Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2021-B-044 Faricimab

Stand: April 2021

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Kriterien gemäß 5. Kapitel § 6 VerfO	**Faricimab [DMÖ]**
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	• Vitrektomie (bei zusätzlich vorliegender vitreomakulärer Traktion) • Laser-/ Fotokoagulation (nur ohne Beteiligung der Fovea)
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschlüsse zur frühen Nutzenbewertung nach §35 a SGB V: • Aflibercept (Beschluss vom 5. März 2015) Visusbeeinträchtigung aufgrund eines diabetischen Makulaödems
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Faricimab	<u>Geplantes Anwendungsgebiet laut Beratungsanforderung:</u> Behandlung einer Visusbeeinträchtigung aufgrund eines diabetischen Makulaödems (DMÖ)
Aflibercept S01LA05 Eylea®	Eylea wird angewendet bei Erwachsenen zur Behandlung […] • einer Visusbeeinträchtigung aufgrund eines diabetischen Makulaödems (DMÖ) (siehe Abschnitt 5.1) (Stand der Fachinformation: Juni 2020)
Fluocinolonacetonid S01BA15 ILUVIEN®	ILUVIEN ist zur Behandlung von Sehstörungen in Verbindung mit chronischem diabetischem Makulaödem (DMÖ) indiziert, das auf verfügbare Therapien nur unzureichend anspricht (siehe Abschnitt 5.1). (Stand der Fachinformation: April 2019)
Dexamethason S01BA01 OZURDEX®	OZURDEX wird angewendet zur Behandlung von Erwachsenen mit: • einer Sehbeeinträchtigung aufgrund eines diabetischen Makulaödems (DMÖ), die pseudophak sind oder auf eine Therapie mit Nicht-Kortikosteroiden unzureichend ansprechen oder bei denen diese als unpassend angesehen wird (Stand der Fachinformation: September 2020)
Ranibizumab S01LA04 Lucentis®	Lucentis wird angewendet bei Erwachsenen zur: • Behandlung einer Visusbeeinträchtigung infolge eines diabetischen Makulaödems (DMÖ) (Stand der Fachinformation: Juli 2020)

Quellen: AMice-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2021-B-044 (Faricimab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	24. Februar 2021

Inhaltsverzeichnis

Abkürzungsverzeichnis

AOA	American Optometric Association
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BCVA	Best corrected visual acuity
CMT	Central macular thickness
CRT	Central retinal thickness
CSMO	Clinically significant macular oedema
CST	Central subfield thickness
DEX	Dexamethasone
DME	Diabetic macular edema
DMO	Diabetic macular oedema
DR	Diabetic retinopathy
ECRI	ECRI Guidelines Trust
ETDRS	Early Treatment Diabetic Retinopathy Study
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IVB	Intravitreal bevacizumab
IVR	Intravitreal ranibizumab
KI	Konfidenzintervall
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
NVAMD	Neovascular age-related macular degeneration
OCT	Optical coherence tomography
OR	Odds Ratio
RR	Relatives Risiko
RVO	Retinal vein occlusion

SIGN	Scottish Intercollegiate Guidelines Network
SSAE	Systemic serious adverse event
TRIP	Turn Research into Practice Database
VEGF	Vascular endothelial growth factor
WHO	World Health Organization

1 Indikation

Zur Behandlung einer Visusbeeinträchtigung aufgrund eines diabetischen Makulaödems bei Erwachsenen

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation diabetisches Makulaödem durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 12.11.2020 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 656 Quellen. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 10 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2015 [2].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 05. März 2015 - Aflibercept (neues Anwendungsgebiet: Visusbeeinträchtigung aufgrund eines diabetischen Makulaödems)

Anwendungsgebiet

Eylea® wird angewendet bei Erwachsenen zur Behandlung einer Visusbeeinträchtigung aufgrund eines diabetischen Makulaödems (DMÖ).

Zweckmäßige Vergleichstherapie

Ranibizumab

Fazit / Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

3.2 Cochrane Reviews

Jorge E et al., 2018 [4].

Monotherapy laser photocoagulation for diabetic macular oedema

Fragestellung

To assess the efficacy and safety of laser photocoagulation as monotherapy in the treatment of diabetic macular oedema.

Methodik

Population:

- adults (aged 18 years or older) diagnosed with type I or II diabetes mellitus with macular oedema as defined by the ETDRS Research Group, regardless of gender and ethnicity

Intervention / Komparator:

- any type of focal/grid macular laser photocoagulation (i.e. argon, diode, micropulse) as monotherapy; we considered trials where comparisons had been made between laser treatment and no intervention or sham treatment.
- We also compared the effects of different types of laser/ wavelengths (e.g. argon blue/green versus krypton red) and subthreshold (e.g. micropulse, non-visible conventional) versus standard macular photocoagulation.

Endpunkte:

- Primary outcomes
  - Improvement or worsening of best-corrected visual acuity (BCVA) defined as gain or loss of 3 lines (0.3 logMAR or 15 ETDRS letters) of BCVA, recorded at 12 months (plus or minus six months) and then yearly.
- Secondary outcomes
  - Continuous BCVA on the logMAR scale (more negative was better; ETDRS letter visual acuity was converted to logMAR).
  - Anatomic measures: partial to complete resolution of macular oedema with stereoscopic fundus photography or biomicroscopy; retinal macular thickness with OCT (thinner was better) and leakage on fluorescein angiography (intravenous fluorescein angiography - IVFA).
  - Contrast sensitivity.
  - Quality of life measures: any validated measurement scale which aimed to measure the impact of visual function loss on participants' quality of life.
  - Local or systemic adverse events or both.
  - Economic data: we performed comparative cost analyses when data were available.

Recherche/Suchzeitraum:

- The Cochrane Eyes and Vision Information Specialist conducted systematic searches in the following databases for RCTs and controlled clinical trials. There were no language or publication year restrictions. The date of the search was 24 July 2018.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 6) (which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (searched 24 July 2018).
- MEDLINE Ovid (1946 to 24 July 2018).
- Embase Ovid (1980 to 24 July 2018).
- LILACS (Latin American and Caribbean Health Science Information database (1982 to 24 July 2018).
- ISRCTN registry (www.isrctn.com/editAdvancedSearch; searched 24 July 2018).
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 24 July 2018).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp; searched 24 July 2018).

Qualitätsbewertung der Studien:

- We assessed the following criteria: random sequence generation, allocation concealment, blinding (masking), incomplete outcome data and other bias (i.e. eyes, rather than participant, unit of analysis without adjustment for correlated data). We also assessed the study to see if it was free from any suggestion of selective outcome reporting. For performance bias, we only evaluated the participants, and for detection bias we evaluated the assessors.

Ergebnisse

Anzahl eingeschlossener Studien:

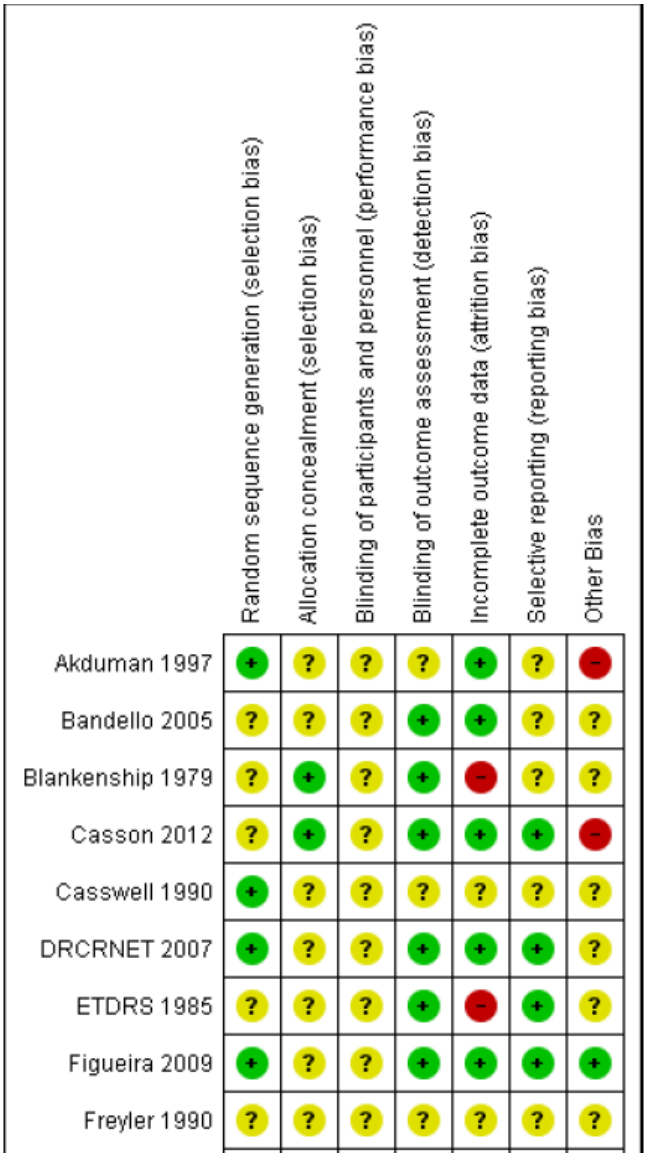
- We included 24 studies (28 reports) with 2650 randomised participants (4416 eyes) in this review.

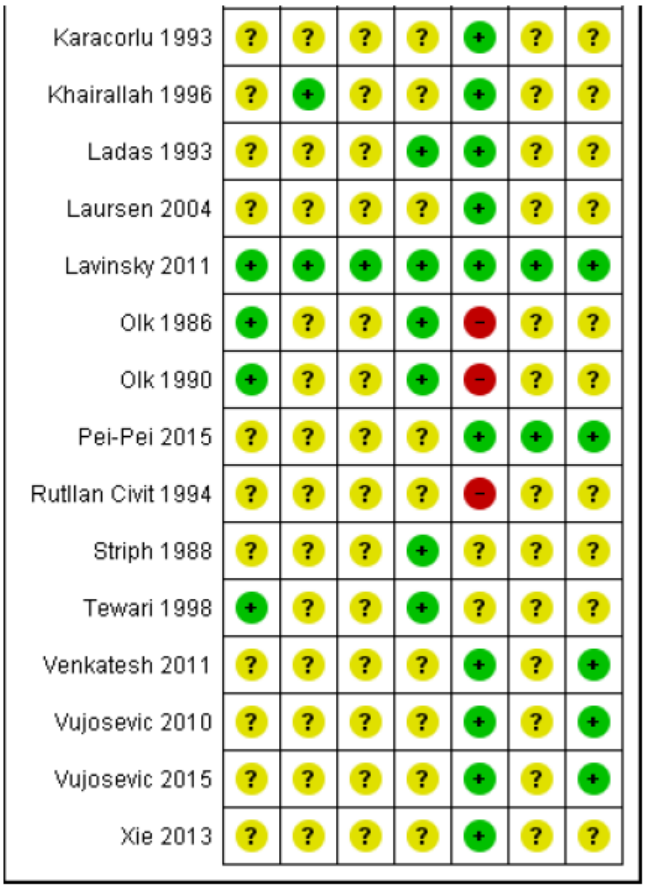
Charakteristika der Population:

- Participants and duration of trials
  - Fifteen studies followed participants for 12 months or less (Akduman 1997; Bandello 2005; Casson 2012; DRCRNET 2007; Figueira 2009; Karacorlu 1993; Khairallah 1996; Laursen 2004; Lavinsky 2011; Pei-Pei 2015; Rutllan Civit 1994; Tewari 1998; Venkatesh 2011; Vujosevic 2010; Xie 2013).
  - Six studies followed participants for more than 12 months (Blankenship 1979; Casswell 1990; ETDRS 1985; Ladas 1993; Olk 1986; Olk 1990).
  - One study did not report the follow-up (Striph 1988), and one study presented a follow-up of six to 24 months (Freyler 1990).
- Types of intervention
  - Four studies randomised participants to macular grid/focal argon laser or no intervention (Blankenship 1979; ETDRS 1985; Ladas 1993; Olk 1986).
  - Nine studies randomised participants to either argon or other types of laser (Akduman 1997; Casswell 1990; Freyler 1990; Karacorlu 1993; Khairallah 1996; Olk 1990; Rutllan Civit 1994; Striph 1988; Tewari 1998).
  - Two studies compared argon versus diode laser (Akduman 1997; Tewari 1998);

- Four studies compared argon versus krypton laser (Casswell 1990; Khairallah 1996; Olk 1990; Striph 1988);
- and three studies compared argon versus dye laser (Freyler 1990; Karacorlu 1993; Rutllan Civit 1994).
- One study compared standard modified ETDRS grid technique with a mild macular grid (MMG) technique (DRCRNET 2007).
- One study compared subthreshold micropulse yellow laser versus subthreshold micropulse infrared laser (Vujosevic 2015).

Qualität der Studien:




Karacorlu 1993
Khairallah 1996
Ladas 1993
Laursen 2004
Lavinsky 2011
Olk 1986
Olk 1990
Pei-Pei 2015
Rutllan Civit 1994
Striph 1988
Tewari 1998
Venkatesh 2011
Vujosevic 2010
Vujosevic 2015
Xie 2013

Studienergebnisse:

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Laser photocoagulation versus no intervention for diabetic macular oedema

Laser photocoagulation versus no intervention for diabetic macular oedema						
Participant or population: diabetic macular oedema **Settings:** hospitals **Intervention:** laser **Comparison:** no intervention						
Outcomes	**Illustrative comparative risks* (95% CI)** **Assumed risk** Macular laser	**Corresponding risk** No intervention	**Relative effect (95% CI)**	**No of eyes (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
Improvement of BCVA defined as ≥ 15 ETDRS letters (i.e. 3 ETDRS lines or 0.3 logMAR Follow-up: 12 months	None of the included studies reported this outcome.					
Worsening of BCVA defined as ≥ 15 ETDRS letters (i.e. 3 ETDRS lines or 0.3 logMAR Follow-up: 12 months	**116 per 1000**	**67 fewer per 1000** (93 fewer to 12 fewer)	**RR 0.42** (0.20 to 0.90)	3703 eyes (4 studies)	⊕⊕⊕⊖ **Moderate**	Assumed risk taken from ETDRS 1985 study.¤ Limitation due to incomplete outcome data (–1).
Continuous BCVA on the logMAR scale (lower logMAR scores represent better visual acuity)	None of the included studies reported this outcome.					
Anatomic measures: partial to complete resolution of the macular oedema with stereoscopic fundus photography or biomicroscopy; leakage on fluorescein angiography (IVFA); and, if available, retinal macular thickness with OCT Follow-up: 36 months	**460 per 1000**	**253 more per 1000** (138 more to 396 more)	**RR 1.55** (1.30 to 1.86)	350 (1 study)	⊕⊕⊕⊖ **Moderate**	Limitation due to incomplete outcome data (–1).
Clinically significant macular oedema						
Central retinal thickness (µm)	None of the included studies reported this outcome.					
Quality of life measures	None of the included studies reported this outcome.					
Adverse events	ETDRS 1985 observed very few adverse effects of focal photocoagulation (not statistically significant) on central visual fields and no adverse effects on colour vision. Olk 1986 reported 1 case or premacular fibrosis possibly due to "too heavy" laser burns in the macula.					

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

BCVA: best-corrected visual acuity; **CI:** confidence interval; **ETDRS:** Early Treatment of Diabetic Retinopathy Study; **IVFA:** intravenous fluorescein angiography; **logMAR:** logarithm of the minimal angle of resolution; **OCT:** optical coherence tomography; **RR:** risk ratio.

GRADE Working Group grades of evidence

High-certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate-certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low-certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low-certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

¤The assumed risk was taken from the study that provided the most evidence, i.e. had the largest weight in the meta-analysis.

