg every 16 weeks on retinal hemorrhage when compared with aflibercept 2 mg in patients with treatment naive neovascular age-related macular degeneration. *(Lanzetta, 2024)*
Any TEAE of intraocular inflammation - 8 mg aflibercept every 12 weeks	Relative risk: 2.01 (CI 95% 0.37 – 10.88) Based on data from 671 participants in 1 study	**6** per 1000 **12** per 1000 Difference: **6 more per 1000** (CI 95%CI 4 fewer – 59 more)	**Very low GRADE** Due to risk of bias and very serious imprecision[3]	The evidence is very uncertain about the effect of aflibercept 8 mg every 12 weeks on any treatment-emergent adverse event of intraocular inflammation when compared with aflibercept 2 mg in patients with treatment naive neovascular age-related macular degeneration. *(Lanzetta, 2024)*
Any TEAE of intraocular inflammation - 8 mg aflibercept every 16 weeks	Relative risk: 0.50 (CI 95% 0.05 – 5.46) Based on data from 674 participants in 1 study	**6** per 1000 **3** per 1000 Difference: **3 fewer per 1000** (CI 95% 6 fewer – 27 more)	**Very low GRADE** Due to risk of bias and very serious imprecision[3]	The evidence is very uncertain about the effect of aflibercept 8 mg every 16 weeks on any treatment-emergent adverse event of intraocular inflammation when compared with aflibercept 2 mg in patients with treatment naive neovascular age-related macular degeneration. *(Lanzetta, 2024)*

Increased intraocular pressure - 8 mg aflibercept every 12 weeks	Relative risk: 1.58 (CI 95% 0.62 – 4.02) Based on data from 671 participants in 1 study	**21** per 1000 **33** per 1000 Difference: **12 more per 1000** (CI 95%CI 8 fewer – 63 more)	**Very low GRADE** Due to risk of bias and very serious imprecision[3]	The evidence is very uncertain about the effect of aflibercept 8 mg every 12 weeks on increased intraocular pressure when compared with aflibercept 2 mg in patients with treatment naive neovascular age-related macular degeneration. *(Lanzetta, 2024)*
Increased intraocular pressure - 8 mg aflibercept every 12 weeks	Relative risk: 1.28 (CI 95% 0.48 – 3.39) Based on data from 674 participants in 1 study	**21** per 1000 **27** per 1000 Difference: **6 more per 1000** (CI 95% 11 fewer – 50 more)	**Very low GRADE** Due to risk of bias and very serious imprecision[3]	The evidence is very uncertain about the effect of aflibercept 8 mg every 16 weeks on increased intraocular pressure when compared with aflibercept 2 mg in patients with treatment naive neovascular age-related macular degeneration. *(Lanzetta, 2024)*
Injection frequency (important)	Based on data from 106 participants in 1 study	Difference: **0.00 lower (MD)** (CI 95%CI 0.52 lower to 0.52 higher)	**Very low GRADE** Due to risk of bias and very serious imprecision[4]	The evidence is very uncertain about the effect of aflibercept 8 mg every 12 weeks on injection frequency when compared with aflibercept 2 mg in patients with treatment naive neovascular age-related macular degeneration. *(Wykoff, 2023)*

1. ***Risk of bias: serious.*** *Due to concerns about conflicts of interest (pharmaceutical sponsoring).*
   Inconsistency: serious. *Because of differences in the direction of the effect.*
2. ***Risk of bias: serious****. Due to concerns about conflicts of interest (pharmaceutical sponsoring).*
3. ***Risk of bias: serious****. Due to concerns about conflicts of interest (pharmaceutical sponsoring).*
   Imprecision: very serious. *Due to overlap of the lower and upper limit of the 95% confidence interval with the minimal clinically important difference.*
4. ***Risk of bias: serious****. Due to concerns about conflicts of interest (pharmaceutical sponsoring).*
   Imprecision: very serious. *Because the optimal information size was not achieved and no events occurred.*

Kennisvragen

Tijdens de ontwikkeling van deze module is gebleken dat er binnen deze module nog te weinig bewijs is voor de onderbouwing van de aanbeveling en dus kennisvragen bestaan. De werkgroep meent dat (vervolg)onderzoek wenselijk is om in de toekomst een duidelijker antwoord te kunnen geven op vragen uit de praktijk.

Kennisvraag:

- Wat is de kosteneffectiviteit van behandeling met anti-VEGF middelen bij patiënten met LMD in Nederland?

Toelichting:

De huidige literatuur biedt met name inzicht in de kortetermijneffectiviteit (follow-up 1 jaar) van de verschillende anti-VEGF-behandelingen bij LMD. Gegevens over de langetermijneffecten zijn beperkt. Hierdoor is er ook onvoldoende duidelijkheid over de kosten-effectiviteit en duurzaamheid van de verschillende middelen. Voor sommige middelen wordt verondersteld dat minder injecties en ziekenhuisbezoeken nodig zijn, maar de daadwerkelijke invloed hiervan op kosten en zorgbelasting is nog onvoldoende onderzocht.

Implementeren-tabel

De implementatietabel brengt in kaart welke factoren de uitvoering van een aanbeveling bevorderen of belemmeren, en welke aanvullende acties nodig zijn voor succesvolle invoering. De adviseur en (cluster)werkgroep vullen de tabel in op basis van gerichte vragen over het onderliggende probleem, relevante randvoorwaarden en mogelijke knelpunten. Op basis hiervan wordt geconcludeerd of een extra implementatie-impuls wenselijk is.

Vraag	***Antwoord:*** *Kruis aan en licht toe/ beschrijf*		***Toelichting keuze:***
I1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?		**Ongewenste praktijkvariatie**	
	X	**Nieuwe evidentie**	Nieuwe middelen op de markt
		Anders	
I2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?		**< 1000**	
		< 5000	
		5000-40.000	
	X	**> 40.000**	
I3. Is de aanbeveling onderdeel van een bredere set interventies of verwant aan andere richtlijnen of modules? Zo ja, hoe verhoudt zij zich daartoe en moet hiermee rekening worden gehouden bij de implementatie, of kan de aanbeveling als losstaand worden beschouwd?	**X**	**Ja**	Module beschrijft eerste keuze, daarna modules veranderen anti-VEGF middel.
		Nee	
I4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:		**Belemmerende factoren**	**Bevorderende factoren/ kansen**
Richtlijn/ klinisch traject (innovatie)		Aanbeveling geldt alleen voor nieuw LMD patiënten, niet voor patiënten die reeds onder behandeling zijn.	Aanbeveling scherp geformuleerd en biedt ruimte voor verschillende behandelkeuzes.
Zorgverleners (artsen en verpleegkundigen)		Voor een oogarts is het vaak onduidelijk wel middel het goedkoopst is in ziekenhuis. Dit ligt bij de ziekenhuisapotheker. Er dient contact te zijn tussen de ziekenhuisapotheker en oogarts over de (kosten van de) anti-VEGF middelen.	
Patiënt/ cliënt (naasten)		Overtuigingen van patiënten over anti-VEGF middelen: duurdere medicatie leidt tot betere resultaten?	
Sociale context			Oogarts wil bijdragen aan lage zorgkosten voor de maatschappij.
Organisatorische context		Onduidelijke prijsafspraken binnen ziekenhuizen. Afspraken kunnen over de tijd worden gewijzigd. Verschillende prijsafspraken	

		per zorgverzekeraar en per ziekenhuis.	
Financiële en juridische context			
I5. A) Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk? (kruis aan) **B) Wat is er nodig van deze personen/partijen om de aanbeveling in de praktijk te kunnen brengen?** *Denk aan aanpassingen in gedrag, werkwijzen, beleid, samenwerking of andere randvoorwaarden.*		**A**	**B**
		Patiënt/ cliënt (naaste)	
	X	Professional	Afstemming tussen ziekenhuisapotheker en oogarts over prijs per middel
	X	Beroepsvereniging, nl	Verspreiding van de richtlijn
		Ziekenhuis (raad van bestuur/UMCNL (voorheen NFU)/NVZ)	
		Zorgverzekeraars/ NZa	
		Zorginstituut [duiding nodig]	
		Anders	
I6. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?	**X**	< 1 jaar	Aanbeveling sluit grotendeels aan bij huidige praktijk
		binnen 2-3 jaar	
I7. Conclusie: is er extra actie en/of ondersteuning nodig voor implementatie van de aanbeveling? *De reguliere implementatieroutes (publicatie en disseminatie via officiele kanalen, opname in professionele standaarden, scholing en nascholing, gebruik van bestaande ICT systemen, audits en visitaties) van de richtlijnmodule alleen is onvoldoende.*		Ja	
	X	Nee	De aanbeveling sluit aan bij de huidige klinische praktijk van oogartsen en vereist daarom geen aanvullende implementatie-activiteiten. De nieuwe aanbeveling biedt meer ruimte voor oogartsen om een afgewogen keuze te maken tussen verschillende behandelopties, maar er worden geen nieuwe of andere middelen aanbevolen. Daarom zal de overgang naar deze aanbeveling naar verwachting zonder noemenswaardige knelpunten zal verlopen.
I8. Plaatsing op de Landelijke Implementatieagenda Medisch Specialistische zorg is gewenst. *Het gaat om zorg die (grotendeels) wordt uitgevoerd binnen de ziekenhuismuren. Succesvolle implementatie vraagt om actieve betrokkenheid en samenwerking*		Ja *	
	X	Nee	Zie bovenstaande.

van meerdere relevante partijen binnen de zorgpraktijk.			

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Quist SW, de Jong LA, van Asten F, Knoester P, Postma MJ, Freriks RD. Cost-minimisation analysis of a treat-and-extend regimen with anti-VEGFs in patients with neovascular age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol. 2022 Apr;260(4):1083-1095. doi: 10.1007/s00417-021-05359-x. Epub 2021 Oct 13. PMID: 34643793; PMCID: PMC8511619.

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Sharma A, Kumar N, Parachuri N, Bandello F, Kupperman BD, Loewenstein A. Ranibizumab Biosimilar (Razumab) vs Innovator Ranibizumab (Lucentis) in neovascular age-related macular degeneration (n-AMD)- efficacy and safety (BIRA study). 2021 Eye (Lond) Jun 22. DOI: 10.1038/s41433-021-01616-9

Solomon SD, Lindsley K, Vedula SS, Krzystolik MG, Hawkins BS. Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. Cochrane Database Syst Rev. 2019 Mar 4;3(3):CD005139. doi: 10.1002/14651858.CD005139.pub4. PMID: 30834517; PMCID: PMC6419319.

Van Asten, CT J Michels 2, Carel B Hoyng 1, Gert Jan van der Wilt 2, B Jeroen Klevering 1, Maroeska M Rovers 2, Janneke P C Grutters. The cost-effectiveness of bevacizumab, ranibizumab and aflibercept for the treatment of age-related macular degeneration-A cost-effectiveness analysis from a societal perspective. PLoS One 2018 May 17;13(5):e0197670.

Woo SJ, Veith M, Hamouz J, Ernest J, Zalewski D, Studnicka J, Vajas A, Papp A, Gabor V, Luu J, Matuskova V, Yoon YH, Pregun T, Kim T, Shin D, Bressler NM. Efficacy and Safety of a Proposed Ranibizumab Biosimilar Product vs a Reference Ranibizumab Product for Patients With Neovascular Age-Related Macular Degeneration: A Randomized Clinical Trial. JAMA Ophthalmol. 2021 Jan 1;139(1):68-76. doi: 10.1001/jamaophthalmol.2020.5053. PMID: 33211076; PMCID: PMC7677876.

Wykoff CC, Brown DM, Reed K, Berliner AJ, Gerstenblith AT, Breazna A, Abraham P, Fein JG, Chu KW, Clark WL, Leal S, Schmelter T, Hirshberg B, Yancopoulos GD, Vitti R; CANDELA Study Investigators. Effect of High-Dose Intravitreal Aflibercept, 8 mg, in Patients With Neovascular Age-Related Macular Degeneration: The Phase 2 CANDELA Randomized Clinical Trial. JAMA Ophthalmol. 2023 Sep 1;141(9):834-842. doi: 10.1001/jamaophthalmol.2023.2421. PMID: 37535382; PMCID: PMC12278850.

Yen WT, Wu CS, Yang CH, Chen YH, Lee CH, Hsu CR. Efficacy and safety of intravitreal faricimab for neovascular age-related macular degeneration: a systematic review and meta-analysis. Sci Rep. 2024 Jan 30;14(1):2485. doi: 10.1038/s41598-024-52942-3. PMID: 38291069; PMCID: PMC10827713.

Bijlagen bij module Keuze anti-VEGF middel

Risk of bias table for intervention studies (randomized controlled trials; based on Cochrane risk of bias tool and suggestions by the CLARITY Group at McMaster University)

Study reference (first author, publication year)	**Was the allocation sequence adequately generated?** Definitely yes Probably yes Probably no Definitely no	**Was the allocation adequately concealed?** Definitely yes Probably yes Probably no Definitely no	**Blinding: Was knowledge of the allocated interventions adequately prevented?** **Were patients blinded?** **Were healthcare providers blinded?** **Were data collectors blinded?** **Were outcome assessors blinded?** **Were data analysts blinded?** Definitely yes Probably yes Probably no Definitely no	**Was loss to follow-up (missing outcome data) infrequent?** Definitely yes Probably yes Probably no Definitely no	**Are reports of the study free of selective outcome reporting?** Definitely yes Probably yes Probably no Definitely no	**Was the study apparently free of other problems that could put it at a risk of bias?** Definitely yes Probably yes Probably no Definitely no	**Overall risk of bias** **If applicable/necessary, per outcome measure** **LOW** **Some concerns** **HIGH**
Lanzetta, 2024	Probably yes; Reason: Randomization was performed by an	Probably yes; Reason: Sham injections were given during visits	Probably yes; Reason: Patients, all study personnel	Probably yes; Reason: Loss to follow-up was infrequent.	Definitely yes; Reason: All relevant outcomes were reported.	Probably yes; Reason: No other problems noted.	Low

	interactive web response system.	when an active injection was not planned to maintain masking.	(other than those performing unmasked roles), and the central reading centre were masked to treatment assignment.				
Wykoff, 2022	Probably yes; Reason: A central randomization scheme was provided by an interactive web response system.	No information	Probably no; Reason: Open-label and single-blinded study. The participants, visual acuity examiners, and reading center were masked to treatment assignment but study investigators and study site personnel were not.	Probably yes; Reason: Loss to follow-up was infrequent in intervention and control group. Missing values were imputed.	Definitely yes; Reason: All relevant outcomes were reported.	Probably yes; Reason: No other problems noted.	Some concerns Reason: Proof-of-concept study with concerns about randomization and blinding.

For the risk of bias assessment of the studies included in Yen (2024), see the original paper.

Table of excluded studies

Reference	Reason for exclusion
Butler ETS, Arnold-Vangsted A, Schou MG, Anguita R, Bjerager J, Borrelli E, Cehofski LJ, Ferro Desideri L, van Dijk EHC, Faber C, Grauslund J, Hajari JN, Huemer J, Klefter ON, Krogh Nielsen M, Sabaner MC, Schneider M, Subhi Y. Comparative efficacy of intravitreal anti-VEGF therapy for neovascular age-related macular degeneration: A systematic review with network meta-analysis. Acta Ophthalmol. 2025 Apr 17. doi: 10.1111/aos.17506. Epub ahead of print. PMID: 40241463.	Wrong comparison: ranibizumab as reference
Cheung CMG, Lim JI, Priglinger S, Querques G, Margaron P, Patel S, Souverain A, Willis JR, Yang M, Guymer R. Anatomic Outcomes with Faricimab vs Aflibercept in Head-to-Head Dosing Phase of the TENAYA/LUCERNE Trials in Neovascular Age-related Macular Degeneration. Ophthalmology. 2025 May;132(5):519-526. doi: 10.1016/j.ophtha.2024.11.023. Epub 2024 Nov 30. PMID: 39617060.	Post hoc analysis of TENAYA en LUCERNE
Evans W, Evans M, Eissa M. Efficacy and Safety of High-Dose Intravitreal Aflibercept in Neovascular Age-Related Macular Degeneration (nAMD): A Systematic Review. Cureus. 2025 Jan 24;17(1):e77906. doi: 10.7759/cureus.77906. PMID: 39991354; PMCID: PMC11847406.	Only two studies included matching with PICO. No meta-analysis
Galeone C, Turati F, Nicolò M, Parravano M, Vujosevic S, Bianchino L, Sicari E, Lanzetta P. Faricimab versus the standard of care for neovascular age-related macular degeneration in Italy: an indirect treatment comparison. Drug Target Insights. 2024 Dec 12;18:105-111. doi: 10.33393/dti.2024.3213. PMID: 39677855; PMCID: PMC11638843.	Indirect treatment comparison of TENAYA and LUCERNE; versus standard of care
Heier JS, Khanani AM, Quezada Ruiz C, Basu K, Ferrone PJ, Brittain C, Figueroa MS, Lin H, Holz FG, Patel V, Lai TYY, Silverman D, Regillo C, Swaminathan B, Viola F, Cheung CMG, Wong TY; TENAYA and LUCERNE Investigators. Efficacy, durability, and safety of intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration (TENAYA and LUCERNE): two randomised, double-masked, phase 3, non-inferiority trials. Lancet. 2022 Feb 19;399(10326):729-740. doi: 10.1016/S0140-6736(22)00010-1. Epub 2022 Jan 24. PMID: 35085502.	Included in SR Yen 2024
Khanani AM, Kotecha A, Chang A, Chen SJ, Chen Y, Guymer R, Heier JS, Holz FG, Iida T, Ives JA, Lim JI, Lin H, Michels S, Quezada Ruiz C, Schmidt-Erfurth U, Silverman D, Singh R, Swaminathan B, Willis JR, Tadayoni R; TENAYA and LUCERNE Investigators. TENAYA and LUCERNE: Two-Year Results from the Phase 3 Neovascular Age-Related Macular Degeneration Trials of Faricimab with Treat-and-Extend Dosing in Year 2. Ophthalmology. 2024 Aug;131(8):914-926. doi: 10.1016/j.ophtha.2024.02.014. Epub 2024 Feb 19. PMID: 38382813.	2-year analysis of TENAYA and LUCERNE trial
Koizumi H, Gomi F, Tsujikawa A, Honda S, Mori R, Ochi H, Iwasaki K, Okada AA; TENAYA and LUCERNE Investigators. Efficacy, durability, and safety of faricimab up to every 16 weeks in patients with neovascular age-related macular degeneration: 2-year results from the Japan subgroup of the phase III TENAYA trial. Graefes Arch Clin Exp Ophthalmol. 2024 Aug;262(8):2439-2448. doi: 10.1007/s00417-024-06377-1. Epub 2024 Mar 14. PMID: 38483611; PMCID: PMC11271316.	2-year analysis TENAYA; subgroup Japan
Mori R, Honda S, Gomi F, Tsujikawa A, Koizumi H, Ochi H, Ohsawa S, Okada AA; TENAYA and LUCERNE Investigators. Efficacy, durability, and safety of faricimab up to every 16 weeks in patients with neovascular age-related macular degeneration: 1-year results from the Japan subgroup of the phase 3 TENAYA trial. Jpn J Ophthalmol. 2023 May;67(3):301-310. doi: 10.1007/s10384-023-00985-w. Epub 2023 Apr 11. Erratum in: Jpn J Ophthalmol. 2023 May;67(3):311. doi: 10.1007/s10384-023-00996-7. PMID: 37039948; PMCID: PMC10098238.	1-year analysis TENAYA; subgroup Japan
Nichani PAH, Popovic MM, Mihalache A, Pathak A, Muni RH, Wong DTW, Kertes PJ. Efficacy and Safety of Intravitreal Faricimab in Neovascular Age-Related Macular Degeneration, Diabetic Macular Edema, and Retinal Vein Occlusion: A Meta-Analysis. Ophthalmologica. 2024;247(5-6):355-372. doi: 10.1159/000541662. Epub 2024 Oct 3. PMID: 39362194; PMCID: PMC11614417.	Better review available; broader population and also observational studies. No comparison between different VEGFs.

Samacá-Samacá D, Hernández-Castillo C, Prieto-Pinto L, Rodríguez F, Sardi C, Ocampo H, Kock J, Hernández F. Efficacy and safety of faricimab for neovascular age-related macular degeneration: a systematic review and network meta-analysis. BMJ Open Ophthalmol. 2024 Jul 23;9(1):e001702. doi: 10.1136/bmjophth-2024-001702. PMID: 39043575; PMCID: PMC11268043.	Network meta-analysis; more recent review available
Stevanovic M, Koulisis N, Chen T, Moysidis SN, Burkemper B, Toy BC, Rao NA, Eliott D, Humayun MS. Intraocular Inflammation, Safety Events, and Outcomes After Intravitreal Injection of Ranibizumab, Aflibercept, Brolucizumab, Abicipar Pegol, and Faricimab for nAMD. J Vitreoretin Dis. 2025 Apr 21:24741264251332515. doi: 10.1177/24741264251332515. Epub ahead of print. PMID: 40271423; PMCID: PMC12012493.	Network meta-analysis; more recent review available
Takahashi K, Cheung CMG, Iida T, Lai TYY, Ohji M, Yanagi Y, Kawano M, Ohsawa S, Suzuki T, Kotecha A, Lin H, Patel V, Swaminathan B, Lee WK; TENAYA, LUCERNE Investigators. Efficacy, durability, and safety of faricimab in patients from Asian countries with neovascular age-related macular degeneration: 1-Year subgroup analysis of the TENAYA and LUCERNE trials. Graefes Arch Clin Exp Ophthalmol. 2023 Nov;261(11):3125-3137. doi: 10.1007/s00417-023-06071-8. Epub 2023 Jun 9. PMID: 37294433; PMCID: PMC10251323.	1-year analysis TENAYA and LUCERNE; Asian subgroup
Wojciechowski P, Wdowiak M, Panek M, Lunk I, Carrasco J, Zhang X, Wu O, Korobelnik JF, Lanzetta P. Efficacy, Safety, and Injection Frequency with Novel Aflibercept 8 mg in Neovascular Age-Related Macular Degeneration: A Comparison with Existing Anti-VEGF Regimens Using a Bayesian Network Meta-Analysis. Ophthalmol Ther. 2025 Apr;14(4):733-753. doi: 10.1007/s40123-025-01098-y. Epub 2025 Feb 24. PMID: 39994103; PMCID: PMC11920537.	Network meta-analysis; also studies included about 2 mg
Zou W, Jiang Q, Wang Y, Wei W, Sun X, Basu K, Chen Q, Kotecha A, Li S, Liu R, Patel V, Chen Y. Efficacy, durability and safety of faricimab for patients with neovascular age-related macular degeneration: 48-week results from the phase 3 LUCERNE China subpopulation. Asia Pac J Ophthalmol (Phila). 2025 Jan-Feb;14(1):100142. doi: 10.1016/j.apjo.2025.100142. Epub 2025 Jan 14. PMID: 39818248.	Subgroup China

Literature search strategy

Cluster/richtlijn: Cluster oog/ RL Leeftijdsgebonden maculadegeneratie (LMD)	
Uitgangsvraag/modules: UV1 Wat is de plaats van de verschillende anti-VEGF middelen bij de behandeling van neovasculaire leeftijdsgebonden macula degeneratie?	
Database(s): Embase.com, Ovid/Medline all	Datum: 23 mei 2025
Periode: vanaf 2021	Talen: geen restrictie
Literatuurspecialist: Alies Oost	Rayyan: https://new.rayyan.ai/reviews/1468165/screening
BMI-zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/	
Toelichting: De sleutelartikelen worden gevonden met deze search.	
Te gebruiken voor richtlijntekst: A systematic literature search was performed by a medical information specialist using the following bibliographic databases: Embase.com and Ovid/Medline all. Both databases were searched from 2021 to May 23th, 2025 for systematic reviews and RCTs. Systematic searches were completed using a combination of controlled vocabulary and natural language keywords. The overall search strategy was derived from the following primary search concepts: (1) age-related macular degeneration; (2)faricimab OR aflibercept. Duplicates were removed using EndNote software. After deduplication a total of 554 records were imported for title/abstract screening.	

5 ***Zoekopbrengst***

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**
SR	119	60	126
RCT	350	200	428

Totaal	469	260	**554***

in Rayyan

Zoekstrategie

5 **Embase.com**

No.	Query	Results
#1	'age related macular degeneration'/exp OR 'wet macular degeneration'/exp OR (('macula* degeneration' OR 'macula* atrophy') NEAR/3 ('age-related' OR senile OR exudative)):ti,ab,kw) OR ((macula* NEAR/4 (senile OR 'age-related') NEAR/4 (degenerat* OR atrophy)):ti,ab,kw) OR amd:ti,ab,kw OR wamd:ti,ab,kw OR warmd:ti,ab,kw OR armd:ti,ab,kw OR namd:ti,ab,kw OR 'subretinal neovascularization'/exp OR ((neovasculari*ation NEAR/3 (choroid* OR subretinal)):ti,ab,kw) OR cnv:ti,ab,kw	76566
#2	'faricimab'/exp OR 'faricimab':ti,ab,kw OR 'rg 7716':ti,ab,kw OR 'rg7716':ti,ab,kw	728
#3	'aflibercept'/exp OR aflibercept:ti,ab,kw OR 'vegf trap':ti,ab,kw OR 'ave0005':ti,ab,kw OR 'bay865321':ti,ab,kw OR 'eylea':ti,ab,kw OR 'vascular endothelial growth factor trap':ti,ab,kw OR 'zaltrap':ti,ab,kw	11501
#4	#1 AND (#2 OR #3) NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'clinical trial':dtype) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	3211
#5	#4 AND [2021-2025]/py	1562
#6	'meta analysis'/exp OR 'systematic review'/exp OR 'scoping review'/exp OR 'rapid review'/exp OR 'umbrella review'/exp OR 'cochrane database of systematic reviews'/jt OR 'network meta-analysis'/exp OR 'networkmeta analy*':ti,ab,kw OR 'networkmetaanaly*':ti,ab,kw OR metaanaly*:ti,ab,kw OR 'meta analy*':ti,ab,kw OR metanaly*:ti,ab,kw OR prisma:ti,ab,kw OR prospero:ti,ab,kw OR metaanali*:ti,ab,kw OR 'meta anali*':ti,ab,kw OR metanali*:ti,ab,kw OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab,kw) OR (((structured OR systemic*) NEAR/3 (review* OR overview* OR synth*) NEAR/3 literature):ti,ab,kw) OR ((systemic* NEAR/1 review*):ti,ab,kw) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab,kw) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab,kw) OR (((literature NEAR/3 (review* OR overview*)):ti,ab,kw) AND (search*:ti,ab,kw OR database*:ti,ab,kw OR 'data base*':ti,ab,kw)) OR (('data extraction*':ti,ab,kw OR 'data source*':ti,ab,kw) AND ('study selection*':ti,ab,kw OR 'studies selection*':ti,ab,kw)) OR ('search strateg*':ti,ab,kw AND 'selection criteria*':ti,ab,kw) OR ('data source*':ti,ab,kw AND 'data synth*':ti,ab,kw) OR medline*:ti,ab,kw OR pubmed*:ti,ab,kw OR 'pub med*':ti,ab,kw OR embase:ti,ab,kw OR cochrane*:ti,ab,kw OR (((critical* OR rapid*) NEAR/2 (review* OR overview* OR synth*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synth*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynth*:ti,ab,kw OR 'meta synth*':ti,ab,kw OR 'review* of review*':ti,ab,kw	1080937
#7	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti	4559542
#8	#5 AND #6	119
#9	#5 AND #7 NOT #8	350
#10	#8 OR #9	469

Ovid/Medline

#	Searches	Results
1	Macular Degeneration/ or exp Wet Macular Degeneration/ or (('macula* degeneration' or 'macula* atrophy') adj3 ('age-related' or senile or exudative)).ti,ab,kf. or (macula* adj4 (senile or 'age-related') adj4 (degenerat* or atrophy)).ti,ab,kf. or amd.ti,ab,kf. or wamd.ti,ab,kf. or warmd.ti,ab,kf. or	51952

	armd.ti,ab,kf. or namd.ti,ab,kf. or exp Choroidal Neovascularization/ or (neovasculari*ation adj3 (choroid* or subretinal)).ti,ab,kf. or cnv.ti,ab,kf.	
2	('faricimab' or 'rg 7716' or 'rg7716').ti,ab,kf.	339
3	(aflibercept or 'vegf trap' or 'ave0005' or 'bay865321' or 'eylea' or 'vascular endothelial growth factor trap' or 'zaltrap').ti,ab,kf.	3925
4	(1 and (2 or 3)) not (comment/ or editorial/ or letter/) not ((exp animals/ or exp models, animal/) not humans/)	1789
5	limit 4 to yr="2021 -Current"	883
6	exp Meta-Analysis/ or exp Network Meta-Analysis/ or exp Systematic Review/ or (networkmeta analy* or networkmetaanaly* or metaanaly* or meta analy* or metanaly* or prisma or prospero or metaanali* or meta anali* or metanali*).ti,ab,kf. or ((systemati* or scoping or umbrella or structured literature) adj3 (review* or overview*)).ti,ab,kf. or ((structured or systemic*) adj3 (review* or overview* or synth*) adj3 literature).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 (review* or overview*)) and (search* or database* or data base*)).ti,ab,kf. or ((data extraction* or data source*) and (study selection* or studies selection*)).ti,ab,kf. or (search strateg* and selection criteria*).ti,ab,kf. or (data source* and data synth*).ti,ab,kf. or (medline* or pubmed* or pub med* or embase or cochrane*).ti,ab,kf. or cochrane.jw. or ((critical* or rapid*) adj2 (review* or overview* or synth*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synth*)) and (search* or database* or data base*)).ab. or metasynth*.ti,ab,kf. or meta synth*.ti,ab,kf.	830415
7	exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.	2890157
8	5 and 6	60
9	(5 and 7) not 8	200
10	8 or 9	260

Bijlage 3 Verantwoording module 2 - Behandeling met conventionele synthetische (cs) DMARD's

Verantwoording

Voor meer details over de gebruikte richtlijnmethodologie verwijzen wij u naar de Werkwijze. Relevante informatie voor de ontwikkeling/herziening van deze richtlijnmodule is hieronder weergegeven.

Initiatief

Initiatief: cluster oog

Samenstelling van de werkgroep

Voor het ontwikkelen van de richtlijnmodule is in 2022 een multidisciplinair cluster ingesteld. Het cluster oog bestaat uit meerdere richltijnen, zie hier voor de actuele clusterindeling. De stuurgroep bewaakt het proces van modulair onderhoud binnen het cluster. De expertisegroepsleden geven hun expertise in, indien nodig. De volgende personen uit het cluster zijn betrokken geweest bij de herziening van deze module.

Clusterstuurgroepleden

- Dr. N.C. (Nicole) Naus, voorzitter cluster oog, oogarts, NOG, Erasmus MC
- Dr. M.C. (Marjolijn) Bartels, Voorzitter Cluster Oog, oogarts, NOG, Deventer Ziekenhuis
- Dr. A.J. (Arlette) van Sorge, oogarts, NOG, Koninklijke Visio,
- Drs. L.J. (Leo) Noordzij, oogarts, NOG, Oog op Zuid Oogkliniek
- Dr. R. (Redmer) van Leeuwen, oogarts, NOG, UMC Utrecht
- Dr. Ir M. (Marleen) van Aartrijk, Klinisch Fysicus NVKF, Koninklijke Visio
- C. (Caroline) Osterholt-Bel, Adviseur oogzorg Oogvereniging

Betrokken clusterexpertisegroepleden

Module 2: behandeling met conventionele synthetische (cs) DMARD's.

- Drs. F.H. (Fleurieke) Verhagen, oogarts, NOG, UMC Utrecht
- Dr. M.E.J. (Mirjam) van Velthoven, oogarts, NOG, Oogziekenhuis Rotterdam
- Prof. dr. I.E. (Irene) van der Horst-Bruinsma, reumatoloog, NVR, Radboud UMC
- S.M. (Saskia) Rombach, internist-allergoloog/immunoloog, NIV, Erasmus MC en Oogziekenhuis Rotterdam
- Prof. dr. J.H. (Joke) de Boer, oogarts, NOG, UMC Utrecht
- A.J.W. (Anne-Mieke) Haasnoot, oogarts, NOG, Deventer Ziekenhuis
- P. (Pauline) de Heer, afgevaardigd op persoonlijke titel

Met ondersteuning van

- Dr. A.C.J. (Astrid) Balemans, senior-adviseur, Kennisinstituut van Medisch Specialisten
- MSc. D.G. (Dian) Ossendrijver, adviseur, Kennisinstituut van Medisch Specialisten
- A. (Alies) Oost, informatiespecialist, Kennisinstituut van de Federatie Medisch Specialisten

Belangenverklaringen

Een overzicht van de belangen van de clusterleden en het oordeel over het omgaan met eventuele belangen vindt u in onderstaande tabel. De ondertekende belangenverklaringen zijn op te vragen bij het secretariaat van het Kennisinstituut van de Federatie Medisch Specialisten via secretariaat@kennisinstituut.nl.