Summary of findings 2. Subthreshold versus standard macular photocoagulation for diabetic macular oedema

Subthreshold versus standard macular photocoagulation for diabetic macular oedema						
Participant or population: diabetic macular oedema **Settings:** hospitals **Intervention:** subthreshold **Comparison:** standard macular photocoagulation						
Outcomes	**Illustrative comparative risks* (95% CI)** **Assumed risk**	**Corresponding risk**	**Relative effect (95% CI)**	**No of eyes (studies)**	**Certainty of the evidence (GRADE)**	**Comments**

	Standard macular photocoagulation	Subthreshold photocoagulation				
Improvement of BCVA defined as ≥ 15 ETDRS letters (i.e. 3 ETDRS lines or 0.3 logMAR, recorded at 12 months (plus or minus 6 months).	**71 per 1000**	**49 fewer per 1000** (70 fewer to 432 more)	**RR 0.31** (0.01 to 7.09)	29 (1)	⊕⊖⊖⊖ **Very low**	Conventional laser used for subthreshold photocoagulation. Assumed risk taken from Bandello 2005 study.[a] Limitation due to unclear risk of bias (-1) Serious limitation due to imprecision (–2).
Worsening of BCVA defined as ≥ 15 ETDRS letters (i.e. 3 ETDRS lines or 0.3 logMAR, recorded at 12 months (plus or minus 6 months). Follow-up: 12 months	**142 per 1000**	10 fewer per 1000 (121 fewer to 676 more)	**RR 0.93** (0.15 to 5.76)	29 (1)	⊕⊖⊖⊖ **Very low**	Conventional laser used for subthreshold photocoagulation. Assumed risk taken from Bandello 2005 study.[a] Limitation due to unclear risk of bias (-1) Serious limitation due to imprecision (–2).
Continuous BCVA: final (or change of) visual acuity Follow-up: 12 months **Overall** (lower logMAR scores represent better visual acuity)	The mean change in continuous BCVA was **–0.03 logMAR** (change 0.04 to –0.08 logMAR and final BCVA 0.3 to 0.55 logMAR)	The mean change in continuous BCVA in the intervention group was on mean **–0.02 logMAR better (–0.07 better to 0.03 worse)**	-	385 (7)	⊕⊕⊖⊖ **Low**	Standard, micropulse and nanopulse laser used for subthreshold photocoagulation. Limitation due to unclear risk of bias (–1). Limitation due to heterogeneity (–1). Micropulse laser was possibly better than standard laser: –0.08 logMAR (95% CI –0.16 to 0.0), and also better as compared to the subgroup analysis on nanopulse and non-visible conventional subthreshold lasers (change 0.0 and 0.04 logMAR respectively, P = 0.07 for subgroup differences).
Anatomic measures: partial to complete resolution of the macular oedema with stereoscopic fundus photography or biomicroscopy; retinal macular thickness with OCT and leakage on fluorescein angiography (IVFA) Follow-up: 12 months	**714 per 1000**	**378 fewer per 1000** (564 fewer to 21 more)	**RR 0.47** (0.21 to 1.03)	29 (1)	⊕⊕⊖⊖ **Low**	Conventional laser used for subthreshold photocoagulation. Assumed risk taken from Bandello 2005 study.[a] Limitation due to unclear risk of bias (-1) Serious limitation due to imprecision (–2).
Final (or change of) central retinal thickness (µm): Follow-up: 12 months **Overall**	The mean change in central retinal thickness was **-126** µm (change -129 to 43 µm and final 289 to 310 µm)	The mean difference in central retinal thickness was on average **-9.1 µm thinner (-26.2 thinner to 8.0 thicker)**	-	385 (7)	⊕⊕⊕⊖ **Moderate**	Conventional, micropulse and nanopulse laser used for subthreshold photocoagulation. Assumed risk from Lavinsky 2011. Limitation related to unclear risk of bias (–1). A thickness change of more than 10% or 50 µm is considered clinically important.
Quality of life measures	None included studies reported this outcome.					
Adverse events	Bandello 2005 found no central 10° visual loss using perimetry for both subthreshold and standard macular photocoagulation. Vujosevic 2010 used microperimetry and found no decrease in central sensitivity with micropulse laser, but a significant decrease in the standard photocoagulation group.					

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

BCVA: best-corrected visual acuity; **CI:** confidence interval; **IVFA:** intravenous fluorescein angiography; **logMAR:** logarithm of the minimal angle of resolution; **NA:** not available; **OCT:** optical coherence tomography; **RR:** risk ratio.

GRADE Working Group grades of evidence

High-certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate-certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low-certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low-certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]The assumed risk was taken from the study that presented the bigger weight in the meta-analysis.

Anmerkung/Fazit der Autoren

Macular grid or focal laser has been used for decades to prevent visual loss in people with diabetic macular oedema (DMO), and has been replaced by intravitreal injection of antiangiogenic drugs. The benefit achieved with macular laser is of moderate-certainty evidence mostly due to inadequate reporting in trials conducted many years ago.

There is moderate-certainty evidence that subthreshold photocoagulation is probably similar to standard photocoagulation, but any benefit is very imprecisely estimated. Moreover, a post-hoc subgroup analysis suggested that subthreshold photocoagulation is more effective when delivered using a micropulse laser.

Mehta H et al., 2018 [6].

Anti-vascular endothelial growth factor combined with intravitreal steroids for diabetic macular oedema

Fragestellung

To assess the effects of intravitreal agents that block vascular endothelial growth factor activity (anti-VEGF agents) plus intravitreal steroids versus monotherapy with macular laser, intravitreal steroids or intravitreal anti-VEGF agents for managing diabetic macular oedema

Methodik

Population:

- people with diabetic macular oedema (DMO) of all ages and both sexes as diagnosed in the included studies. We included trials where the eyes from one participant had received different treatments

Intervention / Komparator:

- We included RCTs comparing intravitreal anti-VEGF plus intravitreal steroids versus intravitreal anti-VEGF alone, intravitreal steroids alone or macular laser alone for managing DMO

Endpunkte:

- Primary outcomes
  - Visual acuity (The primary outcome for this review was mean change in best corrected visual acuity (BCVA) from baseline in the treated eye. We also assessed the proportion of eyes with at least 10 ETDRS letters' (equivalent to 2 ETDRS lines') change (Bailey 1976). Our primary analysis was at one year after randomisation.)
- Secondary outcomes
  - Visual acuity (We also assessed the above visual acuity outcomes at six months and at two years.)
  - Anatomical outcomes (Mean change in central macular thickness (µm) as measured by optical coherence tomography (OCT) at six months, one year and two years.)
- Safety
  - We reported the frequency and severity of ocular or systemic adverse outcomes in the studies. In particular, we identified the following ocular adverse events reported in included randomised clinical trials: endophthalmitis, retinal tears or detachment,

intraocular inflammation, development of cataract, raised intraocular pressure and need for glaucoma drainage surgery. We also recorded systemic side effects including thromboembolic events (as defined by the Antiplatelet Trialists' Collaboration), non-ocular haemorrhage and hypertension (APTC 1994; Boyer 2009).

- Economic data
  - We reported any cost benefit data in the included studies.
- Quality of life data
  - We reported any quality of life data in the included studies.

Recherche/Suchzeitraum:

- The Cochrane Eyes and Vision Information Specialist conducted systematic searches in the following databases for RCTs and controlled clinical trials. There were no language or publication year restrictions. The date of the search was 21 February 2018.
  - Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 1) (which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (searched 21 February 2018);
  - MEDLINE Ovid (1946 to 21 February 2018);
  - Embase Ovid (1980 to 21 February 2018);
  - LILACS (Latin American and Caribbean Health Science Information database (1982 to 21 February 2018);
  - ISRCTN registry (www.isrctn.com/editAdvancedSearch; searched 21 February 2018);
  - US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 21 February 2018);
  - World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp; searched 21 February 2018).

Qualitätsbewertung der Studien:

- Two review authors independently assessed the risk of bias of the selected trials according to Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We considered the following main criteria:
  - Selection bias: random sequence generation, allocation concealment.
  - Performance bias: masking of participants, researchers and outcome assessors.
  - Attrition bias: loss to follow-up, rates of compliance.
  - Reporting bias: selective outcome reporting.Cochrane Risk of Bias

Ergebnisse

Anzahl eingeschlossener Studien:

- We included 13 publications of eight RCTs in this review (DRCRnet U 2018; Lim 2012; Maturi 2015; Neto 2017; Riazi-Esfahani 2017; Shoeibi 2013; Soheilian 2012; Synek 2011). Most studies used the unlicensed anti-VEGF agent bevacizumab and one study used ranibizumab (DRCRnet U 2018). Regarding the use of intravitreal steroid, six studies used intravitreal triamcinolone, whilst two studies used the intravitreal dexamethasone implant (DRCRnet U 2018; Maturi 2015).

- The included studies assessed the combination of intravitreal bevacizumab (off-label) or ranibizumab and either intravitreal triamcinolone (off-label) or dexamethasone implants for the management of diabetic macular oedema (DMO). There were no published randomised clinical trial results on the combination of licensed VEGF inhibitors with intravitreal steroid agents.
- DRCRnet U 2018:

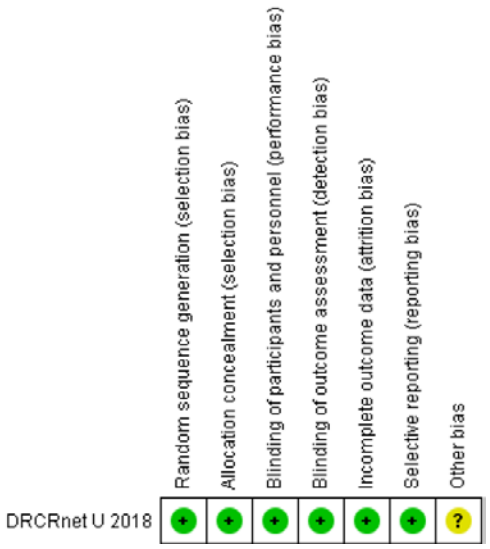
  Maturi RK, Glassman AR, Liu D, Beck RW, Bhavsar AR, Bressler NM, et al. Effect of adding dexamethasone to continued ranibizumab treatment in patients with persistent diabetic macular edema: a DRCR network phase 2 randomized clinical trial. JAMA Ophthalmology 2018;136(1):29-38.

  NCT01945866. Phase II combination steroid and anti-VEGF for persistent DME [Short-term evaluation of combination corticosteroid+anti-VEGF treatment for persistent central-involved diabetic macular edema following anti-VEGF therapy]. clinicaltrials.gov/ct2/show/NCT01945866 (first received 19 September 2013).

Charakteristika der Population:

- Two of the RCTs (Shoeibi 2013; Soheilian 2012) had used selected population subgroups referencing participants from previous trials (Ahmadieh 2008; Soheilian 2009;Yaseri 2014).

Qualität der Studien:



Studienergebnisse:

Aus DRCRnet U 2018

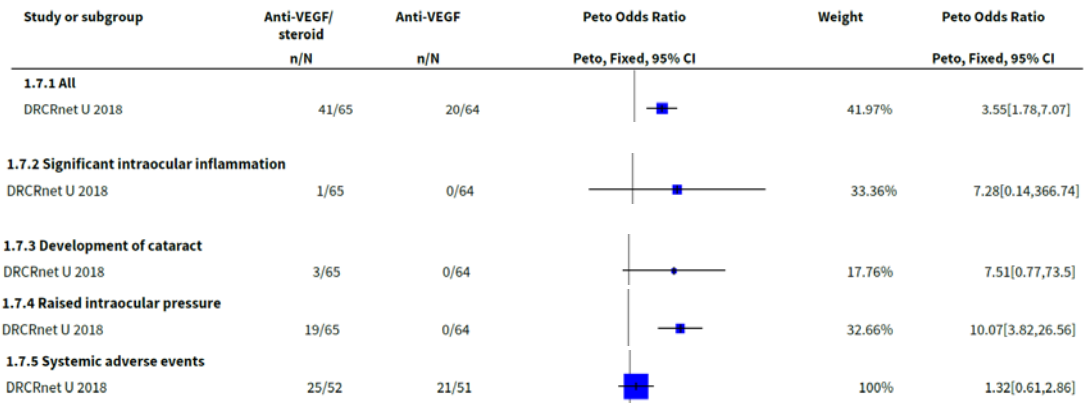
Analysis 1.1. Comparison 1 Anti-VEGF and steroid versus anti-VEGF alone, Outcome 1 Mean change in visual acuity at 6 months.

Study or subgroup	Anti-VEGF/steroid N	Anti-VEGF/steroid Mean(SD)	Anti-VEGF N	Anti-VEGF Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
DRCRnet U 2018	63	2.7 (9.8)	64	3 (7.1)		31.89%	-0.3[-3.28,2.68]

Analysis 1.4. Comparison 1 Anti-VEGF and steroid versus anti-VEGF alone, Outcome 4 Mean change in central macular thickness at 6 months.

Study or subgroup	Anti-VEGF/steroid N	Anti-VEGF/steroid Mean(SD)	Anti-VEGF N	Anti-VEGF Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
DRCRnet U 2018	63	-110 (86)	64	-62 (97)		26.49%	-48[-79.87,-16.13]

Analysis 1.7. Comparison 1 Anti-VEGF and steroid versus anti-VEGF alone, Outcome 7 Adverse events.



Anmerkung/Fazit der Autoren

Combination of intravitreal anti-VEGF plus intravitreal steroids does not appear to offer additional visual benefit compared with monotherapy for DMO; at present the evidence for this is of low certainty.

There was an increased rate of cataract development and raised intraocular pressure in eyes treated with anti-VEGF plus steroid versus anti-VEGF alone. Patients were exposed to potential side effects of both these agents without reported additional benefit. The majority of the evidence comes from studies of bevacizumab and triamcinolone used as primary therapy for DMO.

Kommentare zum Review

Im Cochrane Review wurden auch Wirkstoffe untersucht, für die im vorliegenden Anwendungsgebiet keine Zulassung vorliegt. Es wurden nur Ergebnisse zu im Anwendungsgebiet zugelassenen Therapieoptionen extrahiert. Das Fazit der Autorinnen und Autoren des Cochrane Reviews bezieht sich auf alle darin eingeschlossenen Primärstudien.

Virgili G et al., 2018 [10].

Anti-vascular endothelial growth factor for diabetic macular oedema: a network meta-analysis

Fragestellung

The objective of this updated review is to compare the effectiveness and safety of the different anti-VEGF drugs in preserving and improving vision and quality of life using network meta-analysis methods.

Methodik

Population:

- People with DMO for whom anti-VEGF treatment is indicated.

Intervention / Komparator:

- Any antiangiogenic drug with anti-VEGF modalities compared with another drug with anti-VEGF modalities, laser treatment, sham treatment or no treatment.

Endpunkte:

- Primary outcomes
  - Best-corrected visual acuity (BCVA) expressed as the proportion of participants with at least 15 ETDRS letters (3 ETDRS lines or 0.3 logMAR) of improvement in BCVA from baseline to 12 months.
- Secondary outcomes
  - Mean change in BCVA from baseline to 12 months, measured using ETDRS charts.
  - Mean change in central retinal thickness (CRT), from baseline to 12 months, measured using optical coherence tomography (OCT).
  - Mean change in quality of life from baseline to 12 months, measured using a validated instrument.
- Adverse events
  - All-cause mortality.
  - Arterial thromboembolic events.
  - Systemic serious adverse events (SSAEs).

Recherche/Suchzeitraum:

- The Cochrane Eyes and Vision Information Specialist conducted systematic searches in the following databases for randomised controlled trials and controlled clinical trials. There were no language or publication year restrictions. The date of the search was 26 April 2017.
  - Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 3) (which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (searched 26 April 2017);
  - MEDLINE Ovid (1946 to 26 April 2017);
  - Embase Ovid (1980 to 26 April 2017);
  - LILACS (Latin American and Caribbean Health Science Information database (1982 to 26 April 2017);
  - ISRCTN registry (www.isrctn.com/editAdvancedSearch; searched 26 April 2017);
  - US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 26 April 2017);
  - World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp; searched 26 April 2017).

Qualitätsbewertung der Studien:

- Two review authors independently assessed the included trials for bias according to the methods described in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011b). The following parameters were assessed: sequence generation; allocation concealment; masking (blinding) of participants, personnel and outcome assessors; incomplete outcome data; selective outcome reporting.
- We followed Salanti 2014 to assess the risk of bias of mixed evidence (mixed evidence not defined previously).
  - 1. Summary risk of bias for each trial: we considered all domains but gave more importance to allocation concealment and masking of outcome assessor.

- 2. Summary risk of bias for the mixed evidence: based on the percentage contribution of each direct comparison to each network estimate using the contribution plot (Chaimani 2013). We finally integrated the risk of bias of a given comparison with the assessment of transitivity, or similarity of the characteristics of the studies. We expected the transitivity assumption would hold as long as treatment comparisons were not related to:
    - acute versus chronic DMO, defined using the cut-off of
    - three or more years of duration;
    - average severity of DMO using OCT CRT of 400 micrometres as a cut-off;
    - treatment regimen, such as monthly versus less than monthly and number of injections in the first year;
    - drug dose for ranibizumab, since this is commercially available in two doses (0.3 mg in the USA, 0.5 mg otherwise);
    - whether the trial was industry sponsored.

Ergebnisse

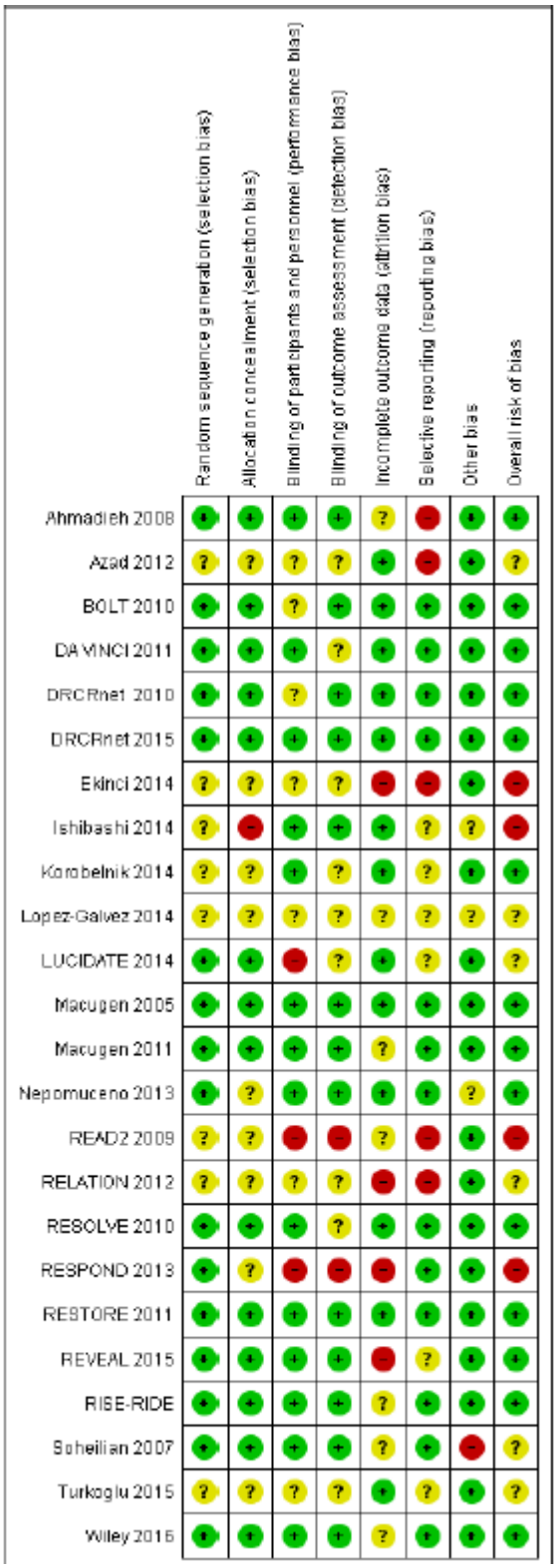
Anzahl eingeschlossener Studien:

- We included a total of 24 studies in this updated systematic review and network meta-analysis. BOLT 2010, DA VINCI 2011, Ishibashi 2014, Korobelnik 2014, Macugen 2005, Macugen 2011, READ2 2009, RELATION 2012, RESOLVE 2010, RESPOND 2013, RESTORE 2011, and RISE-RIDE were industry-sponsored, multicenter RCTs conducted in the USA or Europe, whereas REVEAL 2015 was industry-sponsored but conducted in Asia.
- Ahmadieh 2008, Azad 2012, Ekinci 2014, LUCIDATE 2014, Nepomuceno 2013, Soheilian 2007, and Turkoglu 2015 were independent studies conducted in Brazil, India, Iran, Turkey, and the UK, five of which included bevacizumab. DRCRnet 2010, DRCRnet 2015, Wiley 2016 were publicly-sponsored studies, mainly by the US National Eye Institute, and conducted in the USA or UK. DRCRnet 2015 was the only large parallel-arm study that compared all commercially available drugs (aflibercept, bevacizumab, ranibizumab) and was a large publicly-funded trial comparing aflibercept, bevacizumab and ranibizumab with monthly monitoring and treatment as needed (PRN). Wiley 2016 was a cross-over trial comparing the same three drugs. Lopez-Galvez 2014 was an open-label trial comparing ranibizumab with laser; it was conducted in Spain and results were available only in abstract form.

Charakteristika der Population:

- Trials included participants with DMO diagnosed clinically, and often these trials used OCT for confirming macular centre involvement. Baseline visual acuity of participants was generally between 20/200 and 20/40. Most trials required a three- to six-month interval from previous central or peripheral laser, and a few small studies required that participants had not received previous antiangiogenic treatment.

Qualität der Studien:



Studienergebnisse:

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Antiangiogenic therapy versus control

Patient or population: people with diabetic macular oedema
Settings: ophthalmology clinics
Interventions: laser photocoagulation, aflibercept, bevacizumab, ranibizumab

Outcomes	Assumed risk*	Corresponding risk and relative risk** (95% CI), mixed evidence			Certainty of evidence and reason for downgrading
	Laser photocoagulation	Aflibercept	Bevacizumab	Ranibizumab	
Gain 3+ lines of visual acuity at 1 year	**100 per 1000**	**366 per 1000** (279 to 479) **RR: 3.66 (2.79 to 4.79)**	**247 per 1000** (181 to 337) **RR: 2.47 (1.81 to 3.37)**	**276 per 1000** (212 to 359) **RR: 2.76 (2.12 to 3.59)**	⊕⊕⊕⊕ high
Visual acuity change at 1 year Measured on the logMAR scale, range −0.3 to 1.3. Higher values represent worse visual acuity.	On average visual acuity improved by **−0.01 logMAR** units in the laser group between the start of treatment and 1 year (effectively no change)	Average change in visual acuity was **−0.20 (−0.22 to −0.17) logMAR units better** with aflibercept compared with laser photocoagulation	Average change in visual acuity was **−0.12 (−0.15 to −0.09) logMAR units better** with bevacizumab compared with laser photocoagulation	Average change in visual acuity was **−0.12 (−0.14 to −0.10) logMAR units better** with ranibizumab compared with laser photocoagulation	⊕⊕⊕⊕ high for aflibercept and ranibizumab ⊕⊕⊕ moderate for bevacizumab (−1 for inconsistency of indirect versus direct evidence)
Central retinal thickness μm (CRT) change at 1 year The aim of treatment is to reduce central retinal thickness so thinner is better.	On average CRT changed by **−64 μm** in the laser group between the start of treatment and 1 year (became thinner)	Average change in CRT was **−114 (−147 to −81) μm more (thinner) with aflibercept** compared with laser photocoagulation	Average change in CRT was **−46 (−78 to −14) μm more (thinner)** with bevacizumab compared with laser photocoagulation	Average change in CRT was **−75 (−100 to −50) μm more (thinner)** with ranibizumab compared with laser photocoagulation	⊕⊕⊕⊕ high
Quality of life: NEI-VFQ composite score at 6 to 12 months An improvement by 5 units is clinically significant.	On average the composite score improved by +2 units in the laser group between the start of treatment and 6 to 12 months			Average change in composite score was 5.14 (2.96 to 7.32) with ranibizumab compared with laser photocoagulation	⊕⊕⊕ moderate (−1 for risk of bias)
All serious systemic adverse events at 1 to 2 years	**200 per 1000**	**196 per 1000** (166 to 232) **RR: 0.98 (0.83 to 1.16)**	**186 per 1000** (146 to 238) **RR: 0.93 (0.73 to 1.19)**	**194 per 1000** (160 to 234) **RR: 0.97 (0.80 to 1.17)**	⊕⊕⊕⊕ high
Arterial thromboembolic events at 1 to 2 years	**45 per 1000**	**38 per 1000** (16 to 94) **RR: 0.88 (0.37 to 2.13)**	**41 per 1000** (15 to 117) **RR: 0.94 (0.33 to 2.66)**	**48 per 1000** (23 to 101) **RR: 1.09 (0.52 to 2.29)**	⊕⊕ low (−2 for imprecise estimates)
Death at 1 to 2 years	**20 per 1000**	**20 per 1000** (7 to 61) **RR: 1.01 (0.34 to 3.03) a**	**32 per 1000** (9 to 114) **RR: 1.61 (0.45 to 5.69)**	**18 per 1000** (8 to 40) **RR: 0.90 (0.40 to 2.01)**	⊕⊕ low for bevacizumab and aflibercept (−2 for imprecise estimates) ⊕ very low for aflibercept (additional −1 direct evidence inconsistent, higher risk)

The **assumed risk** in the laser group was estimated as the row sum of the events divided by the row sum of the participants (eyes) for dichotomous variables, and as the (unweighted) median change of visual acuity or central retina thickness
The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
** The risk ratio was estimated from mixed (direct and indirect) comparisons.
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High-certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate-certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low-certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low-certainty: we are very uncertain about the estimate.

Ranibizumab versus aflibercept for diabetic macular oedema

Patient or population: people with diabetic macular oedema
Settings: ophthalmology clinics
Interventions: aflibercept, ranibizumab

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI), mixed evidence**	Certainty of the evidence (GRADE)	Reason for downgrading certainty of evidence
	Assumed risk	Corresponding risk			
	Aflibercept	Ranibizumab			
Gain 3+ lines of visual acuity at 1 year	370 per 1000	278 per 1000 (222 to 348)	RR: 0.75 (0.60 to 0.94)	⊕⊕⊕ moderate	−1 for imprecision as confidence intervals include both clinically important and clinically unimportant effects
Visual acuity change at 1 year Measured on the logMAR scale, range −1.3 to 1.3. Higher values represent worse visual acuity.	On average visual acuity improved by −0.23 logMAR units in the aflibercept group between the start of treatment and 1 year	Average change in visual acuity was **0.08 (0.05 to 0.11) logMAR units worse** with ranibizumab compared with aflibercept		⊕⊕⊕ moderate	−1 for imprecision as confidence intervals include both clinically important and clinically unimportant effects
Central retinal thickness μm (CRT) change at 1 year The aim of treatment is to reduce central macular thickness so thinner is better.	On average CRT changed by −181 μm in the aflibercept group between the start of treatment and 1 year (became thinner)	Average change in CRT was **39 (2 to 76) μm more (thicker) with ranibizumab** compared with aflibercept		⊕⊕ low	−1 for high heterogeneity in two direct comparisons and large predictive intervals −1 for imprecision
Quality of life at 1 year	No data available.				
All serious systemic adverse events at 1 to 2 years	345 per 1000	338 per 1000 (283 to 411)	RR 0.98 (0.82 to 1.19)	⊕⊕⊕⊕ high	
Arterial thromboembolic events at 1 to 2 years	60 per 1000	74 per 1000 (29 to 191)	RR 1.24 (0.48 to 3.19)	⊕ very low	Inconsistency between direct and indirect evidence (−1), and imprecise estimates (−2)
Death at 1 to 2 years	30 per 1000	35 per 1000 (11 to 108)	RR 1.16 (0.38 to 3.58)	⊕ very low	Inconsistency between direct and indirect evidence (−1), and imprecise estimates (−2)

The **assumed risk** in the aflibercept group was estimated as the row sum of the events divided by the row sum of the participants (eyes) for dichotomous variables, and as the (unweighted) median change of visual acuity or central retina thickness
The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
** The risk ratio was estimated from mixed (direct and indirect) comparisons.
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High-certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate-certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low-certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low-certainty: we are very uncertain about the estimate.

Table 3. Gain of 3 or more lines of visual acuity at 12 months: direct (upper-right triangle) and mixed (lower-left triangle) estimates

LASER	**3.82 (2.61 to 5.58)**	**2.74 (1.34 to 5.61)**		**2.82 (1.82 to 4.38)**	**1.88 (1.31 to 2.70)**	**2.30 (1.74 to 3.03)**	
3.66 (2.79 to 4.79)	**AFLI**	**0.68 (0.52 to 0.90)**		**0.77 (0.59 to 0.99)**			
2.47 (1.81 to 3.37)	**0.68 (0.53 to 0.86)**	**BEVA**		1.14 (0.88 to 1.48)			
1.70 (0.58 to 4.94)	0.46 (0.16 to 1.34)	0.69 (0.24 to 1.89)	**PEGA**				**0.51 (0.30 to 0.89)**
2.76 (2.12 to 3.59)	**0.75 (0.60 to 0.94)**	1.11 (0.87 to 1.43)	1.62 (0.58 to 4.57)	**RANI**		0.90 (0.67 to 1.21)	**0.31 (0.13 to 0.76)**
2.02 (1.46 to 2.81)	**0.55 (0.37 to 0.82)**	0.82 (0.54 to 1.24)	1.19 (0.40 to 3.58)	0.73 (0.51 to 1.06)	**RANI-DL**	1.10 (0.80 to 1.51)	
2.33 (1.81 to 3.00)	**0.64 (0.47 to 0.86)**	0.94 (0.68 to 1.31)	1.37 (0.47 to 3.99)	0.85 (0.65 to 1.09)	1.15 (0.85 to 1.56)	**RANI-PL**	
0.87 (0.35 to 2.17)	**0.24 (0.10 to 0.59)**	**0.35 (0.14 to 0.87)**	**0.51 (0.30 to 0.89)**	**0.32 (0.13 to 0.76)**	0.43 (0.17 to 1.11)	**0.37 (0.15 to 0.93)**	**SHAM**

P value for overall inconsistency = 0.883 in the network meta-analysis.
Values in the table are risk ratios and 95% confidence intervals. Values in **bold** are ones where the 95% confidence intervals does not include 1 (null effect).