5

Cluster stuurgroepleden

Tabel 3 Gemelde (neven)functies en belangen stuurgroep

Naam	Hoofdfunctie	Nevenwerkzaamheden	Persoonlijke financiële belangen	Persoonlijke relaties	Extern gefinancierd onderzoek	Intellectuele belangen en reputatie	Overige belangen	Datum	Restrictie
Dr. N.C. (Nicole) Naus,	Oogarts Erasmus MC Rotterdam	Geen	Geen	Geen	Geen	Geen	Geen	1-08-2025	Geen restricties
Dr. M.C. (Marjolijn) Bartels	Oogarts Deventer ziekenhuis	Lid van Concilium, lid van commissie kwaliteit en voorzitter van cornea werkgroep (NOG).	Geen	Geen	ja, 1. PHIC (PIONEERS IN HEALTH CARE INNOVATIEFONDS) voucher voor onderzoek in samenwerking Universiteit Twente ZonMWstudies: 2. BICAT-NL studie 3. EPICAT studie	persoonlijk belang van goed op de hoogte zijn van alles, hetgeen gebruikt wordt in de dagelijkse praktijk en als opleider, lid van Concilium, lid van commissie kwaliteit en voorzitter van cornea werkgroep.	Geen	1-08-2025	Geen restricties

Dr. A.J. (Arlette) van Sorge	Oogarts koninklijke Visio	Voorzitter VRS (vereniging voor revalidatie bij slechtziendheid, onbetaald). Stuurgroeplid bij cluster OOG (NOG). Visitator visitatiecommissie NOG. Bestuurslid Oogcontact (onbetaald).	Geen	Geen	Geen	Geen	Geen	6-05-2025	Geen restricties
Drs. L.J. (Leo) Noordzij	Oogarts bij Cooperatie Oogheelkunde op Zuid voor 3.5 dag in de week. Voor 1.5 dag in de week bestuurslid van de Cooperatie Oogheelkunde op Zuid, de Stichting Oogheelkunde op Zuid en medisch directeur het zelfstandig behandel centrum Oog op Zuid oogkliniek.	Lid richtlijn werkgroep FMS/ NOG betreffende leeftijdsgebonden macula degeneratie (tm juli 2023). Vaste programma commissie InSights symposium, Novartis (gestopt juni 2022). Lid medical innovation academy, Novartis (gestopt augustus 2022).	Geen	Geen	Geen	Geen	Geen	20-04-2025	Geen restricties ('advieswerk' neergelegd per juni/augustus 2022)
Dr. R. (Redmer) van Leeuwen	Oogarts UMC Utrecht	Geen	Geen	Geen	ESCH-R 1. NWO - Circulaire zorg (Projectleider NEE)	Geen	Geen	02-02-2025	Geen restricties

Dr. Ir M. (Marleen) van Aartrijk	Klinisch Fysicus bij Koninklijke Visio (Revalidatie & Advies): betaald, - beheer Oogheelkundige apparatuur - ondersteuning zorgprofessionals bij individuele patienttrajecten (bijv. op gebied van verlichting, autorijden) - producteigenaar elektronisch patientendossier	Geen	Geen persoonlijk financieel belang. Indien een richtlijn verwijzing naar revalidatiezorg stimuleert kan dat impact hebben op mijn werkgever (en dan indirect op mijzelf	Geen	Binnen de revalidatiezorg zijn er fondsen (oa Novum, ZonMW) die exptertiseprojecten ondersteunen. Aan een aantal van deze projecten draag ik bij, maar dat gaat om een zeer beperkt deel van mijn tijd (ben geen hoofdonderzoeker oid)	Verduidelijking van rol revalidatiezorg in de zorgketen	Geen	22-04-2025	Geen restricties
C. (Caroline) Osterholt-Bel	TOA Ikazia	Geen	Geen	Geen	Geen	Geen	Geen	29-04-2025	Geen restricties

Betrokken clusterexpertisegroepleden

Tabel 4 Gemelde (neven)functies en belangen expertisegroep

Naam	Hoofdfunctie	Nevenwerkzaamheden	Persoonlijke financiële belangen	Persoonlijke relaties	Extern gefinancierd onderzoek	Intellectuele belangen en reputatie	Overige belangen	Datum	Restrictie
Drs. F.H. (Fleurieke) Verhagen	AIOS oogheelkunde, UMC Utrecht	Geen	Geen	Geen	Geen	Geen	Geen	01-08-2025	Geen restricties
Dr. M.E.J. (Mirjam) van Velthoven	Oogarts, uveitis specialist - Oogziekenhuis, Rotterdam : betaald	Waarnemend voorzitter infectiepreventie commissie Oogziekenhuis	Sprekersvergoeding van Roche (2024), Bayer (2025), onderwerpen anders dan uveitis; in 2023 presentatie voor Canon over OCT beeldvorming (niet vergoed).	Geen	1. RCT: Association of retinal structural features with angiographic abnormalities in Behcet's disease (Financier Roche, SWOO, RSB) 2. Detection of perifoveal microvascular changes in Behçet Disease measured with OCT-A (Financier Roche, SWOO, RSB)	Geen	Geen	01-08-2025	Geen restricties. Onderwerp van commercieel gefinancierd onderzoek niet gerelateerd aan richtlijn.

Prof. dr. I.E. (Irene) van der Horst-Bruinsma	Afdelingshoofd reumatologie Radboudumc (100%)	Geen	Betaalde adviseurschappen/disclosures > 2 jaar geleden gestopt: Consultant for Abbvie, UCB, MSD, Novartis, Lilly until 2021. Fees received for Lectures from BMS, AbbVie, Pfizer, MSD, UCB.	Geen	Financier 1: Reuma Nederland Financier 2: EuroSpa Inhoud onderzoek 1: Sexe and gender differences in AxSpa Inhoud onderzoek 2: Seks differences in efficacy of biologicals in AxSpA Projectleidersrol 1: ja Projectleidersrol 2: ja	Geen	Geen	21-07-2025	Geen restricties
S.M. (Saskia) Rombach	Internist-allergoloog/immunoloog in het Erasmus MC en het Oogziekenhuis Rotterdam	Geen	Geen	Geen	Geen	Geen	Geen	18-08-2025	Geen restricties
Prof. dr. J.H. (Joke) de Boer	Oogarts UMC Utrecht, aandachtsgebied uveitis	Richtlijnwerkgroep herziening richtiljn uveitis	Geen	Geen	1) Uveitis bij kinderen, financiers: Fischerstichting, ODAS stichting, ANVVB, LSBS. (Ik begeleid als PI een promovendus die onderzoek doet naar uveitis bij kinderen. De	Geen	Geen	22-04-2025	Geen restricties

					promovendus wordt gefinancierd vanuit ODAS, Fischer, LSBS en de ANVVB. Ik ontvang geen persoonlijke vergoeding. Het betreft een fundamenteel onderzoek naar uveitis bij kinderen waarbij er geen raakvlak is met de onderwerpen uit de richtlijn.) 2) Ontsteking bij retinitis pigmentosa, financier: ZonMw via Bartimeus. Ik begeleid als PI een promovendus die onderzoek doet naar retinitis pigmentosa vanuit Bartimeus. De promovendus wordt vanuit Zonmw gefinancierd. Ik ontvang geen persoonlijke vergoeding. 3) De effectiviteit van tocilizumab, financier: Rol: Lokaal PI: inclusie van 3-5 patiënten gaan includeren waar het UMC een vergoeding voor				

					krijgt. UMC krijgt onkostenvergoeding voor gemaakte kosten in het UMCU, apotheek, lab, functie onderzoeken en personeel. 4) Copromotor bij onderzoek 'Ocular surface disease in atopic dermatitis and the effect of dupilumab treatment'. Dit proefschrift is deels gebaseerd op data uit de Registratie Bioday, gefinancierd door Sanofi Genzyme. Sanofi genzyme heeft geen producten die in de richtlijn aan bod komen.				
A.J.W. (Anne-Mieke)	Oogarts Deventer Ziekenhuis	Richtlijnwerkgroep herziening richtiljn uveitis	Vergoeding voor Medewerking aan de Herziening Richtlijn Uveitis Sprekersvergoeding voor presentatie over de richtlijn uveitis (Abbvie). Betreft niet de modules die in cluster oog worden herzien. Financier heeft geen invloed op richtiljn of inhoud van presentatie.	Geen	Geen	Geen	Geen	10-04-2025	Geen restricties

P. (Pauline) de Heer	Strategisch adviseur bij Zorginstituut Nederland Adviseren over passende zorg, duurzaamheid, maatschappelijke opgaven, signalering en agendering.	Geen	Geen	Geen	Geen	Geen	Geen	08-04-2025	Geen resticties

Kwalitatieve raming van mogelijke financiële gevolgen in het kader van de Wkkgz

Bij de richtlijnmodule voerden de clusterleden conform de Wet kwaliteit, klachten en geschillen zorg (Wkkgz) een kwalitatieve raming uit om te beoordelen of de aanbevelingen mogelijk leiden tot substantiële financiële gevolgen. Bij het uitvoeren van deze beoordeling is de richtlijnmodule op verschillende domeinen getoetst (zie het stroomschema bij Werkwijze).

Module	Uitkomst raming	Toelichting
Module behandeling met conventionele synthetische (cs) DMARDS	Geen financiële gevolgen	Uit de toetsing volgt dat de aanbeveling(en) niet breed toepasbaar zijn (<5.000 patiënten) en zal daarom naar verwachting geen substantiële financiële gevolgen hebben voor de collectieve uitgaven.

Bijlage 4 Literatuursamenvatting module 2 - Behandeling met conventionele synthetische (cs) DMARD's

Leeswijzer: de voorliggende herziene tekst vervangt de bestaande module over behandeling met conventionele synthetische (cs)DMARDS.

Introduction (English)

Non-infectious uveitis comprises a group of chronic intraocular inflammatory conditions in which no infectious cause can be identified and if left untreated, can lead to irreversible ocular damage and visual impairment. As a group it accounts for approximately 10% of preventable blindness among the working-age population in western countries. If systemic treatment is necessary to control the inflammation, corticosteroids were historically first in line. However, due to their systemic and ocular side effects, long-term use is not desirable. Current guidelines advise starting steroid sparing medication when it is not possible to taper oral steroids to a low dose (prednisolone 7.5mg a day or less) within 3 months. Early initiation of corticosteroid-sparing therapy appears to improve the prognosis of uveitis, resulting in fewer ocular and systemic side effects. Various conventional synthetic Disease-Modifying Antirheumatic Drugs (csDMARDs) have proven effective in the treatment of uveitis. The introduction of biological DMARDS (biologicals or bDMARDs) have provided an additional repertoire of possibilities for systemic immunomodulatory treatment: these are discussed in the module behandeling met biological (b) en targeted synthetic (ts) DMARD's. Despite the increased use of bDMARDs the use of csDMARDs is still widespread, but preferences are changing due to differences in side effect profile and effectiveness. In this module we will discuss which csDMARD is most effective and safe in the treatment of non-infectious uveitis, which can vary depending on the anatomical location and type of uveitis.

Search and select

A systematic review of the literature was performed to answer the following question(s):
What is the effectiveness and safety of different conventional synthetic DMARDs in patients with non-infectious uveitis?

Table 1. PICO

Patients	Adult patients with non-infectious uveitis
Intervention	Methotrexate, mycophenolate mofetil, azathioprine
Control	All medication mentioned under I
Outcomes	inflammation (anterior chamber cells/vitreous haze), recurrence rate, relapse rate, cystoid macular edema (CME), retinal vasculitis, retinal lesions, choroidal lesions, adverse effects of medication (cataract, glaucoma)
Other selection criteria	Study design: systematic reviews and randomized controlled trials

Relevant outcome measures

The guideline panel considered reduction of inflammation as a **critical** outcome measure for decision making; and cystoid macular edema (CME), retinal vasculitis, retinal lesions, choroidal lesions, recurrence rate, relapse rate, and systemic complications as **important** outcome measures for decision making.

For the outcome *reduction of inflammation*, the guideline development group used the definition as described in the individual studies, if at least one of the variables below was mentioned:

- Anterior chamber cells/flare grading
  - Number of cells: 0 (no cells); 0.5+ (trace); 1+; 2+; 3+; 4+; or
- Vitreous haze, graded as Haze, using:

    - Standardization of Uveitis Nomenclature scale (SUN) (Hornbeak, 2014): 0, clear view of fundus, 1+, faint, 2+, moderate, 3+ marked (hazy optic nerve details), intense (minimal/no optic nerve details);
    - Miami 9-step Scale (Davis, 2010): 0 (no haze) – 8 (maximum haze)
- Cystoid Macular Edema (CME) assessed using optical coherence tomography (OCT central retinal thickness)
- Retinal vasculitis or capillary leakage, assessed with a fluorescence angiography (FA) (grading system by Tugal-Tutkun, 2010)

Reduction of inflammation was considered if at least a 2-step improvement from baseline was achieved at the study's primary endpoint.

For the outcomes recurrence rate, relapse rate, retinal lesions, choroidal lesions, systemic complications, the guideline development group used the definitions in the studies.

The guideline development group defined a mean difference (MD) of 10% for continuous outcomes (<0 favors MTX), a relative risk (RR) of <0.80 or >1.25 for dichotomous outcomes, and a risk difference (RD) of 25% for dichotomous outcomes with a few events (systemic complications), as a minimal clinically (patient) important difference.

Search and select (Methods)
In 2014, a systematic literature search was conducted to select literature that was published between 2006-2014. At that time, there were no studies that matched the PICO.

In 2025, the search was updated. In both search periods similar search strategies and selection criteria were used. The systematic literature search was performed by a medical information specialist using the following bibliographic databases: Embase.com and Ovid/Medline. Both databases were searched from 2014 to the 8th of April 2025 for systematic reviews and RCTs. Systematic searches were completed using a combination of controlled vocabulary/subject headings (e.g., Emtree-terms, MeSH) wherever they were available and natural language keywords. The overall search strategy was derived from two primary search concepts: (1) uveitis; (2) DMARDS. Duplicates were removed using EndNote software. After deduplication a total of 574 records were imported for title/abstract screening. Initially, 21 studies were selected based on title and abstract screening. After reading the full text, 18 studies were excluded (see the exclusion table under the tab 'Evidence tabellen'), and 3 studies were included.

Summary of literature
Description of studies
A total of three studies were included in the analysis of the literature. Important study characteristics and results are summarized in table 2. The assessment of the risk of bias is summarized in the risk of bias tables (under the tab 'Evidence tabellen').

Edwards Mayhew (2022) conducted a Cochrane systematic review and meta-analysis in which the effectiveness and safety of non-biologic, steroid-sparing therapies for adults with non-infectious intermediate, posterior, and panuveitis (from here: non-anterior uveitis) were investigated. The review focused on five commonly used conventional synthetic disease-modifying antirheumatic drugs (csDMARDs): methotrexate (MTX), mycophenolate mofetil (MMF), azathioprine, cyclosporine, and tacrolimus. The authors aimed to evaluate and compare the efficacy of these agents—used either alone or alongside corticosteroids—against each other, placebo, or standard steroid therapy. Considering the purpose of this guideline, only MTX, MMF and azathioprine compared against each other, are considered relevant. To identify relevant studies, the authors carried out an extensive

literature search on April 16, 2021. They searched multiple databases including CENTRAL, MEDLINE, Embase, LILACS, ClinicalTrials.gov, and the WHO ICTRP. No restrictions were applied regarding language or publication date. Additionally, references from relevant reviews and articles were hand-searched. Only randomized controlled trials (RCTs) were eligible for inclusion. Studies were required to involve adult patients (≥18 years) diagnosed with non-anterior uveitis, based on internationally accepted definitions. Trials involving children only, infectious causes of uveitis, concurrent biologic therapies, or combination treatments with multiple immunosuppressive agents were excluded. The review ultimately included 11 RCTs, of which 3 studies (2 RCTs) were considered relevant for the purpose of this guideline (Rathinam, 2014; Rathinam, 2019; Shen, 2016). The other studies were not relevant because the intervention and/or control did not match the PICO. Relevant outcomes included proportion of participants achieving control of inflammation, proportion of participants with confirmed macular edema, and frequency of systemic complications.

Additionally, **Tsui (2022)** conducted a prespecified subanalysis of the First-line Antimetabolites as Steroid-sparing Treatment (FAST) Uveitis Trial, focusing specifically on patients with uveitic macular edema (UME) secondary to non-anterior uveitis. The goal of this subanalysis was to compare the outcomes of UME in patients treated with either MTX or MMF over a 12-month period. The original FAST trial was a block-randomized, observer-masked, multicenter clinical trial conducted at nine sites across the United States, India, Australia, Saudi Arabia, and Mexico. It enrolled 216 patients between August 2013 and August 2017, all aged 16 years or older, who required corticosteroid-sparing immunosuppressive therapy. The trial compared MTX (up to 25 mg/week orally, n=42 eyes of 30 patients) and MMF (up to 1.5 g twice daily, n=55 eyes of 41 patients), alongside a corticosteroid taper, in patients with active non-infectious uveitis. One relevant outcome for the purpose of this guideline is central subfield thickness (CST).

Additionally, **Acharya (2024)** presented a detailed subanalysis of the FAST Uveitis Trial, focusing specifically on patients diagnosed with Vogt–Koyanagi–Harada (VKH) disease. The authors aimed to evaluate how MTX and MMF perform in terms of controlling inflammation and preserving visual function in this distinct patient population. This study included 93 out of 216 patients who met the diagnostic criteria for VKH from the original FAST trial. In this trial, 72 patients had an acute VKH diagnosis (diagnosis <90 days prior to enrollment) and 21 patients had chronic VKH (diagnosis >90 days prior to enrollment). Patients were randomized to receive either oral MTX (25 mg weekly, n=49 patients) or oral MMF (1.5 g twice daily, n=44 patients) and were placed on a standardized oral corticosteroid taper. The main goal was to achieve corticosteroid-sparing control of intraocular inflammation within 6 months, with continued monitoring up to 12 months. Relevant outcomes for the purpose of this guideline are control of inflammation, change in CST, and frequency of systemic complications.

Table 2. Characteristics of included studies

Study	Participants	Comparison	Follow-up	Outcome measures	Comments	Risk of bias (per outcome measure)*
Included in systematic review Edwards Mayhew, 2022						
Rathinam, 2014	N at baseline Intervention: 41 Control: 39 Number analyzed Intervention: 35 Control: 32 Age (mean, SD) Intervention: 38.6 (SD 10.3) Control: 40.2 (SD 14.2) Sex (m/f) Intervention: 15/26 Control: 17/22	Intervention: methotrexate in combination with topical or oral steroid therapy • Maintenance dose: 25 mg a week oral methotrexate • Induction dose for the first two run-in weeks: 15 mg a week oral methotrexate Control: mycophenolate mofetil in combination with topical or oral steroid therapy • Maintenance dose: 1 g twice daily oral mycophenolate mofetil • Induction dose for the first two run-in weeks: 500 mg twice daily oral mycophenolate mofetil	Up to 6 months	Control of inflammation Resolution of macular edema Frequency of systemic complications	Funding for this trial was provided by That Man May See Foundation at University of California, San Francisco (UCSF), and the South Asia Research Fund. "Dr. Acharya is currently supported by a National Eye Institute grant (no. U10 EY021125-01). The UCSF Department of Ophthalmology is supported by the National Eye Institute (NIH-NEI EY002162 - Core grant for Vision Research) and by the Research to Prevent Blindness Unrestricted grant. The sponsor or funding organization had no role in the design or conduct of this research."	Some concerns *Bias in selection of the reported result and in measurement of the outcome*
Shen, 2016* *VKH patients only	N at baseline Intervention: 27 Control: 16 Number analyzed Intervention: 23 Control: 9815 Age (mean, SD) Intervention: 37.2y (SD 9.0) Control: 40.4y (SD 8.2) Sex (m/f)* Intervention: 7/20 Control: 6/10 *slightly more females in methotrexate group than mycophenolate	Intervention: methotrexate in combination with topical or oral steroid therapy • Maintenance dose: 25 mg a week oral methotrexate • start on >15 mg of systemic corticosteroids, and these were tapered according to guidelines Control: mycophenolate mofetil 2dd1000mg in combination with topical or oral steroid therapy	Up to 6 months	Control of inflammation Frequency of systemic complications	Funding for this trial was provided by That Man May See Foundation and The South Asia Research Fund at UCSF. Dr. Acharya is currently supported by an NEI U10 EY021125-01 grant. The UCSF Department of Ophthalmology is supported by the National Eye Institute and Research to Prevent Blindness Foundation grants.	Some concerns *Bias in selection of the reported result and in measurement of the outcome*

	group (70.1% vs 55.0%)	• Maintenance dose: 1 g twice daily oral mycophenolate mofetil • start on >15 mg of systemic corticosteroids, and these were tapered according to guidelines				
Rathinam, 2019	<u>N at baseline</u> Intervention: 107 Control: 109 <u>Number analyzed</u> Intervention: 96 Control: 98 <u>Age (median, IQR)</u> Intervention: 36 (IQR 26-50) Control: 41 (IQR 31-51) <u>Sex (m/f)*</u> Intervention: 32/75 Control: 49/60 *slightly more females in methotrexate group than mycophenolate group (70.1% vs 55.0%)	<u>Intervention:</u> methotrexate in combination with topical or oral steroid therapy • Initial dose 15 mg by mouth weekly for 2 weeks, then increased to maintenance dose of 25 mg by mouth weekly; dose reductions allowed for intolerability <u>Control:</u> mycophenolate mofetil in combination with topical steroid therapy • Initial dose 500 mg, twice a day, for 2 weeks, then increased to maintenance dose of 1.5 mg by mouth, twice a day; dose reductions allowed for intolerability	Up to 12 months* *Randomization broken after 6 months, so only the results reported at 6 months were pertinent	Control of inflammation Change from baseline in central subfield macular thickness Frequency of systemic complications	this study was supported by NEI cooperative agreement U10 EY021125 (to Dr Acharya, primary investigator). The University of California San Francisco pharmacy provided study drugs for all sites. The Department of Ophthalmology at UCSF is supported by an unrestricted grant from the Research to Prevent Blindness Foundation, a core grant (EY06190) from the NEI, and That Man May See Foundation. The National Institutes of Health (NIH) did not have any direct role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation of the manuscript; and decision to submit the manuscript for publication. The data and safety monitoring committee, appointed by the NIH, reviewed and approved submitting this manuscript for	Low

					publication.	
Individual studies						
Tsui, 2022* *Focusing on patients of the FAST uveitis trial with uveitic macular edema	N at baseline Intervention: 30 (42 eyes) Control: 41 (55 eyes) Number analyzed Intervention: 28 (39 eyes) Control: 38 (51 eyes) Age (median, IQR) Intervention: 46.8y (IQR 34.2-53.2) Control: 39.5y (IQR 26.2-53.3) Sex (m/f)* Intervention: 16/26 (eyes) Control: 25/30 (eyes)	Intervention: methotrexate in combination with topical or oral steroid therapy • Initial dose 15 mg by mouth weekly for 2 weeks, then increased to maintenance dose of 25 mg by mouth weekly; dose reductions allowed for intolerability Control: mycophenolate mofetil in combination with topical steroid therapy • Initial dose 500 mg, twice a day, for 2 weeks, then increased to maintenance dose of 1.5 mg by mouth, twice a day; dose reductions allowed for intolerability	Up to 6 months	Control of inflammation Central subfield thickness	This study was supported by National Eye Institute Cooperative Agreement U10 EY021125 (PI Dr. Acharya). The Department of Ophthalmology at the University of California San Francisco is supported by an unrestricted grant from the Research to Prevent Blindness Foundation, a core grant from the National Eye Institute at the National Institutes of Health (EY06190) and the That Man May See Foundation	Low (all outcomes)
Acharya, 2024* *VKH patients	N at baseline Intervention: 49 (98 eyes) Control: 44 (88 eyes) Number analyzed Intervention: 46 (92 eyes) Control: 39 (78 eyes) Age (median, IQR) Intervention: 35 (IQR 28-46) Control: 38y (IQR 31-52) Sex (m/f)* Intervention: 11/38 Control: 16/28 Disease stage (%) *Acute VKH* Intervention: 74 Control: 82	Intervention: methotrexate in combination with topical or oral steroid therapy • Initial dose 15 mg by mouth weekly for 2 weeks, then increased to maintenance dose of 25 mg by mouth weekly; dose reductions allowed for intolerability Control: mycophenolate mofetil in combination with topical steroid therapy • Initial dose 500 mg, twice a day, for 2 weeks, then increased to	Up to 6 months	Control of inflammation Change in central subfield thickness (CST) Frequency of systemic complications	This study was supported by the National Eye Institute (NEI) grant U10 EY021125 (Dr. Acharya, principal investigator). The University of California, San Francisco (UCSF) pharmacy provided study drugs for all sites. The Department of Ophthalmology at UCSF is supported by an unrestricted grant from the Research to Prevent Blindness Foundation, a core grant (EY06190) from the NEI, and All May See Foundation.	Low (all outcomes)

	Chronic VKH Intervention: 26 Control: 18	maintenance dose of 1.5 mg by mouth, twice a day; dose reductions allowed for intolerability			The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Nisha Acharya has served as a consultant to Roche, Inc. and has received non-monetary support (study medication donation) from AbbVie, Inc. for an NIH-funded trial.	

*For further details, see risk of bias table in the appendix

Results

Control of inflammation (crucial)

All non-anterior uveitis patients

Two studies included in the Cochrane review of Edwards Mayhew (2022) reported the outcome proportion of participants achieving control of inflammation (higher number of events is better) up to six months follow-up (Rathinam, 2014; Rathinam, 2019) comparing MTX with MMF. In both studies, control of inflammation was defined as less than or equal to 0.5+ anterior chamber cells, less than or equal to 0.5+ vitreous haze, and no active retinal/choroidal lesions in both eyes, and required that participants were on a low dose of oral steroid (oral prednisone 7.5 mg daily at 6 months) and two drops or fewer per day of topical 1% prednisolone acetate.

Rathinam (2014) reported 24/35 (68.6%) successful events in the MTX group vs. 15/32 (46.9%) successful events in the MMF group. This corresponded to a calculated risk ratio (RR) of 1.46 (95% CI, 0.95 to 2.25) in favor of the MTX group and clinically relevant. Rathinam (2019) reported 64/96 (66.7%) successful events in the MTX group vs. 56/98 (57.1%) successful events in the MMF group. This corresponded to a calculated risk ratio (RR) of 1.17 (95% CI, 0.93 to 1.46) in favor of the MTX group, but not clinically relevant (Figure 1).

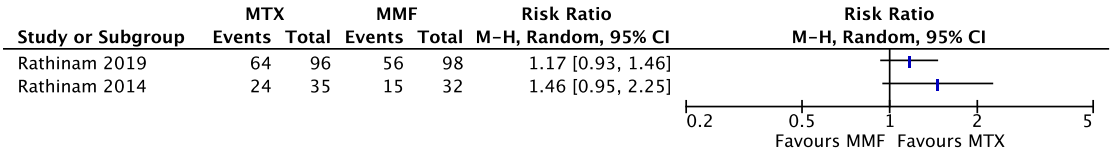

Figure 1. MTX vs. MMF, outcome: control of inflammation. Follow-up: 6 months. Study population: all non-anterior uveitis patients.

Subset of VKH patients

One study included in the Cochrane review of Edwards Mayhew (2022) reported the outcome proportion of participants achieving control of inflammation (higher number of events is better) up to six months follow-up in VKH patients (Shen, 2016). One additional study published after the search date of Edwards Mayhew (2022), reported the same outcome in the subset of VKH patients at six months follow-up (Acharya, 2024). Both studies defined control of inflammation as follows: less than or equal to 0.5+ anterior chamber cells, less than or equal to 0.5+ vitreous cells, less than or equal to

0.5+ vitreous haze, and no active retinal/choroidal lesions, less than or equal to 10 mg of oral prednisone daily and less than or equal to 2 drops of prednisolone acetate 1% a day, and no declaration of treatment failure because of intolerability or safety concerns.

Shen (2016) reported 17/23 (74%) successful events in the MTX group vs. 8/15 (53%) successful events in the MMF group. This corresponded to a calculated risk ratio (RR) of 1.39 (95% CI, 0.85 to 2.36) in favor of the MTX group and clinically relevant. Acharya (2024) reported 37/46 (80.4%) successful events in the MTX group vs. 25/39 (64.1%) successful events in the MMF group. This corresponded to a calculated risk ratio (RR) of 1.25 (95% CI, 0.95 to 1.65) in favor of the MTX group but not considered clinically relevant (Figure 2).

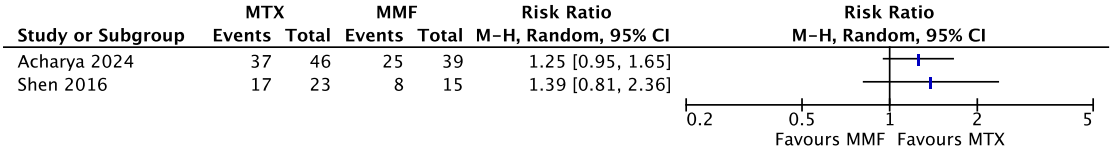

Figure 2 MTX vs. MMF, outcome: control of inflammation. Follow-up: 6 months. Study population: subset of VKH patients.

Acharya (2024) also reported the outcome at 12 months follow-up. Of the 62 VKH patients who had treatment success at 6 months, 34 patients on MTX and 23 patients on MMF were followed up to 12 months. Successful events were reported for 26/34 (76.4%) patients on MTX and for 21/23 (91.3%) patients on MMF. This corresponded to a calculated risk ratio (RR) of 0.84 (95% CI, 0.67 to 1.05) in favor of the MMF group but not considered clinically relevant.

Subset of patients with uveitic macular edema

One study published after the search date of Edwards Mayhew (2022), reported the same outcome in the subset of patients with uveitic macular edema at six months follow-up (Tsui, 2022). Also here, the same definition of control of inflammation was used (prednisone of 7.5 mg, two-step decrease in anterior chamber, vitreous haze and retinal/choroidal activity).

Tsui (2022) reported 15/30 (50%) successful events in the MTX group vs. 20/41 (48.8%) successful events in the MMF group. This corresponded to a calculated risk ratio (RR) of 1.02 (95% CI, 0.64 to 1.65), which is not clinically relevant (Figure 3).

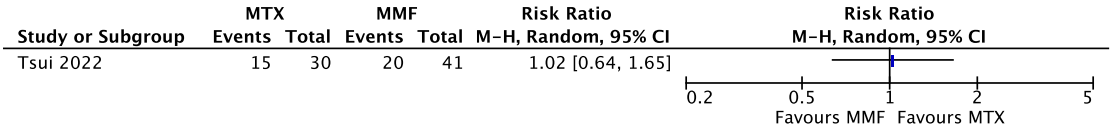

Figure 3 MTX vs. MMF, outcome: control of inflammation. Follow-up: 6 months. Study population: subset of patients with uveitic macular edema.

Cystoid macular edema (important)

All non-anterior uveitis patients

One study included in the Cochrane review of Edwards Mayhew (2022) reported the outcome change in central macular thickness (<0 favors MTX) up to six months follow-up in all non-anterior uveitis patients (Rathinam, 2019). Rathinam (2019) reported a mean change of -26 (SD 69.63) μm in the MTX group (n=55 eyes) vs. a mean change of -14 (SD 61.66) μm in the MMF group (n=42 eyes). This corresponded to a calculated mean difference (MD) of -12.00 μm (95% CI, -38.20 to 14.20) in favor of the MTX group, but not clinically relevant (Figure 4).

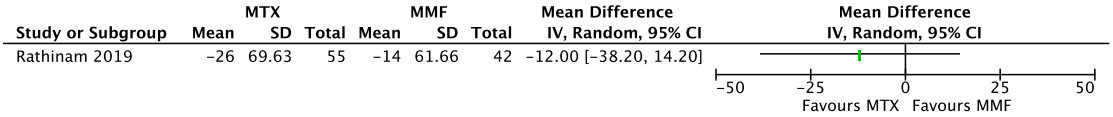

Figure 4 MTX vs. MMF, outcome: change in central macular thickness (μm). Follow-up: 6 months. Study population: all non-anterior uveitis patients.