Table 4. Mean visual acuity change at 12 months: direct (upper-right triangle) and mixed (lower-left triangle) estimates

LASER	**−0.20 (−0.24 to −0.17)**	**−0.20 (−0.28 to −0.12)** [a]		**−0.11 (−0.13 to −0.08)**	**−0.12 (−0.16 to −0.075)**	**−0.10 (−0.13 to −0.08)**	
−0.20 (−0.22 to −0.17)	**AFLI**	**0.07 (0.03 to 0.11)**		**0.04 (0.00 to 0.08)**			
−0.12 (−0.15 to −0.09) [a]	**0.08 (0.05 to 0.11)**	**BEVA**		−0.02 (−0.05 to 0.01)			
0.01 (−0.09 to 0.07)	**0.19 (0.11 to 0.27)**	**0.11 (0.04 to 0.19)**	**PEGA**				**0.08 (0.03 to 0.13)**
−0.12 (−0.14 to −0.10)	**0.08 (0.05 to 0.11)**	0.00 (−0.02 to 0.03)	**−0.11 (−0.19 to −0.04)**	**RANI**		0.01 (−0.02 to 0.03)	**0.23 (0.15 to 0.32)**
−0.11 (−0.13 to −0.09)	**0.08 (0.04 to 0.13)**	0.01 (−0.04 to 0.06)	**−0.11 (−0.19 to −0.02)**	0.00 (−0.04 to 0.05)	**RANI-DL**	0.00 (−0.05 to 0.05)	
−0.11 (−0.14 to −0.08)	**0.09 (0.06 to 0.12)**	0.01 (−0.02 to 0.05)	**−0.10 (−0.18 to −0.02)**	0.01 (−0.01 to 0.03)	0.01 (−0.04 to 0.05)	**RANI-PL**	
0.08 (0.01 to 0.15)	**0.28 (0.21 to 0.35)**	**0.20 (0.13 to 0.27)**	**0.09 (0.06 to 0.12)**	**0.20 (0.13 to 0.27)**	**0.20 (0.11 to 0.28)**	**0.19 (0.12 to 0.26)**	**SHAM**

[a] P value for differences between direct and indirect estimates = 0.031 in the network meta-analysis.
P value for overall inconsistency = 0.665.

Table 5. Mean central retinal thickness change at 12 months: direct (upper-right triangle) and mixed (lower-left triangle) estimates

LASER	**−119 (−143 to −95)**	**−44 (−82 to −5)**	**−71 (−120 to −22)^**	**−35 (−62 to −8)**	**−64 (−103 to −25)[b]***	
−114 (−147 to −81)	**AFLI**	**68 (43 to 94)**	22 (−4 to 48)			
−46 (−78 to −14)	**68 (29 to 108)**	**BEVA**	**−38 (−56 to −20)**			**132 (72 to 187)**
−75 (−100 to −50)	**39 (2 to 76)**	**−29 (−58 to −1)**	**RANI**		−19 (−39 to 2) [a]	**1470 (95 to 196)**
−57 (−111 to −2)	57 (−6 to 120)	−11 (−73 to 51)	18 (−40 to 76)	**RANI-DL**	6 (−22 to 34)	
−72.90 (−103 to −42)[b]	41 (−2 to 84)	−27 (−68 to 13)	2 (−31 to 35)[a]	−16 (−71 to 38)	**RANI-PL**	
77 (18 to 137)	**191 (127 to 256)**	**123 (67 to 179)**	**153 (97 to 208)**	**134 (55 to 213)**	**150 (87 to 214)**	**SHAM**

[a] P value for differences between direct and indirect estimates = 0.003.
[b] P value for differences between direct and indirect estimates = 0.044.
* P value for heterogeneity = 0.002; I^2 = 80% in the direct meta-analysis.
^ P value for heterogeneity = 0.000; I^2 = 91% in the direct meta-analysis.
P value for overall inconsistency = 0.209 in the network meta-analysis.

Table 7. All serious systemic adverse events (longest available follow-up)

CONTROL	0.95 (0.75 to 1.20)	1.29 (0.43 to 3.84)	1.02 (0.67 to 1.53)	0.98 (0.76 to 1.25)
0.98 (0.83 to 1.16)	**AFLI**	0.95 (0.75 to 1.20)		1.04 (0.83 to 1.32)
0.93 (0.73 to 1.19)	0.95 (0.76 to 1.18)	**BEVA**		0.96 (0.77 to 1.20)
1.02 (0.64 to 1.64)	1.04 (0.63 to 1.72)	1.09 (0.64 to 1.86)	**PEGA**	
0.97 (0.80 to 1.17)	0.98 (0.82 to 1.19)	1.04 (0.84 to 1.28)	0.95 (0.57 to 1.58)	**RANI**

P value for overall inconsistency = 0.859.

Table 8. Antiplatelet Trialists Collaboration arterial thromboembolic events at the longest available follow-up

CONTROL	1.50 (0.81 to 2.79)	0.92 (0.17 to 5.12)	0.78 (0.31 to 1.97)	0.64 (0.38 to 1.07)
0.88 (0.37 to 2.13)	**AFLI**	1.46 (0.71 to 2.98)		2.26 (1.15 to 4.23)[a]
0.94 (0.33 to 2.66)	1.06 (0.36 to 3.11)	**BEVA**		1.51 (0.85 to 2.69)
0.79 (0.20 to 3.02)	0.89 (0.18 to 4.43)	0.83 (0.15 to 4.61)	**PEGA**	
1.09 (0.52 to 2.29)	1.24 (0.48 to 3.19)[a]	1.17 (0.43 to 3.13)	1.17 (0.43 to 3.16)	**RANI**

[a] P value for differences between direct and indirect estimates = 0.002.
P value for overall inconsistency = 0.274 in the network meta-analysis.

Table 9. All-cause mortality at the longest available follow-up

CONTROL	1.69 (0.30 to 9.42)[a]	0.95 (0.06 to 14.85)	0.82 (0.25 to 2.65)	0.64 (0.32 to 1.25)[d]
1.01 (0.34 to 3.03)[a]	AFLI	2.67 (0.97 to 7.37)[b]		2.26 (0.80 to 6.40)[c]
1.61 (0.45 to 5.69)	1.59 (0.43 to 5.94)[b]	BEVA		0.85 (0.40 to 1.83)
0.81 (0.16 to 4.03)	0.81 (0.12 to 5.62)	0.51(0.07 to 3.90)	PEGA	
0.90 (0.40 to 2.01)	1.16 (0.38 to 3.58)[c]	0.73 (0.22 to 2.37)	1.44 (0.24 to 8.48)	RANI

[a] P value for differences between direct and indirect estimates = 0.011.
[b] P value for differences between direct and indirect estimates = 0.030.
[c] P value for differences between direct and indirect estimates = 0.015.
[d] P value for differences between direct and indirect estimates = 0.022.
P value for overall inconsistency = 0.087 in the network meta-analysis.

Anmerkung/Fazit der Autoren

There is moderate-certainty evidence that aflibercept confers some advantage in improving visual function over ranibizumab and bevacizumab in people with DMO at one year. An anatomic benefit was found with ranibizumab over bevacizumab (low-certainty evidence), but there was little difference on functional outcomes (low- and moderate-certainty evidence). Relative effects among anti-VEGF drugs at two years are less well known, since most studies did not maintain randomisation after one year or were short term. A single large publicly-funded trial found no differences in visual outcomes among these drugs at two years. Evidence from RCTs may not apply to real-world practice, where people in need of antiangiogenic treatment are often under-treated and under-monitored.

We found no signals of differences in safety between the three antiangiogenic drugs that are currently available to treat DMO, particularly for a summary outcome measure such as the sum of all SSAEs (high- or moderate-certainty evidence). However, our estimates were imprecise regarding arterial thromboembolic events and all-cause death (very low-certainty evidence).

Kommentare zum Review

Im Cochrane Review wurde auch Bevacizumab untersucht, für das im vorliegenden Anwendungsgebiet keine Zulassung vorliegt.

3.3 Systematische Reviews

Low A et al., 2019 [5].

Comparative effectiveness and harms of intravitreal antivascular endothelial growth factor agents for three retinal conditions: a systematic review and meta-analysis

siehe auch: Pham B et al. 2019 [8].

Fragestellung

We conducted a systematic review to compare the effects of aflibercept, bevacizumab and ranibizumab on best-corrected visual acuity (BCVA) changes, quality of life and ocular or systemic adverse events in patients with neovascular age-related macular degeneration (NVAMD), diabetic macular oedema (DME) and central or branch retinal vein occlusion (RVO).

Methodik

Population:

- adults with NVAMD, DME or RVO

Intervention / Komparator:

- comparison of at least two anti-VEGF agents (aflibercept, bevacizumab or ranibizumab)

Endpunkte:

- visual acuity
- functional status
- quality of life
- systemic adverse events
- ocular harms
- cost-effectiveness

Recherche/Suchzeitraum:

- Ovid MEDLINE, PubMed, Elsevier EMBASE, Ovid EMB Reviews, trial registries and regulatory agency websites from database inception to 6 February 2017

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias tool
- After group discussion, we classified the overall strength of evidence for each outcome as high, moderate, low or insufficient using an established method that considers study limitations, directness, consistency, precision, reporting bias and applicability of the evidence.

Ergebnisse

Anzahl eingeschlossener Studien:

- Three trials included patients with DME (eine Studie enthält u. a. Untersuchungen zu Aflibercept vs Ranibizumab; die anderen Studien enthalten ausschließlich Untersuchungen zu Aflibercept vs Bevacizumab bzw. zu Bevacizumab vs Ranibizumab)

Charakteristika der Population:

Trial; Author year • ROB • Population; mean age, % male, mean baseline BCVA • No. randomized • Length of follow-up • Country • Other notes	Interventions (no. per group) • Treatment schedule
DRCR.net (Diabetic Retinopathy Clinical Research Network) Protocol T; Wells 2016[31,32,44] • Low ROB • DME involving the macular center; 60.6 years (SD 10), 54% male, 64.8 letters (SD 11.3) • 660 (578 analyzed at 24 months) • 24 months • U.S.	Group 1: Aflibercept 2.0 mg PRN (n=224) Group 2: Bevacizumab 1.25 mg PRN (n=218) Group 3: Ranibizumab 0.3 mg PRN (n=218) • Schedule: Both groups injected every 4 weeks unless visual acuity was 20/20 or better, CST was below the eligibility threshold, and no improvement or worsening observed in response to 2 consecutive injections. • Patients also received focal/grid laser photocoagulation starting at 6-months if DME persisted.

Qualität der Studien:

Trial; Author year	Sequence generation: Was the allocation sequence adequately generated?	Allocation concealment: Was allocation adequately concealed?	Blinding: Was knowledge of the allocated intervention adequately prevented during the study?	Incomplete outcome data: Were incomplete outcome data adequately addressed?	Selective outcome reporting: Are reports of the study free of suggestion of selective outcome reporting?	Other sources of bias: Was the study apparently free of other problems that could put it at a high risk of bias?	Overall assessment: Low/Unclear/High
DRCR.net (Protocol T); Wells 2016[31,32]	Yes: performed at the DRCR.net study website (computer-generated) in permuted blocks and with stratification according to study site and visual acuity in the study eye.	Yes: central randomization at the DRCR.net study website.	Assessors: Yes. Participants and providers: Yes.	Yes: 7% lost to follow-up (similar between groups). Primary analysis used ITT; used Markov chain Monte Carlo method of multiple imputation to impute missing data (sensitivity analyses with different approaches for handling missing data produced similar results). There was no imputation for missing data in secondary analyses.	Yes: all outcomes pre-specified in the protocol are reported.	Yes	Low

31 Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: two-year results from a comparative effectiveness randomized clinical trial. Ophthalmology 2016;123:1351–9.

32 Diabetic Retinopathy Clinical Research Network, Wells JA, Glassman AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. N Engl J Med 2015;372:1193–203.

Studienergebnisse:

Outcome	No. studies (N=total randomised)	Summary of findings; Combined summary estimate (95% CI)	Strength of evidence*	Comments
Aflibercept vs Ranibizumab				
Mean BCVA change†	1 RCT (n=442) ► 1 low ROB	Small benefit with aflibercept over the short term. The difference was small but statistically significant at 12 months (2.1 letters (95% CI 0.1 to 4.2), p=0.034; in subgroup with lower baseline BCVA, 4.7 letters (95% CI 1.4 to 8.0), p=0.003). No difference found between groups by 24 months.	Low	One trial showed no clinically important difference between drugs over the short or long term, including in the subgroup with worse visual acuity at baseline.
≥15 letter gain	1 RCT (n=442) ► 1 low ROB	No significant differences in overall population, but subgroup with lower baseline BCVA saw greater relative benefit with aflibercept over the short (p=0.008) but not long term.	Low	
Ocular AEs	1 RCT (n=442) ► 1 low ROB	No difference. Low rates of most serious ocular AEs. Endophthalmitis: no occurrences. Vitreous haemorrhage and elevated intraocular pressure were more common.	Low	
Systemic AEs	1 RCT (n=442) ► 1 low ROB	Higher rates of ATEs in ranibizumab arm at 24 months: 5.4% vs 11.9% (p=0.047). Rates of other events were high, likely due to poor baseline health, but no differences found between groups.	Low	

*Based on the consistency, coherence, applicability of the body of evidence and internal validity of individual studies. The strength of evidence is classified as follows (details in online supplementary appendix 3): • High = Further research is very unlikely to change our confidence in the estimate of effect. • Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. • Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. • Insufficient = Any estimate of effect is very uncertain.
†The minimal clinically important difference in mean BCVA change was defined as a difference of ≥5 letters between drugs.

Anmerkung/Fazit der Autoren

We found that aflibercept, bevacizumab and ranibizumab had comparable effects on visual acuity and similar rates of ocular and systemic harms. Because the agents had similar effectiveness and safety profiles but had marked differences in price, repackaged bevacizumab was found to be the most cost-effective drug. Clinicians should also consider factors such as patient preference, individual treatment response, convenience of dosing and evolving regulatory standards when choosing among these three anti-VEGF agents.

Kommentare zum Review

Im systematischen Review wurde auch Bevacizumab untersucht, für das im vorliegenden Anwendungsgebiet keine Zulassung vorliegt. Es wurden nur Ergebnisse zu im Anwendungsgebiet zugelassenen Therapieoptionen extrahiert. Das Fazit der Autorinnen und Autoren des systematischen Reviews bezieht sich auf alle darin eingeschlossenen Primärstudien.

He Y et al., 2018 [3].

A meta-analysis of the effect of a dexamethasone intravitreal implant versus intravitreal anti-vascular endothelial growth factor treatment for diabetic macular edema

Fragestellung

This meta-analysis evaluated the effectiveness and safety of dexamethasone (DEX) implant and intravitreal anti-vascular endothelial growth factor (VEGF) treatment for diabetic macular edema (DME).