Subset of VKH patients

One study included in the Cochrane review of Edwards Mayhew (2022) reported the outcome proportion of participants with confirmed (residual) macular edema (lower number of events is better) up to six months follow-up in a subgroup of VKH patients with macular edema at baseline (Rathinam, 2014). Rathinam (2014) reported 5/22 (22.7%) events in the MTX group vs. 6/13 (46.2%) events in the MMF group. This corresponded to a calculated risk ratio (RR) of 0.49 (95% CI, 0.19 to 1.30) in favor of the MTX group and clinically relevant (Figure 5).

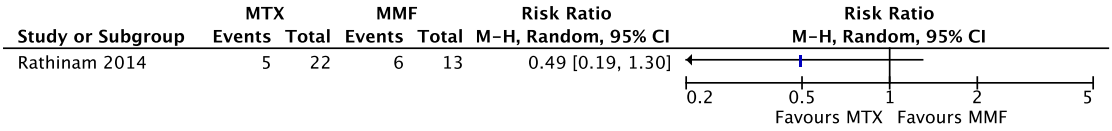

Figure 5 MTX vs. MMF, outcome: confirmed residual macular edema. Follow-up: 6 months. Study population: subset of VKH patients with uveitic macular edema.

Additionally, one study reported the outcome change in central subfield thickness (CST) as a percentage (higher is better) up to six months follow-up in a subset of VKH patients (Acharya, 2024). Acharya (2024) reported a mean change in CST of 20.6% (SD 36.1) in the MTX group (n=92 eyes) vs. 1.4% (SD 35.5) in the MMF group (n=78 eyes). This corresponded to a calculated MD of 19.20% (95% CI, 8.41 to 29.99), in favour of the MTX group and clinically relevant (Figure 6).

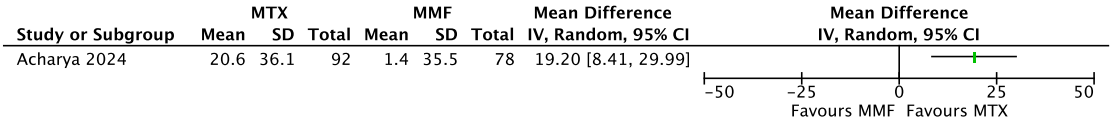

Figure 6 MTX vs. MMF, outcome: change in central subfield thickness (%). Follow-up: 6 months. Study population: subset of VKH patients.

Subset of patients with uveitic macular edema

One study reported the outcome change in central macular thickness (<0 favours MTX) in the subset of patients with uveitic macular edema from baseline to six months follow-up (Tsui, 2022). Tsui (2022) reported a median change of -26 μm (IQR -89 to 5) in the MTX group (n=30) vs. -14 μm (IQR -80 to 3.25) in the MMF group (n=41). The decrease in macular thickness was not significantly different between the two groups. A GRADE assessment could not be applied, since only medians with IQRs were reported.

Retinal vasculitis (important)

The outcome measure retinal vasculitis was not reported.

Retinal lesions (important)

This outcome was not separately reported, because it was included in the definition of the outcome control of inflammation.

Choroidal lesions (important)

This outcome was not separately reported, because it was included in the definition of the outcome control of inflammation.

Recurrence rate (important)

The outcome measure recurrence rate was not reported.

Relapse rate (important)

The outcome measure relapse rate was not reported.

Systemic complications (important)

All non-anterior uveitis patients

Two studies included in the Cochrane review of Edwards Mayhew (2022) reported the outcome proportion of participants experiencing systemic complications (lower number of events is better) up to six months follow-up (Rathinam, 2014; Rathinam, 2019).

Elevated aspartate aminotransferase (AST) or alanine aminotransferase ALT (nonserious)

Rathinam (2014) reported that 4/41 (10%) participants experienced elevated AST or ALT (nonserious) in the MTX group compared to 2/39 (5.13%) in the MMF group. This corresponded to a calculated RD of 0.05 (95% CI, -0.07 to 0.16), in favour of the MMF group, but not clinically relevant.

Rathinam (2019) reported that 14/107 (13.1%) participants experienced elevated AST or ALT (nonserious) in the MTX group compared to 8/109 (7.33%) in the MMF group. This corresponded to a calculated RD of 0.06 (95% CI, -0.02 to 0.14), in favour of the MMF group, but not clinically relevant (Figure 7).

Elevated AST or ALT (serious)

Rathinam (2019) reported that 3/107 (2.80%) participants experienced elevated AST or ALT (serious) in the MTX group compared to 2/109 (1.83%) in the MMF group. This corresponded to a calculated RD of 0.01 (95% CI, -0.03 to 0.05) (Figure 7).

Bone marrow suppression

Abnormal Hb

Rathinam (2014) reported that 0/41 (0%) participants experienced abnormal Hb in the MTX group compared to 2/39 (5.13%) in the MMF group. This corresponded to a calculated RD of -0.05 (95% CI, -0.13 to 0.03), in favour of the MTX group, but not clinically relevant.

Rathinam (2019) reported that 2/107 (1.87%) participants experienced abnormal Hb in the MTX group compared to 3/109 (2.75%) in the MMF group. This corresponded to a calculated RD of -0.01 (95% CI, -0.05 to 0.03) (Figure 7).

Low leukocyte count

Rathinam (2019) reported that 3/107 (2.80%) participants experienced low leukocyte count in the MTX group compared to 1/109 (0.92%) in the MMF group. This corresponded to a calculated RD of 0.02 (95% CI, -0.02 to 0.05) (Figure 7).

Elevated creatinine

Rathinam (2019) reported that 1/107 (0.93%) participants experienced elevated creatinine in the MTX group compared to 0/109 (0%) in the MMF group. This corresponded to a calculated RD of 0.01 (95% CI, -0.02 to 0.03) (Figure 7).

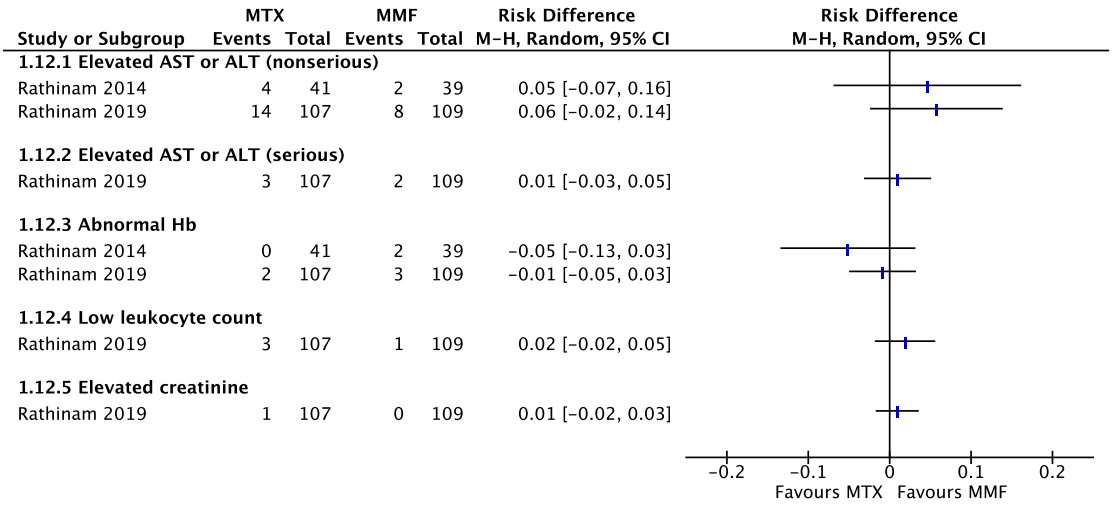

Figure 7 MTX vs. MMF, outcome: proportion of participants experiencing systemic complications (%). Follow-up: 6 months. Study population: all non-anterior uveitis patients.

Subset of VKH patients

Two studies reported the outcome proportion of participants experiencing systemic complications (lower number of events is better) up to six months follow-up in the subset of VKH patients (Shen, 2016; Acharya, 2024).

Elevated AST or ALT

Shen (2016) reported that 2/27 (7%) VKH patients experienced elevated AST or ALT in the MTX group compared to 0/16 (0%) in the MMF group. This corresponded to a calculated RD of 0.07 (95% CI, -0.06 to 0.21), in favour of the MMF group, but not clinically relevant.

Acharya (2024) reported that 10/49 (20.4%) VKH patients experienced elevated AST or ALT (nonserious or serious) in the MTX group compared to 6/44 (13.6%) in the MMF group. This corresponded to a calculated RD of 0.07 (95% CI, -0.08 to 0.22), in favour of the MMF group, but not clinically relevant (Figure 8).

Abnormal Hb

Acharya (2024) reported that 1/49 (2%) VKH patients experienced abnormal Hb in the MTX group compared to 2/44 (4.5%) in the MMF group. This corresponded to a calculated RD of -0.03 (95% CI, -0.10 to 0.05) (Figure 8).

Low leukocyte count

Acharya (2024) reported that 1/49 (2%) VKH patients experienced low leukocyte count in the MTX group compared to 0/44 (0%) in the MMF group. This corresponded to a calculated RD of 0.02 (95% CI, -0.04 to 0.08) (Figure 8).

Elevated creatinine

Acharya (2024) reported that 1/49 (2%) VKH patients experienced elevated creatinine in the MTX group compared to 0/44 (0%) in the MMF group. This corresponded to a calculated RD of 0.02 (95% CI, -0.04 to 0.08) (Figure 8).

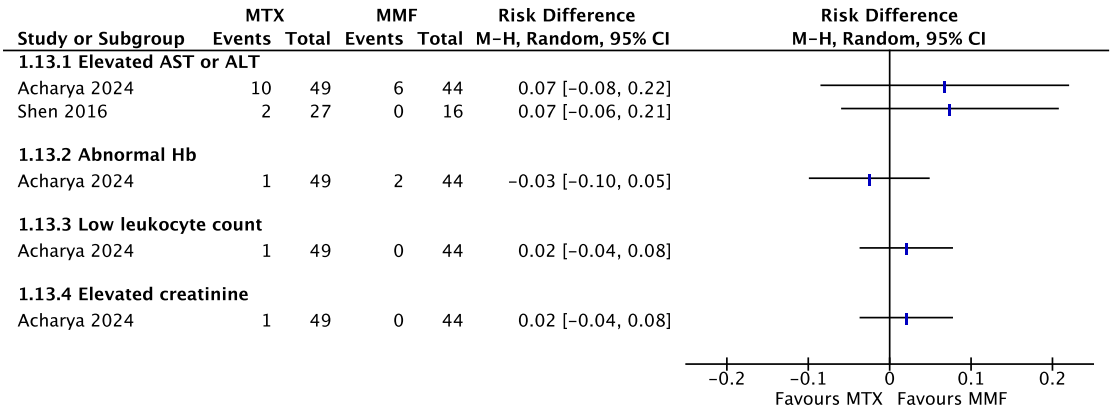

Figure 8 MTX vs. MMF, outcome: proportion of participants experiencing systemic complications (%). Follow-up: 6 months. Study population: VKH patients.

5 *Subset of patients with uveitic macular edema*

The outcome measure systemic complications was not reported.

Summary of Findings

Population: non-anterior uveitis patients
Intervention: Methotrexate (MTX)
Comparator: Mycophenolate mofetil (MMF)

Outcome Timeframe	**Study results and measurements**	**Relative effect estimates** MMF MTX	**Certainty of the evidence** (Quality of evidence)	**Summary**
Proportion of participants achieving control of inflammation (crucial) *6 months*	Based on data from 261 participants in 2 studies Follow up 6 months	RR of 1.17 (0.93 to 1.46) (Rathinam, 2019) RR of 1.46 (0.95 to 2.25) (Rathinam, 2014)	**Low** Due to serious risk of bias, Due to serious imprecision[1]	Methotrexate may result in little to no difference in the proportion of participants achieving control of inflammation when compared with mycophenolate mofetil at six months in all non-anterior uveitis patients. *(Rathinam, 2014; Rathinam, 2019)*
Change in central macular thickness (important) *6 months*	Based on data from 97 eyes in 1 study Follow up 6 months	MD of **12 µm lower** (95% CI, 38.20 lower to 14.20 higher)	**Low** Due to serious imprecision[2]	Methotrexate may result in little to no difference in mean change in central macular thickness compared to mycophenolate mofetil at six months in all non-anterior uveitis patients. *(Rathinam, 2019)*
Retinal vasculitis (Important)	-	-	**No GRADE** (No evidence was found)	No evidence was found regarding the effect of methotrexate on retinal vasculitis compared to mycophenolate mofetil in all non-anterior uveitis patients.
Recurrence rate (important)	-	-	**No GRADE** (No evidence was found)	No evidence was found regarding the effect of methotrexate on recurrence rate compared to mycophenolate mofetil in all non-anterior uveitis patients.
Relapse rate (important)	-	-	**No GRADE** (No evidence was found)	No evidence was found regarding the effect of methotrexate on relapse rate compared to mycophenolate mofetil in all non-anterior uveitis patients.

Systemic complications *Elevated AST or ALT (nonserious)* (important)	Based on data from 261 participants in 2 studies Follow up 6 months	RD of **5% higher** (95% CI, 7% lower to 16% higher) (Rathinam, 2014) RD of **6% higher** (95% CI, 2% lower to 14% higher) (Rathinam, 2019)	**Low** Due to serious risk of bias, Due to serious imprecision[3]	Methotrexate may result in little to no difference in proportion of patients experiencing elevated AST or ALT (nonserious) compared to mycophenolate mofetil at six months in all non-anterior uveitis patients. *(Rathinam, 2014; Rathinam, 2019)*
Systemic complications *Elevated AST or ALT (serious)* (important)	Based on data from 216 participants in 1 study Follow up 6 months	RD of **1% higher** (95% CI, 3% lower to 5% higher) (Rathinam, 2019)	**Low** Due to serious risk of bias, Due to serious imprecision[3]	Methotrexate may result in little to no difference in proportion of patients experiencing elevated AST or ALT (serious) compared to mycophenolate mofetil at six months in all non-anterior uveitis patients. *(Rathinam, 2019)*
Systemic complications *Abnormal Hb* (important)	Based on data from 261 participants in 2 studies Follow up 6 months	RD of **5% lower** (95% CI, 13% lower to 3% higher) (Rathinam, 2014) RD of **1% lower** (95% CI, 5% lower to 3% higher) (Rathinam, 2019)	**Low** Due to serious risk of bias, Due to serious imprecision[3]	Methotrexate may result in little to no difference in proportion of patients experiencing abnormal Hb compared to mycophenolate mofetil at six months in all non-anterior uveitis patients. *(Rathinam, 2014; Rathinam, 2019)*
Systemic complications *Low leukocyte count* (important)	Based on data from 216 participants in 1 study Follow up 6 months	RD of **2% higher** (95% CI, 2% lower to 5% higher) (Rathinam, 2019)	**Low** Due to serious risk of bias, Due to serious imprecision[3]	Methotrexate may result in little to no difference in proportion of patients experiencing low leukocyte count compared to mycophenolate mofetil at six months in all non-anterior uveitis patients. *(Rathinam, 2019)*
Systemic complications *Elevated creatinine* (important)	Based on data from 216 participants in 1 study Follow up 6 months	RD of **1% higher** (95% CI, 2% lower to 3% higher) (Rathinam, 2019)	**Low** Due to serious risk of bias, Due to serious imprecision[3]	Methotrexate may result in little to no difference in proportion of patients experiencing elevated creatinine compared to mycophenolate mofetil at six months in all non-anterior uveitis patients. *(Rathinam, 2019)*

5. **Risk of bias: serious.** Some concern in risk of bias in outcome measurement; **Imprecision: serious.** Due to overlap of the 95% CI with the right border of clinical relevance;
6. **Imprecision: serious.** Wide confidence intervals, Only data from one study;
7. **Risk of bias: serious**. Some concerns in risk of bias in outcome measurement; **imprecision: serious.** Small sample size;

Population: VKH patients (subgroup)
Intervention: Methotrexate (MTX)
Comparator: Mycophenolate mofetil (MMF)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** MMF MTX	**Certainty of the evidence** (Quality of evidence)	**Summary**
Proportion of participants achieving control of inflammation (crucial) *6 months*	Based on data from 123 participants in 2 studies Follow up 6 months	RR of 1.25 (95% CI, 0.95 to 1.65) (Acharya, 2024) RR of 1.39 (95% CI, 0.81 to 2.36) (Shen, 2016)	**Low** Due to serious risk of bias, due to serious imprecision[1]	Methotrexate may result in a slight increase in the proportion of participants achieving control of inflammation compared to mycophenolate mofetil at six months in VKH patients. *(Shen, 2016; Acharya, 2024)*
Proportion of participants with confirmed (residual) macular edema (important) *6 months*	Based on data from 35 participants in 1 study Follow up 6 months	RR of 0.49 (95% CI, 0.19 to 1.30) (Rathinam, 2014)	**Very low** Due to serious risk of bias, Due to very serious imprecision[2]	The evidence is very uncertain about the effect of methotrexate on the proportion of participants with confirmed (residual) macular edema when compared with mycophenolate mofetil at six months in VKH patients. *(Rathinam, 2014)*
Percentage of change in central macular thickness (important) *6 months*	Based on data from 170 eyes in 1 study Follow up 6 months	MD of **19.20% higher** (95% CI, 8.41% higher to 29.99% higher)	**Moderate** Due to serious imprecision[3]	Methotrexate probably results in a higher percentage of change in central macular thickness compared to mycophenolate mofetil at six months in VKH patients. *(Acharya, 2024)*
Retinal vasculitis (Important)	-	-	**No GRADE** (No evidence was found)	No evidence was found regarding the effect of methotrexate on retinal vasculitis compared to mycophenolate mofetil in VKH patients.
Recurrence rate (important)	-	-	**No GRADE** (No evidence was found)	No evidence was found regarding the effect of methotrexate on recurrence rate compared to mycophenolate mofetil in VKH patients.
Relapse rate (important)	-	-	**No GRADE** (No evidence was found)	No evidence was found regarding the effect of methotrexate on relapse rate compared to mycophenolate mofetil in VKH patients.

Systemic complications *Elevated AST or ALT* (Important)	Based on data from 136 participants in 2 studies Follow up 6 months	RD of **7% higher** (95% CI, 8% lower to 22% higher) (Acharya, 2024) RD of **7% higher** (95% CI, 6% lower to 21% higher) (Shen, 2016)	**Low** Due to serious risk of bias, due to serious imprecision[4]	Methotrexate may result in little to no difference in proportion of patients experiencing elevated AST or ALT compared to mycophenolate mofetil at six months in all VKH patients. *(Shen, 2016; Acharya, 2024)*
Systemic complications *Abnormal Hb* (Important)	Based on data from 93 participants in 1 study Follow up 6 months	RD of **3% lower** (95% CI, 10% lower to 5% higher) (Acharya, 2024)	**Low** Due to serious risk of bias, due to serious imprecision[4]	Methotrexate may result in little to no difference in proportion of patients experiencing abnormal Hb compared to mycophenolate mofetil at six months in all VKH patients. *(Acharya, 2024)*
Systemic complications *Low leukocyte count* (Important)	Based on data from 93 participants in 1 study Follow up 6 months	RD of **2% higher** (95% CI, 4% lower to 8% higher) (Acharya, 2024)	**Low** Due to serious risk of bias, due to serious imprecision[4]	Methotrexate may result in little to no difference in proportion of patients experiencing low leukocyte count compared to mycophenolate mofetil at six months in all VKH patients. *(Acharya, 2024)*
Systemic complications *Elevated creatinine* (Important)	Based on data from 93 participants in 1 study Follow up 6 months	RD of **2% higher** (95% CI, 4% lower to 8% higher) (Acharya, 2024)	**Low** Due to serious risk of bias, due to serious imprecision[4]	Methotrexate may result in little to no difference in proportion of patients experiencing elevated creatinine compared to mycophenolate mofetil at six months in all VKH patients. *(Acharya, 2024)*

1. **Risk of Bias: serious.** Selective outcome reporting; **Imprecision: serious.** Due to overlap of the 95% CI with the right border of clinical relevance;
2. **Risk of Bias: serious.** Selective outcome reporting; **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study;
3. **Imprecision: serious.** Due to overlap of the 95% CI with the right border of clinical relevance;
4. **Risk of bias: serious**. Selective outcome reporting; **Imprecision: serious.** Low number of patients;

5

Population: patients with uveitic macular edema (subgroup)
Intervention: Methotrexate (MTX)
Comparator: Mycophenolate mofetil (MMF)

Outcome Timeframe	**Study results and measurements**	**Relative effect estimates** MMF MTX	**Certainty of the evidence** (Quality of evidence)	**Summary**
Proportion of participants achieving control of inflammation (crucial) *6 months*	Based on data from 71 participants in 1 study Follow up 6 months	RR of 1.02 (95% CI, 0.64 to 1.65) (Tsui, 2022)	**Low** Due to very serious imprecision[1]	Methotrexate may result in little to no difference in the proportion of participants achieving control of inflammation compared to mycophenolate mofetil in patients with uveitic macular edema. *(Tsui, 2022)*
Change in central macular thickness (important) *6 months*	Based on data from 71 participants in 1 study Follow up 6 months	MTX group: 26 µm lower (IQR, 89 lower to 5 higher) MMF group: 14 µm lower (IQR, 80 lower to 3.25 higher) (Tsui, 2022)	**No GRADE** (Due to lack of data reporting)	The effect of methotrexate on the change in central macular thickness compared to mycophenolate mofetil in patients with uveitic macular edema could not be graded, due to lack of data reporting. *(Tsui, 2022)*
Retinal vasculitis (Important)	-	-	**No GRADE** (No evidence was found)	No evidence was found regarding the effect of methotrexate on retinal vasculitis compared to mycophenolate mofetil in patients with uveitic macular edema.
Recurrence rate (important)	-	-	**No GRADE** (No evidence was found)	No evidence was found regarding the effect of methotrexate on recurrence rate compared to mycophenolate mofetil in patients with uveitic macular edema.
Relapse rate (important)	-	-	**No GRADE** (No evidence was found)	No evidence was found regarding the effect of methotrexate on relapse rate compared to mycophenolate mofetil in patients with uveitic macular edema.
Systemic complications (important)	-	-	**No GRADE** (No evidence was found)	No evidence was found regarding the effect of methotrexate on the proportion of participants with

				systemic complications compared to mycophenolate mofetil in patients with uveitic macular edema.

1. **Imprecision: very serious.** Due to overlap of the 95% CI with both borders of clinical relevance;

Kennisvragen

Tijdens de ontwikkeling van deze module is gebleken dat er binnen deze module nog te weinig bewijs is voor de onderbouwing van de aanbeveling en dus kennisvragen bestaan. De werkgroep meent dat (vervolg)onderzoek wenselijk is om in de toekomst een duidelijker antwoord te kunnen geven op vragen uit de praktijk.

Kennisvraag:

Wat is de effectiviteit van azathioprine vergeleken met MTX of MMF als behandeling bij patiënten met niet-infectieuze uveitis?

Toelichting:

Er bestaat geen recente literatuur over het gebruik van azathioprine in vergelijking met MTX of MMF. Aangezien dit een niet-teratogene manier is om het immuunsysteem te onderdrukken – en aangezien uveitis een grote groep jong-volwassenen in hun vruchtbare jaren treft – is dit een essentieel onderwerp om verder te onderzoeken.

Implementatietabel

Tabel A: (De-)Implementatietabel met impuls analyse

Aanbeveling – 1			
1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?	☐ **Ongewenste praktijkvariatie** ■ **Nieuwe evidentie** ☐ **Anders** Er zijn relatief weinig prospectieve vergelijkende studies naar verschillende csDMARDs in niet-infectieuze uveitis. Daarnaast is niet-infectieuze uveitis een verzamelterm die een heterogene groep oogheelkundige ziektebeelden bevat: studies met andere demografische kenmerken – en daarmee andere subtypes van niet-infectieuze uveitis – kunnen de toepasbaarheid van de data op onze patientenpopulatie in Nederland bemoeilijken. Daarom is er behoefte aan een landelijke richtlijn met gerichte aanbevelingen.		
2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?	■ **< 1000** ☐ **< 5000** ☐ **5000-40.000** ☐ **> 40.000**		
3. Maakt de aanbeveling deel uit van een set van interventies voor hetzelfde probleem?	■ **Ja**: hoe verhoudt deze aanbeveling zich tot de andere aanbevelingen uit deze module/ richtlijn of uit andere richtlijnen(modules)? Dient hier rekening mee gehouden te worden bij de implementatie of kan dit worden gezien als een losstaande aanbeveling? **Toelichting:** Deze module volgt op de de module “systemische behandeling van niet-infectieuze uveitis” en loopt parallel aan de modules “biologicals voor niet-infectieuze uveitis”, module ‘Plaatsbepaling van b/tsDMARDS tov csDMARDs ☐ **Nee**		
4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:	***Voorbeelden***	**Wat zijn mogelijke belemmerende factoren?**	**Wat zijn mogelijke bevorderende factoren?**

a) **Richtlijn/ klinisch traject (innovatie)**	*Voortschrijding/vooruitgang in de praktijk, haalbaarheid, geloofwaardigheid, toegankelijkheid, aantrekkelijkheid*	Het starten van een DMARD zal niet in alle klinieken even makkelijk gaan. Met name de ondersteuning / begeleiding vanuit een immunoloog of reumatoloog is niet in alle ziekenhuizen gewaarborgd.	Het gaat om een aanbeveling die overeenkomt met de reeds geïmplementeerde dagelijkse praktijk.
b) **Zorgverleners (artsen en verpleegkundigen)**	*Bewustzijn, kennis, houding, motivatie om te veranderen, gedragsroutines*	Het gaat om relatief risicovolle medicijnen. Niet alle oogartsen voelen zich competent om dit voor te schrijven en te begeleiden.	Steeds meer samenwerking (maar helaas nog niet overal) met immunologie en/of reumatologie voor begeleiding.
c) **Patiënt/ cliënt (naasten)**	*Kennis, vaardigheden, houding, compliance*	Grote lijst aan bijwerkingen. Niet alle patienten staan hiervoor open.	Goede voorlichtingsfolders bestaan al en kunnen makkelijk aangepast worden naargelang de context.
d) **Sociale context**	*Mening van collega's, cultuur van het netwerk, samenwerking, leiderschap*	Zie punt b.	Zie punt b.
e) **Organisatorische context**	*Organisatie van zorgprocessen, personeel, capaciteiten, middelen, structuren*	Deze medicijnen moeten worden voorgeschreven door een ervaren arts, waarbij er periodiek lab onderzoek plaatsvindt. Dit moet geimplementeerd worden in een poliklinische routine.	Veel ziekenhuizen kennen deze opzet al.
f) **Economische en politieke context**	*Financiële regelingen, regelgeving, beleid (vergoede zorg, betaaltitel)*	Er bestaat op dit moment geen DBC voor periodiek labonderzoek bij risicovolle medicatie, waarvoor het relatief "dure" patientenzorg is en dit door sommige klinieken afgestoten zal worden.	De DBC labonderzoek bij risicovolle medicatie bestaat wel voor reumatologie en immunologie.

5. Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk?	■ Patiënt/ cliënt (naaste) ■ Professional ☐ Beroepsvereniging ■ Ziekenhuis(bestuurder) ■ Zorgverzekeraars/ NZa ☐ Zorginstituut [duiding nodig] ☐
6. Wat zouden deze personen/ partijen moeten veranderen in hun gedrag of organisatie om de aanbeveling toe te passen?	Samenwerking tussen specialismes bevorderen.
7. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?	■ < 1 jaar ☐ < 2 jaar ☐ < 3 jaar De aanbeveling volgt de praktijk al.
8. Conclusie: is er extra aandacht nodig voor implementatie van de aanbeveling (anders dan publicatie van deze richtlijnmodule)?	☐ **Ja*** ■ **Nee** **Toelichting**: er zou ook aandacht voor de richtlijn moeten zijn binnen de reumatologie en / of immunologie.

**Deze aanbeveling komt in aanmerking voor plaatsing op de Implementatie Agenda van het programma Zorg Evaluatie & Gepast Gebruik (ZE&GG). In het programma ZE&GG werken patiënten, zorgverleners, zorgaanbieders, zorgverzekeraars en overheid samen aan de bewezen beste zorg voor de patiënt. Daarmee is ZE&GG een programma van alle betrokken partijen in de Medisch Specialistische Zorg. FMS is één van deze betrokken partijen.*

De implementatieagenda van ZE&GG bevat onderwerpen over wat de bewezen beste zorg is en die in de dagelijkse zorgpraktijk geïmplementeerd zouden moeten worden. Zorgverzekeraars Nederland (ZN) en de Nederlandse Vereniging voor Ziekenhuizen (NVZ) hebben landelijke afspraken gemaakt over de implementatie van de onderwerpen van de implementatieagenda. Deze afspraken zijn onderdeel van de zorginkoopafspraken tussen zorgverzekeraars en zorgaanbieders.

Vanuit FMS worden sterke, goed onderbouwde aanbevelingen, getoetst op de behoefte aan een implementatie impuls aangedragen. Voor de beoordeling van onderwerpen uit richtlijnen wordt gekeken naar bovenstaande tabel voor een inschatting van de implementatie impuls. Met de ingevulde implementatietabel kunnen we vanuit FMS de andere HLA-MSZ partijen goed informeren om zo samen te beslissen of de aanbeveling daadwerkelijk op de implementatie agenda zal worden geplaatst.

Literatuur

Acharya NR, Rathinam SR, Thundikandy R, Kanakath A, Murugan SB, Vedhanayaki R, Gonzales JA, Lim LL, Suhler EB, Al-Dhibi HA, Doan T, Arellanes-Garcia L, Coyne A, Porco TC, Shantha JG; FAST Research Group. Outcomes in Patients With Vogt-Koyanagi-Harada Disease From the First-Line Antimetabolites for Steroid-Sparing Treatment Uveitis Trial. Am J Ophthalmol. 2024 Nov;267:100-111. doi: 10.1016/j.ajo.2024.06.004. Epub 2024 Jun 22. PMID: 38909740.

Bernal-Morales C, Ramanan AV, Pavesio C. Use of immunomodulators in non-infectious uveitis: lights and shadows. Eye (Lond). 2024 Dec;38(17):3231-3242. doi: 10.1038/s41433-024-03294-9. Epub 2024 Aug 19. PMID: 39160332; PMCID: PMC11584895.

Chattopadhyay, A., Rathinam, S., Gonzales, J. A., Kelly, N. K., Thundikandy, R., … Kanakath, A. Association between Quality of Life and Visual Acuity in a Randomized Clinical Trial of Patients with Uveitis Taking Antimetabolites. Ocular Immunology and Inflammation. 2024. *32*(3), 301–309. https://doi.org/10.1080/09273948.2023.2169714

Edwards Mayhew RG, Li T, McCann P, Leslie L, Strong Caldwell A, Palestine AG. Non-biologic, steroid-sparing therapies for non-infectious intermediate, posterior, and panuveitis in adults. Cochrane Database Syst Rev. 2022 Oct 31;10(10):CD014831. doi: 10.1002/14651858.CD014831.pub2. PMID: 36315029; PMCID: PMC9621106.

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Leclercq M, Sève P, Biard L, Vautier M, Maalouf G, Leroux G, Domont F, Toutée A, Fardeau C, Sales de Gauzy T, Touhami S, Kodjikian L, Cacoub P, Bodaghi B, Saadoun D, Desbois AC. Methotrexate versus conventional disease-modifying antirheumatic drugs in the treatment of non-anterior sarcoidosis-associated uveitis. Br J Ophthalmol. 2024 Dec 17;109(1):34-40. doi: 10.1136/bjo-2024-325163. PMID: 39013629.

Niemeyer KM, Gonzales JA, Rathinam SR, Babu M, Thundikandy R, Kanakath A, Porco TC, Browne EN, Rao MM, Acharya NR. Quality-of-Life Outcomes From a Randomized Clinical Trial Comparing Antimetabolites for Intermediate, Posterior, and Panuveitis. Am J Ophthalmol. 2017 Jul;179:10-17. doi: 10.1016/j.ajo.2017.04.003. Epub 2017 Apr 14. PMID: 28414043; PMCID: PMC5504281.

Rathinam SR, Babu M, Thundikandy R, Kanakath A, Nardone N, Esterberg E, Lee SM, Enanoria WT, Porco TC, Browne EN, Weinrib R, Acharya NR. A randomized clinical trial comparing methotrexate and mycophenolate mofetil for noninfectious uveitis. Ophthalmology. 2014 Oct;121(10):1863-70. doi: 10.1016/j.ophtha.2014.04.023. Epub 2014 Jun 7. PMID: 24917273; PMCID: PMC4177935.