Methodik

Population:

- Patients with DME

Intervention / Komparator:

- the DEX implant (Ozurdex) was included as an intervention; there was a comparison between the DEX implant (Ozurdex®) and anti-VEGF

Endpunkte:

- Primary outcomes:
  - mean BCVA and mean improvement from baseline in BCVA [time points: baseline, 6 months, and 12 months]. BCVA was obtained using the Early Treatment Diabetic Retinopathy Study (ETDRS).
- Secondary outcomes:
  - mean CST and mean change from baseline in CST or foveal thickness, and central macular thickness (CMT) was demonstrated on optical coherence tomography (OCT) [time points: baseline, 6 months, and 12 months].
- Additional outcomes:
  - Total number of serious adverse events (SAEs) at the end of each study; elevation of intraocular pressure (IOP>21 mmHg, required glaucoma agents for IOP control, or IOP elevation by at least 5 mmHg from baseline at any follow-up visit; the number of cataracts; mean number of intravitreal injections

Recherche/Suchzeitraum:

- PubMed, Embase, clinicaltrials.gov, and the Cochrane Library, up to August 2017

Qualitätsbewertung der Studien:

- The Cochrane Collaboration's tool was applied to assess the risk of bias in each study based on the Cochrane Handbook

Ergebnisse

Anzahl eingeschlossener Studien:

- Four studies comprising 521 study eyes were used in our meta-analysis (1 study: DEX vs. IVR [Allergan 2015]; 3 studies: DEX vs. IVB)

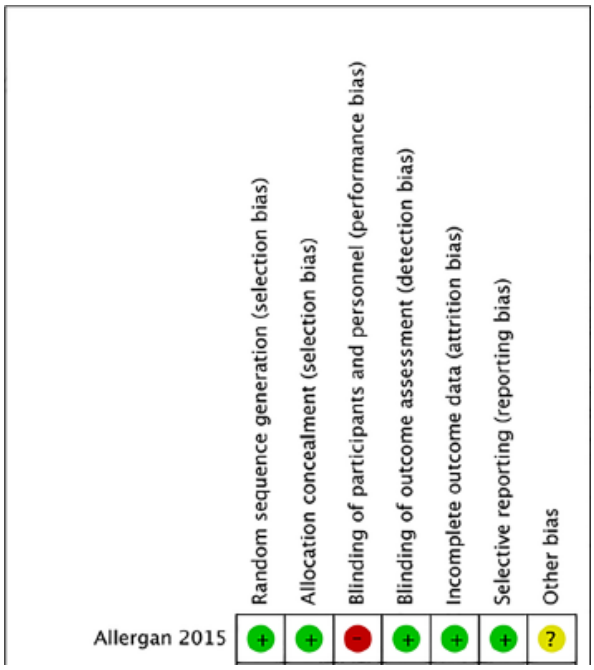
Charakteristika der Population:

Study	Place	Conditions	Participants numbers	Interventions details	Total number of treatments	Age (years)	Female sex, no. (%)	BCVA at baseline	CST/CMT (μm) at baseline	Follow-up duration (months)
Gillies et al. 2014 < The BEVORDEX Study> [23]	Australia	DR	DEX: 46 IVB: 42	DEX: 0.7 mg every 16 weeks + PRN IVB: 0.5 mg every 4 weeks + PRN	DEX: 2.7 IVB: 8.6	DEX: 61.4 ± 9.0 IVB: 62.2 ± 10.5 (*P* = 0.71)	DEX: 16 (35%) IVB: 16 (38%) (*P* = 0.83)	DEX: 55.5 ± 12.5 IVB: 56.3 ± 11.9 (*P* = 0.75)	DEX: 474.3 ± 95.9 IVB: 503 ± 140.9 (*P* = 0.38)	12
Allergan 2015 [27]	Multiple countries: Belgium, Denmark, France, Germany, Israel, Italy, Netherlands, Portugal, South Africa, Spain, United Kingdom, United States	DR	DEX: 181 IVR: 182	DEX: 0.7 mg on Day 1, Month 5, and Month 10 IVR: 0.5 mg into the study eye on Day 1. Patients may receive additional injections on a monthly basis, as needed, for disease progression	NA	NA	DEX: 69 (38%) IVR: 66 (36%)	DEX: 60.2 ± 9.74 IVR: 60.4 ± 9.34	DEX: 465.1 ± 136.09 IVR: 471.2 ± 139.51	12
Shah et al. 2016 [24]	Indiana, United States	DR	DEX: 27 IVB: 23	DEX: 0.7 mg given every 3 months over 6 month period with a maximum of 3 injections IVB: 1.25 mg given monthly during a 6 month period	DEX: 2.7 ± 0.5 IVB: 7.0 ± 0.2 (*P* < 0.001)	DEX: 65 ± 11 IVB: 61 ± 9 (*P* = 0.209)	DEX: 15 (56%) IVB: 10 (44%) (*P* = 0.571)	DEX: 59 ± 12 IVB: 59 ± 13 (*P* = 0.770)	DEX: 458 ± 100 IVB: 485 ± 122 (*P* = 0.508)	7
Gallemore et al. 2017 [26]	California, United States	DR	DEX: 10 IVB: 10	DEX: Ozurdex, 0.7 mg given at initial visit and at month 4 (visit 5) IVB: 1.25 mg given at initial visit and Q1 month for a total of 5 treatments	NA	DEX: 63.9 ± 1.8 IVB: 61.2 ± 2.9	DEX: 5 (50%) IVB: 3 (30%)	DEX: 67.8 ± 3.8 IVB: 71.9 ± 2.9	DEX: 385.9 ± 43.0 IVB: 341.5 ± 11.3	6

NA not available, *PRN* pro re nata

Allergan: Safety and efficacy study of dexamethasone versus ranibizumab in patients with diabetic macular edema. 2015. January 29, 2015 edition: ClinicalTrials.gov.

Qualität der Studien:



Studienergebnisse:

- mean change in BCVA and the associated 95% CI, comparing DEX with Anti-VEGF treatment at 12 months

	DEX			Anti- VEGF				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Allergan 2015	4.34	7.34	181	7.6	6.74	182	93.3%	-3.26 [-4.71, -1.81]

- mean change in CST and the associated 95% CI, comparing DEX with Anti-VEGF treatment at 12 months

	DEX			Anti- VEGF				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Allergan 2015	-173.9	129.64	163	-163.5	161.34	166	57.2%	-10.40 [-42.00, 21.20]

- total serious adverse events

	DEX		Anti- VEGF			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Allergan 2015	40	181	41	182	80.7%	0.98 [0.67, 1.44]

- elevation of IOP

	DEX		Anti- VEGF			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Allergan 2015	65	181	12	182	46.9%	5.45 [3.05, 9.73]

- adverse events: cataract

Study or Subgroup	DEX Events	Total	Anti- VEGF Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Allergan 2015	28	181	8	182	53.9%	3.52 [1.65, 7.51]

Anmerkung/Fazit der Autoren

In summary, this meta-analysis of data from four randomized clinical trials revealed that despite some ocular adverse events, DEX-treated eyes had relatively superior anatomic outcomes compared with anti-VEGF, and showed similar rates of vision improvement, while requiring fewer injections, especially in pseudophakic patients. However, considering for the restrictions of indications, the DEX implant may not be recommended as a first-line therapy for DME.

In the future, randomization of these treatments would allow a definite conclusion about whether switching to a DEX implant is more beneficial rather than anti-VEGF treatment. Additionally, new treatments (monotherapy or combined therapy) should be investigated to optimize clinical efficacy and reduce side-effects.

Kommentare zum Review

Im systematischen Review wurde auch Bevacizumab untersucht, für das im vorliegenden Anwendungsgebiet keine Zulassung vorliegt. Es wurden nur Ergebnisse zu im Anwendungsgebiet zugelassenen Therapieoptionen extrahiert. Das Fazit der Autorinnen und Autoren des systematischen Reviews bezieht sich auf alle darin eingeschlossenen Primärstudien.

Nguyen CL et al., 2018 [7].

Aflibercept for diabetic macular oedema: a meta-analysis of randomized controlled trials

Fragestellung

To evaluate the relative efficacy and safety of aflibercept for treatment of diabetic macular oedema (DMO).

Methodik

Population:

- patients with DR and clinically significant macular oedema (CSMO)

Intervention:

- aflibercept

Komparator:

- another treatment

Endpunkte:

- proportion of patients with at least 15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (equivalent to 3 ETDRS lines or 0.3 logMAR) of gain or loss after one year or two years

- mean change in best corrected visual acuity (BCVA), and mean reduction in central macular thickness (CMT) after one year or two years
- Safety was assessed as the proportions of patients with death, thromboembolic events, and any systemic or ocular serious adverse event after one year or two years

Recherche/Suchzeitraum:

- CENTRAL (The Cochrane Library 2017, Issue 4), Ovid MEDLINE, EMBASE, the Meta Register of Controlled Trials (mRCT), ClinicalTrials.gov, and the WHO International Clinical Trials Registry Platform (ICTRP); the final search was conducted on November 2017

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- A total of 4 studies were included. One study compared aflibercept with bevacizumab and ranibizumab for centre-involved DMO [18-19]. As this was the only study comparing aflibercept with other anti-VEGF agents and there was no photocoagulation control arm, it was excluded from the Meta-analysis. Three trials compared aflibercept with control with up to 148wk of follow up. Meta-analysis was conducted on the trials at follow up of 1 and 2y [26]. In total, there were four RCTs included in this study. Three of these trials were included in the Meta-analysis, and comprised a total of 661 patients: 331 patients in the aflibercept group and 330 patients in the photocoagulation group.

Charakteristika der Population:

Study	Location	Comparator intervention	Follow up (wk)	*n*	Mean age (y)
DA VINCI 2012	United States, Canada, Austria	Laser photocoagulation	52	45/44[a]	61/64[a]
DRCRN 2016	United States	Bevacizumab 1.25 mg, Ranibizumab 0.3 mg	104	208/206/206[b]	61/62/59[b]
VISTA 2015	United States	Laser photocoagulation	148	151/154[a]	63/62[a]
VIVID 2015	Europe, Japan, Australia	Laser photocoagulation	148	135/132[a]	64/64[a]

[a]Aflibercept group/laser photocoagulation group; [b]Aflibercept group/bevacizumab group/ranibizumab group.

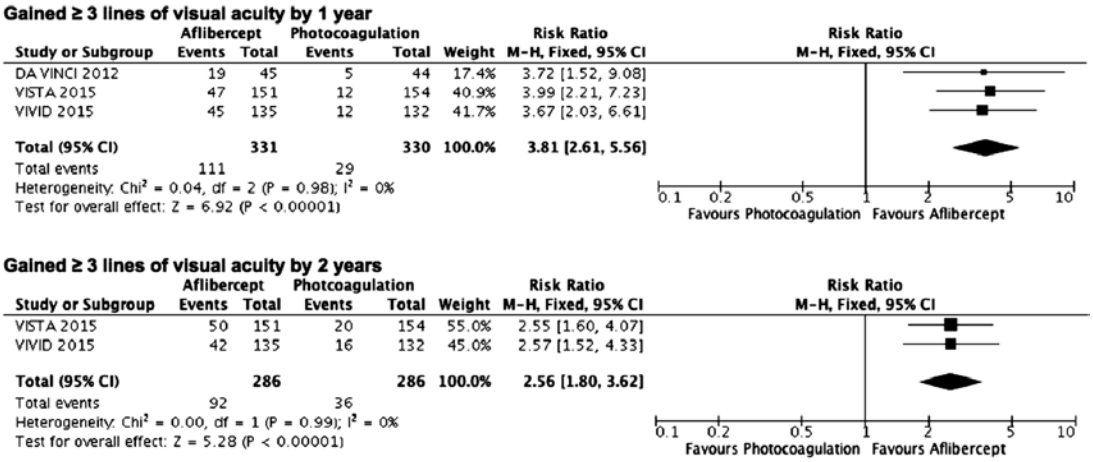
Qualität der Studien:

Studienergebnisse:

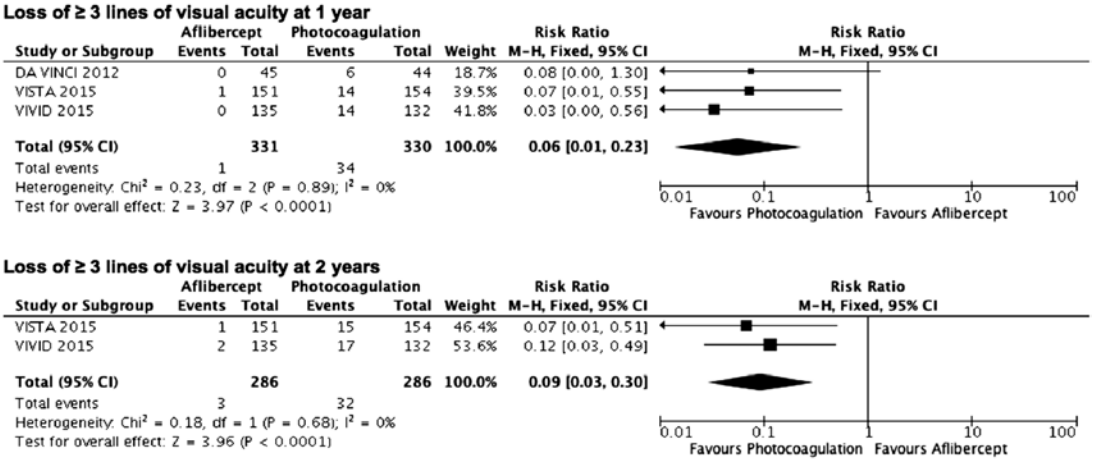
Die Ergebnisse der Studie DRCRN 2016 (d h. der Vergleich zwischen Aflibercept und Ranibizumab) können dem systematischen Review von Low et al. (2017) entnommen werden.

Aflibercept vs. Photocoagulation

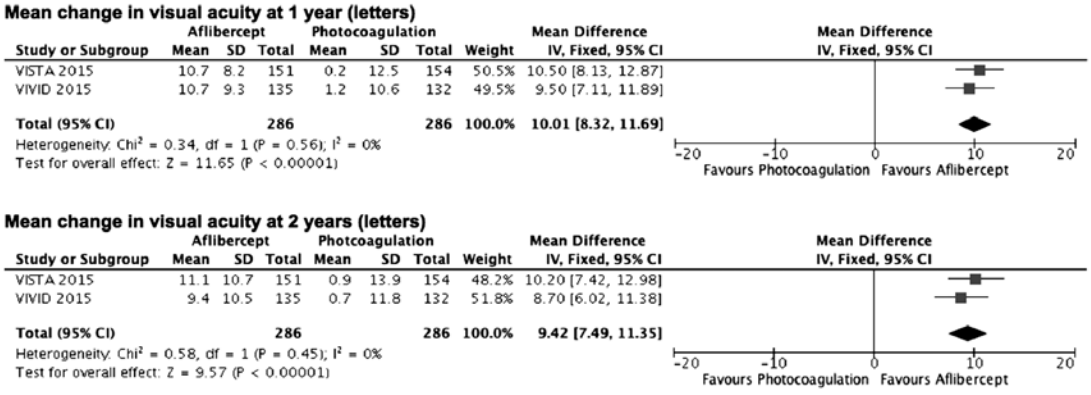
- gains of 3 or more lines of visual acuity from baseline as measured on a logMAR chart



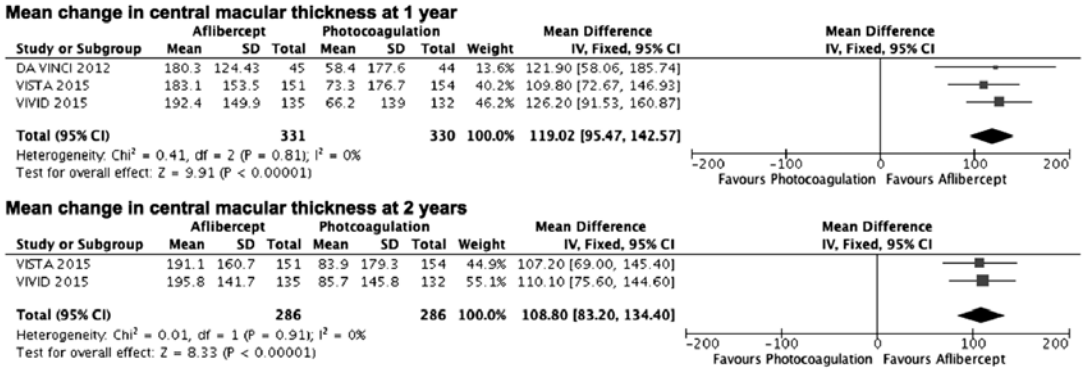
- loss of 3 or more lines of visual acuity from baseline as measured on a logMAR chart



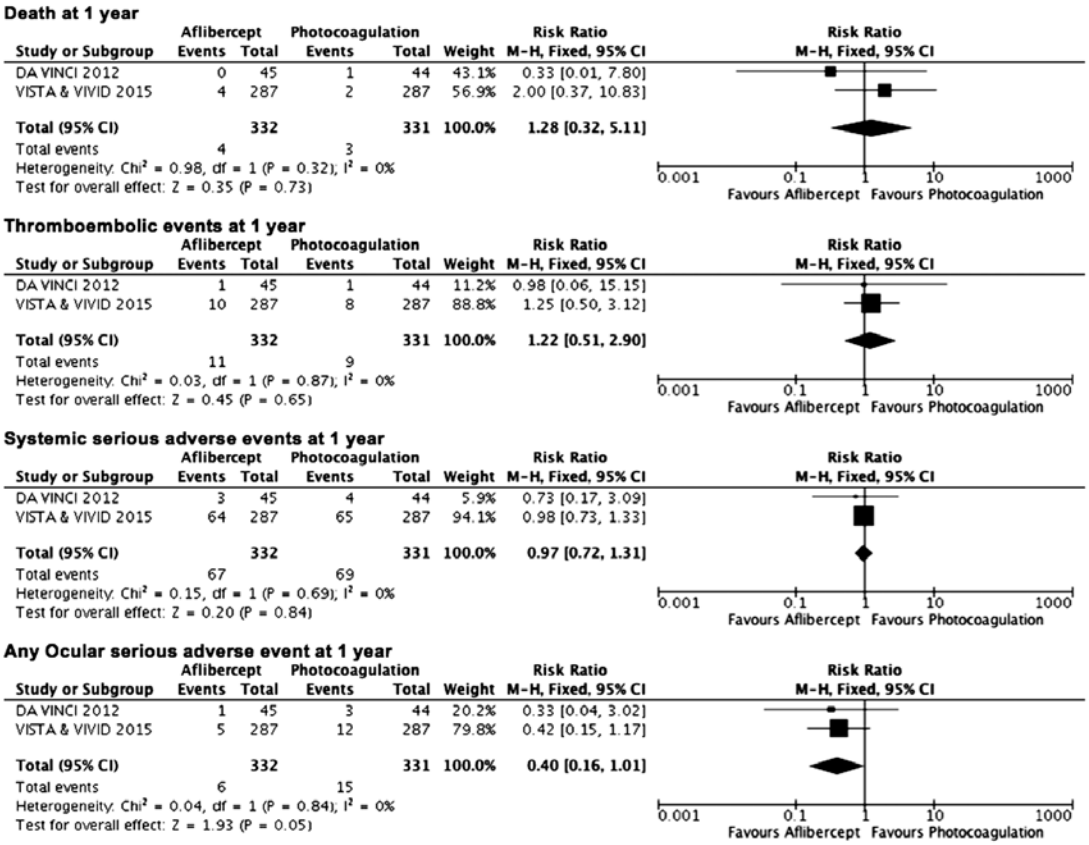
- changes from baseline to follow up best corrected visual acuity (in letters)



- changes from baseline to follow up central macular thickness



- serious adverse events



Anmerkung/Fazit der Autoren

This Meta-analysis confirms the comparable safety and superior efficacy of aflibercept over photocoagulation for patients with DMO. It also highlights the need for further comparative trials of anti-VEGF agents and investigations assessing treatment effects in the real world.