Rathinam SR, Gonzales JA, Thundikandy R, Kanakath A, Murugan SB, Vedhanayaki R, Lim LL, Suhler EB, Al-Dhibi HA, Doan T, Keenan JD, Rao MM, Ebert CD, Nguyen HH, Kim E, Porco TC, Acharya NR; FAST Research Group. Effect of Corticosteroid-Sparing Treatment With Mycophenolate Mofetil vs Methotrexate on Inflammation in Patients With Uveitis: A Randomized Clinical Trial. JAMA. 2019 Sep 10;322(10):936-945. doi: 10.1001/jama.2019.12618. PMID: 31503307; PMCID: PMC6737523.

Shen E, Rathinam SR, Babu M, Kanakath A, Thundikandy R, Lee SM, Browne EN, Porco TC, Acharya NR. Outcomes of Vogt-Koyanagi-Harada Disease: A Subanalysis From a Randomized Clinical Trial of Antimetabolite Therapies. Am J Ophthalmol. 2016 Aug;168:279-286. doi: 10.1016/j.ajo.2016.06.004. Epub 2016 Jun 10. PMID: 27296490; PMCID: PMC4969141.

Southgate G, Clarke P, Harmer MJ. Renal outcomes in tubulointerstitial nephritis and uveitis (TINU) syndrome: a systematic review and meta-analysis. J Nephrol. 2023 Mar;36(2):507-519. doi: 10.1007/s40620-022-01478-8. Epub 2022 Nov 18. PMID: 36396848.

Sura AA, Sun Y, Reddy AK, Rathinam SR, Gonzales JA, Thundikandy R, Vedhanayaki R, Kanakath A, Murugan B, Doan TA, Lim LL, Suhler EB, Al-Dhibi HA, Acharya NR; FAST Research Group. Reduced Dose Methotrexate and Mycophenolate Mofetil in Noninfectious Uveitis: A Sub-Analysis from the First-Line Antimetabolites as Steroid Sparing Therapy (FAST) Trial. Ocul Immunol Inflamm. 2024 Aug;32(6):955-960. doi: 10.1080/09273948.2023.2165949. Epub 2023 Jan 26. PMID: 36701644; PMCID: PMC10368793.

Tsui E, Rathinam SR, Gonzales JA, Thundikandy R, Kanakath A, Balamurugan S, Vedhanayaki R, Lim LL, Suhler EB, Al-Dhibi HA, Doan T, Keenan J, Ebert CD, Kim E, Madow B, Porco TC, Acharya NR; FAST Research Group. Outcomes of Uveitic Macular Edema in the First-line Antimetabolites as Steroid-Sparing Treatment Uveitis Trial. Ophthalmology. 2022 Jun;129(6):661-667. doi: 10.1016/j.ophtha.2022.02.002. Epub 2022 Feb 8. PMID: 35143800.

Bijlagen bij module behandeling met conventionele synthetische (cs)DMARDs.

Risk of Bias tables

Risk of bias table for intervention studies (randomized controlled trials; based on Cochrane risk of bias tool and suggestions by the CLARITY Group at McMaster University)

5

Research question:

Study reference (first author, publication year)	**Was the allocation sequence adequately generated?**	**Was the allocation adequately concealed?**	**Blinding: Was knowledge of the allocated interventions adequately prevented?** **Were patients/ healthcare providers / data collectors / outcome assessors/ data analysts blinded?**	**Was loss to follow-up (missing outcome data) infrequent?**	**Are reports of the study free of selective outcome reporting?**	**Was the study apparently free of other problems that could put it at a risk of bias?**	**Overall risk of bias** If applicable/necessary, per outcome measure **LOW** **Some concerns** **HIGH**
Tsui, 2022	Definitely yes; Reason: permuted block randomization and random allocation sequence was generated using R software	Probably yes; Reason: allocation was concealed until after enrolment, not reported how it was concealed.	Probably yes; Reason: personnel responsible for outcome measurements (ophthalmologists, visual acuity examiners, OCT operators) were masked. Study coordinators and patients were not masked to medication assignment.	Probably no Reason: 22 patients (10.2%) were lost to follow-up, which was equally divided across both groups. ITT analysis not fully applied.	Definitely yes Reason: All relevant outcomes were reported;	Definitely yes; Reason: No other problems noted	**Low (all outcomes)**
Acharya, 2024	Definitely yes; Reason: permuted block randomization and random allocation sequence was generated using R software	Probably yes; Reason: allocation was concealed until after enrolment, not reported how it was concealed.	Probably yes; Reason: personnel responsible for outcome measurements (ophthalmologists, visual acuity examiners, OCT operators) were masked. Study coordinators and patients were not masked to medication assignment.	Definitely yes Reason: 8 patients (8.6%) were lost to follow-up, which was equally divided across both groups ITT analysis for primary outcome was performed and VKH patients with missing primary outcome data were excluded	Definitely yes Reason: All relevant outcomes were reported;	Probably no Imbalance in chronic vs. acute VKH. Chronic VKH cases more common and treatment response differed by disease stage.	**Low (all outcomes)**

Table of excluded studies

Reference	Reason for exclusion
Bernal-Morales C, Ramanan AV, Pavesio C. Use of immunomodulators in non-infectious uveitis: lights and shadows. Eye (Lond). 2024 Dec;38(17):3231-3242. doi: 10.1038/s41433-024-03294-9. Epub 2024 Aug 19. PMID: 39160332; PMCID: PMC11584895.	Wrong study design (narrative review)
Browne EN, Rathinam SR, Kanakath A, Thundikandy R, Babu M, Lietman TM, Acharya NR. A Bayesian Analysis of a Randomized Clinical Trial Comparing Antimetabolite Therapies for Non-Infectious Uveitis. Ophthalmic Epidemiol. 2017 Feb;24(1):63-70. doi: 10.1080/09286586.2016.1255764. Epub 2016 Dec 16. PMID: 27982726; PMCID: PMC5738326.	Wrong study design (study in which results were pooled by experts in the field)
Chattopadhyay A, Rathinam SR, Gonzales JA, Kelly NK, Thundikandy R, Kanakath A, Murugan SB, Vedhanayaki R, Lim LL, Suhler EB, Al-Dhibi HA, Doan T, Ebert CD, Porco TC, Acharya NR; FAST Research Group. Association between Quality of Life and Visual Acuity in a Randomized Clinical Trial of Patients with Uveitis Taking Antimetabolites. Ocul Immunol Inflamm. 2024 Apr;32(3):301-309. doi: 10.1080/09273948.2023.2169714. Epub 2023 Feb 7. PMID: 36749914; PMCID: PMC10404633.	Wrong aim (association between quality of life and visual acuity)
Gómez-Gómez A, Loza E, Rosario MP, Espinosa G, de Morales JMGR, Herrera JM, Muñoz-Fernández S, Rodríguez-Rodríguez L, Cordero-Coma M; Spanish Society of Ocular Inflammation (SEIOC). Efficacy and safety of immunomodulatory drugs in patients with non-infectious intermediate and posterior uveitis, panuveitis and macular edema: A systematic literature review. Semin Arthritis Rheum. 2020 Dec;50(6):1299-1306. doi: 10.1016/j.semarthrit.2020.08.010. Epub 2020 Aug 28. PMID: 33065425.	Only RCTs relevant for the comparison MTX vs. MMF (Rathinam, 2014; Shen, 2016), which are already included in the Cochrane review of Edwards Mayhew (2022)
Jabs DA. Antimetabolite Therapy for Uveitis: Methotrexate or Mycophenolate? JAMA Ophthalmol. 2019 Dec 1;137(12):1449-1451. doi: 10.1001/jamaophthalmol.2019.3964. PMID: 31503274.	Wrong study design (commentary)
Karam M, Alsaif A, Al-Naseem A, Hayre A, Al Jabbouri A, Aldubaikhi A, Kahlar N, Al-Mutairi S. Mycophenolate versus Methotrexate in Non-infectious Ocular Inflammatory Disease: A Systematic Review and Meta-Analysis. Ocul Immunol Inflamm. 2023 Apr;31(3):613-620. doi: 10.1080/09273948.2022.2034166. Epub 2022 Feb 24. PMID: 35201968.	Less extensive reporting of data than in Cochrane review of Edwards Mayhew (2022)
Kelly NK, Chattopadhyay A, Rathinam SR, Gonzales JA, Thundikandy R, Kanakath A, Murugan SB, Vedhanayaki R, Cugley D, Lim LL, Suhler EB, Al-Dhibi HA, Ebert CD, Berlinberg EJ, Porco TC, Acharya NR; FAST Research Group. Health- and Vision-Related Quality of Life in a Randomized Controlled Trial Comparing Methotrexate and Mycophenolate Mofetil for Uveitis. Ophthalmology. 2021 Sep;128(9):1337-1345. doi: 10.1016/j.ophtha.2021.02.024. Epub 2021 Mar 4. PMID: 33675850; PMCID: PMC8384645.	Wrong outcomes
Knickelbein JE, Kim M, Argon E, Nussenblatt RB, Sen NH. Comparative efficacy of steroid-sparing therapies for non-infectious uveitis. Expert Rev Ophthalmol. 2017;12(4):313-319. doi: 10.1080/17469899.2017.1319762. Epub 2017 Apr 26. PMID: 30867672; PMCID: PMC6411306.	Wrong study design (narrative review)
Leclercq M, Sève P, Biard L, Vautier M, Maalouf G, Leroux G, Domont F, Toutée A, Fardeau C, Sales de Gauzy T, Touhami S, Kodjikian L, Cacoub P, Bodaghi B, Saadoun D, Desbois AC. Methotrexate versus conventional disease-modifying antirheumatic drugs in the treatment of non-anterior sarcoidosis-associated uveitis. Br J Ophthalmol. 2024 Dec 17;109(1):34-40. doi: 10.1136/bjo-2024-325163. PMID: 39013629.	Wrong study design (retrospective observational study)
Niemeyer KM, Gonzales JA, Rathinam SR, Babu M, Thundikandy R, Kanakath A, Porco TC, Browne EN, Rao MM, Acharya NR. Quality-	Wrong outcomes

of-Life Outcomes From a Randomized Clinical Trial Comparing Antimetabolites for Intermediate, Posterior, and Panuveitis. Am J Ophthalmol. 2017 Jul;179:10-17. doi: 10.1016/j.ajo.2017.04.003. Epub 2017 Apr 14. PMID: 28414043; PMCID: PMC5504281.	
Rathinam SR, Gonzales JA, Thundikandy R, Kanakath A, Murugan SB, Vedhanayaki R, Lim LL, Suhler EB, Al-Dhibi HA, Doan T, Keenan JD, Rao MM, Ebert CD, Nguyen HH, Kim E, Porco TC, Acharya NR; FAST Research Group. Effect of Corticosteroid-Sparing Treatment With Mycophenolate Mofetil vs Methotrexate on Inflammation in Patients With Uveitis: A Randomized Clinical Trial. JAMA. 2019 Sep 10;322(10):936-945. doi: 10.1001/jama.2019.12618. PMID: 31503307; PMCID: PMC6737523.	Included in the Cochrane review of Edwards Mayhew (2022)
Rathinam SR, Babu M, Thundikandy R, Kanakath A, Nardone N, Esterberg E, Lee SM, Enanoria WT, Porco TC, Browne EN, Weinrib R, Acharya NR. A randomized clinical trial comparing methotrexate and mycophenolate mofetil for noninfectious uveitis. Ophthalmology. 2014 Oct;121(10):1863-70. doi: 10.1016/j.ophtha.2014.04.023. Epub 2014 Jun 7. PMID: 24917273; PMCID: PMC4177935.	Included in the Cochrane review of Edwards Mayhew (2022)
Reddy AK, Miller DC, Sura AA, Rathinam SR, Gonzales JA, Thundikandy R, Kanakath A, Murugan B, Vedhanayaki R, Lim LL, Suhler EB, Doan T, Al-Dhibi HA, Goldstein DA, Arellanes-Garcia L, Acharya NR. Risk of failing both methotrexate and mycophenolate mofetil from the First-line Antimetabolites as Steroid-sparing Treatment (FAST) uveitis trial. J Ophthalmic Inflamm Infect. 2023 Jun 9;13(1):29. doi: 10.1186/s12348-023-00350-5. PMID: 37294447; PMCID: PMC10256664.	Wrong intervention and control: risk factors for failing MTX and MMF
Rossi DC, Ribi C, Guex-Crosier Y. Treatment of chronic non-infectious uveitis and scleritis. Swiss Med Wkly. 2019 Mar 10;149:w20025. doi: 10.4414/smw.2019.20025. PMID: 30852832.	Wrong study design (narrative review)
Shen E, Rathinam SR, Babu M, Kanakath A, Thundikandy R, Lee SM, Browne EN, Porco TC, Acharya NR. Outcomes of Vogt-Koyanagi-Harada Disease: A Subanalysis From a Randomized Clinical Trial of Antimetabolite Therapies. Am J Ophthalmol. 2016 Aug;168:279-286. doi: 10.1016/j.ajo.2016.06.004. Epub 2016 Jun 10. PMID: 27296490; PMCID: PMC4969141.	Included in the Cochrane review of Edwards Mayhew (2022)
Sura AA, Sun Y, Reddy AK, Rathinam SR, Gonzales JA, Thundikandy R, Vedhanayaki R, Kanakath A, Murugan B, Doan TA, Lim LL, Suhler EB, Al-Dhibi HA, Acharya NR; FAST Research Group. Reduced Dose Methotrexate and Mycophenolate Mofetil in Noninfectious Uveitis: A Sub-Analysis from the First-Line Antimetabolites as Steroid Sparing Therapy (FAST) Trial. Ocul Immunol Inflamm. 2024 Aug;32(6):955-960. doi: 10.1080/09273948.2023.2165949. Epub 2023 Jan 26. PMID: 36701644; PMCID: PMC10368793.	Wrong aim: the influence of dose reduction of MTX and MMF (instead of MTX vs. MMF) on ocular outcomes
Tallouzi MO, Moore DJ, Barry RJ, Calvert M, Mathers J, Murray PI, Denniston AK. The Effectiveness of Pharmacological Agents for the Treatment of Uveitic Macular Edema (UMO): A Systematic Review. Ocul Immunol Inflamm. 2019;27(4):658-680. doi: 10.1080/09273948.2019.1569243. Epub 2019 Feb 27. PMID: 30811272.	Only Rathinam (2014) relevant, but this RCT is already included in the Cochrane review of Edwards Mayhew (2022)
Zuo H, Zhang W, Yan Y. Efficacy and Safety of Immunosuppressant Therapy for Noninfectious Uveitis: A Systematic Review and Meta-Analysis. Comput Math Methods Med. 2021 Sep 4;2021:1933604. doi: 10.1155/2021/1933604. PMID: 34527074; PMCID: PMC8437623.	Wrong intervention (biologicals), only Rathinam (2019) relevant, but this RCT is already included in the more recent and complete Cochrane review of Edwards Mayhew (2022)

Literature search strategy

Algemene informatie

Cluster/richtlijn: Cluster Oog - Uveitis - module csDMARDS	
Uitgangsvraag/modules: Wat is de meest effectieve corticosteroïd-sparende non-biological behandeling van niet-infectieuze uveitis?	
Database(s): Embase.com, Ovid/Medline	Datum: 8 april 2025
Periode: vanaf 2014	Talen: geen restrictie
Literatuurspecialist: Esther van der Bijl	
BMI-zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Deduplication: voor het ontdubbelen is gebruik gemaakt van http://dedupendnote.nl/	
Toelichting: De sleutelartikelen worden gevonden met deze search.	
Te gebruiken voor richtlijntekst: A systematic literature search was performed by a medical information specialist using the following bibliographic databases: Embase.com and Ovid/Medline. Both databases were searched from 2014 to the 8th of April 2025 for systematic reviews and RCTs. Systematic searches were completed using a combination of controlled vocabulary/subject headings (e.g., Emtree-terms, MeSH) wherever they were available and natural language keywords. The overall search strategy was derived from two primary search concepts: (1) uveitis; (2) DMARDS. Duplicates were removed using EndNote software. After deduplication a total of 574 records were imported for title/abstract screening.	

Zoekopbrengst 8 april 2025

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**
SR	310	130	
RCT	171	128	
Totaal	481	258	**574***

voor AS Review

Zoekstrategie Embase.com 8 april 2025

No.	***Query***	***Results***
#1	'uveitis'/exp OR 'panuveitis':ti,ab,kw OR 'uveiti*':ti,ab,kw OR chorioretinitis:ti,ab,kw OR retinitis:ti,ab,kw OR scleritis:ti,ab,kw OR vitritis:ti,ab,kw OR iritis:ti,ab,kw OR iridocyclitis:ti,ab,kw OR 'pars planitis':ti,ab,kw OR chorioiditis:ti,ab,kw	103163
#2	'disease modifying antirheumatic drug'/exp OR 'methotrexate'/exp OR 'mycophenolate mofetil'/exp OR 'azathioprine'/exp OR 'disease modifying antirheumatic*':ti,ab,kw OR 'disease modifying anti rheumatic*':ti,ab,kw OR csdmards:ti,ab,kw OR dmards:ti,ab,kw OR '4 amino 10 methylfolic acid':ti,ab,kw OR '4 amino 10 methylpteroylglutamic acid':ti,ab,kw OR '4 amino n10 methylpteroylglutamic acid':ti,ab,kw OR 'mtx':ti,ab,kw OR 'a methopterine':ti,ab,kw OR 'abitextrate':ti,ab,kw OR 'abitrexate':ti,ab,kw OR 'adx 2191':ti,ab,kw OR 'adx2191':ti,ab,kw OR 'amethopterin':ti,ab,kw OR 'amethopterine':ti,ab,kw OR 'ametopterine':ti,ab,kw OR 'antifolan':ti,ab,kw OR 'biotrexate':ti,ab,kw OR 'brimexate':ti,ab,kw OR 'canceren':ti,ab,kw OR 'cl 14377':ti,ab,kw OR 'cl14377':ti,ab,kw OR 'emt 25299':ti,ab,kw OR 'emt25299':ti,ab,kw OR 'emtexate':ti,ab,kw OR 'emthexat':ti,ab,kw OR 'emthexate':ti,ab,kw OR 'emtrexate':ti,ab,kw OR 'enthexate':ti,ab,kw OR 'farmitrexat':ti,ab,kw OR 'farmitrexate':ti,ab,kw OR 'farmotrex':ti,ab,kw OR 'folex':ti,ab,kw OR 'folex pfs':ti,ab,kw OR 'ifamet':ti,ab,kw OR 'imeth':ti,ab,kw OR 'intradose mtx':ti,ab,kw OR 'jylamvo':ti,ab,kw OR 'lantarel':ti,ab,kw OR 'ledertrexate':ti,ab,kw OR 'lumexon':ti,ab,kw OR 'maxtrex':ti,ab,kw OR 'metatrexan':ti,ab,kw OR 'metex':ti,ab,kw OR 'methoblastin':ti,ab,kw OR 'methohexate':ti,ab,kw OR 'methotrate':ti,ab,kw OR 'methotrexat':ti,ab,kw OR 'methotrexate*':ti,ab,kw OR 'methotrexato':ti,ab,kw OR 'methoxtrexate':ti,ab,kw OR 'methrotrexate':ti,ab,kw OR 'methylaminopterin':ti,ab,kw OR 'methylaminopterine':ti,ab,kw OR 'meticil':ti,ab,kw OR 'metoject':ti,ab,kw OR 'metothrexate':ti,ab,kw OR 'metotrexat':ti,ab,kw OR 'metotrexate':ti,ab,kw OR 'metotrexin':ti,ab,kw OR 'metrex':ti,ab,kw OR 'metrotex':ti,ab,kw OR 'mexate':ti,ab,kw OR 'mexate-aq':ti,ab,kw OR 'mpi 2505':ti,ab,kw OR 'mpi 5004':ti,ab,kw OR 'mpi2505':ti,ab,kw OR 'mpi5004':ti,ab,kw OR	396222

	'neotrexate':ti,ab,kw OR 'nordimet':ti,ab,kw OR 'novatrex':ti,ab,kw OR 'nsc 740':ti,ab,kw OR 'nsc740':ti,ab,kw OR 'otrexup':ti,ab,kw OR 'r 9985':ti,ab,kw OR 'r9985':ti,ab,kw OR 'rasuvo':ti,ab,kw OR 'reditrex':ti,ab,kw OR 'reumatrex':ti,ab,kw OR 'rheumatrex':ti,ab,kw OR 'texate':ti,ab,kw OR 'texorate':ti,ab,kw OR 'tremetex':ti,ab,kw OR 'trexall':ti,ab,kw OR 'trexeron':ti,ab,kw OR 'wr 19039':ti,ab,kw OR 'wr19039':ti,ab,kw OR 'xaken':ti,ab,kw OR 'xatmep':ti,ab,kw OR 'zexate':ti,ab,kw OR 'zlatal':ti,ab,kw OR 'cell cept':ti,ab,kw OR 'cellcept':ti,ab,kw OR 'cellmune':ti,ab,kw OR 'cellsept':ti,ab,kw OR 'mowel':ti,ab,kw OR 'munoloc':ti,ab,kw OR 'myclausen':ti,ab,kw OR 'mycofit':ti,ab,kw OR 'mycolat':ti,ab,kw OR 'mycophenolate mofetil':ti,ab,kw OR 'mycophenolic acid 2 morpholinoethyl ester':ti,ab,kw OR 'mycophenolic acid mofetil':ti,ab,kw OR 'myfenax':ti,ab,kw OR 'myhibbin':ti,ab,kw OR 'r 99':ti,ab,kw OR 'r99':ti,ab,kw OR 'ro 1061443':ti,ab,kw OR 'ro1061443':ti,ab,kw OR 'rs 61443':ti,ab,kw OR 'rs 61443 190':ti,ab,kw OR 'rs61443':ti,ab,kw OR 'rs61443 190':ti,ab,kw OR 'trixin':ti,ab,kw OR 'arathioprin':ti,ab,kw OR 'arathioprine':ti,ab,kw OR 'aza-q':ti,ab,kw OR 'azafalk':ti,ab,kw OR 'azafor':ti,ab,kw OR 'azahexal':ti,ab,kw OR 'azamedac':ti,ab,kw OR 'azamun':ti,ab,kw OR 'azamune':ti,ab,kw OR 'azanin':ti,ab,kw OR 'azapin':ti,ab,kw OR 'azapress':ti,ab,kw OR 'azaprine':ti,ab,kw OR 'azarex':ti,ab,kw OR 'azasan':ti,ab,kw OR 'azathiodura':ti,ab,kw OR 'azathiopine':ti,ab,kw OR 'azathioprim':ti,ab,kw OR 'azathioprin':ti,ab,kw OR 'azathioprine':ti,ab,kw OR 'azathioprine sodium':ti,ab,kw OR 'azathiopurine':ti,ab,kw OR 'azathropsin':ti,ab,kw OR 'azatioprina':ti,ab,kw OR 'azatox':ti,ab,kw OR 'azatrilem':ti,ab,kw OR 'azopi':ti,ab,kw OR 'azoran':ti,ab,kw OR 'azothioprin':ti,ab,kw OR 'azothioprine':ti,ab,kw OR 'bw 57 322':ti,ab,kw OR 'bw 57-322':ti,ab,kw OR 'bw 57322':ti,ab,kw OR 'bw57-322':ti,ab,kw OR 'bw57322':ti,ab,kw OR 'colinsan':ti,ab,kw OR 'immuran':ti,ab,kw OR 'immurel':ti,ab,kw OR 'immuthera':ti,ab,kw OR 'imunen':ti,ab,kw OR 'imuprin':ti,ab,kw OR 'imuran':ti,ab,kw OR 'imurane':ti,ab,kw OR 'imurek':ti,ab,kw OR 'imurel':ti,ab,kw OR 'imuren':ti,ab,kw OR 'jayempi':ti,ab,kw OR 'methylnitroimidazolylmercaptopurine':ti,ab,kw OR 'nsc 39084':ti,ab,kw OR 'nsc39084':ti,ab,kw OR 'oraprine':ti,ab,kw OR 'ozathuia':ti,ab,kw OR 'thioazeprine':ti,ab,kw OR 'thioprine':ti,ab,kw OR 'transimune':ti,ab,kw OR 'zytrim':ti,ab,kw	
#3	(corticosteroid* NEAR/3 (spar* OR avoid* OR replac* OR substitut*)):ti,ab,kw	2692
#4	#2 OR #3	398131
#5	#1 AND #4	11687
#6	#5 AND [2014-2025]/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	4653
#7	'meta analysis'/exp OR 'systematic review'/exp OR 'scoping review'/exp OR 'rapid review'/exp OR 'umbrella review'/exp OR 'cochrane database of systematic reviews'/jt OR 'network meta-analysis'/exp OR 'networkmeta analy*':ti,ab,kw OR 'networkmetaanaly*':ti,ab,kw OR metaanaly*:ti,ab,kw OR 'meta analy*':ti,ab,kw OR metanaly*:ti,ab,kw OR prisma:ti,ab,kw OR prospero:ti,ab,kw OR metaanali*:ti,ab,kw OR 'meta anali*':ti,ab,kw OR metanali*:ti,ab,kw OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab,kw) OR (((structured OR systemic*) NEAR/3 (review* OR overview* OR synth*) NEAR/3 literature):ti,ab,kw) OR ((systemic* NEAR/1 review*):ti,ab,kw) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab,kw) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab,kw) OR (((literature NEAR/3 (review* OR overview*)):ti,ab,kw) AND (search*:ti,ab,kw OR database*:ti,ab,kw OR 'data base*':ti,ab,kw)) OR (('data extraction*':ti,ab,kw OR 'data source*':ti,ab,kw) AND ('study selection*':ti,ab,kw OR 'studies selection*':ti,ab,kw)) OR ('search strateg*':ti,ab,kw AND 'selection criteria*':ti,ab,kw) OR ('data source*':ti,ab,kw AND 'data synth*':ti,ab,kw) OR medline*:ti,ab,kw OR pubmed*:ti,ab,kw OR 'pub med*':ti,ab,kw OR embase:ti,ab,kw OR cochrane*:ti,ab,kw OR (((critical* OR rapid*) NEAR/2 (review* OR overview* OR synth*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synth*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynth*:ti,ab,kw OR 'meta synth*':ti,ab,kw OR 'review* of review*':ti,ab,kw	1098073
#8	'randomized controlled trial'/exp OR ((random* NEAR/3 (trial* OR trail* OR study OR studies)):ti,ab,kw,tt) OR (random*:ti,ab,kw,tt AND (group*:ti,ab,kw,tt OR criteria*:ti,ab,kw,tt)) OR ((randomized:ti,ab,kw,tt OR randomised:ti,ab,kw,tt) AND (trial*:ti,ab,kw,tt OR trail*:ti,ab,kw,tt OR study:ti,ab,kw,tt OR studies:ti,ab,kw,tt)) OR ((('cross over*' OR crossover*) NEAR/2 (randomiz* OR randomis*)):ti,ab,kw,tt) OR (((pragmatic OR practical) NEAR/1 ('clinical trial*' OR 'clinical trail*')):ti,ab,kw) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 (trial* OR trail*)):ti,ab,kw) OR rct:ti,ab,kw,tt OR rcts:ti,ab,kw,tt OR 'random* control*':ti,ab,kw,tt OR 'random* clinical*':ti,ab,kw,tt OR 'random* comparative*':ti,ab,kw,tt OR ((randomly NEAR/4 (devid* OR divid* OR assign* OR allocat*)):ti,ab) OR ((randomly NEAR/3 (placed OR receiv*)):ti,ab) OR ((random* NEAR/1 assign*):ti,ab)	1908367
#9	#6 AND #7 - SR	310
#10	#6 AND #8 NOT #9 - RCT	171
#11	#9 OR #10 - Totaal	481

Zoekstrategie Ovid/Medline 8 april 2025

#	Searches	Results
1	exp Uveitis/ or exp Panuveitis/ or uveiti*.ti,ab,kf. or chorioretinitis.ti,ab,kf. or retinitis.ti,ab,kf. or scleritis.ti,ab,kf. or vitritis.ti,ab,kf. or iritis.ti,ab,kf. or iridocyclitis.ti,ab,kf. or pars planitis.ti,ab,kf. or chorioiditis.ti,ab,kf.	63584
2	exp Antirheumatic Agents/ or exp Methotrexate/ or exp Mycophenolic Acid/ or exp Azathioprine/ or disease modifying antirheumatic*.ti,ab,kf. or disease modifying anti rheumatic*.ti,ab,kf. or csdmards.ti,ab,kf. or dmards.ti,ab,kf. or 4 amino 10 methylfolic acid.ti,ab,kf. or 4 amino 10 methylpteroylglutamic acid.ti,ab,kf. or 4 amino n10 methylpteroylglutamic acid.ti,ab,kf. or mtx.ti,ab,kf. or a methopterine.ti,ab,kf. or abitextrate.ti,ab,kf. or abitrexate.ti,ab,kf. or adx 2191.ti,ab,kf. or adx2191.ti,ab,kf. or amethopterin.ti,ab,kf. or amethopterine.ti,ab,kf. or ametopterine.ti,ab,kf. or antifolan.ti,ab,kf. or biotrexate.ti,ab,kf. or brimexate.ti,ab,kf. or canceren.ti,ab,kf. or cl 14377.ti,ab,kf. or cl14377.ti,ab,kf. or emt 25299.ti,ab,kf. or emt25299.ti,ab,kf. or emtexate.ti,ab,kf. or emthexat.ti,ab,kf. or emthexate.ti,ab,kf. or emtrexate.ti,ab,kf. or enthexate.ti,ab,kf. or farmitrexat.ti,ab,kf. or farmitrexate.ti,ab,kf. or farmotrex.ti,ab,kf. or folex.ti,ab,kf. or folex pfs.ti,ab,kf. or ifamet.ti,ab,kf. or imeth.ti,ab,kf. or intradose mtx.ti,ab,kf. or jylamvo.ti,ab,kf. or lantarel.ti,ab,kf. or ledertrexate.ti,ab,kf. or lumexon.ti,ab,kf. or maxtrex.ti,ab,kf. or metatrexan.ti,ab,kf. or metex.ti,ab,kf. or methoblastin.ti,ab,kf. or methohexate.ti,ab,kf. or methotrate.ti,ab,kf. or methotrexat.ti,ab,kf. or methotrexate*.ti,ab,kf. or methotrexato.ti,ab,kf. or methoxtrexate.ti,ab,kf. or methrotrexate.ti,ab,kf. or methylaminopterin.ti,ab,kf. or methylaminopterine.ti,ab,kf. or meticil.ti,ab,kf. or metoject.ti,ab,kf. or metothrexate.ti,ab,kf. or metotrexat.ti,ab,kf. or metotrexate.ti,ab,kf. or metotrexin.ti,ab,kf. or metrex.ti,ab,kf. or metrotex.ti,ab,kf. or mexate.ti,ab,kf. or mexate-aq.ti,ab,kf. or mpi 2505.ti,ab,kf. or mpi 5004.ti,ab,kf. or mpi2505.ti,ab,kf. or mpi5004.ti,ab,kf. or neotrexate.ti,ab,kf. or nordimet.ti,ab,kf. or novatrex.ti,ab,kf. or nsc 740.ti,ab,kf. or nsc740.ti,ab,kf. or otrexup.ti,ab,kf. or r 9985.ti,ab,kf. or r9985.ti,ab,kf. or rasuvo.ti,ab,kf. or reditrex.ti,ab,kf. or reumatrex.ti,ab,kf. or rheumatrex.ti,ab,kf. or texate.ti,ab,kf. or texorate.ti,ab,kf. or tremetex.ti,ab,kf. or trexall.ti,ab,kf. or trexeron.ti,ab,kf. or wr 19039.ti,ab,kf. or wr19039.ti,ab,kf. or xaken.ti,ab,kf. or xatmep.ti,ab,kf. or zexate.ti,ab,kf. or zlatal.ti,ab,kf. or cell cept.ti,ab,kf. or cellcept.ti,ab,kf. or cellmune.ti,ab,kf. or cellsept.ti,ab,kf. or mowel.ti,ab,kf. or munoloc.ti,ab,kf. or myclausen.ti,ab,kf. or mycofit.ti,ab,kf. or mycolat.ti,ab,kf. or mycophenolate mofetil.ti,ab,kf. or mycophenolic acid 2 morpholinoethyl ester.ti,ab,kf. or mycophenolic acid mofetil.ti,ab,kf. or myfenax.ti,ab,kf. or myhibbin.ti,ab,kf. or r 99.ti,ab,kf. or r99.ti,ab,kf. or ro 1061443.ti,ab,kf. or ro1061443.ti,ab,kf. or rs 61443.ti,ab,kf. or rs 61443 190.ti,ab,kf. or rs61443.ti,ab,kf. or rs61443 190.ti,ab,kf. or trixin.ti,ab,kf. or arathioprin.ti,ab,kf. or arathioprine.ti,ab,kf. or aza-q.ti,ab,kf. or azafalk.ti,ab,kf. or azafor.ti,ab,kf. or azahexal.ti,ab,kf. or azamedac.ti,ab,kf. or azamun.ti,ab,kf. or azamune.ti,ab,kf. or azanin.ti,ab,kf. or azapin.ti,ab,kf. or azapress.ti,ab,kf. or azaprine.ti,ab,kf. or azarex.ti,ab,kf. or azasan.ti,ab,kf. or azathiodura.ti,ab,kf. or azathiopine.ti,ab,kf. or azathioprim.ti,ab,kf. or azathioprin.ti,ab,kf. or azathioprine.ti,ab,kf. or azathioprine sodium.ti,ab,kf. or azathiopurine.ti,ab,kf. or azathropsin.ti,ab,kf. or azatioprina.ti,ab,kf. or azatox.ti,ab,kf. or azatrilem.ti,ab,kf. or azopi.ti,ab,kf. or azoran.ti,ab,kf. or azothioprin.ti,ab,kf. or azothioprine.ti,ab,kf. or bw 57 322.ti,ab,kf. or bw 57-322.ti,ab,kf. or bw 57322.ti,ab,kf. or bw57-322.ti,ab,kf. or bw57322.ti,ab,kf. or colinsan.ti,ab,kf. or immuran.ti,ab,kf. or immurel.ti,ab,kf. or immuthera.ti,ab,kf. or imunen.ti,ab,kf. or imuprin.ti,ab,kf. or imuran.ti,ab,kf. or imurane.ti,ab,kf. or imurek.ti,ab,kf. or imurel.ti,ab,kf. or imuren.ti,ab,kf. or jayempi.ti,ab,kf. or methylnitroimidazolylmercaptopurine.ti,ab,kf. or nsc 39084.ti,ab,kf. or nsc39084.ti,ab,kf. or oraprine.ti,ab,kf. or ozathuia.ti,ab,kf. or thioazeprine.ti,ab,kf. or thioprine.ti,ab,kf. or transimune.ti,ab,kf. or zytrim.ti,ab,kf.	526734
3	(corticosteroid* adj3 (spar* or avoid* or replac* or substitut*)).ti,ab,kf.	1824
4	2 or 3	528055
5	1 and 4	4885
6	limit 5 to yr="2014 -Current"	2168
7	6 not (comment/ or editorial/ or letter/) not ((exp animals/ or exp models, animal/) not humans/)	1975
8	exp Meta-Analysis/ or exp Network Meta-Analysis/ or exp Systematic Review/ or (networkmeta analy* or networkmetaanaly* or metaanaly* or meta analy* or metanaly* or prisma or prospero or metaanali* or meta anali* or metanali*).ti,ab,kf. or ((systemati* or scoping or umbrella or structured literature) adj3 (review* or overview*)).ti,ab,kf. or ((structured or systemic*) adj3 (review* or overview* or synth*) adj3 literature).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 (review* or overview*)) and (search* or database* or data base*)).ti,ab,kf. or ((data extraction* or data source*) and (study selection* or studies selection*)).ti,ab,kf. or (search strateg* and selection criteria*).ti,ab,kf. or (data source* and data synth*).ti,ab,kf. or (medline* or pubmed* or pub med* or embase or cochrane*).ti,ab,kf. or cochrane.jw. or ((critical* or rapid*) adj2 (review* or	817706

	overview* or synth*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synth*)) and (search* or database* or data base*)).ab. or metasynth*.ti,ab,kf. or meta synth*.ti,ab,kf.	
9	exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.	1816006
10	7 and 8 - SR	130
11	(7 and 9) not 10 - RCT	128
12	10 or 11 - Totaal	258

Bijlage 5 Verantwoording module 3 - Ontstekingsprofylaxe cataractchirurgie bij uveitispatiënten

Verantwoording

Voor meer details over de gebruikte richtlijnmethodologie verwijzen wij u naar de Werkwijze. Relevante informatie voor de ontwikkeling/herziening van deze richtlijnmodule is hieronder weergegeven.