Kommentare zum Review

Die Ergebnisse der Studie DRCRN 2016 (d. h. der Vergleich zwischen Aflibercept und Ranibizumab) können dem systematischen Review von Low et al. (2019) entnommen werden.

Qian TW et al., 2017 [9].

Efficiency and safety of laser photocoagulation with or without intravitreal ranibizumab for treatment of diabetic macular edema: a systematic review and meta-analysis

Fragestellung

To compare the therapeutic effect and safety of laser photocoagulation along with intravitreal ranibizumab (IVR) versus laser therapy in treatment of diabetic macular edema (DME)

Methodik

Population:

- adult participants (minimum age of 18y) with any type of DME of any sex and race

Intervention:

- IVR + laser treatment

Komparator:

- laser photocoagulation alone

Endpunkte:

- best-corrected visual acuity (BCVA), central retinal thickness (CRT), and adverse events (AEs)

Recherche/Suchzeitraum:

- PubMed, EMBASE, Web of Science, Cochrane Library, and ClinicalTrials.gov were searched for patients from January 2010 to March 2016

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias tool

Ergebnisse

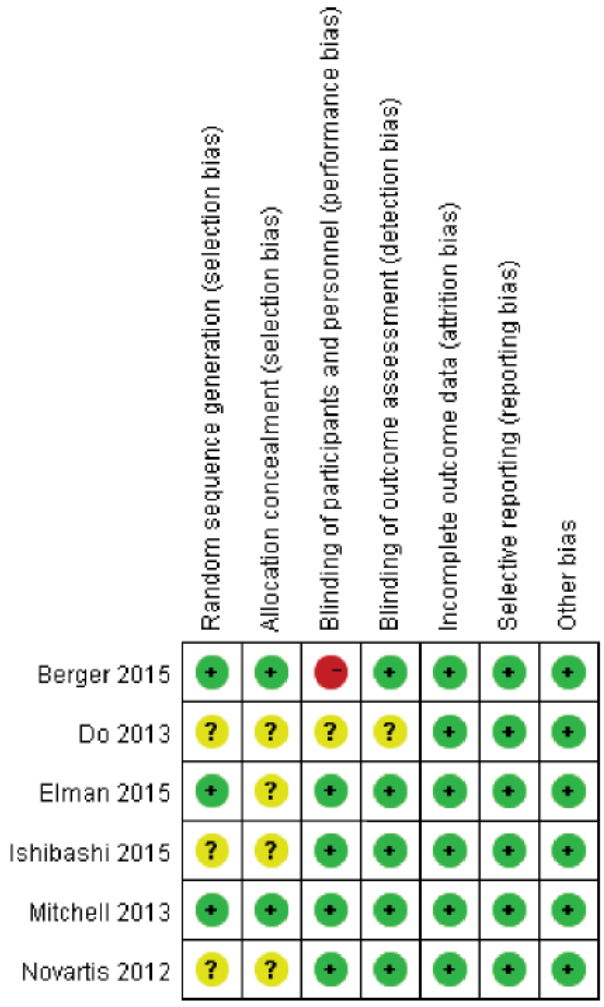
Anzahl eingeschlossener Studien:

- Six RCTs with a total of 2069 patients with DME were included in Meta-analysis

Charakteristika der Population:

Trials (first author, year)	Location	Design	Treatment group (patients, *n*)	Age (mean years)	Gender male, *n* (%)	Follow-up (mo)
Berger A[16], 2015	Canada	RCT	IVR (75)	61.5	42 (56.0)	
			IVR+laser (73)	60.8	47 (64.4)	3, 6, 9, 12
			Laser (72)	62.8	43 (59.7)	
Elman MJ[20], 2015	United States	RCT	IVR+deferred (≥24wk) laser (188)	64	110 (58.5)	
			IVR+prompt laser (187)	62	102 (54.5)	12, 24, 36, 60
			Prompt laser (293)	63	170 (58.0)	
			Triamcinolone+prompt laser (186)	62	100 (53.8)	
Ishibashi T[21], 2015	East Asia	RCT	IVR (133)	60.7	81 (60.9)	
			IVR+laser (132)	61.2	67 (50.8)	12
			Laser (131)	61.5	75 (57.3)	
Mitchell P[23], 2013	Europe, Australia, Canada, Turkey	RCT	IVR (116)	62.9	73 (62.9)	
			IVR+laser (118)	64.0	70 (59.3)	12
			Laser (111)	63.5	58 (52.3)	
Do DV[26], 2013	United States	RCT	IVR (42)	62	13 (31.0)	
			IVR+laser (42)	62	19 (45.2)	6, 12, 18, 24, 36
			Laser (42)	62	20 (47.6)	
Novartis[27], 2012	Germany	RCT	IVR+laser (85)	63.5	53 (62.4)	12
			Laser (43)	63.5	27 (62.8)	

Qualität der Studien:



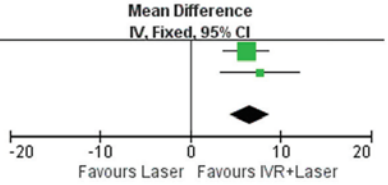
Studienergebnisse:

- The mean change in BCVA from baseline of each study (A: 6mo; B: 12mo; C: 24mo)

A

Study or Subgroup	IVR+Laser Mean	SD	Total	Laser Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Berger 2015	7.1	8.04	75	0.9	7.66	72	75.0%	6.20 [3.66, 8.74]
Do 2013	7.24	10.29	42	-0.43	10.29	42	25.0%	7.67 [3.27, 12.07]
Total (95% CI)			**117**			**114**	**100.0%**	**6.57 [4.37, 8.77]**

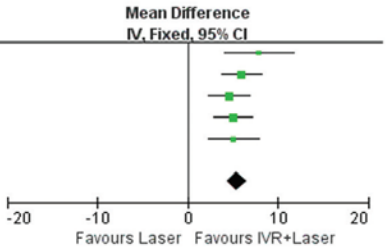
Heterogeneity: Chi² = 0.32, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 5.85 (P < 0.00001)



B

Study or Subgroup	IVR+Laser Mean	SD	Total	Laser Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Berger 2015	8.2	9.43	73	0.3	13.62	72	8.5%	7.90 [4.08, 11.72]
Elman 2015	9	11	187	3	13	293	26.4%	6.00 [3.83, 8.17]
Ishibashi 2015	6.4	10.67	129	1.8	8.27	128	22.8%	4.60 [2.27, 6.93]
Mitchell 2013	5.9	7.92	118	0.8	8.56	110	27.0%	5.10 [2.96, 7.24]
Novartis 2012	6.5	8.6	85	1.4	7.3	43	15.3%	5.10 [2.25, 7.95]
Total (95% CI)			**592**			**646**	**100.0%**	**5.46 [4.35, 6.58]**

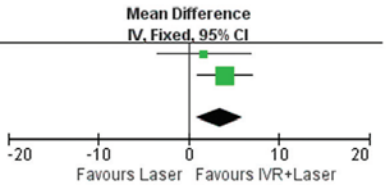
Heterogeneity: Chi² = 2.50, df = 4 (P = 0.64); I² = 0%
Test for overall effect: Z = 9.61 (P < 0.00001)



C

Study or Subgroup	IVR+Laser Mean	SD	Total	Laser Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Do 2013	6.8	11.4	34	5.1	10.1	34	25.3%	1.70 [-3.42, 6.82]
Elman 2015	7	13	136	3	15	211	74.7%	4.00 [1.02, 6.98]
Total (95% CI)			**170**			**245**	**100.0%**	**3.42 [0.84, 5.99]**

Heterogeneity: Chi² = 0.58, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 2.60 (P = 0.009)

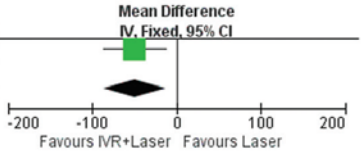


- CRT (A: 6mo; B: 12mo; C: 24mo)

A

Study or Subgroup	IVR+Laser Mean	SD	Total	Laser Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Berger 2015	-114.2	110.88	70	-64.4	110.77	65	100.0%	-49.80 [-87.21, -12.39]
Total (95% CI)			**70**			**65**	**100.0%**	**-49.80 [-87.21, -12.39]**

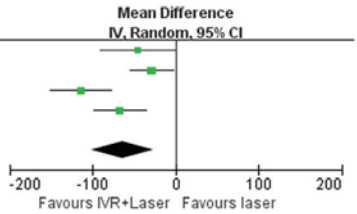
Heterogeneity: Not applicable
Test for overall effect: Z = 2.61 (P = 0.009)



B

Study or Subgroup	IVR+Laser Mean	SD	Total	Laser Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Berger 2015	-152.2	139.27	73	-107.1	143.86	72	21.7%	-45.10 [-91.20, 1.00]
Elman 2015	-131	129	171	-102	151	271	27.7%	-29.00 [-55.40, -2.60]
Ishibashi 2015	-171.8	160.85	115	-57.2	118.6	115	24.6%	-114.60 [-151.13, -78.07]
Mitchell 2013	-128.3	114.34	118	-61.3	132.29	110	26.0%	-67.00 [-99.20, -34.80]
Total (95% CI)			**477**			**568**	**100.0%**	**-63.46 [-101.19, -25.73]**

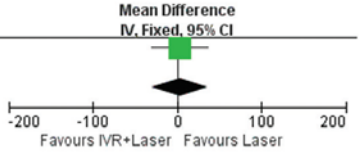
Heterogeneity: Tau² = 1156.30; Chi² = 14.45, df = 3 (P = 0.002); I² = 79%
Test for overall effect: Z = 3.30 (P = 0.0010)



C

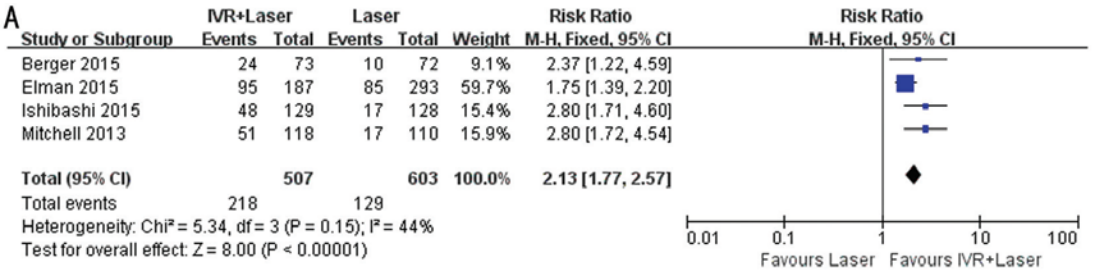
Study or Subgroup	IVR+Laser Mean	SD	Total	Laser Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Elman 2015	-138	149	211	-141	155	136	100.0%	3.00 [-29.91, 35.91]
Total (95% CI)			**211**			**136**	**100.0%**	**3.00 [-29.91, 35.91]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.18 (P = 0.86)

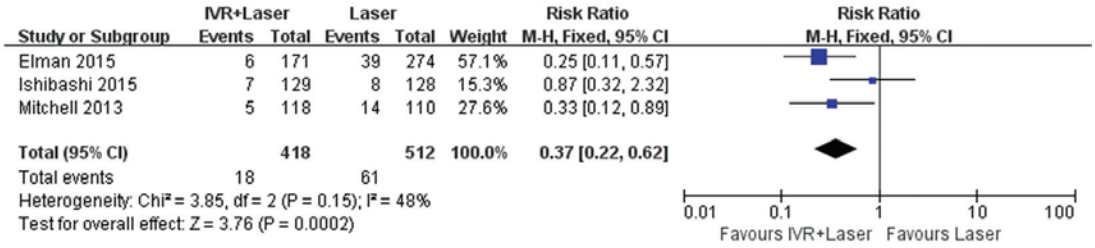


- proportion of the patients with at least 10 letters improvement at 12mo

A



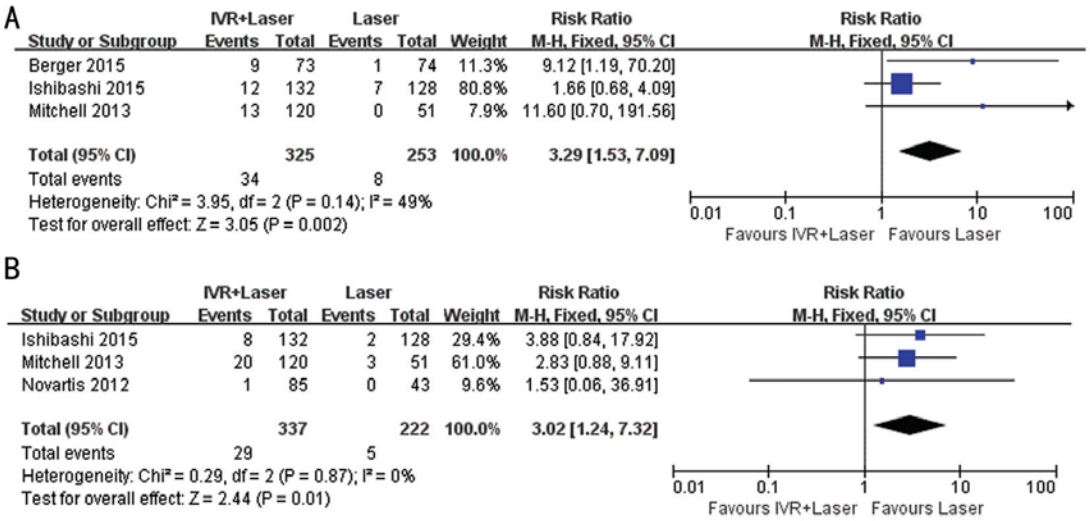
B



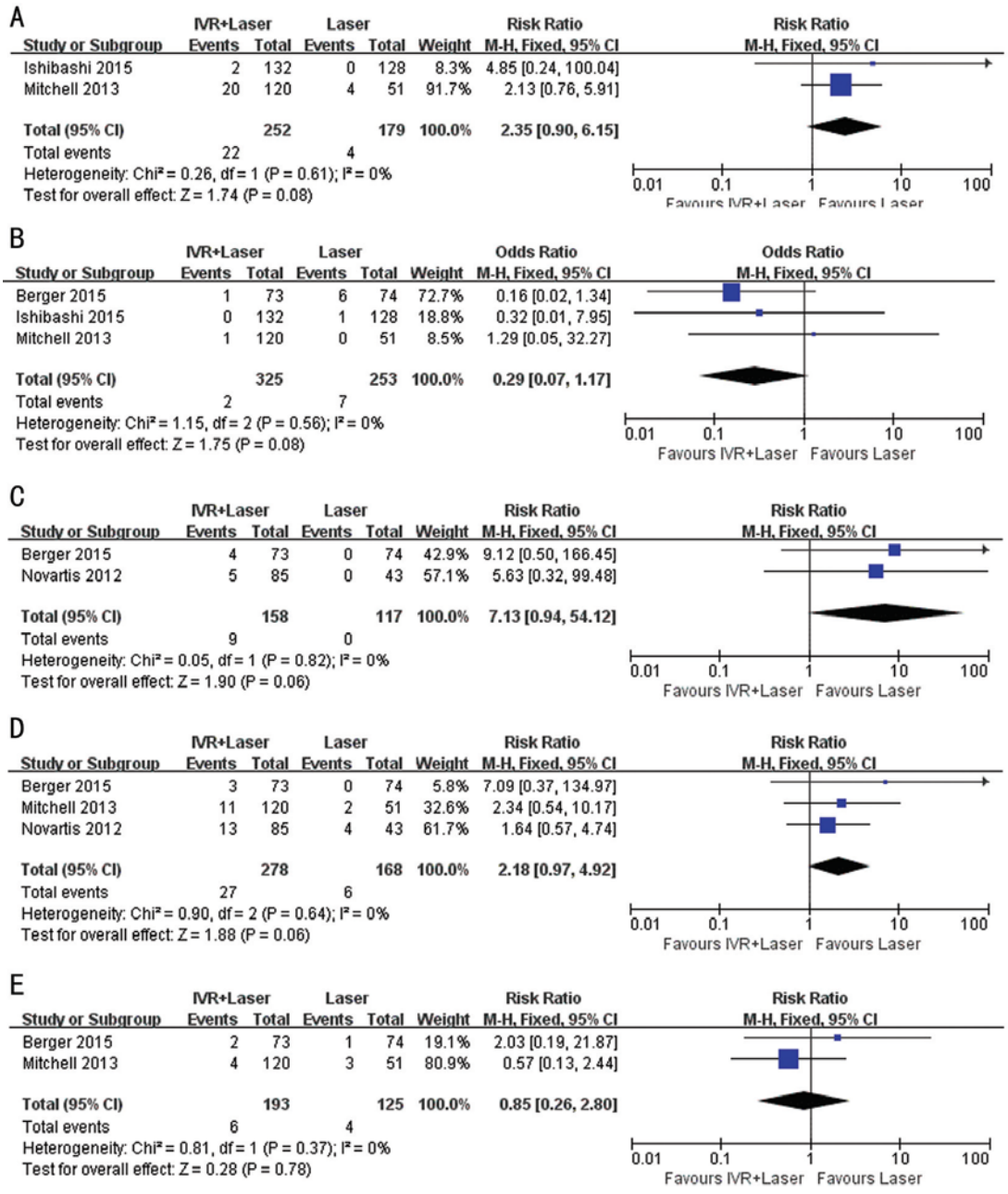
- Main ocular adverse events and nonocular adverse events

Adverse events	Berger *et al*[16], 2015		Ishibashi *et al*[21], 2015		Mitchell *et al*[23], 2013		Novartis[27], 2012	
	IVR+Laser	Laser	IVR+Laser	Laser	IVR+Laser	Laser	IVR+Laser	Laser
Total	73	74	132	128	120	51	85	43
Serious adverse events	9	5	22	19	43	7	14	5
Ocular adverse events								
Cataract (study eye)			2	0	20	4		
Retinal detachment (study eye)			1	0				
Conjunctival hemorrhage (study eye)	9	1	12	7	13	0		
Vitreous hemorrhage (study eye)	1	6	0	1	1	0		
Eye irritation (study eye)	4	0					5	0
Eye pain (study eye)	3	0			11	2	13	4
Dry eye (study eye)	2	1			4	3		
Diabetic retinal edema (fellow eye)			8	2	20	3	1	0
Nonocular adverse events								
Cardiovascular disorders	1	3	4	1	10	2	1	2
Infections and infestations	7	5	18	12	42	18	15	6
Metabolism and nutrition disorders	2	1	0	4			4	1
Vascular disorders	2	5	8	6	15	6	8	4

- Meta-analysis with statistically significant difference between IVR+laser and laser group in the RR (A: Conjunctival hemorrhage; B: Diabetic retinal edema)



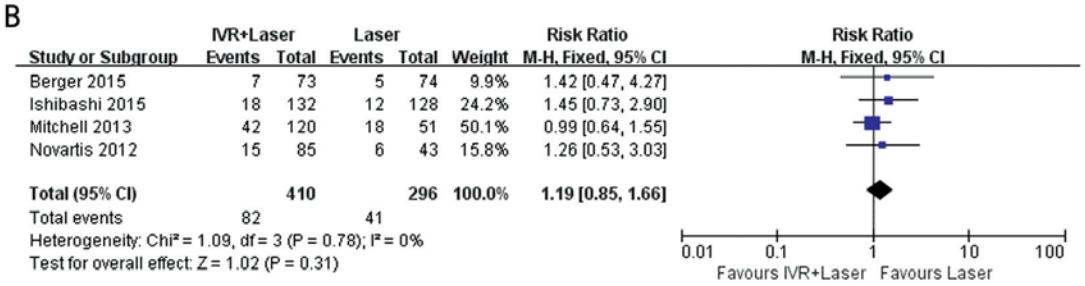
- Comparison between IVR+laser versus laser for the incidence of five ocular adverse events in patients with DME (A: Cataract; B: Vitreous hemorrhage; C: Eye irritation; D: Eye pain; E: Dry eye)



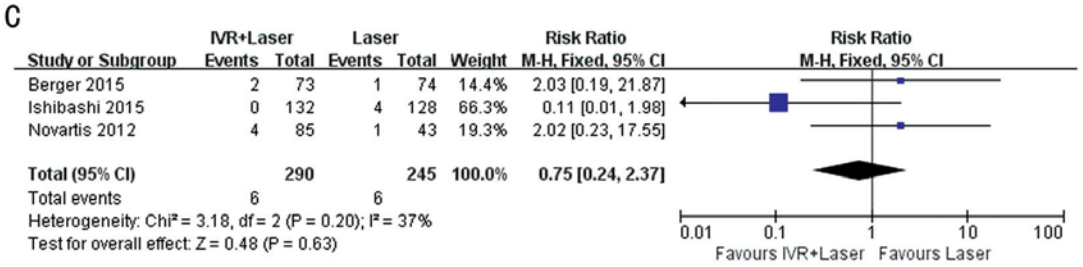
- Comparison between IVR+laser versus laser for the incidence of four non-ocular adverse events in patients with DME (A: Cardiovascular disorders; B: Infections and infestations; C: Metabolism and nutrition disorders; D: Vascular disorders)

A

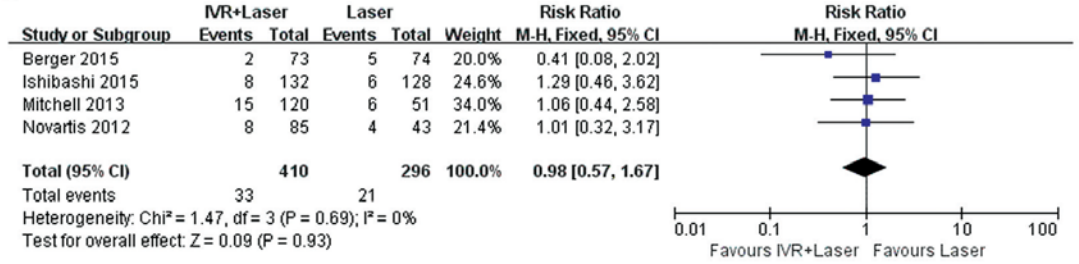
B



C



D



Anmerkung/Fazit der Autoren

The results of our analysis show that IVR+laser has better availability in functional (improving BCVA) and anatomic (reducing CRT) outcomes than laser monotherapy for the treatment of DME. However, the patients who received the treatment of IVR+laser may get a higher risk of suffering from conjunctival hemorrhage (study eye) and diabetic retinal edema (fellow eye).

3.4 Leitlinien

AOA Evidence-Based Optometry Guideline Development Group, 2019 [1].

American Optometric Association (AOA)

Eye care of the patient with diabetes mellitus, second edition

Zielsetzung/Fragestellung

The objectives of this Guideline are to assist doctors of optometry in achieving the following:

[…]

- Preservation of vision by reducing the risk of vision loss in persons with diabetes through timely diagnosis, intervention, determination of need for future evaluation, and appropriate referral
- Improvement in the quality of care rendered to persons with diabetes

[…]

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche und Auswahl der Evidenz; systematische Bewertung der Evidenz: teilweise;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- 1976 through January 2019 using the following electronic databases:
  - American Diabetes Association
  - Centers for Disease Control and Prevention, National Center for Health Statistics
  - Cochrane Library
  - Diabetes Care
  - Google Scholar
  - Healthy People 2020
  - Investigative Ophthalmology and Visual Science
  - JAMA Ophthalmology
  - Medline Plus
  - National Eye Institute
  - PLoS One
  - PubMed
  - Retina

LoE / GoR

The following table provides the grading system used in this guideline for rating evidence-based clinical statements. Grades are provided for both quality of the evidence and strength of clinical recommendations.

Key to Quality of Evidence and Strength of Clinical Recommendation Grading	
Quality of Evidence Levels	
Grade	**Study Type**

A	• **Meta-Analysis**
	• **Systematic Review**
	• **Randomized Clinical Trial**
	• **Diagnostic Studies** (Grade A)
	  ○ Do not have a narrow population
	  ○ Do not use a poor reference standard
	  ○ No case control studies of diseases or conditions

B	• **Randomized Clinical Trial** (weaker design)
	• **Cohort Studies**
	  ○ Retrospective
	  ○ Prospective
	• **Diagnostic Studies** (Grade B - only *one* of the following)
	  ○ Narrow population
	  ○ Sample used does not reflect the population to whom the test would apply
	  ○ Uses a poor reference standard
	  ○ Comparison between the test and reference standard is not blinded
	  ○ Case control studies of diseases or conditions

C	• **Case Control Studies**
	  ○ Study of sensitivity and specificity of a diagnostic test, population-based descriptive study of diseases or conditions
	  ○ Retrospective or prospective
	• **Diagnostic Studies** (Grade C - at least two or more of the following)
	  ○ Narrow population
	  ○ Sample used does not reflect the population to whom the test would apply
	  ○ Uses a poor reference standard
	  ○ Comparison between the test and reference standard is not blinded
	• **Studies of Strong Design**
	  ○ With substantial uncertainty about conclusions or serious doubts about generalizations, bias, research design, or sample size
	• **Nonrandomized Trials**

D	• **Cross Sectional Studies** • **Case Reports/Series** • **Reviews** • **Position Papers** • **Expert Opinion** • **Reasoning from Principle**

Strength of Clinical Recommendation Levels
Strong Recommendation: The benefits of the recommendation clearly exceed the harms (or the harms clearly exceed the benefits in the case of a negative recommendation) and the quality of evidence is excellent (Grade A or B). In some clearly identified circumstances, a strong recommendation may be made on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms. *This recommendation should be followed unless clear and compelling rationale for an alternative approach is present.*
Recommendation: The benefits of the recommendation exceed the harms (or the harms exceed the benefits in the case of a negative recommendation) but the quality of evidence is not as strong (Grade B or C). In some clearly identified circumstances, a recommendation may be made on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms. *This recommendation should generally be followed, but remain alert for new information.*
Discretional: The current evidence is insufficient to assess the balance of benefits and harms of the recommendation. Evidence may be lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined. *There should be an awareness of this recommendation, but a flexibility in clinical decision-making, as well as remaining alert for new information.*

Clinical Notes and Statements

Quality of evidence grades (A, B, C, or D) are shown throughout the guideline for clinical notes and statements. For example, a clinical note or statement with a quality of evidence grade of "B" is shown as "(Evidence Grade: B)".

Evidence-Based Action Statements will be highlighted in an "Action" box, with the quality of evidence, level of confidence, and clinical recommendation grading information listed. For example:

Consensus-Based Action Statements, based on consensus by the Guideline Development Reading Group, are also highlighted in an "Action" box, but without any quality of evidence or strength of clinical recommendation grading information listed. For example:

Empfehlungen

3. Treatment of Persons with Retinal Complications

c. Diabetic Macular Edema

EVIDENCE-BASED ACTION STATEMENT: Patients with central-involved diabetic macular edema (DME) should be referred to an ophthalmologist experienced in the management of diabetic retinal disease for treatment with anti-VEGF agents and/or subsequent or deferred focal/grid macular laser therapy.[65,69,71,72,74,75,77,82,298,300,311,313-317,319-324,327,329]
Evidence Quality: Grade A. Randomized Clinical Trials, Systematic Reviews, Cohort-prospective Studies, Cohort-retrospective Study, Case Series **Level of Confidence:** High **Clinical Recommendation Strength:** Strong Recommendation. This recommendation should be followed unless clear and compelling rationale for an alternative approach is present.
Evidence Statements: Clinical studies to evaluate the efficacy of aflibercept, bevacizumab (BVZ), or ranibizumab (RBZ) for the treatment of central-involved DME have concluded that all three agents improved vision and were equally or more effective than focal/grid photocoagulation or sham treatment.[65,74,298,300,314-316,317,319,320,321,324] (All Evidence Grade: A)[322,327,329] (All Evidence Grade: B) A study of long-term outcomes of ranibizumab (RBZ) injections given as needed based on functional and anatomical responses for 48 months in an ordinary clinical setting reported a substantial and continuous visual benefit in patients with DME.[313] (Evidence Grade: C) Patients with DME who have early response (after one injection) to anti-VEGF treatment by reduction in central retinal thickness will have significant response to treatment by three months.[311] (Evidence Grade: D) In eyes with initial visual acuity of 20/40 or better at baseline, there was no significant difference among aflibercept, bevacizumab (BVZ), or ranibizumab (RBZ) for the treatment of central-involved DME. In eyes with 20/50 visual acuity or worse, aflibercept provided greater average gains in visual acuity compared to BVZ and RBZ.[71] (Evidence Grade: A) [75] (Evidence Grade: A) [77] (Evidence Grade: B) [82] (Evidence Grade: A) Most eyes treated with ranibizumab (RBZ) and either prompt or deferred laser maintain vision gains obtained by the first year through five years with little additional treatment after three years.[72] (Evidence Grade: A) The use of focal/grid laser treatment at the time of initiation of intravitreous RBZ is not better, and possibly worse, for vision outcomes than deferring laser treatment for 24 weeks or more in eyes with DME involving the fovea.[69] (Evidence Grade: A) Patients treated with RBZ experienced fewer complications such as vitreous hemorrhage and fewer developed proliferative diabetic retinopathy (PDR) or underwent panretinal photocoagulation (PRP).[323] (Evidence Grade: A)
Potential Benefits: Preservation of vision / **Potential Risks/Harms:** Complications from intravitreous injections or laser treatment
Benefit and Harm Assessment: Benefits significantly outweigh harms
Potential Costs: Direct cost of treatment
Value Judgments: None
Role of Patient Preferences: Moderate
Intentional Vagueness: None
Gaps in Evidence: None identified

65. Diabetic Retinopathy Clinical Research Network, Elman MJ, Aiello LP, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology 2010;117(6):1064-77.
69. Diabetic Retinopathy Clinical Research Network, Elman MJ, Qin H, et al. Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: Three-year randomized trial results. Ophthalmology 2012;119(11):2312-18.
71. Diabetic Retinopathy Clinical Research Network, Wells JA, Glassman AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. N Engl J Med 2015;372(13):1193-203.
72. Elman MJ, Ayala A, Bressler NM, et al. Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: 5-year randomized trial results. Ophthalmology 2015;122(2):375-81.