Initiatief

Initiatief: cluster oog

Samenstelling van de werkgroep

Voor het ontwikkelen van de richtlijnmodule is in 2022 een multidisciplinair cluster ingesteld. Het cluster oog bestaat uit meerdere richltijnen, zie hier voor de actuele clusterindeling. De stuurgroep bewaakt het proces van modulair onderhoud binnen het cluster. De expertisegroepsleden geven hun expertise in, indien nodig. De volgende personen uit het cluster zijn betrokken geweest bij de herziening van deze module.

Clusterstuurgroepleden

- Dr. N.C. (Nicole) Naus, voorzitter cluster oog, oogarts, NOG, Erasmus MC
- Dr. M.C. (Marjolijn) Bartels, Voorzitter Cluster Oog, oogarts, NOG, Deventer Ziekenhuis
- Dr. A.J. (Arlette) van Sorge, oogarts, NOG, Koninklijke Visio,
- Drs. L.J. (Leo) Noordzij, oogarts, NOG, Oog op Zuid Oogkliniek
- Dr. R. (Redmer) van Leeuwen, oogarts, NOG, UMC Utrecht
- Dr. Ir M. (Marleen) van Aartrijk, Klinisch Fysicus NVKF, Koninklijke Visio
- C. (Caroline) Osterholt-Bel, Adviseur oogzorg Oogvereniging

Betrokken clusterexpertisegroepleden

Module 3: ontstekingsprofylaxe cataractchirurgie bij uveitis patiënten

- Prof. dr. J.H. (Joke) de Boer, oogarts, NOG, UMC Utrecht
- A.J.W. (Anne-Mieke) Haasnoot, oogarts, NOG, Deventer Ziekenhuis
- Drs. F.H. (Fleurieke) Verhagen, oogarts, NOG, UMC Utrecht
- Dr. M.E.J. (Mirjam) van Velthoven, oogarts, NOG, Oogziekenhuis Rotterdam
- P. (Pauline) de Heer, afgevaardigd op persoonlijke titel

Met ondersteuning van

- Dr. A.C.J. (Astrid) Balemans, senior-adviseur, Kennisinstituut van Medisch Specialisten
- MSc. D.G. (Dian) Ossendrijver, adviseur, Kennisinstituut van Medisch Specialisten
- A. (Alies) Oost, informatiespecialist, Kennisinstituut van de Federatie Medisch Specialisten

Belangenverklaringen

Een overzicht van de belangen van de clusterleden en het oordeel over het omgaan met eventuele belangen vindt u in onderstaande tabel. De ondertekende belangenverklaringen zijn op te vragen bij het secretariaat van het Kennisinstituut van de Federatie Medisch Specialisten via secretariaat@kennisinstituut.nl.

5

Cluster stuurgroepleden

Tabel 5 Gemelde (neven)functies en belangen stuurgroep

Naam	Hoofdfunctie	Nevenwerkzaamheden	Persoonlijke financiële belangen	Persoonlijke relaties	Extern gefinancierd onderzoek	Intellectuele belangen en reputatie	Overige belangen	Datum	Restrictie
Dr. N.C. (Nicole) Naus,	Oogarts Erasmus MC Rotterdam	Geen	Geen	Geen	Geen	Geen	Geen	1-08-2025	Geen restricties
Dr. M.C. (Marjolijn) Bartels	Oogarts Deventer ziekenhuis	Lid van Concilium, lid van commissie kwaliteit en voorzitter van cornea werkgroep (NOG).	Geen	Geen	ja, 1. PHIC (PIONEERS IN HEALTH CARE INNOVATIEFONDS) voucher voor onderzoek in samenwerking Universiteit Twente ZonMWstudies: 2. BICAT-NL studie 3. EPICAT studie	persoonlijk belang van goed op de hoogte zijn van alles, hetgeen gebruikt wordt in de dagelijkse praktijk en als opleider, lid van Concilium, lid van commissie kwaliteit en voorzitter van cornea werkgroep.	Geen	1-08-2025	Geen restricties

Dr. A.J. (Arlette) van Sorge	Oogarts koninklijke Visio	Voorzitter VRS (vereniging voor revalidatie bij slechtziendheid, onbetaald). Stuurgroeplid bij cluster OOG (NOG). Visitator visitatiecommissie NOG. Bestuurslid Oogcontact (onbetaald).	Geen	Geen	Geen	Geen	Geen	6-05-2025	Geen restricties
Drs. L.J. (Leo) Noordzij	Oogarts bij Cooperatie Oogheelkunde op Zuid voor 3.5 dag in de week. Voor 1.5 dag in de week bestuurslid van de Cooperatie Oogheelkunde op Zuid, de Stichting Oogheelkunde op Zuid en medisch directeur het zelfstandig behandel centrum Oog op Zuid oogkliniek.	Lid richtlijn werkgroep FMS/ NOG betreffende leeftijdsgebonden macula degeneratie (tm juli 2023). Vaste programma commissie InSights symposium, Novartis (gestopt juni 2022). Lid medical innovation academy, Novartis (gestopt augustus 2022).	Geen	Geen	Geen	Geen	Geen	20-04-2025	Geen restricties ('advieswerk' neergelegd per juni/augustus 2022)
Dr. R. (Redmer) van Leeuwen	Oogarts UMC Utrecht	Geen	Geen	Geen	ESCH-R 1. NWO - Circulaire zorg (Projectleider NEE)	Geen	Geen	02-02-2025	Geen restricties

Dr. Ir M. (Marleen) van Aartrijk	Klinisch Fysicus bij Koninklijke Visio (Revalidatie & Advies): betaald, - beheer Oogheelkundige apparatuur - ondersteuning zorgprofessionals bij individuele patienttrajecten (bijv. op gebied van verlichting, autorijden) - producteigenaar elektronisch patientendossier	Geen	Geen persoonlijk financieel belang. Indien een richtlijn verwijzing naar revalidatiezorg stimuleert kan dat impact hebben op mijn werkgever (en dan indirect op mijzelf	Geen	Binnen de revalidatiezorg zijn er fondsen (oa Novum, ZonMW) die exptertiseprojecten ondersteunen. Aan een aantal van deze projecten draag ik bij, maar dat gaat om een zeer beperkt deel van mijn tijd (ben geen hoofdonderzoeker oid)	Verduidelijking van rol revalidatiezorg in de zorgketen	Geen	22-04-2025	Geen restricties
C. (Caroline) Osterholt-Bel	TOA Ikazia	Geen	Geen	Geen	Geen	Geen	Geen	29-04-2025	Geen restricties

Betrokken clusterexpertisegroepleden

Tabel 6 Gemelde (neven)functies en belangen expertisegroep

Naam	Hoofdfunctie	Nevenwerkzaamheden	Persoonlijke financiële belangen	Persoonlijke relaties	Extern gefinancierd onderzoek	Intellectuele belangen en reputatie	Overige belangen	Datum	Restrictie
Prof. dr. J.H. (Joke) de Boer	Oogarts UMC Utrecht, aandachtsgebied uveitis	Richtlijnwerkgroep herziening richtiljn uveitis	Geen	Geen	1) Uveitis bij kinderen, financiers: Fischerstichting, ODAS stichting, ANVVB, LSBS. (Ik begeleid als PI een promovendus die onderzoek doet naar uveitis bij kinderen. De promovendus wordt gefinancierd vanuit ODAS, Fischer, LSBS en de ANVVB. Ik ontvang geen persoonlijke vergoeding. Het betreft een fundamenteel onderzoek naar uveitis bij kinderen waarbij er geen raakvlak is met de onderwerpen uit de richtlijn.) 2) Ontsteking bij retinitis pigmentosa, financier: ZonMw via Bartimeus. Ik begeleid als PI een promovendus die onderzoek doet naar retinitis pigmentosa vanuit Bartimeus. De promovendus wordt vanuit Zonmw gefinancierd. Ik	Geen	Geen	22-04-2025	Geen restricties

					ontvang geen persoonlijke vergoeding. 3) De effectiviteit van tocilizumab, financier: Rol: Lokaal PI: inclusie van 3-5 patiënten gaan includeren waar het UMC een vergoeding voor krijgt. UMC krijgt onkostenvergoeding voor gemaakte kosten in het UMCU, apotheek, lab, functie onderzoeken en personeel. 4) Copromotor bij onderzoek 'Ocular surface disease in atopic dermatitis and the effect of dupilumab treatment'. Dit proefschrift is deels gebaseerd op data uit de Registratie Bioday, gefinancierd door Sanofi Genzyme. Sanofi genzyme heeft geen producten die in de richtlijn aan bod komen.				

A.J.W. (Anne-Mieke)	Oogarts Deventer Ziekenhuis	Richtlijnwerkgroep herziening richtiljn uveitis	Vergoeding voor Medewerking aan de Herziening Richtlijn Uveitis Sprekersvergoeding voor presentatie over de richtlijn uveitis (Abbvie). Betreft niet de modules die in cluster oog worden herzien. Financier heeft geen invloed op richtiljn of inhoud van presentatie.	Geen	Geen	Geen	Geen	10-04-2025	Geen restricties
Drs. F.H. (Fleurieke) Verhagen	AIOS oogheelkunde, UMC Utrecht	Geen	Geen	Geen	Geen	Geen	Geen	01-08-2025	Geen restricties
Dr. M.E.J. (Mirjam) van Velthoven	Oogarts, uveitis specialist - Oogziekenhuis, Rotterdam : betaald	Waarnemend voorzitter infectiepreventie commissie Oogziekenhuis	Sprekersvergoeding van Roche (2024), Bayer (2025), onderwerpen anders dan uveitis; in 2023 presentatie voor Canon over OCT beeldvorming (niet vergoed).	Geen	1. RCT: Association of retinal structural features with angiographic abnormalities in Behcet's disease (Financier Roche, SWOO, RSB) 2. Detection of perifoveal microvascular changes in Behçet Disease measured with OCT-A (Financier Roche, SWOO, RSB)	Geen	Geen	01-08-2025	Geen restricties. Onderwerp van commercieel gefinancierd onderzoek niet gerelateerd aan richtlijn.

P. (Pauline) de Heer	Strategisch adviseur bij Zorginstituut Nederland Adviseren over passende zorg, duurzaamheid, maatschappelijke opgaven, signalering en agendering.	Geen	Geen	Geen	Geen	Geen	Geen	08-04-2025	Geen resticties

Kwalitatieve raming van mogelijke financiële gevolgen in het kader van de Wkkgz

Bij de richtlijnmodule voerden de clusterleden conform de Wet kwaliteit, klachten en geschillen zorg (Wkkgz) een kwalitatieve raming uit om te beoordelen of de aanbevelingen mogelijk leiden tot substantiële financiële gevolgen. Bij het uitvoeren van deze beoordeling is de richtlijnmodule op verschillende domeinen getoetst (zie het stroomschema bij Werkwijze).

Module	Uitkomst raming	Toelichting
Module behandeling met ontstekingsprofylaxe cataract chirugie bij uveits	Geen financiële gevolgen	Hoewel uit de toetsing volgt dat de aanbeveling(en) breed toepasbaar zijn (5.000-40.000 patiënten), volgt ook uit de toetsing dat [het overgrote deel (±90%) van de zorgaanbieders en zorgverleners al aan de norm voldoet

Bijlage 6 literatuursamenvatting module 3 - Ontstekingsprofylaxe cataractchirurgie bij uveitispatiënten

Leeswijzer: de voorliggende tekst wordt als nieuwe module toegevoegd aan de richtlijn uveitis.

Introduction (English)

Cataract surgery carries a risk of postoperative inflammation, synechiae formation and cystoid macular edema (CME). To reduce this risk, the prophylactic use of corticosteroid eye drops and nonsteroidal anti-inflammatory drugs (NSAIDs) after cataract surgery is recommended. Patients with a history of non-infectious uveitis have an increased likelihood of postoperative complications and a higher risk of uveitis recurrence, vitreous membranes, cocoon formation around the intra-ocular lens (IOL). Therefore, adequate anti-inflammatory prophylaxis and mydriatic eye drops is essential in this patient population. However, the optimal anti-inflammatory regimen for cataract surgery in patients with a history of non-infectious uveitis remains unclear. The choice of prophylactic strategy depends on several factors, control of inflammation and current treatment with csDMARDs and bDMARDs. It is possible that these patients may benefit from a less intensive perioperative prophylactic regimen.

Search and select

A systematic review of the literature was performed to answer the following question(s):
What is the efficacy and safety of orbital, peri-ocular and topical corticosteroids compared with systemic corticosteroids in adult patients with non-infectious uveitis inactive for 3 months undergoing cataract surgery?

Table 2. PICO

Patients	Patients >18y with non-infectious uveitis (inactive for 3 months) undergoing cataract surgery • Subgroup: patients with non-infectious uveitis undergoing cataract surgery and under treatment with adalimumab or tocilizumab
Intervention	Intravitreal/parabulbar/peri-ocular/topical corticosteroids: triamcinolone parabulbar 40 mg (= kenacort), triamcinolone intravitreal 4 mg, celestone chronodose, dexamethason intravitreal implant (= ozurdex), fluocinolonacetenoide implant (= Illuvien).
Control	Systemic corticosteroids (prednisone)
Outcomes	Postoperative inflammation (cells in anterior chamber, tyndall/flare), cystoid macular edema after 4-6 weeks, 3 months, posterior synechiae, complications of medication (e.g. posterior capsule opacification), glaucoma
Other selection criteria	Study design: systematic reviews and randomized controlled trials

<u>Relevant outcome measures</u>

The guideline panel considered postoperative inflammation as a **critical** outcome measure for decision making; and cystoid macular edema (CME) and (ocular) complications as an **important** outcome measure for decision making.

A priori, the guideline panel did not define the outcome measures listed above but used the definitions used in the studies.

The guideline panel defined a mean difference (MD) of 10% for continuous outcomes, a relative risk (RR) <0.80 or >1.25 for dichotomous outcomes, and a risk difference (RD) of 25% for dichotomous outcomes with a few events, as a minimal clinically (patient) important difference.

<u>Search and select (Methods)</u>

A systematic literature search was performed by a medical information specialist using the following bibliographic databases: Embase.com and Ovid/Medline. Both databases were searched from 2005

to July 28, 2025 for systematic reviews and RCTs. Systematic searches were completed using a combination of controlled vocabulary/subject headings (e.g., Emtree-terms, MeSH) wherever they were available and natural language keywords. The overall search strategy was derived from the following primary search concepts: (1) cataract surgery; (2) uveitis; (3) inflammation prophylaxis. Duplicates were removed using EndNote software. After deduplication a total of 423 records were imported for title/abstract screening. Initially, 9 studies were selected based on title and abstract screening. After reading the full text, 3 studies were excluded (see the exclusion table under the tab 'Evidence tabellen'), and 4 studies were included.

Summary of literature

Description of studies

A total of one systematic review (including two relevant RCTs) and three additional RCTs were included in the analysis of the literature. Important study characteristics and results are summarized in table 2. The assessment of the risk of bias is summarized in the risk of bias tables (under the tab 'Evidence tabellen').

Hsieh (2023) performed a systematic review (SR) and meta-analysis (MA) in which the aim was to compare the effects of intravitreal corticosteroids with systemic anti-inflammatory agents in patients with uveitis who underwent cataract surgery. Randomized controlled trials (RCTs), comparative cohort studies and case-control studies comparing intraoperative intravitreal injection of corticosteroid or steroid implant with systemic steroid with or without immunomodulatory therapy (IMT) among patients with infectious or non-infectious uveitis were included. This SR finally included 5 studies (Dada, 2007; Gupta, 2013; Gupta, 2019; Roesel, 2008; Belair, 2009), of which 2 RCTs were considered relevant for the purpose of this guideline (Dada, 2007; Gupta, 2013. The studies of Belair (2009) and Roesel (2008) were not relevant, because the respective study design did not match the pre-defined selection criteria of this guideline. Gupta (2019) was not considered relevant because the interventions did not match the predefined PICO. The databases of PubMed, EMBASE, and Cochrane Library were searched from inception through May 2021.

Jamil (2024), published after the search date of Hsieh (2023), performed an RCT comparing the effects of intravitreal injection of 4 mg triamcinolone acetonide (TA) with 0.5 mg/kg/day of oral prednisolone. This RCT was conducted at Layton Rahmatulla Benevolent Trust Tertiary Teaching Eye Hospital in Karachi. Patients with a diagnosis of uveitis according to SUN criteria were included, as well as uveitis patients with quiescent inflammation for at least 3 months prior to cataract surgery. In this group, 5/19 cases in the intervention group and 5/19 cases in the control group had infectious uveitis.

Sudhalkar (2020) was not included in the SR and MA of Hsieh (2023) (reason is unclear), but did match the PICO of this guideline and was therefore considered relevant. The aim of this RCT was to compare the effects of the intravitreal dexamethasone implant (Ozurdex) with systemic corticosteroids among patients with non-infectious uveitis. This study was conducted at the Raghudeep Eye Hospital, Ahmedabad, India. Adult patients aged 18y or older, with a diagnosis of previous unilateral recurrent noninfectious intermediate uveitis or posterior uveitis with cystoid macular edema and cataract of sufficient degree to warrrant surgery, with well-controlled uveitis for at least 3 months prior to surgery, were included in the trial.

Roesel (2010) was not included in the SR and MA of Hsieh (2023) (reason unclear), but it did match the PICO of this guideline and was therefore considered relevant. The aim of this RCT was to compare the effects of a single intraoperative orbital floor TA injection with 4-week postoperative oral prednisolone in patients with chronic non-infectious uveitis undergoing cataract surgery. The RCT was a monocentric study. Eligible patients for inclusion were patients suffering from non-

infectious uveitis and vision-impairing lens opacification, with quiescence of inflammation for at least 3 months prior to cataract surgery.

Table 2. Characteristics of included studies

Study	Participants	Comparison	Follow-up	Outcome measures	Comments	Risk of bias (per outcome measure)*
Included in systematic review Hsieh, 2023						
Dada, 2007 (RCT)	N at baseline Intervention: 20 eyes Control: 20 eyes Age (mean, SD) Intervention: 34.85y (no SD reported) Control: 34.95y (no SD reported) Sex *Total population* Male: 47.5%	Intervention: Intraoperatively intravitreal injection of preservative-free Triamcinolone Acetonide (TA) Aurocort), 4 mg in 0.1 mL; no systemic steroids were given in the postoperative period. Control: Postoperative oral prednisolone 1 mg/kg body weight/day for 2 weeks, subsequently tapered over 6 weeks	6 months	Postoperative anterior chamber cells and flares at day 30 (4 wk) and day 180 (6 months) Uveitis recurrence Postoperative central macular edema development (%)	No financial disclosures	High *Due to problems with blinding of participants and personnel (performance bias)*
Gupta, 2013 (RCT)	N at baseline Intervention: 10 eyes Control: 10 eyes *3/10 cases in implant group and 4/10 cases in steroid group are infectious uveitis* Age (mean, SD) Intervention: 42.80y (SD 16.24) Control: 44.90y (SD 11.50) Sex *Total population* Male: 15%	Intervention: Intraoperative 0.7 mg dexamethasone intravitreal implant (Ozurdex). Control: Postoperative oral steroids (prednisolone 1 mg/kg) as a tapering dose, which was reduced per week and stopped by the end of 8 weeks.	6 months	Uveitis recurrence Postoperative central macular edema development (%)	No conflicts of interest	High *Due to problems with blinding of participants and personnel (performance bias)*
Individual studies						
Jamil, 2024 (RCT)	N at baseline Intervention: 20 patients Control: 20 patients	Intervention: Intraoperatively intravitreal injection of 4 mg TA.	3 months	Postoperative inflammation at 4 wk and 12 wk	No conflict of interest reported and no funding associated with the work featured	HIGH (all outcomes)

	5/19 cases in the intervention group and 5/19 cases in the control group is infectious uveitis Age (mean, SD) Intervention: 45.21y (SD 8.90) Control: 44.95y (10.80) Sex Intervention: 57.9% male Control: 42.1% male Immunosuppressive therapy Intervention: 42.1% Control: 47.4%	Control: Peri-operative oral steroids (prednisolone 0.5 mg/kg/day, commencing 5 days before surgery, for 2 weeks and tapered over 6 weeks).		Uveitis recurrence Cystoid macular edema development (%) Posterior synechiae Systemic adverse effects Posterior capsule opacification (PCO) = complication		
Sudhalkar, 2020 (RCT)	N at baseline Intervention: 20 patients Control: 23 patients Age (median, SD) Intervention: 47.3y (SD 4.23) Control: 49.12y (SD 5.32) Sex (m/f) Intervention: 9/11 Control: 10/13	Intervention: Intravitreal dexamethasone implant (Ozurdex) + postoperative topical prednisolone drops + cycloplegic therapy + nepafenac eye drops Control: Systemic corticosteroids, beginning 2 days prior to surgery tapered over 3-4 weeks (oral prednisolone, 1 mg/kg body weight/day)	6 months	Postoperative cystoid macular edema Complications	Grant support and study injections were received for the intervention from Allergan India Pvt. Ltd, the marketers and distributors of the intravitreal dexamethasone implant (Ozurdex, Allergan, Irvine,CA). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript	High (all outcomes)
Roesel, 2010	N at baseline Intervention: 20 Control: 20 Age (mean, SD) Intervention: 40.5y (SD 13.68) Control: 46.5y (SD 13.43) Sex (m/f)	Intervention: Intraoperative orbital floor TA, 1 ml (40mg) (parabular) Control: 4-wk postoperative oral prednisolone	6 months	Postoperative inflammation (flare, anterior chamber cells) Cystoid macular edema Posterior capsule opacification (PCO)	No financial interest reported in any of the reagents used in the study	HIGH (all outcomes)

	Intervention: 93/39 Control: 30/9					

*For further details, see risk of bias table in supplementary data 6 of the systematic review by Hsieh (2023)

Results

The results were subdivided in Three subcomparisons:

- *Comparison 1: **Intravitreal injection** of Triamcinolone Acetonide (TA) compared to oral prednisolone. Two studies were included: Dada (2007) and Jamil (2024)*
- *Comparison 2: **Intravitreal implant** of dexamethasone versus oral prednisolone. Two studies were included Gupta, (2013), Sudhalkar (2020)*
- *Comparison 3: **Parabulbair Triamcinolone Acetonide** compared to oral prednisolone. One study was included Roesel (2010)*

Per subcomparison the results on the different predefined outcomes (postoperative inflammation; cystoid macular edema and complications) were presented.

COMPARISON 1: INTRAVITREAL INJECTION TRIAMCINOLONE ACETONIDE VS ORAL PREDNISOLONE

Postoperative inflammation (crucial)

One RCT included in the SR and MA of Hsieh (2023) and two individual RCTs reported the outcome postoperative inflammation (Dada, 2007; Jamil, 2024). Postoperative inflammation was reported as 'uveitis recurrence', and 'anterior chamber cell and flare' in the various studies.

Uveitis recurrence

Two RCTs reported the outcome uveitis recurrence (Dada, 2007; Jamil, 2024). Uveitis recurrence was defined according to SUN criteria. In the study of Dada (2007), 4/20 (20%) patients in the TA group developed a uveitis recurrence, compared to 5/20 (25%) patients in the steroid group during 6 months of follow-up. This corresponded to a calculated RR of 0.80 (95% CI, 0.25 to 2.55), which is not clinically relevant. In the study of Jamil (2024), none of the patients in each group developed a uveitis recurrence during 3 months of follow-up.

Anterior chamber cell at 1 month follow-up

In the RCT of Dada (2007), the mean anterior chamber cell grading was 0.3 (SD 0.5) in the TA group compared to 0.6 (SD 0.7) in the steroid group at 1 month follow-up. This corresponded to a calculated MD of 0.30 lower (95% CI, 0.68 lower to 0.08 higher) in the TA group, which is not clinically relevant.

Jamil (2024) reported that 19/19 (100%) patients in the TA group had 0 or +0.5 anterior chamber cells compared to 16/19 (84.2%) patients in the oral steroid group. This corresponded to a calculated RR of 1.18 (95% CI 0.95 to 1.46), in favor of the TA group, but not clinically relevant.

Anterior chamber cell at 3 months follow-up

In the RCT of Dada (2007), the mean anterior chamber cell grading was 0.2 (SD 0.6) in the TA group compared to 0.1 (SD 0.3) in the steroid group at 3 months follow-up. This corresponded to a calculated MD of 0.10 higher (95% CI, 0.19 lower to 0.39 higher) in the TA group, which is not clinically relevant.

Jamil (2024) reported that 19/19 (100%) patients in the TA group had 0 or +0.5 anterior chamber cells compared to 18/19 (94.7%) patients in the oral steroid group. This corresponded to a calculated RR of 1.05 (95% CI 0.91 to 1.22), which is not clinically relevant.

Anterior chamber flare at 1 month follow-up

In the RCT of Dada (2007), the mean anterior chamber flare was 0.7 (SD 0.6) in the TA group compared to 1.0 (SD 0.6) in the steroid group at 1 month follow-up. This corresponded to a calculated MD of 0.30 lower (95% CI, 0.67 lower to 0.07 higher) in the TA group, which is not clinically relevant.

Jamil (2024) reported that 18/19 (94.7%) patients in the TA group had 0 or +0.5 anterior chamber flare compared to 12/19 (63.2%) patients in the oral steroid group. This corresponded to a calculated RR of 1.50 (95% CI, 1.05 to 2.15), in favor of the TA group, and clinically relevant.

Anterior chamber flare at 3 months follow-up
In the RCT of Dada (2007), the mean anterior chamber flare was 0.5 (SD 0.7) in the TA group compared to 0.35 (SD 0.5) in the steroid group at 3 months follow-up. This corresponded to a calculated MD of 0.15 higher (95% CI, 0.23 lower to 0.53 higher) in the TA group, which is not clinically relevant.

Jamil (2024) reported that 19/19 (100%) patients in the TA group had 0 or +0.5 anterior chamber flare compared to 18/19 (94.7%) patients in the oral steroid group. This corresponded to a calculated RR of 1.05 (95% CI, 0.91 to 1.22), which is not clinically relevant.

Cystoid macular edema (important)
One RCT included in the SR of Hsieh (2023) and one individual RCT reported the outcome cystoid macular edema (CME) (Dada, 2007; Jamil, 2024).

In the RCT of Dada (2007), CME occurred in 1/20 (5%) patients in the TA group at 3 months follow-up compared to 3/20 (15%) patients in the oral steroids group after 3-6 months follow-up. This corresponded to a calculated RD of 10% lower (95% CI, 28% lower to 8% higher) in the TA group, which is not clinically relevant. In the RCT of Jamil (2024), none of the patients in both groups developed postoperative CME.

Complications (important)
Posterior synechiae
The study of Dada (2007) did not report this specific complication. The study of Jamil (2024) reported posterior synechiae at baseline only.

Posterior capsule opacification (PCO)
One study reported the complication PCO (Jamil, 2024). In the study of Jamil (2024), none of the patients in both groups developed PCO.

Intraocular hypertension/glaucoma
One RCT included in the SR and MA of Hsieh (2023) and one individual RCT reported the outcome intraocular hypertension (Dada, 2007; Jamil, 2024). Dada (2007) and Jamil (2024) used a definition of >21 mmHg.

In the RCT of Dada (2007), intraocular hypertension occurred in 5/20 (25%) patients in the TA group at 2 weeks to 3 months follow-up compared to 1/20 (5%) patients in the oral steroids group after 6 months follow-up. This corresponded to a calculated RD of 20% higher (95% CI, 1% lower to 41% higher) in the TA group, which is not clinically relevant. In the RCT of Jamil (2024), 0/19 (0%) patients in the TA group developed intraocular hypertension compared to 5/19 (26.3%) patients in the oral steroids group.

COMPARISON 2: INTRAVITREAL IMPLANT DEXAMETHASONE VS ORAL PREDNISOLONE

Postoperative inflammation (crucial)
Uveitis recurrence

One RCT reported the outcome uveitis recurrence (Gupta, 2013). Uveitis recurrence was defined according to SUN criteria. In the study of Gupta (2013), none of the patients in each group developed a uveitis recurrence during 1 year of follow-up (0/14 and 0/16 patients respectively).

Anterior chamber inflammation (at 1 week and at 3 months)
One RCT included in the SR of Hsieh (2023) reported the outcome postoperative inflammation, but absolute numbers were not reported (Gupta, 2013). The study reported the following: "*Anterior chamber inflammation decreased progressively in both the groups in a similar pattern. At the end of 1 week, anterior chamber inflammation reduced in both groups and the anterior chamber was quiet in both groups at 3 months. One eye in the steroid group developed severe postoperative anterior chamber inflammation with fibrin. The case was kept under close follow-up and managed with intensive topical steroids*." Because absolute data were lacking, a GRADE assessment for this outcome could not be performed.

Cystoid macular edema (important)
One RCT included in the SR and MA of Hsieh (2023) reported the outcome cystoid macular edema (CME) (Gupta, 2013). In total, 1/10 (10%) patients in the dexamethasone implant group compared to 1/10 (10%) patients in the oral steroids group developed postoperative CME at 3-6 months follow-up. The calculated RD of CME was 0% (95% CI, 26% lower to 26% higher), which is not clinically relevant.

In the study of Sudhalkar (2020), 1/20 (5%) patients in the dexamethasone implant group compared to 2/23 (8.7%) patients in the oral steroids group developed postoperative CME at 3 months follow-up. This corresponded to a calculated RD of 4% lower (95% CI, 19% lower to 11% higher) in the dexamethasone + topical steroids group, which is not clinically relevant.

Complications (important)
Posterior synechiae
The complication posterior synechiae was not reported.

Anterior capsule opacification (ACO)
The study of Gupta (2013) reported the following about the complication ACO: "Visual acuity of less than 20/40 was found in only 3 of the 20 patients at the final follow-up visit. Two patients (2 eyes) had an epiretinal membrane, while the other developed anterior capsular opacification for which the patient underwent surgical capsulotomy and regained good vision (6/9)." A GRADE assessment for this outcome could not be performed, because it was not clear in which group the anterior capsular opacification occurred.

Intraocular hypertension
One RCT included in the SR and MA of Hsieh (2023) reported the complication intraocular hypertension (defined as IOP >21 mmHg) (Gupta, 2013). In the study of Gupta (2013), 2/10 (20%) patients in the dexamethasone group compared to 3/10 (30%) patients in the oral steroids group had intraocular hypertension after 3 months follow-up. This corresponded to a calculated RD of 10% lower (95% CI, 48% lower to 28% higher) in the dexamethasone group, which is not clinically relevant.

In the study of Sudhalkar (2020), 4/20 (20%) patients in the dexamethasone + topical steroids group compared to 0/23 (0%) patients oral steroids group developed intraocular hypertension (defined as >25 mmHg) at 1-2 months follow-up. This corresponded to a calculated RD of 20% higher (95% CI, 2% higher to 38% higher), in favor of the oral steroids + IMT group, which is not clinically relevant.

COMPARISON 3: PARABULBAR TRIAMCINOLONE ACETONIDE COMPARED TO ORAL PREDNISOLONE

Postoperative inflammation (crucial)

Anterior chamber cell at 1 month follow-up.

Roesel (2010) reported that 15/20 (75%) patients in the TA group had 0 or +0.5 anterior chamber cells compared to 13/20 (65%) patients in the oral steroid group. This corresponded to a calculated RR of 1.15 (95% CI 0.77 to 1.74), in favor of the TA group, but not clinically relevant.

Anterior chamber cell at 3 months follow-up

Roesel (2010) reported that 16/20 (80%) patients in the TA group had 0 or +0.5 anterior chamber cells compared to 11/20 (55%) patients in the oral steroid group. This corresponded to a calculated RR of 1.45 (95% CI 0.92 to 2.29), in favor of the TA group, and clinically relevant.

Anterior chamber flare at 1 month follow-up

Roesel (2010) reported that the mean LFP was 31.9 Ph/s (SD 15.8) in the TA group compared to 26.9 (SD 17.3) in the oral steroid group. This corresponded to a calculated MD of 5.00 Ph/s higher (95% CI, 5.27 lower to 15.27 higher), in favor of the oral steroids group, but not clinically relevant.
Pre-operative the mean LFP before surgery was 24.6 (SD 10.7) in the TA group and 25.1 (SD 14.3) in the oral prednisolone group.

Anterior chamber flare at 3 months follow-up

Roesel (2010) reported that the mean LFP was 27.5 Ph/s (SD 13.9) in the TA group compared to 32.2 Ph/s (SD 23.0) in the oral steroid group. This corresponded to a calculated MD of 4.70 Ph/s lower (95% CI, 16.48 lower to 7.08 higher), in favor of the TA group, but not clinically relevant
Pre-operative the mean LFP before surgery was 24.6 (SD 10.7) in the TA group and 25.1 (SD 14.3) in the oral prednisolone group.

Cystoid macular edema (important)

In the RCT of Roesel (2010), CME occurred in 12/20 (60%) patients in the TA group compared to 12.8/20 (64%) patients in the oral steroids group at 3 months follow-up. This corresponded to a calculated RD of 5% lower (95% CI, 35% lower to 25% higher) in the TA group (Figure 3), which is not clinically relevant

Complications (important)

Posterior synechiae

In the study of Roesel (2010), 0/20 (0%) patients in the TA group compared to 1/20 (5%) patients in the steroid group, developed postoperative posterior synechiae. This corresponded to a calculated RD of 5% lower (95% CI, 18% lower to 8% higher) in the TA group, which is not clinically relevant.

Posterior capsule opacification (PCO)

In the study of Roesel (2010), 14.2/20 (71%) patients in the TA group compared to 15.4/20 (77%) patients in the oral steroids group, developed PCO after 6 months follow-up. This corresponded to a calculated RD of 5% lower (95% CI, 33% lower to 23% higher) in the TA group, which is not clinically relevant.

Intraocular hypertension/glaucoma

In the RCT of Roesel (2010), intraocular hypertension occurred in 2/20 (12%) patients in the TA group compared to 5/20 (25%) patients in the oral steroids group at 6 months follow-up. This corresponded to a calculated RD of 15% lower (95% CI, 38% lower to 8% higher) in the TA group (Figure 4), which is not clinically relevant.

In one study only, the outcome glaucoma surgery was reported (Roesel, 2010). In this study, 0/20 (0%) patients in the TA group compared to 3/20 (15%) patients in the oral steroids group required glaucoma surgery. This corresponded to a calculated RD of 15% lower (95% CI, 32% lower to 2% higher) in the TA group, which is not clinically relevant.

Summary of Findings

COMPARISON 1: INTRAVITREAL INJECTION TRIAMCINOLONE ACETONIDE VS ORAL PREDNISOLONE

Population: Patients with non-infectious uveitis requiring cataract surgery
Intervention: Intravitreal injection of triamcinolone acetonide
Comparator: Oral prednisolone

Outcome Timeframe	Study results and measurements	Absolute effect estimates Intravitreal injection TA — Oral prednisolone	Certainty of the evidence (Quality of evidence)	Summary
Postoperative inflammation				
Uveitis recurrence 6 months	Based on data from 120 participants in 2 studies Follow-up 3-6 months	• RR of 0.80 (95% CI, 0.25 to 2.55) (Dada, 2007) • None of the patients developed uveitis recurrence (Jamil, 2024)	Very low Due to serious risk of bias, Due to very serious imprecision[1]	The evidence is very uncertain about the effect of intravitreal injection of TA on uveitis recurrence after 6 months follow-up when compared with oral prednisolone in patients with non-infectious uveitis requiring cataract surgery. *(Dada, 2007; Jamil, 2024)*
Anterior chamber cell 1 month	Based on data from 120 participants in 2 studies Follow up 1 month	• Cell: MD of 0.30 lower (95% CI, 0.68 lower to 0.08 higher) (Dada, 2007) • 0 or +0.5 cells: RR of 1.18 (95% CI, 0.95 to 1.46) (Jamil, 2024)	Low Due to serious risk of bias, due to serious imprecision[2]	The evidence suggests that an intravitreal injection of TA does not reduce of increase postoperative inflammation (anterior chamber cell) at 1 month, when compared with oral prednisolone in patients with non-infectious uveitis requiring cataract surgery. *(Dada, 2007; Jamil, 2024)*
Anterior chamber cell 3 months	Based on data from 120 participants in 2 studies Follow up 3 months	• Cell: MD of 0.10 higher (95% CI 0.19 lower to 0.39 higher) (Dada, 2007) • 0 or +0.5 cells: RR of 1.05 (95% CI, 0.91 to 1.22) (Jamil, 2024)	Low Due to serious risk of bias, due to serious imprecision[2]	The evidence suggests that an intravitreal injection of TA does not reduce of increase postoperative inflammation (anterior chamber cell) at 3 months, when compared with oral prednisolone in patients with non-infectious uveitis requiring cataract surgery. *(Dada, 2007; Jamil, 2024)*
Anterior chamber flare 1 month	Based on data from 120 participants in 2 studies	• Flare: MD of 0.30 lower (95% CI, 0.67 lower to	Very low	The evidence is very uncertain about the effect of intravitreal injection of TA on anterior chamber flare after 1 month follow-up when

	Follow up 1 month	0.07 higher) (Dada, 2007) • 0 or 0.5+ flare: RR of 1.50 (95% CI, 1.05 to 2.15) (Jamil, 2024)	Due to serious risk of bias, due to serious inconsistency, due to serious imprecision[3]	compared with oral prednisolone in patients with non-infectious uveitis requiring cataract surgery. *(Dada, 2007; Jamil, 2024)*
Anterior chamber flare 3 months	Based on data from 120 participants in 2 studies Follow up 3 months	• Flare: MD of 0.15 higher (95% CI, 0.23 lower to 0.53 higher) (Dada, 2007) • 0 or 0.5+ flare: RR of 1.05 (95% CI, 0.91 to 1.22) (Jamil, 2024)	Low Due to serious risk of bias, due to serious imprecision[2]	The evidence suggests that an intravitreal injection of TA does not reduce of increase postoperative inflammation (anterior chamber flare at 3 months), when compared with oral prednisolone in patients with non-infectious uveitis requiring cataract surgery. *(Dada, 2007; Jamil, 2024)*
Cystoid macular edema				
Cystoid macular edema 3-6 months	Based on data from 120 participants in 2 studies Follow up 3-6 months	• RD of 10% lower (95% CI, 28% lower to 8% higher (Dada, 2007) • No CME in both groups (Jamil, 2024)	Low Due to serious risk of bias, due to serious imprecision[2]	The evidence suggests that an intravitreal injection of TA does not reduce of increase cystoid macular edema when compared with oral prednisolone in patients with non-infectious uveitis requiring cataract surgery. *(Dada, 2007; Jamil, 2024)*
Complications				
Posterior capsule opacification (PCO) 6 months	Based on data from 80 participants in 1 study Follow up 6 months	• No PCO development in both groups (Jamil, 2024)	Low Due to serious risk of bias, Due to serious imprecision[4]	The evidence suggests that an intravitreal injection of TA does not reduce of increase PCO, when compared with oral prednisolone in patients with non-infectious uveitis requiring cataract surgery. *(Jamil, 2024)*
Intraocular hypertension 6 months	Based on data from 118 participants in 2 studies Follow up 6 months	• RD of 20% higher (95% CI, 1% lower to 41% higher) (Dada, 2007) • RD of 26% lower (95% CI, 47% lower to 6% lower) (Jamil, 2024)	Very low Due to serious risk of bias, Due to serious inconsistency, Due to very serious imprecision[5]	The evidence is very uncertain about the effect of intravitreal injection of TA on intraocular hypertension after 6 months follow-up when compared with oral prednisolone in patients with non-infectious uveitis requiring cataract surgery. *(Dada, 2007; Jamil, 2024)*

8. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; **Imprecision: very serious**. Due to overlap of the 95% CI with both limits of clinical relevance;
9. **Risk of Bias**: serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; **Imprecision: serious**. Due to overlap of the 95% CI with one limit of clinical relevance;
10. **Risk of Bias**: serious. Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Inconsistency: serious**. The direction of the effect is not consistent between the included studies; **Imprecision: serious**. Due to overlap of the 95% CI of both studies with one limit of clinical relevance;
11. **Risk of Bias**: serious. Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision**: serious. Due to low sample size (<100);
12. **Risk of Bias**: serious. Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Inconsistency**: serious. The direction of the effect is not consistent between the included studies; **Imprecision**: very serious. Due to overlap of the 95% CI with the both limits of clinical relevance

COMPARISON 2: INTRAVITREAL IMPLANT DEXAMETHASONE VS ORAL PREDNISOLONE

Population: Patients with (non-)infectious uveitis requiring cataract surgery
Intervention: Dexamethasone implant
Comparator: Oral prednisolone

5

Outcome Timeframe	Study results and measurements	Absolute effect estimates Intravitreal implant dexamethasone	 Oral prednisolone	Certainty of the evidence (Quality of evidence)	Summary
Postoperative inflammation					
Uveitis recurrence 12 months	Based on data from 30 participants in 1 study Follow up 12 months	*"none of the patients in each group developed a uveitis recurrence during 1 year of follow-up (0/14 and 0/16 patients)"*		No GRADE (lack of data)	Due to lack of data, a GRADE assessment for the outcome anterior chamber inflammation could not be performed. *(Gupta, 2013)*
Anterior chamber inflammation 3 months	Based on data from 20 participants in 1 study Follow up 3 months	*"Anterior chamber inflammation decreased progressively in both the groups in a similar pattern. At the end of 1 week, anterior chamber inflammation reduced in both groups and the anterior chamber was quiet in both groups at 3 months. One eye in the steroid group developed severe postoperative anterior chamber inflammation with fibrin. The case was kept under close follow-up and managed with intensive topical steroids"*		No GRADE (lack of data)	Due to lack of data, a GRADE assessment for the outcome anterior chamber inflammation could not be performed. *(Gupta, 2013)*
Cystoid macular edema					
Cystoid macular edema 3-6 months	Based on data from 63 participants in 2 studies Follow up 3-6 months	• RD of 0% (95% CI, 26% lower to 26% higher) – Gupta (2013)		Very low Due to serious risk of bias, Due to very serious imprecision[1]	The evidence is very uncertain about the effect of a dexamethasone implant on cystoid macular edema after 3-6 months follow-up when

		• RD of 4% lower (95% CI, 19% lower to 11% higher) (Sudhalkar, 2020)		compared with oral prednisolone in patients with (non-)infectious uveitis requiring cataract surgery. *(Gupta, 2013; Sudhalkar 2020)*
Complications				
Posterior synechiae	-	-	No GRADE (outcome not reported)	No evidence was found regarding the effect of a dexamethasone implant on posterior synechiae when compared with oral prednisolone in patients with (non-)infectious uveitis requiring cataract surgery.
Anterior capsule opacification (ACO)	Based on data from 20 participants in 1 study	*"Visual acuity of less than 20/40 was found in only 3 of the 20 patients at the final follow-up visit. Two patients (2 eyes) had an epiretinal membrane, while the other developed anterior capsular opacification for which the patient underwent surgical capsulotomy and regained good vision (6/9)"*	No GRADE (lack of data)	Due to lack of data, a GRADE assessment for the outcome anterior capsule opacification could not be performed. *(Gupta, 2013)*
Intraocular hypertension 3 months	Based on data from 63 participants in 2 study Follow up 3 months	• RD of 10% lower (95% CI, 48% lower to 28% higher) (Gupta, 2019) • RD of 20% higher (95% CI, 2% higher to 38% higher) (Sudhalkar, 2020)	Very low Due to serious risk of bias, Due to serious inconsistency, Due to very serious imprecision[2]	The evidence is very uncertain about the effect of a dexamethasone implant on intraocular hypertension after 3 months follow-up when compared with oral prednisolone in patients with (non-)infectious uveitis requiring cataract surgery. *(Gupta, 2013; Sudhalkar 2020)*

1. **Risk of Bias**: serious. No information about concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: very serious**. Due to overlap of the 95% CI with both limits of clinical relevance;
2. **Risk of Bias:** serious. Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Inconsistency**: serious. The direction of the effect is not consistent between the included studies;**Imprecision**: very serious. Due to overlap of the 95% CI with both limits of clinical relevance;

COMPARISON 3: PARABULBAR TRIAMCINOLONE ACETONIDE COMPARED TO PREDNISOLONE

Population: Patients with non-infectious uveitis requiring cataract surgery
Intervention: parabulbar triamcinolone acetonide (TA)
Comparator: oral prednisolone

5

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Summary
		Intravitreal implant dexamethason	Oral prednisolone		
Postoperative inflammation					
Uveitis recurrence 6 months	-	-		No GRADE (outcome not reported)	No evidence was found regarding the effect of a parabulbar TA on posterior synechiae when compared with oral prednisolone in patients with (non-)infectious uveitis requiring cataract surgery.
Anterior chamber cell 1 month	Based on data from 40 participants in 1 studies Follow up 1 month	0 or +0.5 cells: RR of 1.15 (95% CI, 0.77 to 1.74) (Roesel, 2010)		Very low Due to serious risk of bias, due to very serious imprecision[1]	The evidence is very uncertain about the effect of intravitreal injection of TA on anterior chamber cells after 1 month follow-up when compared with oral prednisolone in patients with non-infectious uveitis requiring cataract surgery. *(Roesel, 2010)*
Anterior chamber cell 3 months	Based on data from 40 participants in 1 study Follow up 3 months	0 or +0.5 cells: RR of 1.45 (95% CI, 0.92 to 2.29) (Roesel, 2010)		Very low Due to serious risk of bias, due to very serious imprecision[1]	The evidence is very uncertain about the effect of intravitreal injection of TA on anterior chamber cells after 3 months follow-up when compared with oral prednisolone in patients with non-infectious uveitis requiring cataract surgery. *(Roesel, 2010)*
Anterior chamber flare 1 month	Based on data from 40 participants in 1 study Follow up 1 month	LFP: MD of 5.00 Ph/s higher (95% CI, 5.27 lower to 15.27 higher) (Roesel, 2010)		Very low Due to serious risk of bias, due to very serious imprecision[2]	The evidence is very uncertain about the effect of intravitreal injection of TA on anterior chamber flare after 1 month follow-up when compared with oral prednisolone in patients with non-infectious uveitis requiring cataract surgery. *(Roesel, 2010)*

Anterior chamber flare 3 months	Based on data from 40 participants in 1 study Follow up 3 months	LFP: 4.70 Ph/s lower (95% CI, 16.48 lower to 7.08 higher) (Roesel, 2010)	Very low Due to serious risk of bias, due to very serious imprecision[1]	The evidence is very uncertain about the effect of intravitreal injection of TA anterior chamber flare after 3 months follow-up when compared with oral prednisolone in patients with non-infectious uveitis requiring cataract surgery. *(Roesel, 2010)*
Cystoid macular edema				
Cystoid macular edema 3-6 months	Based on data from 40 participants in 1 study Follow up 3-6 months	RD of 5% lower (95% CI, 35% lower to 25% higher) (Roesel, 2010)	Very low Due to serious risk of bias, due to very serious imprecision[1]	The evidence is very uncertain about the effect of intravitreal injection of TA on cystoid macular edema after 3-6 months follow-up when compared with oral prednisolone in patients with non-infectious uveitis requiring cataract surgery. *(Roesel, 2010)*
Complications				
Posterior synechiae 6 months	Based on data from 40 participants in 1 study Follow-up 6 months	RD of 5% lower (95% CI, 18% lower to 8% higher) (Roesel, 2010)	Very low Due to serious risk of bias, due to very serious imprecision[1]	The evidence is very uncertain about the effect of intravitreal injection of TA on posterior synechiae after 6 months follow-up when compared with oral prednisolone in patients with non-infectious uveitis requiring cataract surgery. *(Roesel, 2010)*
Posterior capsule opacification (PCO) 6 months	Based on data from 40 participants in 1 study Follow up 6 months	RD of 5% lower (95% CI, 33% lower to 23% higher) (Roesel, 2010)	Very low Due to serious risk of bias, due to very serious imprecision[1]	The evidence is very uncertain about the effect of intravitreal injection of TA on posterior capsule opacification after 6 months follow-up when compared with oral prednisolone in patients with non-infectious uveitis requiring cataract surgery. *(Roesel, 2010)*
Intraocular hypertension 6 months	Based on data from 40 participants in 1 study Follow up 6 months	RD of 15% lower (95% CI, 38% lower to 8% higher) (Roesel, 2010)	Very low Due to serious risk of bias, due to very serious imprecision[1]	The evidence is very uncertain about the effect of intravitreal injection of TA on intraocular hypertension after 6 months follow-up when compared with oral prednisolone in patients with non-infectious uveitis requiring cataract surgery. *(Roesel, 2010)*

1. Risk of Bias: serious. Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Imprecision: very serious. Due to overlap of the 95% CI with the limit(s) of clinical relevance and the low sample size (<100);

Kennisvragen

Tijdens de ontwikkeling van deze module is gebleken dat er binnen deze module nog te weinig bewijs is voor de onderbouwing van de aanbeveling en dus kennisvragen bestaan. De werkgroep meent dat (vervolg)onderzoek wenselijk is om in de toekomst een duidelijker antwoord te kunnen geven op vragen uit de praktijk.

Kennisvraag:

> Wat is de aangewezen ontstekingsprofylaxe bij cataractchirurgie voor verschillende subgroepen uveitispatiënten, waaronder: patiënten met een eenmalige, milde en langdurig in remissie zijnde uveïtis versus patiënten met recidiverende of bilaterale uveïtis?

Toelichting:

Het is onduidelijk of voor alle uveitispatiënten, de ontstekingsprofylaxe er hetzelfde uit dient te zien. Voor veel subgroepen, vormt de beschreven anti-inflammatoire therapie mogelijk een overbehandeling en volstaat uitsluitend topicale behandeling. Het is onduidelijke voor welke groep de beschreven therapie een overbehandeling vormt, en wanneer over kan worden gegaan op uitsluitend topicale behandeling.

Implementeren-tabel

De implementatietabel brengt in kaart welke factoren de uitvoering van een aanbeveling bevorderen of belemmeren, en welke aanvullende acties nodig zijn voor succesvolle invoering. De adviseur en (cluster)werkgroep vullen de tabel in op basis van gerichte vragen over het onderliggende probleem, relevante randvoorwaarden en mogelijke knelpunten. Op basis hiervan wordt geconcludeerd of een extra implementatie-impuls wenselijk is.

Vraag	***Antwoord:*** *Kruis aan en licht toe/ beschrijf*		***Toelichting keuze:***
I1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?	**X**	**Ongewenste praktijkvariatie**	
		Nieuwe evidentie	
		Anders	
I2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?		**< 1000**	
		< 5000	
	X	**5000-40.000**	
		> 40.000	
I3. Is de aanbeveling onderdeel van een bredere set interventies of verwant aan andere richtlijnen of modules? Zo ja, hoe verhoudt zij zich daartoe en moet hiermee rekening worden gehouden bij de implementatie, of kan de aanbeveling als losstaand worden beschouwd?		**Ja**	
		Nee	
I4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:		**Belemmerende factoren**	**Bevorderende factoren/ kansen**
Richtlijn/ klinisch traject (innovatie)		Lage bewijskracht en onduidelijk welk middel de beste resultaten geeft.	Belangrijk dat er intensieve ontstekingsprofylaxe wordt gegeven. Verschillende manieren van toediening lijken geschikt.
Zorgverleners (artsen en verpleegkundigen)		Behandelkeuze vraagt om klinische ervaring en maatwerk.	Aanbeveling sluit grotendeels aan bij de huidige praktijk.
Patiënt/ cliënt (naasten)		Verschillende aanbevelingen voor verschillende subgroepen.	Samen beslissen, keuze kan worden afgestemd op voorkeuren van patiënt.
Sociale context		n.v.t	n.v.t
Organisatorische context		Beschikbaarheid van verschillende vormen van antiprofylaxe.	Aanbeveling sluit grotendeels aan bij de huidige praktijk.

Financiële en juridische context		Implantaten zijn duurder dan orale of parabulbaire therapie	Alle vormen van antiprofylaxe vallen binnen de verzekerde zorg.
I5. A) Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk? (kruis aan) **B) Wat is er nodig van deze personen/partijen om de aanbeveling in de praktijk te kunnen brengen?** *Denk aan aanpassingen in gedrag, werkwijzen, beleid, samenwerking of andere randvoorwaarden.*		**A**	**B**
		Patiënt/ cliënt (naaste)	
	X	Professional	Kennis van de richtlijn, gesprek met patiënt over verschillende opties. Samen beslissen.
	X	Beroepsvereniging, nl	Verspreiding van de richtlijn
		Ziekenhuis (raad van bestuur/UMCNL (voorheen NFU)/NVZ)	
	X	Zorgverzekeraars/ NZa	Voortzetten van vergoeding voor alle vormen van ontstekingsprofylaxe.
		Zorginstituut [duiding nodig]	
		Anders	
I6. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?	**X**	< 1 jaar	Aanbeveling sluit grotendeels aan bij huidige praktijk.
		binnen 2-3 jaar	
I7. Conclusie: is er extra actie en/of ondersteuning nodig voor implementatie van de aanbeveling? *De reguliere implementatieroutes (publicatie en disseminatie via officiele kanalen, opname in professionele standaarden, scholing en nascholing, gebruik van bestaande ICT systemen, audits en visitaties) van de richtlijnmodule alleen is onvoldoende.*		Ja	
	X	Nee	Aanbeveling sluit aan bij huidige praktijk.
I8. Plaatsing op de Landelijke Implementatieagenda Medisch Specialistische zorg is gewenst. *Het gaat om zorg die (grotendeels) wordt uitgevoerd binnen de ziekenhuismuren. Succesvolle implementatie vraagt om actieve betrokkenheid en samenwerking van meerdere relevante partijen binnen de zorgpraktijk.*		Ja *	
	X	Nee	

**Deze aanbeveling komt mogelijk in aanmerking voor plaatsing op de Landelijke Implementatieagenda van het programma Zorg Evaluatie & Gepast Gebruik (ZE&GG), waarin alle betrokken partijen in de medisch-specialistische zorg samenwerken aan de implementatie van bewezen beste zorg. De Federatie levert namens*

het veld goed onderbouwde aanbevelingen aan, die zijn getoetst op de behoefte aan een implementatie-impuls. De onderwerpen op de Implementatieagenda zijn onderdeel van landelijke zorginkoopafspraken tussen zorgverzekeraars en zorgaanbieders. Voor de beoordeling van aanbevelingen uit richtlijnen wordt gebruikgemaakt van de implementatietabel. Op basis hiervan kunnen we de andere partijen goed informeren en gezamenlijk besluiten of plaatsing op de Implementatieagenda passend is.

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Bijlagen bij module profylaxe cataract chirurgie bij uveitis

Risk of Bias tables

Study reference (first author, publication year)	**Was the allocation sequence adequately generated?** Definitely yes Probably yes Probably no Definitely no	**Was the allocation adequately concealed?** Definitely yes Probably yes Probably no Definitely no	**Blinding: Was knowledge of the allocated interventions adequately prevented?** **Were patients blinded?** **Were healthcare providers blinded?** **Were data collectors blinded?** **Were outcome assessors blinded?** **Were data analysts blinded?** Definitely yes Probably yes Probably no Definitely no	**Was loss to follow-up (missing outcome data) infrequent?** Definitely yes Probably yes Probably no Definitely no	**Are reports of the study free of selective outcome reporting?** Definitely yes Probably yes Probably no Definitely no	**Was the study apparently free of other problems that could put it at a risk of bias?** Definitely yes Probably yes Probably no Definitely no	**Overall risk of bias** **If applicable/necessary, per outcome measure** **LOW** **Some concerns** **HIGH**
Jamil, 2024	No information;	No information;	No information;	Definitely yes; Reason: All patients completed the 12-week follow-up. There was no missing data.	Definitely yes; Reason: All relevant outcomes were reported	Definitely yes; Reason: No other problems noted	**HIGH (all outcomes)** Reason: there is no information about allocation sequence generation, concealment of allocation and blinding.

Sudhalkar, 2020	Definitely yes; Reason: Randomization was achieved with the help of a random number table.	**Probably no;** Reason: The allocation list was not stored.	**Definitely no** Reason: The primary investigator and the data analyst were masked to both groups for data interpretation about photographs or imaging studies, IOP studies and visual acuity changes. Patients were not masked to the treatment.	No information	Definitely yes Reason: All relevant outcomes were reported;	Definitely yes; Reason: No other problems noted	**HIGH** (all outcomes) Reason: problems with allocation concealment and blinding
Roesel, 2010	No information	No information	**Probably no** Reason: Presence of CME was confirmed using a fluorescein angiography (FLA). FLA pictures were assessed by two masked observers. No information about blinding status of patients, data analysts and data collectors.	No information	Definitely yes Reason: All relevant outcomes were reported;	Definitely yes; Reason: No other problems noted	**HIGH (all outcomes)** Reason: lack of information about how randomization is conducted

For risk of bias assessment of the studies included in Hsieh (2023), see Hsieh (2023).

Table of excluded studies

Reference	Reason for exclusion
Bunjo LJ, Bacchi S, Pietris J, Chan WO. Current management options for the treatment of refractory postoperative cystoid macular edema: A systematic review. Surv Ophthalmol. 2024 Jul-Aug;69(4):606-621. doi: 10.1016/j.survophthal.2024.03.005. Epub 2024 Mar 14. PMID: 38490455.	Wrong population + no clear selection criteria for intervention and control
Roesel M, Tappeiner C, Heinz C, Koch JM, Heiligenhaus A. Comparison between intravitreal and orbital floor triamcinolone acetonide after phacoemulsification in patients with endogenous uveitis. Am J Ophthalmol. 2009 Mar;147(3):406-12. doi: 10.1016/j.ajo.2008.09.011. Epub 2008 Dec 3. PMID: 19054496.	Wrong comparator
Sen HN, Abreu FM, Louis TA, Sugar EA, Altaweel MM, Elner SG, Holbrook JT, Jabs DA, Kim RY, Kempen JH; Multicenter Uveitis Steroid Treatment (MUST) Trial and Follow-up Study Research Group. Cataract Surgery Outcomes in Uveitis: The Multicenter Uveitis Steroid Treatment Trial. Ophthalmology. 2016 Jan;123(1):183-90. doi: 10.1016/j.ophtha.2015.09.022. Epub 2015 Oct 20. PMID: 26499920; PMCID: PMC5554451.	Wrong outcome

Literature search strategy

Zoekverantwoording

Algemene informatie

Cluster/richtlijn: Cluster oog (2e cyclus)	
Uitgangsvraag/modules: UV5 Welke profylaxe dient bij een cataractoperatie gebruikt te worden bij patiënten met een niet-infectieuze uveitis in de voorgeschiedenis?	
Database(s): Embase.com, Ovid/Medline all	Datum: 28 juli 2025
Periode: vanaf 2005	Talen: geen restrictie
Literatuurspecialist: Alies Oost	Rayyan: https://new.rayyan.ai/reviews/1556817/screening
BMI-zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/	
Toelichting: Het sleutelartikel wordt gevonden met de search.	
Te gebruiken voor richtlijntekst: A systematic literature search was performed by a medical information specialist using the following bibliographic databases: Embase.com and Ovid/Medline all. Both databases were searched from 2005 to July 28th 2025 for systematic reviews and RCTs. Systematic searches were completed using a combination of controlled vocabulary and natural language keywords. The overall search strategy was derived from the following primary search concepts: (1) cataract surgery; (2) uveitis; (3) inflammation prophylaxis. Duplicates were removed using EndNote software. After deduplication a total of 423 records were imported for title/abstract screening.	

Zoekopbrengst

	EMBASE	OVID/MEDLINE	Ontdubbeld
SR	88	25	86
RCT	285	113	337
Totaal	373	138	**423***

in Rayyan

Zoekstrategie

Embase.com

No.	Query	Results
#1	'cataract'/exp OR 'cataract extraction'/exp OR ((lens* NEAR/2 opacit*):ti,ab,kw) OR cataract*:ti,ab,kw OR pseudophakia*:ti,ab,kw OR capsulorhexis:ti,ab,kw OR	136911

	capsulorrhexis:ti,ab,kw OR phacoemulsification*:ti,ab,kw OR 'phaco emulsification*':ti,ab,kw	
#2	'uveitis'/exp OR 'panuveitis':ti,ab,kw OR 'uveiti*':ti,ab,kw OR chorioretinitis:ti,ab,kw OR retinitis:ti,ab,kw OR scleritis:ti,ab,kw OR vitritis:ti,ab,kw OR iritis:ti,ab,kw OR iridocyclitis:ti,ab,kw OR 'pars planitis':ti,ab,kw OR chorioiditis:ti,ab,kw	105902
#3	'triamcinolone'/exp OR 'triamcinolone acetonide'/exp OR 'triamcinolon*':ti,ab,kw OR kenacort:ti,ab,kw OR 'betamethasone acetate plus betamethasone sodium phosphate'/exp OR ((betamethasone NEAR/6 acetate NEAR/6 phosphate):ti,ab,kw) OR (((celestene OR celestone) NEAR/3 (chronodose OR cronodose OR soluspan)):ti,ab,kw) OR 'intravitreal implant'/exp OR 'intravitreal implant':ti,ab,kw OR 'dexamethasone'/exp OR 'dexametason*':ti,ab,kw OR 'dexamethason*':ti,ab,kw OR 'ozurdex':ti,ab,kw OR 'fluocinolone acetonide'/exp OR 'fluocinolon* acetonid*':ti,ab,kw OR 'fluocinonid* acetonid*':ti,ab,kw OR fluocinolonacetonid*:ti,ab,kw OR 'iluvien*':ti,ab,kw OR (((parabulbar OR 'para bulbar' OR peribulbar OR 'peri bulbar' OR subconjunctiv* OR 'sub conjunctiv*' OR perbulbar OR 'per bulbar' OR subtenon* OR 'sub tenon*' OR periocular* OR 'peri ocular*' OR intravitreal OR ivi OR topical*) NEAR/6 (corticosteroid* OR steroid* OR glucocortico* OR corticoid* OR 'anti inflamm*' OR prophyla*)):ti,ab,kw)	300110
#4	#1 AND #2 AND #3 NOT ('conference abstract'/it OR 'clinical trial':dtype) NOT (('editorial'/it OR 'letter'/it OR 'note'/it) NOT 'evidence based medicine'/exp) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) AND [2005-2025]/py	1541
#5	'meta analysis'/exp OR 'systematic review'/exp OR 'scoping review'/exp OR 'rapid review'/exp OR 'umbrella review'/exp OR 'cochrane database of systematic reviews'/jt OR 'network meta-analysis'/exp OR 'networkmeta analy*':ti,ab,kw OR 'networkmetaanaly*':ti,ab,kw OR metaanaly*:ti,ab,kw OR 'meta analy*':ti,ab,kw OR metanaly*:ti,ab,kw OR prisma:ti,ab,kw OR prospero:ti,ab,kw OR metaanali*:ti,ab,kw OR 'meta anali*':ti,ab,kw OR metanali*:ti,ab,kw OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab,kw) OR (((structured OR systemic*) NEAR/3 (review* OR overview* OR synth*) NEAR/3 literature):ti,ab,kw) OR ((systemic* NEAR/1 review*):ti,ab,kw) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab,kw) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab,kw) OR (((literature NEAR/3 (review* OR overview*)):ti,ab,kw) AND (search*:ti,ab,kw OR database*:ti,ab,kw OR 'data base*':ti,ab,kw)) OR (('data extraction*':ti,ab,kw OR 'data source*':ti,ab,kw) AND ('study selection*':ti,ab,kw OR 'studies selection*':ti,ab,kw)) OR ('search strateg*':ti,ab,kw AND 'selection criteria*':ti,ab,kw) OR ('data source*':ti,ab,kw AND 'data synth*':ti,ab,kw) OR medline*:ti,ab,kw OR pubmed*:ti,ab,kw OR 'pub med*':ti,ab,kw OR embase:ti,ab,kw OR cochrane*:ti,ab,kw OR (((critical* OR rapid*) NEAR/2 (review* OR overview* OR synth*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synth*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynth*:ti,ab,kw OR 'meta synth*':ti,ab,kw OR 'review* of review*':ti,ab,kw	1143068
#6	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti	4862973
#7	#4 AND #5	88
#8	#4 AND #6 NOT #7	285
#9	#7 OR #8	373

Ovid/Medline

#	Searches	Results
1	exp Cataract/ or exp Cataract Extraction/ or (lens* adj2 opacit*).ti,ab,kf. or cataract*.ti,ab,kf. or pseudoaphakia*.ti,ab,kf. or capsulorhexis.ti,ab,kf. or capsulorrhexis.ti,ab,kf. or phacoemulsification*.ti,ab,kf. or 'phaco emulsification*'.ti,ab,kf.	89403
2	exp Uveitis/ or exp Panuveitis/ or uveiti*.ti,ab,kf. or chorioretinitis.ti,ab,kf. or retinitis.ti,ab,kf. or scleritis.ti,ab,kf. or vitritis.ti,ab,kf. or iritis.ti,ab,kf. or iridocyclitis.ti,ab,kf. or pars planitis.ti,ab,kf. or chorioiditis.ti,ab,kf.	64364

3	exp Triamcinolone/ or 'triamcinolon*'.ti,ab,kf. or kenacort.ti,ab,kf. or (betamethasone adj6 acetate adj6 phosphate).ti,ab,kf. or ((celestene or celestone) adj3 (chronodose or cronodose or soluspan)).ti,ab,kf. or exp Drug Implants/ or 'intravitreal implant'.ti,ab,kf. or exp Dexamethasone/ or 'dexametason*'.ti,ab,kf. or 'dexamethason*'.ti,ab,kf. or 'ozurdex'.ti,ab,kf. or exp Fluocinolone Acetonide/ or 'fluocinolon* acetonid*'.ti,ab,kf. or 'fluocinonid* acetonid*'.ti,ab,kf. or fluocinolonacetonid*.ti,ab,kf. or 'iluvien*'.ti,ab,kf. or ((parabulbar or 'para bulbar' or peribulbar or 'peri bulbar' or subconjunctiv* or 'sub conjunctiv*' or perbulbar or 'per bulbar' or subtenon* or 'sub tenon*' or periocular* or 'peri ocular*' or intravitreal or ivi or topical*) adj6 (corticosteroid* or steroid* or glucocortico* or corticoid* or 'anti inflamm*' or prophyla*)).ti,ab,kf.	129457
4	(1 and 2 and 3) not ((exp animals/ or exp models, animal/) not humans/) not ((letter/ or comment/ or editorial/) not (exp Clinical Trial/ or exp Meta-Analysis/ or exp Scoping Review/ or exp Systematic Review/))	679
5	limit 4 to yr="2005 -Current"	543
6	exp Meta-Analysis/ or exp Network Meta-Analysis/ or exp Systematic Review/ or (networkmeta analy* or networkmetaanaly* or metaanaly* or meta analy* or metanaly* or prisma or prospero or metaanali* or meta anali* or metanali*).ti,ab,kf. or ((systemati* or scoping or umbrella or structured literature) adj3 (review* or overview*)).ti,ab,kf. or ((structured or systemic*) adj3 (review* or overview* or synth*) adj3 literature).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 (review* or overview*)) and (search* or database* or data base*)).ti,ab,kf. or ((data extraction* or data source*) and (study selection* or studies selection*)).ti,ab,kf. or (search strateg* and selection criteria*).ti,ab,kf. or (data source* and data synth*).ti,ab,kf. or (medline* or pubmed* or pub med* or embase or cochrane*).ti,ab,kf. or cochrane.jw. or ((critical* or rapid*) adj2 (review* or overview* or synth*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synth*)) and (search* or database* or data base*)).ab. or metasynth*.ti,ab,kf. or meta synth*.ti,ab,kf.	847679
7	exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.	2921650
8	5 and 6	25
9	(5 and 7) not 8	113
10	8 or 9	138

Bijlage 7 Verantwoording module 4 – Torische intra-oculaire lenzen

Verantwoording

Voor meer details over de gebruikte richtlijnmethodologie verwijzen wij u naar de Werkwijze. Relevante informatie voor de ontwikkeling/herziening van deze richtlijnmodule is hieronder weergegeven.

Initiatief

Initiatief: cluster oog

Samenstelling van de werkgroep

Voor het ontwikkelen van de richtlijnmodule is in 2022 een multidisciplinair cluster ingesteld. Het cluster oog bestaat uit meerdere richltijnen, zie hier voor de actuele clusterindeling. De stuurgroep bewaakt het proces van modulair onderhoud binnen het cluster. De expertisegroepsleden geven hun expertise in, indien nodig. De volgende personen uit het cluster zijn betrokken geweest bij de herziening van deze module.

Clusterstuurgroepleden

- Dr. N.C. (Nicole) Naus, voorzitter cluster oog, oogarts, NOG, Erasmus MC
- Dr. M.C. (Marjolijn) Bartels, Voorzitter Cluster Oog, oogarts, NOG, Deventer Ziekenhuis
- Dr. A.J. (Arlette) van Sorge, oogarts, NOG, Koninklijke Visio,
- Drs. L.J. (Leo) Noordzij, oogarts, NOG, Oog op Zuid Oogkliniek
- Dr. R. (Redmer) van Leeuwen, oogarts, NOG, UMC Utrecht
- Dr. Ir M. (Marleen) van Aartrijk, Klinisch Fysicus NVKF, Koninklijke Visio
- C. (Caroline) Osterholt-Bel, Adviseur oogzorg Oogvereniging

Betrokken clusterexpertisegroepleden

Module 4: torische intra-oculaire lenzen

- Dr. N. (Nienke) Visser, oogarts, NOG, Maastricht UMC
- Drs. R.H.J. (Robert Jan) Wijdh, oogarts, NOG, UMC Groningen

Met ondersteuning van

- Dr. A.C.J. (Astrid) Balemans, senior-adviseur, Kennisinstituut van Medisch Specialisten
- MSc. D.G. (Dian) Ossendrijver, adviseur, Kennisinstituut van Medisch Specialisten
- A. (Alies) Oost, informatiespecialist, Kennisinstituut van de Federatie Medisch Specialisten

Belangenverklaringen

Een overzicht van de belangen van de clusterleden en het oordeel over het omgaan met eventuele belangen vindt u in onderstaande tabel. De ondertekende belangenverklaringen zijn op te vragen bij het secretariaat van het Kennisinstituut van de Federatie Medisch Specialisten via secretariaat@kennisinstituut.nl.

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Cluster stuurgroepleden

Tabel 7 Gemelde (neven)functies en belangen stuurgroep

Naam	Hoofdfunctie	Nevenwerkzaamheden	Persoonlijke financiële belangen	Persoonlijke relaties	Extern gefinancierd onderzoek	Intellectuele belangen en reputatie	Overige belangen	Datum	Restrictie
Dr. N.C. (Nicole) Naus,	Oogarts Erasmus MC Rotterdam	Geen	Geen	Geen	Geen	Geen	Geen	1-08-2025	Geen restricties
Dr. M.C. (Marjolijn) Bartels	Oogarts Deventer ziekenhuis	Lid van Concilium, lid van commissie kwaliteit en voorzitter van cornea werkgroep (NOG).	Geen	Geen	ja, 1. PHIC (PIONEERS IN HEALTH CARE INNOVATIEFONDS) voucher voor onderzoek in samenwerking Universiteit Twente ZonMWstudies: 2. BICAT-NL studie 3. EPICAT studie	persoonlijk belang van goed op de hoogte zijn van alles, hetgeen gebruikt wordt in de dagelijkse praktijk en als opleider, lid van Concilium, lid van commissie kwaliteit en voorzitter van cornea werkgroep.	Geen	1-08-2025	Geen restricties

Dr. A.J. (Arlette) van Sorge	Oogarts koninklijke Visio	Voorzitter VRS (vereniging voor revalidatie bij slechtziendheid, onbetaald). Stuurgroeplid bij cluster OOG (NOG). Visitator visitatiecommissie NOG. Bestuurslid Oogcontact (onbetaald).	Geen	Geen	Geen	Geen	Geen	6-05-2025	Geen restricties
Drs. L.J. (Leo) Noordzij	Oogarts bij Cooperatie Oogheelkunde op Zuid voor 3.5 dag in de week. Voor 1.5 dag in de week bestuurslid van de Cooperatie Oogheelkunde op Zuid, de Stichting Oogheelkunde op Zuid en medisch directeur het zelfstandig behandel centrum Oog op Zuid oogkliniek.	Lid richtlijn werkgroep FMS/ NOG betreffende leeftijdsgebonden macula degeneratie (tm juli 2023). Vaste programma commissie InSights symposium, Novartis (gestopt juni 2022). Lid medical innovation academy, Novartis (gestopt augustus 2022).	Geen	Geen	Geen	Geen	Geen	20-04-2025	Geen restricties ('advieswerk' neergelegd per juni/augustus 2022)
Dr. R. (Redmer) van Leeuwen	Oogarts UMC Utrecht	Geen	Geen	Geen	ESCH-R 1. NWO - Circulaire zorg (Projectleider NEE)	Geen	Geen	02-02-2025	Geen restricties

Dr. Ir M. (Marleen) van Aartrijk	Klinisch Fysicus bij Koninklijke Visio (Revalidatie & Advies): betaald, - beheer Oogheelkundige apparatuur - ondersteuning zorgprofessionals bij individuele patienttrajecten (bijv. op gebied van verlichting, autorijden) - producteigenaar elektronisch patientendossier	Geen	Geen persoonlijk financieel belang. Indien een richtlijn verwijzing naar revalidatiezorg stimuleert kan dat impact hebben op mijn werkgever (en dan indirect op mijzelf	Geen	Binnen de revalidatiezorg zijn er fondsen (oa Novum, ZonMW) die exptertiseprojecten ondersteunen. Aan een aantal van deze projecten draag ik bij, maar dat gaat om een zeer beperkt deel van mijn tijd (ben geen hoofdonderzoeker oid)	Verduidelijking van rol revalidatiezorg in de zorgketen	Geen	22-04-2025	Geen restricties
C. (Caroline) Osterholt-Bel	TOA Ikazia	Geen	Geen	Geen	Geen	Geen	Geen	29-04-2025	Geen restricties

Betrokken clusterexpertisegroepleden

Tabel 8 Gemelde (neven)functies en belangen expertisegroep

Naam	Hoofdfunctie	Nevenwerkzaamheden	Persoonlijke financiële belangen	Persoonlijke relaties	Extern gefinancierd onderzoek	Intellectuele belangen en reputatie	Overige belangen	Datum	Restrictie
Dr. N. (Nienke) Visser	Oogarts MUMC Maastricht	Lid cornea werkgroep ESCRS	**Geen**	**Geen**	Hoofdonderzoeker Europese klinische studie naar dropless cataract surgery (Effectiveness of periocular drug injection in cataract surgery). Deze studie is gefinancierd door de ESCRS en zal begin 2025 zijn afgerond.	**Geen**	**Geen**	**01-08-2025**	**Geen restricties**
Drs. R.H.J. (Robert Jan) Wijdh	UMCG Groningen	Geen	Geen	Geen	Geen	Geen	Geen	**01-08-2025**	**Geen restricties**

5

Kwalitatieve raming van mogelijke financiële gevolgen in het kader van de Wkkgz

Bij de richtlijnmodule voerden de clusterleden conform de Wet kwaliteit, klachten en geschillen zorg (Wkkgz) een kwalitatieve raming uit om te beoordelen of de aanbevelingen mogelijk leiden tot substantiële financiële gevolgen. Bij het uitvoeren van deze beoordeling is de richtlijnmodule op verschillende domeinen getoetst (zie het stroomschema bij Werkwijze).

Module	Uitkomst raming	Toelichting
Module torische intra-oculaire lenzen	Geen financiële gevolgen	Hoewel uit de toetsing volgt dat de aanbeveling(en) breed toepasbaar zijn (>40.000 patiënten), volgt uit de toetsing dat het overgrote deel (±90%) van de zorgaanbieders en zorgverleners al aan de norm voldoet. Er worden daarom geen financiële gevolgen verwacht.

Bijlage 8 literatuursamenvatting module 4 – Torische intra-oculaire lenzen

Leeswijzer: de voorliggende herziene tekst vervangt de bestaande module over torische intra-oculaire lenzen bij cataract. De tekst in blauw is afkomstig uit de huidige module en ongewijzigd overgenomen.

Introduction (English)

Torische intra-oculaire lenzen kunnen tijdens een cataractoperatie worden geïmplanteerd. Dit type lens is ontworpen om naast cataract, ook **astigmatisme (cilinderafwijking)** te corrigeren, waardoor de patiënt na de operatie vaak scherper en bril-onafhankelijker kan zijn voor veraf. Cornea astigmatisme van 1D of meer is aanwezig bij ongeveer 28% van de patiënten (Hoffmann, 2010). Uit de cataractregistratie van 2023 blijkt dat in slechts 2,6% van de gevallen een torische lens wordt geïmplanteerd, terwijl de patiënt vaak wel de wens heeft bril-onafhankelijker voor veraf te zijn na een cataractoperatie. Patiënten beschrijven dat de optie om voor een torische lens te kiezen niet altijd wordt besproken. Het is onduidelijk vanaf welk astigmatische patiënten in aanmerking komen voor torische intra-oculaire lenzen en de afweging om voor een torische intra-oculaire lens te kiezen samen met de patiënt gemaakt dient te worden.

Search and select

Om de uitgangsvraag te kunnen beantwoorden is er een systematische literatuuranalyse verricht naar de volgende zoekvraag:

Wat zijn de gunstige en ongunstige effecten van torische intraoculaire lenzen (IOLs) vergeleken met sferische intraoculaire lenzen bij een cataractoperatie?

Table 1. PICO

Patients	patiënten > 18 jaar die cataractchirurgie ondergaan;
Intervention	torische lenzen;
Control	sferische lenzen;
Outcomes	ongecorrigeerde visus voor verte afstand, restcilinder, brilafhankelijkheid, secundaire interventies (laser touch up of realignment).
Other selection criteria	Study design: systematic reviews and randomized controlled trials [Minimal follow-up: …]

Relevant outcome measures

De werkgroep achtte visus met doelrefractie voor veraf en restcilinder voor de besluitvorming cruciale uitkomstmaten; en brilafhankelijkheid en secundaire interventies (laser touch up/ realignment) voor de besluitvorming belangrijke uitkomstmaten.

De werkgroep definieerde de uitkomstmaten als volgt: visus voor veraf diende gerapporteerd te zijn op een continue (log)MAR schaal, brilafhankelijkheid (op enige afstand) patiënt-gerapporteerd.

De werkgroep definieerde een verschil in visus van 0,1 logMAR voor als een klinisch (patiënt) relevant verschil. Een risk ratio van < 0,8 en > 1,25 werd als klinisch relevant gezien voor brilafhankelijkheid. Een risk ratio van < 0,91 en > 1,1 werd als klinisch relevant gezien voor het eruit halen van de lens. Voor restcilinder werd een verschil van >0,5 dioptrie als klinisch relevant gedefinieerd.

Search and select (Methods)

De zoekstrategie voor de module multifocale intraoculaire lenzen en torische lenzen werd gecombineerd.

In de databases Medline (via OVID) en Embase (via Embase.com) is op 5 maart 2020 met relevante zoektermen gezocht naar systematische reviews en gerandomiseerd gecontroleerd onderzoek (RCT's). De zoekverantwoording is weergegeven onder het tabblad Verantwoording. De literatuurzoekactie leverde 402 treffers op. Studies werden geselecteerd op grond van de volgende selectiecriteria: systematische review (gezocht in ten minste twee relevante databases, risk of bias beoordeling aanwezig en de resultaten van individuele studies voldoende gepresenteerd) of RCT waarin een vergelijking is gemaakt tussen torische intraoculaire lenzen en sferische lenzen bij patiënten. Daarnaast moest tenminste één van de bovengenoemde uitkomstmaten zijn gerapporteerd.

Er werden op basis van titel en abstract in eerste instantie 9 studies voorgeselecteerd. Na raadpleging van de volledige tekst, werden vervolgens 4 studies voor geëxcludeerd (zie exclusietabel onder het tabblad Verantwoording) en 5 studies definitief geselecteerd.

Summary of literature

Description of studies

Zestien onderzoeken zijn opgenomen in de literatuuranalyse: 13 RCT's werden beschreven in één systematische review en twee RCT's werden gepubliceerd na het verschijnen van de systematische review. De belangrijkste studiekarakteristieken en resultaten zijn opgenomen in de evidencetabellen. De beoordeling van de individuele studieopzet (risk of bias) is opgenomen in de risk-of-biastabellen.

Beschrijving studies

Systematische reviews

Kessel (2016) is een systematische review waarin dertien RCT's werden geïncludeerd (Freitas, 2014; Gangwani, 2014; Hirnschall, 2014; Holland, 2010; Lam, 2015; Liu, 2014; Maedel, 2014; Mendicute, 2009; Mingo-Botin, 2010; Titiyal, 2014; Visser, 2014; Waltz, 2015 en Zhang, 2011). De systematische review includeerde RCT's waarin patiënten met leeftijdsgerelateerde cataract en regulair astigmatisme werden onderzocht die een cataractoperatie ondergingen aan één of beide ogen en de vergelijking werd gemaakt tussen 1) torische intraoculaire lenzen en 2) non-torische intraoculaire lenzen. Er werd niets vermeld over minimale corneale astigmatisme. Er werd gezocht tot augustus 2015 en er werd een GRADE-beoordeling uitgevoerd. In de controlegroep werd een onderverdeling gemaakt in non-torische lenzen en non-torische lenzen met relaxerende incisies. Ook werd voor één studie een multifocale torische intraoculaire lens vergeleken met een multifocale non-torische intraoculaire lens met relaxerende incisies. Voor de volgende voor de werkgroep relevante uitkomsten werd een meta-analyse uitgevoerd: ongecorrigeerde visus voor veraf, restcilinder, brilafhankelijkheid en adverse events.

RCT's

Emesz (2015) was een RCT uit Oostenrijk waarin bij patiënten die met bilaterale seniele cataract en pre-existerend regelmatig topografisch corneaal astigmatisme met cylindrische waarden van 1,5 tot 6 dioptrieën die voor beide ogen in aanmerking kwamen voor een cataract operatie de vergelijking werd gemaakt tussen 1) een laag (1,5 tot 2,35 D) torische intraoculaire lens (N=32 ogen); 2) een hoog (3,00-6,00 D) torische intraoculaire lens (N=22 ogen) en 3) een non-torische intraoculaire lens (N=24 ogen). Exclusiecriteria waren onder andere oculaire comorbiditeiten. De volgende voor de werkgroep relevante uitkomsten werden gerapporteerd: ongecorrigeerde visus voor veraf en restcilinder. De loss-to- follow up werd niet gerapporteerd en er werd niets vermeld over blindering van patiënten en outcome assessors.

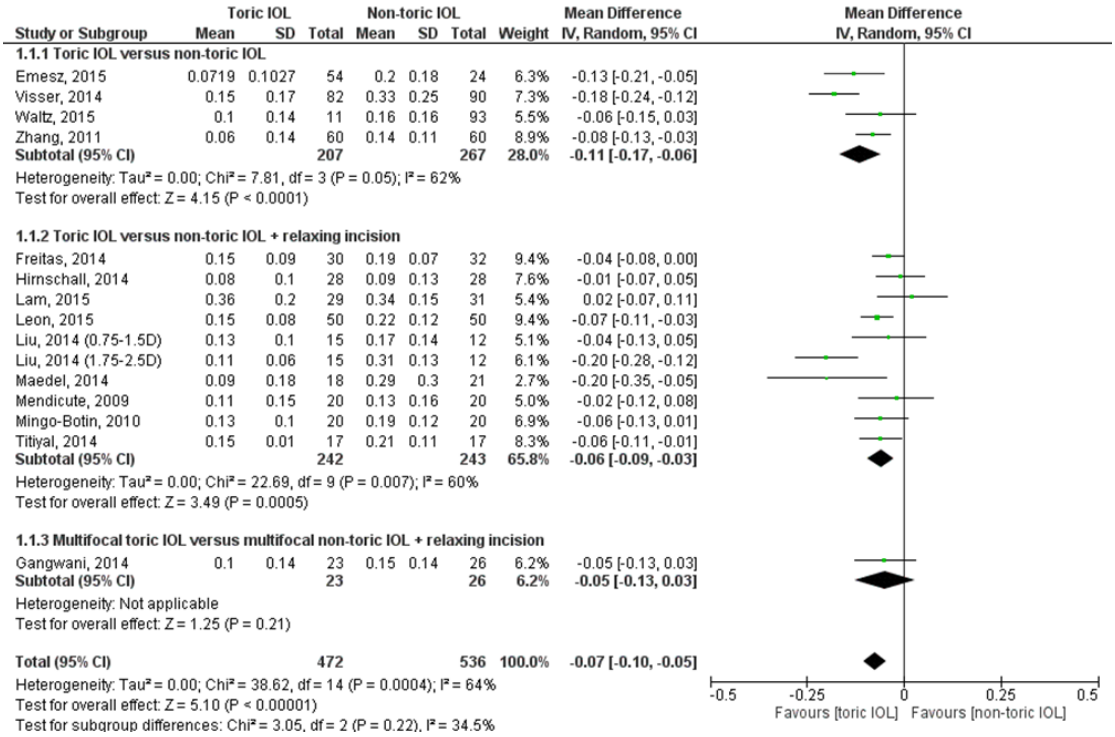
Leon (2015) was een RCT uit Italië waarin bij patiënten die met significante cataract en pre-existerende regelmatig corneaal astigmatisme met cylindrische waarden van 1,0 tot 2,0 dioptrieën die voor één oog in aanmerking kwamen voor een cataractoperatie de vergelijking werd gemaakt tussen 1) torische intraoculaire lenzen (N=50 patiënten) en 2) non-torische intraoculaire lenzen met

relaxerende incisies (N=50 patiënten). Exclusiecriteria waren onder andere oculaire comorbiditeiten. De volgende voor de werkgroep relevante uitkomsten werden gerapporteerd: ongecorrigeerde visus voor veraf, restcilinder en postoperatieve complicaties waaronder re-operaties voor geroteerde lenzen. De loss-to- follow up werd niet gerapporteerd en er werd niets vermeld over blindering van patiënten en outcome assessors.

Results

1. Uitkomstmaat ongecorrigeerde visus voor verte afstand

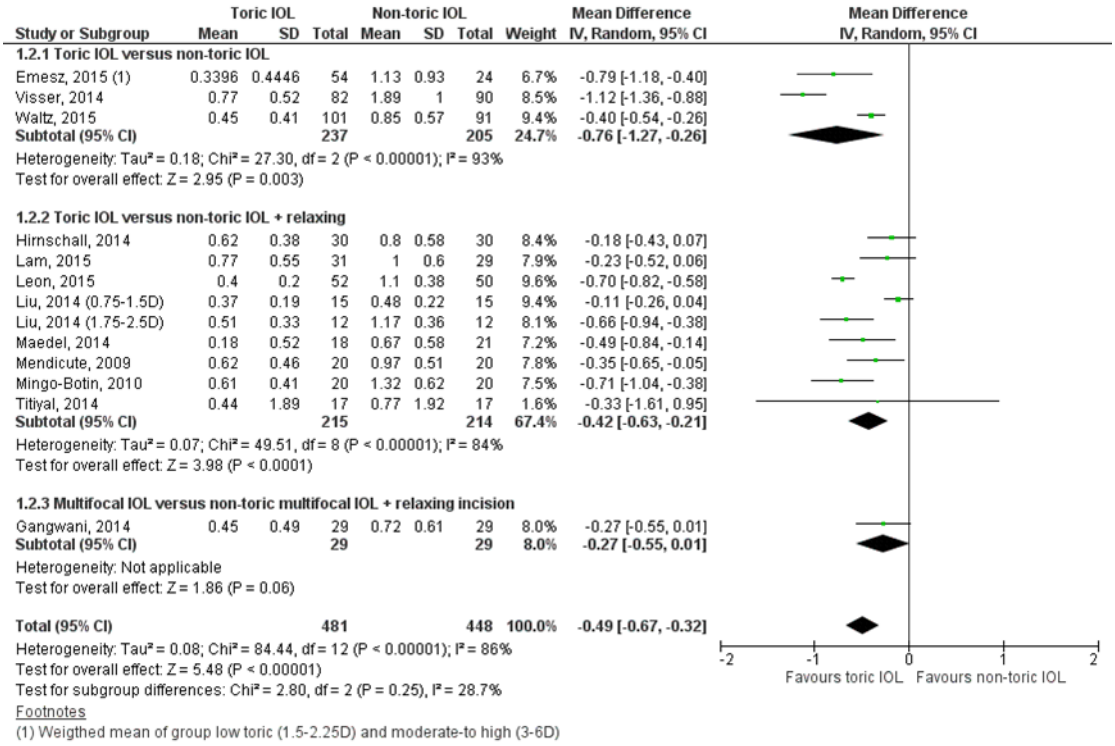
Ongecorrigeerde visus voor veraf werd in 14 studies onderzocht (Emesz, 2015; Freitas, 2014; Gangwani, 2014; Hirnschall, 2014; Lam, 2015; Leon, 2015; Liu, 2014; Maedel, 2014; Mendicute, 2009; Mingo-Botin, 2010; Titiyal, 2014; Visser, 2014; Waltz, 2015 en Zhang, 2011). Het gemiddelde verschil in ongecorrigeerde visus voor veraf, tussen de torische groep en de non-torische groep was MD= -0,11; 95%BI= (-0,17;-0,06); p<0,00001; ntotaal=474), met een random effect model en een matige heterogeniteit (I2 62%) (figuur 1, vergelijking 1.1.1), een betere ongecorrigeerde visus voor veraf in de torische groep.



Figuur 1 Uitkomstmaat ongecorrigeerde visus voor veraf. Z: p-waarde van het gepoolde effect; df: degrees of freedom (vrijheidsgraden); I2: statistische heterogeniteit; CI: betrouwbaarheidsinterval

2. Uitkomstmaat restcilinder

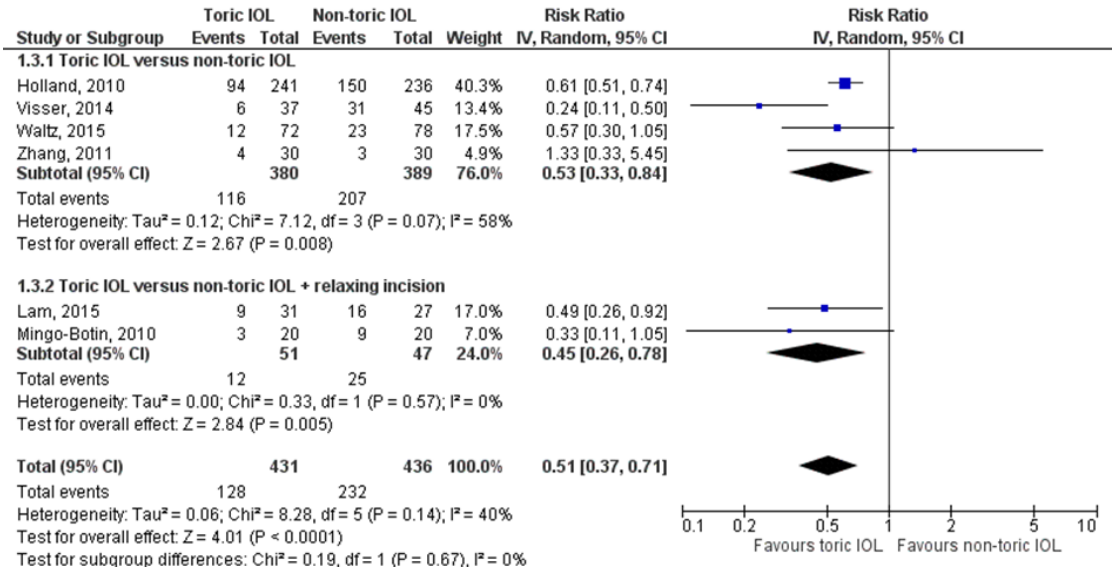
Restcilinder werd in 12 studies onderzocht (Emesz, 2015; Gangwani, 2014; Hirnschall, 2014; Lam, 2015; Leon, 2015; Liu, 2014; Maedel, 2014; Mendicute, 2009; Mingo-Botin, 2010; Titiyal, 2014; Visser, 2014 en Waltz, 2015). Het gemiddelde verschil in restcilinder, tussen de torische groep en de non-torische groep was MD= -0,76; 95%BI= (-1,27;-0,26); p=0,003; ntotaal=442), met een random effect model en een matige heterogeniteit (I2 93%) (figuur 2, vergelijking 1.2.1), een kleinere restcilinder in de torische groep.



Figuur 2 Uitkomstmaat restcilinder Z: p-waarde van het gepoolde effect; df: degrees of freedom (vrijheidsgraden); I^2: statistische heterogeniteit; CI: betrouwbaarheidsinterval

3. Uitkomstmaat brilafhankelijkheid

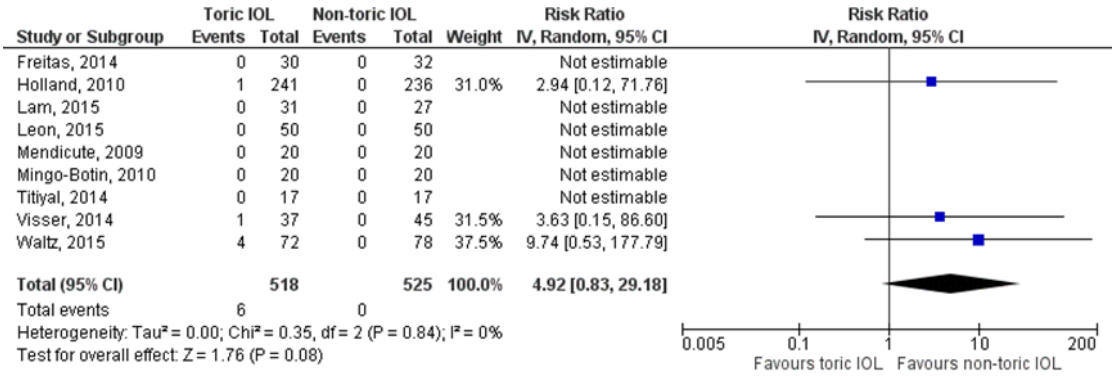
Brilafhankelijkheid werd in 6 studies onderzocht (Holland, 2010; Lam, 2015; Mingo-Botin, 2010; Visser, 2014; Waltz, 2015 en Zhang, 2011). De gepoolde resultaten laten zien dat de incidentie van brilafhankelijkheid (op enig moment van de dag/ op enige afstand) 29,7% (128/431) was in de torische groep en 53,2% (232/436) in de non-torische groep (figuur 3). Het gemiddelde relatieve risico (RR) van de gepoolde studies voor brilafhankelijkheid was RR: 0,51 (95%BI= (0,37, 0,71); p<0,0001; ntotaal =867), met een random effect model en een lage heterogeniteit.



Figuur 3 Uitkomstmaat brilafhankelijkheid. Z: p-waarde van het gepoolde effect; df: degrees of freedom (vrijheidsgraden); I^2: statistische heterogeniteit; CI: betrouwbaarheidsinterval

4. Uitkomstmaat secundaire interventies (laser touch up/ realignment)

Secundaire interventies werd in 9 studies onderzocht (Freitas, 2014; Holland, 2010; Lam, 2015; Leon, 2015; Mendicute, 2009; Mingo-Botin, 2010; Titiyal, 2014; Visser, 2014 en Waltz, 2015). De gepoolde resultaten laten zien dat de incidentie van een re-operatie vanwege de rotatie van een torische lens (realignment) 1,16% (6/518) was in de torische groep en logischerwijs 0% (0/525) in de non-torische groep (figuur 4). Het gemiddelde relatieve risico (RR) van de gepoolde studies voor realignment was RR: 4,92 (95%BI= (0,83, 29,18); p=0,84; ntotaal =1043), met een random effect model en een lage heterogeniteit (I2 0%), patiënten met een torische lens hebben een hoger risico op een realignment, echter is dit verschil niet statistisch significant. In de non-torische groep is het risico uiteraard niet aanwezig. Laser-touch ups werden in geen van de studies vermeld.



Figuur 4 Uitkomstmaat secundaire interventies (realignment). Z: p-waarde van het gepoolde effect; df: degrees of freedom (vrijheidsgraden); I^2: statistische heterogeniteit; CI: betrouwbaarheidsinterval

Summary of Findings

1. Uitkomstmaat ongecorrigeerde visus voor veraf

Laag GRADE	Ongecorrigeerde visus voor veraf lijkt beter bij een torische intraoculaire lens vergeleken met een non-torische intraoculaire lens (met of zonder relaxerende incisies). Bronnen: (Emesz, 2015; Visser, 2014; Waltz, 2015 en Zhang, 2011)

2. Restcilinder

Laag GRADE	De restcilinder lijkt kleiner bij een torische intraoculaire lens vergeleken met een non-torische intraoculaire lens (met of zonder relaxerende incisies). Bronnen: (Emesz, 2015; Visser, 2014; Waltz, 2015 en Zhang, 2011)

3. Uitkomstmaat brilafhankelijkheid

Redelijk GRADE	Patiënten met astigmatisme met een torische intraoculaire lens zijn waarschijnlijk minder afhankelijk van een bril dan patiënten met een non-torische lens. Bronnen: (Holland, 2010; Lam, 2015; Mingo-Botin, 2010; Visser, 2014; Waltz, 2015 en Zhang, 2011)

4. Uitkomstmaat realignment

Laag GRADE	Realignment komt nooit voor bij een niet torische lens en bij een torische lens is dit aantal zeer laag, zo laag dat het klinisch niet relevant is.

	Bronnen: (Freitas, 2014; Holland, 2010; Lam, 2015; Leon, 2015; Mendicute, 2009; Mingo-Botin, 2010; Titiyal, 2014; Visser, 2014 en Waltz, 2015)

Kennisvragen

Tijdens de ontwikkeling van deze module is gebleken dat er binnen deze module nog te weinig bewijs is voor de onderbouwing van de aanbeveling en dus kennisvragen bestaan. De werkgroep meent dat (vervolg)onderzoek wenselijk is om in de toekomst een duidelijker antwoord te kunnen geven op vragen uit de praktijk.

Kennisvraag:

- Wat is de minimale mate van corneaal astigmatisme waarbij implantatie van een torische intraoculaire lens leidt tot (een klinisch relevante verbetering) van visuele uitkomsten?
-

Toelichting:

Er is weinig literatuur beschikbaar over de minimale mate van astigmatisme dat aanwezig moet zijn voor effectieve implantatie van een torische IOL. Het is onduidelijk of torische IOLs ook overwogen kunnen worden bij patiënten met een laag astigmatische (<0.75 D).

Tabel A: (De-)Implementatietabel met impuls analyse

Aanbeveling – 1			
1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?	**X Ongewenste praktijkvariatie** □ **Nieuwe evidentie** □ **Anders** **Toelichting:** Uit de praktijk bleek dat bij slechts een klein deel van de patiënten de mogelijkheden voor torische IOLs werd besproken.		
2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?	□ < **1000** □ < **5000** *X* **5000-40.000** □ **> 40.000**		
3. Maakt de aanbeveling deel uit van een set van interventies voor hetzelfde probleem?	□ **Ja**: hoe verhoudt deze aanbeveling zich tot de andere aanbevelingen uit deze module/ richtlijn of uit andere richtlijnen(modules)? Dient hier rekening mee gehouden te worden bij de implementatie of kan dit worden gezien als een losstaande aanbeveling? **Toelichting:** [toelichting] **X Nee**		
4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:	***Voorbeelden***	**Wat zijn mogelijke belemmerende factoren?**	**Wat zijn mogelijke bevorderende factoren?**
g) **Richtlijn/ klinisch traject (innovatie)**	*Voortschrijding/vooruitgang in de praktijk, haalbaarheid, geloofwaardigheid, toegankelijkheid, aantrekkelijkheid*		Verspreiding van de richtlijn. Delen van hulpmiddelen om restcilinder te berekenen
h) **Zorgverleners (artsen en verpleegkundigen)**	*Bewustzijn, kennis, houding, motivatie om te veranderen, gedragsroutines*	Heersende overtuigingen en routine. Kennisniveau van de oogarts en paramedisch personeel over torische IOL Het idee niet te kunnen voldoen aan de hogere verwachten van de patiënt die worden gecreëerd door bijbetaling voor de procedure	Laagdrempelige doorverwijzing naar collega's bij gebrek aan expertise.

		Moeilijkheden bij de behandeling van een postoperatieve refractie-afwijking	
i) **Patiënt/ cliënt (naasten)**	*Kennis, vaardigheden, houding, compliance*	Kennis en overtuigingen over de voor- en nadelen van verschillende typen lenzen. Vaardigheden om de voor- en nadelen te begrijpen. Patiënt moet kosten van torische IOL zelf betalen, hoge verwachtingen t.a.v. torische IOLs die worden gecreëerd door bijbetaling voor de procedure	Vergroten gezondheidsvaardigheden van de patiënten. Minder brilafhankelijkheid
j) **Sociale context**	*Mening van collega's, cultuur van het netwerk, samenwerking, leiderschap*		
k) **Organisatorische context**	*Organisatie van zorgprocessen, personeel, capaciteiten, middelen, structuren*	Grotere belasting in het vooronderzoek om juiste IOL sterkte en as te bepalen. Extra apparatuur en extra instrumentarium en disposables. Extra tijd nodig voor uitleg en voor de procedure zelf	
l) **Economische en politieke context**	*Financiële regelingen, regelgeving, beleid (vergoede zorg, betaaltitel)*	De meerkosten voor het implanteren van een torische IOL worden in de meeste gevallen niet vergoed door de verzekeraar	

5. Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk?	X Patiënt/ cliënt (naaste) X Professional X Beroepsvereniging X Ziekenhuis(bestuurder) □ Zorgverzekeraars/ NZa □ Zorginstituut [duiding nodig] □ ……. *(graag aanvullen met alle relevante partijen, e.g., industrie)*

6. Wat zouden deze personen/ partijen moeten veranderen in hun gedrag of organisatie om de aanbeveling toe te passen?	*Patiënt: zich goed laten informeren door de oogarts, open staan voor de genoemde voor- en nadelen *Professional: kennis uitbreiden over torische IOL, ook ten aanzien van berekening van de sterkte en bepaling van de as. Bij gebrek aan kennis of mogelijkheden om torische IOL te plaatsen de patiënt wel informeren en e.v.t doorverwijzen naar collega. *Beroepsvereniging: verspreiding van de richtlijn, vergroten van bewustzijn over torische IOLs na cataractoperatie *Ziekenhuis(bestuurder): beschikbaar maken van apparatuur en instrumentarium om torische IOLs te plaatsen
7. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?	X < 1 jaar □ < 2 jaar □ < 3 jaar
8. Conclusie: is er extra aandacht nodig voor implementatie van de aanbeveling (anders dan publicatie van deze richtlijnmodule)?	□ **Ja* X Nee** **Toelichting:**

**Deze aanbeveling komt in aanmerking voor plaatsing op de Implementatie Agenda van het programma Zorg Evaluatie & Gepast Gebruik (ZE&GG). In het programma ZE&GG werken patiënten, zorgverleners, zorgaanbieders, zorgverzekeraars en overheid samen aan de bewezen beste zorg voor de patiënt. Daarmee is ZE&GG een programma van alle betrokken partijen in de Medisch Specialistische Zorg. FMS is één van deze betrokken partijen.*

De implementatieagenda van ZE&GG bevat onderwerpen over wat de bewezen beste zorg is en die in de dagelijkse zorgpraktijk geïmplementeerd zouden moeten worden. Zorgverzekeraars Nederland (ZN) en de Nederlandse Vereniging voor Ziekenhuizen (NVZ) hebben landelijke afspraken gemaakt over de implementatie van de onderwerpen van de implementatieagenda. Deze afspraken zijn onderdeel van de zorginkoopafspraken tussen zorgverzekeraars en zorgaanbieders.

Vanuit FMS worden sterke, goed onderbouwde aanbevelingen, getoetst op de behoefte aan een implementatie impuls aangedragen. Voor de beoordeling van onderwerpen uit richtlijnen wordt gekeken naar bovenstaande tabel voor een inschatting van de implementatie impuls. Met de ingevulde implementatietabel kunnen we vanuit FMS de andere HLA-MSZ partijen goed informeren om zo samen te beslissen of de aanbeveling daadwerkelijk op de implementatie agenda zal worden geplaatst.

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Bijlagen bij module torische intra-oculaire lenzen

Risk of Bias tables

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Kessel, 2016	SR and meta-analysis of RCTs *Literature search up to* August 26, 2015 **A**: Freitas, 2014 **B**: Gangwani, 2014 **C**: Hirnschall, 2014 **D**: Holland, 2010 **E**: Lam, 2015 **F**: Liu, 2014 **G**: Maedel, 2014 **H**: Mendicute, 2009 **I**: Mingo-Botin, 2010 J: Titiyal, 2014 K: Visser, 2014 L: Waltz, 2015 M: Zhang, 2011 Study design: RCT [parallel / cross-over], cohort [prospective / retrospective], case-control Setting and Country: Review: Denmark Source of funding and conflicts of interest: [commercial / non-commercial / industrial co-authorship]	Inclusion criteria SR: to examine the effect of toric IOL implantation (I) versus non-toric IOL implantation (C) in patients with agerelated cataracts and preoperative corneal astigmatism undergoing phacoemulsification (P) (PICO). The implantation of non-toric IOLs could be combined with limbal or cornealrelaxing incisions Exclusion criteria SR: References that reported only on outcome after toric IOL implantation in patients with corneal ectasia, such as keratoconus, or marginal pellucid degenerations were excluded *13 studies included*	Describe intervention: **A**: Toric IOL in both eyes (AcrySof Toric TM, Alcon, Fort Worth, TX) **B**: Multifocal toric IOL (Mflex-T multifocal toric IOL, Rayner IOLs, East Sussex, UK) in 1 eye of a patient **C**: Rayner T-Flex toric IOL (Rayner) in 1 eye **D**: Acrysof Toric (SA60T3-T5, Alcon) **E**: TECNIS Toric IOL (Abbott Medical Optics (Santa Ana, CA) **F**: Toric IOL (model and manufacturer not specified) **G**: Aspheric toric IOL (Lentis Unico L-312T, Oculentis GmbH, Berlin, Germany) **H**: Toric IOL (Acrysof Toric SN60T3, SN60T4, SN60T5, Alcon) **I**: Toric IOL (Acrysof Toric, Alcon) J: Toric IOL (AcrySof IQ Toric, Alcon) K: Toric IOL (AcrySof aspheric toric, SN6AT3-T9, Alcon)	Describe control: **A**: Non-toric IOL (AcrySof Natural, Alcon) þ limbal-relaxing incisions in both eyes **B**: Non-toric multifocal IOL (Mflex, Rayner IOLs) in the other eye þ peripheral cornealrelaxing incision **C**: C-Flex or Superflex non-toric IOL (Rayner) þ 1 or 2 relaxing peripheral corneal incisions in the other eye **D**: Non-toric IOL (Acrysof SA60AT, Alcon) **E**: TECNIS 1-piece IOL with limbal-relaxing incision **F**: Non-toric IOL (model and manufacturer not specified) þ peripheral corneal-relaxing incisions Aspheric non-toric IOL (Lentis Unico L-312, Oculentis GmbH) þ opposite clear corneal incisions **H**: Non-toric IOL (AcrySof SN60AT, Alcon) þ opposite clear corneal incisions	End-point of follow-up: **A**: 1, 3,6 mo **B**: 3 mo **C**: 1, 6 mo **D**: 1 yr **E**: 1, 3 mo **F**: 1, 6 mo **G**: 1hr, 1wk, 3, 9 mo **H**: 3 mo **I**: 3 mo J: 1d, 1 wk, 1,3 mo K: 1wk, 1,3,6 mo L: 1d, 1wk, 1,3,6 mo M: 1,3,6 mo If included studies reported outcomes at more than 1 time point, the last reported time point was used in the analyses For how many participants were no complete outcome data available? (intervention/control) **A:** **B**: 58 eyes of 29 patients were included but 3 were lost to follow-up **C**: 30 patients were included, 2 were lost to follow-up	Outcome measure-1 UDVA A-M: see forest plot Outcome measure-2 Residual astigmatism A-M: See forest plot Outcome measure-3 Spectacle independency D, K, L, M: see forest plot Outcome measure-4 number of operative and postoperative complications including reoperations for rotated IOL **A: 0** **B**: NR **C**: NR **D**: Toric: 1 repositioning because of rotation; followed by second surgery for IOL replacement. Other:: 1 eye had retinal detachment,; 1 eye had paracentesis for elevated postoperative IOP; 1 eye underwent focal laser treatment for diabetic macular edema; 1 eye had laser photocoagulation for	Facultative: Brief description of author's conclusion: toric IOLs provided better UCDVA, greater spectacle independence, and lower amounts of residual astigmatism than non-toric IOLs even when relaxing incisions were used Level of evidence: GRADE (per comparison and outcome measure) including reasons for down/upgrading Cochrane Risk of Bias tool **A:** **random seq: low** **allocation: unclear** **blinding parti and perso: unclear** **blinding outcome ass: unclear** **incomplete outcome data:low** **selective rep: unclear** **other bias:low** **B**: **random seq: low** **allocation: unclear**

	The author(s) have made the following disclosure(s): L.K.: Personal fees from Danish Health and Medicines Authorities during the conduct of this study. The study was initiated and funded by the National Danish Health and Medicines Authorities, but the sponsor had no role in the design or conduct of this research. **A:** Alcon provided all IOLs free of cost. The Municipal Health Authority of Uberlândia provided cataract service costs **B**: Supported by an unrestricted grant from Rayner Surgical, United Kingdom and National Institute of Health Research award **C**: Funding by National Institute of Health Research award + unrestricted grant from Rayner Surgical, London **D**: The study was sponsored by Alcon	Important patient characteristics at baseline: *Number of patients; characteristics important to the research question and/or for statistical adjustment (confounding in cohort studies); for example, age, sex, bmi,...* N, mean age **A**: 15 (30eyes). 65.7y / 16 (32 eyes) 71.8y **B**: 29 eyes / 29 eyes, 74.8y **C**: 30 (60eyes) 71.0 (8.4)y **D**: 241 eyes / 236 eyes, 71y **E**: 31 (31 eyes), 64.8 y (10.3), / 29 (29 eyes), 67.7y (6.9) **F**: group A: 15p / 15p Group B: 12p / 12p 67.3 (10.3) / 70.5 (8.0) **G**: 18 eyes / 21 eyes, 70.1y, 11.8 **H**: 20, 69.3 (8.2) / 20 eyes, 71.9 (6.8)	L: Toric IOL (TECNIS toric ZTC150, Abbott Medical Optics) M: Toric IOL (AcrySof Toric SN60T3-5, Alcon)	**I**: Non-toric IOL (Acrysof Natural, Alcon) þ peripheral cornealrelaxing incision J: Non-toric IOL (AcrySof IQ, Alcon) þ astigmatic keratotomy K: Non-toric IOL (AcrySof aspheric non-toric, Alcon, SN60WF) L: Non-toric IOL (TECNIS 1-piece ZCB00 IOL, Abbott Medical Optics) M: Non-toric (AcrySof non-toric SN60AT, Alcon)	**D**: "Of the 541 enrolled subjects, 24 did not receive implants owing to preoperative or intraoperative exclusions; 517 received the AcrySof Toric IOL (n=256) or the control IOL (n=261). Results exclude subjects who received IOLs but discontinued (Toric n=4, control n=2) or were lost to follow-up (Toric n=9, control n=22)" Thus, 5% in the toric and 9% in the control group were lost after randomization. **E**: "One patient suffered a stroke 2 months postoperatively and was not able to attend the clinic … two patients were lost to follow-up." **F**: 0 **G**: 56 patients were included, 17 were lost to follow-up (30%) **H**: Not reported if any patient was excluded after randomization or if any patients were lost to follow-up **I**: Number of patients lost to follow-up or exclusion not reported J:0	treatment of a retinal tear Non-toric group: 1 eye had crystalline lens fragment removal **E**: 0 **F**: NR **G**: NR **H**: 0 **I**: 0 J:0 K: Toric: 1 eye had IOL repositioning. Other: 1 eye with posterior vitreous detachment with a retinal defect Non-toric group: none encountered L: 1 eye with a rotated IOL (that was not repositioned) had a retinal tear and received treatment; 4 eyes had IOL repositioning; 2 eyes had retinal repair procedures M: NR	**blinding parti and perso:low** **blinding outcome ass: low** **incomplete outcome data: low** **selective rep:low** **other bias:low** **C**: **random seq: low** **allocation:low** **blinding parti and perso:low** **blinding outcome ass:low** **incomplete outcome data:low** **selective rep:low** **other bias:low** **D**: **random seq: low** **allocation:low** **blinding parti and perso:unclear** **blinding outcome ass: unclear** **incomplete outcome data: unclear** **selective rep:low** **other bias:low** E: **random seq: low** **allocation: unclear** **blinding parti and perso:low** **blinding outcome ass: unclear** **incomplete outcome data:low** **selective rep:low**

	Laboratories Inc. Data from the study were considered during the approval process of the AcrySof Toric IOL by the United States Food and Drug Administration. **E**: **F**: **G**: It was planned that 60 patients should be included but inclusion was stopped after 36 patients because of severe rotation. Funded by an unrestricted grant from Askin & Co, GmbH, Vienna **H**: Funding not reported. No conflict of interests reported **I**: Funding was not reported. No conflict of interests was reported J: Funding and conflict of interests not reported K: Supported by a grant from the Ministry of Health, Welfare and Sports and The Netherlands Organization for Scientific Research. Several authors had received payment from Alcon as consultants, lecture fees or study grant.	**I**: 20 eyes, 71.5 (11.1) / 20 eyes, 75.6 (5.9) yrs J: 17 eyes, 60.7 (5.99) / 17 eyes (62.23 yrs (3.29) K: 41p (82 eyes) / 45p (90 eyes), 74y L: 102 p, 71.3 (9.1)y / 95 p, 69.9y (7.6) M: 30p (60 eyes), 67 (10)y / 30p (60 eyes), 65 (12)y Pre-operative astigmatism **A**: 0.75-2.5 (both eyes) **B**: 1.0-2.5D **C**: 1.0-2.5D **D**: ≥0.75 D with the rule ast or ≥ 1.0D against the rule ast **E**: ≤ 3.0 D **F**: Group A: 0.75-1.5 Group B: 1.75-2.5D **G**: 1.04-2.11 D (mean 1.69 SD 0.41) **H**: 1-3 **I**: 1-3 J: 1.25-3 K: ≥1.25 L: 0.75-1.5D M: ≥0.5 - ≤ 3 in both eyes Groups comparable at baseline?			K: Low rate of patients lost to follow-up (4 out of 86 randomized) L: 1 patient was lost to 6 months follow-up in the toric group and 2 in the non-toric group M:0		**other bias:low** **F**: **random seq: high** **allocation: unclear** **blinding parti and perso: unclear** **blinding outcome ass: unclear** **incomplete outcome data:low** **selective rep:low** **other bias:low** **G**: **random seq: low** **allocation:low** **blinding parti and perso:low** **blinding outcome ass:low** **incomplete outcome data:high** **selective rep:high** **other bias:low** H: **random seq: unclear** **allocation: unclear** **blinding parti and perso: unclear** **blinding outcome ass: unclear** **incomplete outcome data: unclear** **selective rep: low** **other bias:low** I: **random seq: unclear** **allocation: unclear**

	L: Sponsored by Abbott Medical Optics, California. Sponsor designed the study, participated in analysis of data and data management and interpretation, reviewed and approved the final manuscript M: Funding and conflict of interests not reported						**blinding parti and perso: unclear** **blinding outcome ass: unclear** **incomplete outcome data: unclear** **selective rep: low** **other bias:low** J: **random seq: high** **allocation: unclear** **blinding parti and perso: unclear** **blinding outcome ass: unclear** **incomplete outcome data:low** **selective rep:low** **other bias:low** K: **random seq: low** **allocation:low** **blinding parti and perso:low** **blinding outcome ass:low** **incomplete outcome data:low** **selective rep:low** **other bias:unclear** L: **random seq: low** **allocation:low** **blinding parti and perso:low** **blinding outcome ass:low** **incomplete outcome data:low**

							selective rep:low **other bias:low** **M random seq: unclear** **allocation: unclear** **blinding parti and perso: unclear** **blinding outcome ass: unclear** **incomplete outcome data:low** **selective rep:low** **other bias:low** GRADE: Outcome measure 1: UDVA: Toric – vs non-toric: high Toric – vs non-toric:+ relaxing incision: high Multifocal toric: moderate (imprecision) Residual astigmatism: Toric – vs non-toric: high Toric – vs non-toric:+ relaxing incision: high Multifocal toric: high(imprecision) Spectacle ind Toric – vs non-toric Toric – vs non-toric:+ relaxing incision: high

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments

Emesz, 2015	Type of study: RCT Setting and country: Department of Ophthalmology, Austria Funding and conflicts of interest: Fuchs Foundation for the Promotion of Research in Ophthalmology, Salzburg, Austria. Alcon Inc. financially supports the Fuchs-Foundation as the clinical research center of the Department of Ophthalmology of the Paracelsus Medical University Salzburg, Salzburg, Austria (Grant Number 2010-37). No author has a financial or proprietary interest in any material or method mentioned.	Inclusion criteria: e bilateral senile cataract and preexisting regular topographic corneal astigmatism demanding a toric IOL implantation, with cylindric values between 1.5 diopters (D) and 6.0 D. Exclusion criteria: pregnancy, lactation, irregular corneal astigmatism, diabetic retinopathy, iris neovascularization, congenital eye abnormality, glaucoma, pseudoexfoliation syndrome, amblyopia, uveitis, long-term anti-inflammatory treatment, advanced age-related macular degeneration, retinal detachment, previous ocular surgery, severe corneal and retinal disease, and history of eye trauma N total at baseline: Intervention1: 16p (32 eyes) I2: 11p (22 eyes) Control: 12p (24 eyes) Important prognostic factors[2]: *For example* *age ± SD:* *I1: 64.86 ± 10.65* *I2: 64.82 ±10.68* *C: 74.72 ±6.72* Refr Ast: I1: 1.45 *±1.18* I2: 1.92 *±1.08* C: 0.97 *±0.89* Groups comparable at baseline?	Describe intervention (treatment/procedure/test): The Acrysof IQ toric SN6AT (Alcon Laboratories, Inc.) 2 groups: I1: low toric I2: high toric The model SN6AT3 (torus 1.50 D) or SN6AT4 (2.25 D) was implanted in eyes in the low toric IOL group, and the SN6AT5 (3.00 D), SN6AT6 (3.75 D), SN6AT7 (4.50 D) SN6AT8 (5.25 D), or SN6AT9 (6.0 D) was implanted in eyes in the moderate-to-high toric IOL group All patients received a corneoscleral incision of 2. 2 mm at the 12 o'clock position	Describe control (treatment/procedure/test): nontoric SN60WF IOL (Alcon Laboratories, Inc.), All patients received a corneoscleral incision of 2. 2 mm at the 12 o'clock position	Length of follow-up: 1d, 6w Loss-to-follow-up: none Incomplete outcome data: none	Outcome measure-1 UDVA I1:0.08*±0.08* I2: 0.06*±0.13* C: 0.2*±0.18* Outcome measure-2 Residual astigmatism I1: 0.36*±0.44* I2: 0.31*±0.46* C: 1.13*±0.93* Outcome measure-3 Spectacle independency NR Outcome measure-4 number of operative and postoperative complications including reoperations for rotated IOL NR Only IOL rotation in degrees	

Leon, 2015	Type of study: RCT Setting and country: University eye clinic Italy Funding and conflicts of interest: no conflicts	Inclusion criteria: significant cataract (II-IV group LOCS IIIThe Lens Opacities Classification System III [21]), regular corneal astigmatism (1.0-2.0 D), with-the-rule (WTR) astigmatism, mean axial length 23-24 mm 依0.81, regular and symmetric astigmatism shape at the corneal topographic map, regular and WTR astigmatism of the posterior corneal surface, pharmacologic mydriasis >6.00 mm diameter to allow intraoperative and postoperative visualization of axis marks on the toric IOLs. Exclusion criteria: previous surgery in the eye under study, irregular astigmatisms of the anterior or the posterior corneal surfaces, against-the-rule (ATR) astigmatism, ocular diseases (pupil or zonular abnormalities, corneal scaring, uveitis, glaucoma, neuro-ophthalmic diseases, significant macular disease or other retinopathy). N total at baseline: Intervention: 52 Control: 50 Important prognostic factors[2]: *For example* *age ± SD:* *I: 69.6±5.9* *C: 70.9± 7.3* *Sex:* *I: 50% M* *C: 22/28 M* Groups comparable at baseline?	Describe intervention (treatment/procedure/test): toric IOL (AcrySof詩 IQ Toric IOL, Alcon Inc.)	Describe control (treatment/procedure/test): monofocal IOL (AcrySof詩 IQ Aspheric IOL, Alcon Inc.) + limbal relaxing incisions	

Risk of Bias tables

Systematic review

Study First author, year	Appropriate and clearly focused question?[1] Yes/no/unclear	Comprehensive and systematic literature search?[2] Yes/no/unclear	Description of included and excluded studies?[3] Yes/no/unclear	Description of relevant characteristics of included studies?[4] Yes/no/unclear	Appropriate adjustment for potential confounders in observational studies?[5] Yes/no/unclear/notapplicable	Assessment of scientific quality of included studies?[6] Yes/no/unclear	Enough similarities between studies to make combining them reasonable?[7] Yes/no/unclear	Potential risk of publication bias taken into account?[8] Yes/no/unclear	Potential conflicts of interest reported?[9] Yes/no/unclear
Kessel, 2016	Yes	Yes	Yes	Yes	NA	Yes	Yes	Yes	yes

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study reference (first author, publication year)	Describe method of randomisation[1]	Bias due to inadequate concealment of allocation?[2] (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?[3] (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?[3] (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome accessors to treatment allocation?[3] (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?[4] (unlikely/likely/unclear)	Bias due to loss to follow-up?[5] (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?[6] (unlikely/likely/unclear)
Emesz, 2015	NR; Consecutive patients had binocular randomized implantation of a nontoric IOL, a low toric IOL, or a medium-tohigh toric IOL after phacoemulsification. Patients received the same IOL type in both eyes.	Unclear, NR	Unclear, NR	Unclear, NR	Unclear, NR	Unlikely	Likely (not clear if patients were lost to FU)	Unclear

Leon, 2015	Patients were randomly assigned to one of the two treatments computer. A randomized number was assigned to each patient when the inclusion and exclusion criteria were satisfied	Unclear, NR	Unclear, NR	Unclear, NR	Unclear, NR	the need for spectacles is mentioned in methods of abstract but not further reported	Likely, not reported	Unclear

Table of excluded studies

Reference	Reason for exclusion
Agresta, 2012	Includeert ook observationeel onderzoek en geincludeerde RCT's ook in Kessel, 2016 beschreven
Ferreira, 2012	Vergelijking 2 typen torische lenzen
Oshika, 2018	Design voldoet niet: cohort
Simons, 2019	Kosten-effectiviteitsstudie en effectmaten al in Visser, 2014 beschreven

5 Literature search strategy

Algemene informatie

Richtlijn: Cataract	
Uitgangsvraag: Welke intra-oculaire lenzen (IOLs) dienen bij voorkeur gebruikt te worden bij een cataractoperatie om het optimale resultaat te behalen?	
Database(s): Medline, Embase	Datum: 5-3-2020
Periode: 2011- maart 2020	Talen: Engels
Literatuurspecialist: Miriam van der Maten	
Toelichting en opmerkingen: Voor deze search is gezocht op de P en de I van de PICOs behorende bij deze uitgangsvraag. Dat wil zeggen dat cataract gecombineerd is met multifocale IOLs of torische IOLs. Alle genoemde artikelen worden gevonden met de zoekopdracht wanneer er niet beperkt wordt met studiefilters op de niet-vergelijkende studie van Chang (2017) na. Deze gaat niet specifiek over cataract. Wanneer er op SRs en RCTs wordt gezocht, worden de drie opgegeven sleutelartikelen van Kessen (2016), Simons (2019) en Cochener (2018) ook gevonden.	

Zoekopbrengst

	EMBASE	OVID/MEDLINE	Ontdubbeld
SRs	37	41	52
RCTs	291	189	350
Totaal	328	230	**402**

Database	Zoektermen		
Embase	#8	#6 OR #7	3
	#7	#3 AND #5 NOT #6	2
	#6	#3 AND #4	3
	#5	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti	2 2
	#4	'meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de	4 6
	#3	#1 AND #2 AND [english]/lim AND [2011-2020]/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	7
	#2	'multifocal intraocular lens'/exp OR 'toric intraocular lens'/exp OR (('lens implant'/exp OR 'intraocular lens':ti,ab,kw OR iol:ti,ab,kw) AND (multifocal:ti,ab,kw OR 'multi-focal':ti,ab,kw OR bifocal:ti,ab,kw OR 'bi-focal':ti,ab,kw OR trifocal:ti,ab,kw OR 'tri-focal':ti,ab,kw	5

		OR accomodative:ti,ab,kw OR toric:ti,ab,kw)) OR ((extended NEAR/3 range):ti,ab,kw) OR ((extended NEAR/3 depth):ti,ab,kw)	
	#1	'cataract'/exp/mj OR cataract*:ti,ab,kw OR ((lens* NEAR/2 (opacit* OR clouding)):ti,ab,kw) OR (('posterior capsule' NEAR/2 opacification):ti,ab,kw) OR 'refractive surgery'/exp/mj OR ((refractive NEAR/3 (surgery OR surgical)):ti,ab)	
Medline (OVID)	1 exp Cataract/ or cataract*.ti,ab,kf. or (lens* adj2 (opacit* or clouding)).ti,ab,kf. or ('posterior capsule' adj2 opacification).ti,ab,kf. or exp Refractive Surgical Procedures/ or (refractive adj3 (surgery or surgical)).ti,ab. (97820) 2 exp "Multifocal Intraocular Lenses"/ or ((exp Lenses, Intraocular/ or exp Lens Implantation, Intraocular/ or 'intraocular lens'.ti,ab,kf. or iol.ti,ab,kf.) and (multifocal or 'multi-focal' or bifocal or 'bi-focal' or trifocal or 'tri-focal' or accomodative or toric).ti,ab,kf.) or (extended adj3 range).ti,ab,kf. or (extended adj3 depth).ti,ab,kf. (5084) 3 1 and 2 (1804) 4 limit 3 to (english language and yr="2011 -Current") (1052) 5 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (433858) 6 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1952535) 7 4 and 5 (41) 8 (4 and 6) not 7 (189) 9 7 or 8 (230)		