74. Bressler SB, Glassman AR, Almukhtar T, et al. Five-year outcomes of ranibizumab with prompt or deferred laser versus laser or triamcinolone plus deferred ranibizumab for diabetic macular edema. Am J Ophthalmol 2016;164:57-68.
75. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: Two-year results from a comparative effectiveness randomized clinical trial. Ophthalmology 2016;123(6):1351-59.
77. Jampol LM, Glassman AR, Bressler NM, et al. Anti-vascular endothelial growth factor comparative effectiveness trial for diabetic macular edema: Additional efficacy post hoc analyses of a randomized clinical trial. JAMA Ophthalmol 2016;134(12):1429-34.
82. Wells JA, Glassman AR, Jampol LM, et al. Association of baseline visual acuity and retinal thickness with 1-year efficacy of aflibercept, bevacizumab, and ranibizumab for diabetic macular edema. JAMA Ophthalmol 2016;134(2):127-34.
298. Virgili G, Parravano M, Evans JR, et al. Anti-vascular endothelial growth factor for diabetic macular oedema: A network meta-analysis. Cochrane Database Syst Rev 2017;6:CD007419.
300. Rajendram R, Fraser-Bell S, Kaines A, et al. A 2-year prospective randomized controlled trial of intravitreal bevacizumab or laser therapy (BOLT) in the management of diabetic macular edema: 24-month data: Report 3. Arch Ophthalmol 2012;130(8):972-79.
311. Shah AR, Yonekawa Y, Todorich B, et al. Prediction of anti-VEGF response in diabetic macular edema after 1 injection. J Vitreoretin Dis 2017;1(3):169-74.
313. Epstein D, Amren U. Long-time outcome in patients treated with ranibizumab for diabetic macular edema: A 4-year study. Retina 2018;38(1):183-86.
314. Wiley HE, Thompson DJ, Bailey C, et al. A crossover design for comparative efficacy: A 36-week randomized trial of bevacizumab and ranibizumab for diabetic macular edema. Ophthalmology 2016;123(4):841-49.
315. Zhang L, Wang W, Gao Y, et al. The Efficacy and Safety of Current Treatments in Diabetic Macular Edema: A Systematic Review and Network Meta-Analysis. PLoS One 2016;11(7):e0159553.
316. Massin P, Bandello F, Garweg JG, et al. Safety and efficacy of ranibizumab in diabetic macular edema (RESOLVE Study): A 12-month, randomized, controlled, double-masked, multicenter phase II study. Diabetes Care 2010;33(11):2399-405.
317. Nguyen QD, Shah SM, Khwaja AA, et al. Two-year outcomes of the ranibizumab for edema of the mAcula in diabetes (READ-2) study. Ophthalmology 2010;117(11):2146-51.
319. Mitchell P, Bandello F, Schmidt-Erfurth U, et al. The RESTORE Study: Ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmology 2011;118(4):615-25.
320. Schmidt-Erfurth U, Lang GE, Holz FG, et al. Three-year outcomes of individualized ranibizumab treatment in patients with diabetic macular edema: The RESTORE extension study. Ophthalmology 2014;121(5):1045-53.
321. Brown DM, Nguyen QD, Marcus DM, et al. Long-term outcomes of ranibizumab therapy for diabetic macular edema: The 36-month results from two phase III trials: RISE and RIDE. Ophthalmology 2013;120(10):2013-22.
322. Boyer DS, Nguyen QD, Brown DM, et al. Outcomes with as-needed ranibizumab after initial monthly therapy: Long-term outcomes of the phase III RIDE and RISE trials. Ophthalmology 2015;122(12):2504-13.
323. Nguyen QD, Brown DM, Marcus DM, et al. Ranibizumab for diabetic macular edema: Results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology 2012;119(4):789-801.
324. Ishibashi T, Li X, Koh A, et al. The REVEAL Study: Ranibizumab monotherapy or combined with laser versus laser monotherapy in Asian patients with diabetic macular edema. Ophthalmology 2015;122(7):1402-15.
327. Sivaprasad S, Crosby-Nwaobi R, Esposti SD, et al. Structural and functional measures of efficacy in response to bevacizumab monotherapy in diabetic macular oedema: Exploratory analyses of the BOLT Study (Report 4). PLoS One 2013;8(8):e72755.
329. Do DV, Nguyen QD, Boyer D, et al. One-year outcomes of the DA VINCI Study of VEGF Trap-Eye in eyes with diabetic macular edema. Ophthalmology 2012;119(8):1658-65.

EVIDENCE-BASED ACTION STATEMENT: Persons who experience persistent diabetic macular edema (DME) following laser and/or anti-vascular endothelial growth factor (anti-VEGF) therapy for DME should be referred to an ophthalmologist experienced in the management of diabetic retinal disease for possible treatment with intraocular steroids.[62,65,302,345,346,348]
Evidence Quality: Grade A. Randomized Clinical Trials, Systematic Review, Cohort-prospective Studies **Level of Confidence:** High **Clinical Recommendation Strength:** Strong Recommendation. This recommendation should be followed unless clear and compelling rationale for an alternative approach is present.
Evidence Statements: Intravitreous triamcinolone acetonide (IVTA) combined with prompt focal/grid laser therapy was reported to be equally effective as ranibizumab monotherapy at improving visual acuity and reducing retinal thickening in pseudophakic persons, but was less effective in those who had not had cataract surgery.[65] (Evidence Grade: A) The use of IVTA injections and intraocular corticosteroid sustained-release drug delivery systems for the treatment of DME have been shown effective in decreasing macular thickness and improving visual acuity. Results of a meta-analysis of studies that evaluated the efficacy of IVTA for the treatment of DME refractory to laser photocoagulation reported a temporary improvement of visual acuity, with a peak benefit of approximately three lines of visual acuity one month post injection.[302] (Evidence Grade: A) An evaluation of the efficacy and safety of 1 mg and 4 mg doses of IVTA in comparison with focal/grid photocoagulation for the treatment of DME found focal/grid photocoagulation to be more effective with respect to both visual acuity and retinal thickening and has fewer side effects, particularly elevation of intraocular pressure and lens changes, than IVTA for most patients with DME at two years.[62] (Evidence Grade: A) Intravitreous treatment with dexamethasone implant has been shown to safely reduce DME and improve visual acuity in difficult to treat and long-standing DME. One injection of dexamethasone was found to provide anatomical and functional effectiveness for the treatment of DME as reported in a six-month study and side effects were reported to be rare and manageable.[345] (Evidence Grade: B) A study to evaluate the long-term anatomical and functional outcomes in patients with DME treated with intravitreous dexamethasone implant reported it to be a safe and effective treatment for DME in patients' refractory to previous anti-VEGF injections.[348] (Evidence Grade: B) An assessment of the long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for DME found that both low- and high-dose inserts significantly improved best corrected visual acuity in patients with DME over two years, and the risk-to-benefit ratio was superior for the low-dose insert.[346] (Evidence Grade: A)
Potential Benefits: Preservation of vision / **Potential Risks/Harms:** Development of cataracts and increased intraocular pressure, complications of intravitreous injections
Benefit and Harm Assessment: Balance of benefits and harms
Potential Costs: Direct cost of treatment
Value Judgments: None
Role of Patient Preferences: Moderate
Intentional Vagueness: None
Gaps in Evidence: None identified

62. Diabetic Retinopathy Clinical Research Network. A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema. Ophthalmology 2008;115(9):1447-49.
65. Diabetic Retinopathy Clinical Research Network, Elman MJ, Aiello LP, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology 2010;117(6):1064-77.
302. Rudnisky CJ, Lavergne V, Katz D. Visual acuity after intravitreal triamcinolone for diabetic macular edema refractory to laser treatment: A meta-analysis. Can J Ophthalmol 2009;44(5):587-93.
345. Guigou S, Pommier S, Meyer F, et al. Efficacy and safety of intravitreal dexamethasone implant in patients with diabetic macular edema. Ophthalmologica 2015;233(3-4):169-75.
346. Campochiaro PA, Brown DM, Pearson A, et al. Long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for diabetic macular edema. Ophthalmology 2011;118(4):626-35.
348. Chatziralli I, Theodossiadis P, Parikakis E, et al. Dexamethasone intravitreal implant in diabetic macular edema: Real-life data from a prospective study and predictive factors for visual outcome. Diabetes Ther 2017;8(6):1393-404.

EVIDENCE-BASED ACTION STATEMENT: Persons with vitreous hemorrhage, traction retinal detachment, macular traction, or an epiretinal membrane should be referred to an ophthalmologist experienced in the management of diabetic retinal disease for possible vitrectomy.[66,304,305]
Evidence Quality: Grade B. Systematic Review, Cohort-prospective Studies **Level of Confidence:** Medium **Clinical Recommendation Strength:** Recommendation. This recommendation should generally be followed, but remain alert for new information.
Evidence Statements: Vitrectomy performed for diabetic macular edema (DME) and vitreomacular traction has been shown to improve vision with a low surgical complication rate.[66] (Evidence Grade: B) Vitrectomy can result in a reduction in macular thickening[66] and can improve visual acuity in DME when the pre-operative acuity is <20/80 and there is an epiretinal membrane or vitreoretinal adhesion.[304] (Evidence Grade: B) There is little evidence to support the use of vitrectomy as an intervention for DME in the absence of epiretinal membrane or vitreomacular traction. Furthermore, there is no evidence to suggest a superiority of vitrectomy over laser in terms of functional outcomes.[305] (Evidence Grade: B)
Potential Benefits: Preservation of vision / **Potential Risks/Harms:** Complications from vitrectomy surgery
Benefit and Harm Assessment: Benefits significantly outweigh harms
Potential Costs: Direct cost of treatment
Value Judgments: None
Role of Patient Preferences: Large
Intentional Vagueness: None
Gaps in Evidence: None identified

66. Diabetic Retinopathy Clinical Research Network Writing Committee, Haller JA, Qin H, et al. Vitrectomy outcomes in eyes with diabetic macular edema and vitreomacular traction. Ophthalmology 2010;117(6):1087-93.
304. Flaxel CJ, Edwards AR, Aiello LP, et al. Factors associated with visual acuity outcomes after vitrectomy for diabetic macular edema: Diabetic Retinopathy Clinical Research Network. Retina 2010;30(9):1488-95.
305. Simunovic MP, Hunyor AP, Ho IV. Vitrectomy for diabetic macular edema: A systematic review and meta-analysis. Can J Ophthalmol 2014;49(2):188-95.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 11 of 12, November 2020) am 10.11.2020

#	Suchfrage
1	MeSH descriptor: [Diabetic Retinopathy] explode all trees
2	((diabetic OR diabetes) AND (macular OR retinal) AND (edema OR oedema)):ti,ab,kw
3	((diabetic OR diabetes) AND (maculopath* OR retinopath*)):ti,ab,kw
4	#1 OR #2 OR #3
5	#4 with Cochrane Library publication date from Nov 2015 to present, in Cochrane Reviews

Systematic Reviews in Medline (PubMed) am 10.11.2020

#	Suchfrage
1	diabetic retinopathy[MeSH Terms]
2	(diabetic[Title/Abstract] OR diabetes[Title/Abstract]) AND (macular[Title/Abstract] OR retinal[Title/Abstract]) AND (edema[Title/Abstract] OR oedema[Title/Abstract])
3	(diabetic[Title/Abstract] OR diabetes[Title/Abstract]) AND (maculopath*[Title/Abstract] OR retinopath*[Title/Abstract])
4	#1 OR #2 OR #3
5	(#4) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))

#	Suchfrage
6	(#5) AND ("2015/11/01"[PDAT] : "3000"[PDAT])
7	(#6) NOT "The Cochrane database of systematic reviews"[Journal]
8	(#7) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 10.11.2020

#	Suchfrage
1	diabetic retinopathy[MeSH Terms]
2	(diabetic[Title/Abstract] OR diabetes[Title/Abstract]) AND (macular[Title/Abstract] OR retinal[Title/Abstract]) AND (edema[Title/Abstract] OR oedema[Title/Abstract])
3	(diabetic[Title/Abstract] OR diabetes[Title/Abstract]) AND (maculopath*[Title/Abstract] OR retinopath*[Title/Abstract])
4	#1 OR #2 OR #3
5	(#4) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
6	(#5) AND ("2015/11/01"[PDAT] : "3000"[PDAT])
7	(#6) NOT (retracted publication [pt] OR retraction of publication [pt])

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Beteiligung von AkdÄ und Fachgesellschaften nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

2021-B-044

Kontaktdaten

Deutsche Ophthalmologische Gesellschaft (DOG), Deutsche Diabetes Gesellschaft (DDG), Retinologische Gesellschaft (RG), Berufsverband der Augenärzte Deutschlands e.V. BVA)

Mit Zustimmung der DGf Allgemein- und Familienmedizin (DEGAM)

Indikation gemäß Beratungsantrag

…wird angewendet bei Erwachsenen zur Behandlung des diabetischen Makulaödems (DMÖ).

Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?

Die Behandlungsoptionen sind zuletzt ausführlich in der Stellungnahme der augenärztlichen Fachgesellschaften dargestellt worden [1] und in den Praxisempfehlungen der Deutschen Diabetes-Gesellschaft erwähnt [2]. Es müssen verschiedene Therapieoptionen für die Therapie des diabetischen Makulaödems berücksichtigt werden:

- Lasertherapie (*focal/grid laser*)
- Intravitreale operative Medikamentenapplikation (IVOM) mit VEGF-Inhibitoren (*Aflibercept, Bevacizumab*, Ranibizumab*)
- Intravitreale operative Medikamentenapplikation (IVOM) mit Steroiden (*Triamcinolon**) und Steroid-Implantaten (*Dexamethason, Fluocinolon*)

**Bevacizumab* und *Triamcinolon* stellen eine *off label*-Behandlung dar.

Grundsätzlich sollen alle Patienten über die verschiedenen Therapiemodalitäten, insbesondere über die jeweilige Visusprognose, Behandlungsfrequenzen und Komplikationshäufigkeiten informiert werden [1].

Es ist zu beachten, dass verschiedene Untersuchungen wie die Bestimmung des bestkorrigierten Visus, die Spaltlampenuntersuchung der vorderen Augenabschnitte die stereoskopische Untersuchung der gesamten Netzhaut in Mydriasis, die Fluoreszeinangiographie und die optische Kohärenztomographie (OCT) erforderlich sind, um die Indikation, d.h. Chancen und Risiken der Behandlung, im Einzelfall zu bewerten.

Die Behandlung eines diabetischen Makulaödems mit intravitrealen Medikamenten soll nur dann erfolgen, wenn aufgrund des Ausgangsbefunds eine positive Beeinflussung des funktionellen (und morphologischen) Befunds erwartet werden kann. Hinweise auf reduzierte Chancen einer Sehverbesserung können hierbei eine zentrale Atrophie (Netzhautdicke im OCT, zentrale Ischämie in der Fluoreszeinangiographie) oder Sekundärveränderungen wie proliferative Membranen und traktive Veränderungen sein.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung von „Patienten mit Visusbeeinträchtigung infolge eines diabetischen Makulaödems (DMÖ)**“, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?**

Es ist zu berücksichtigen, dass der Großteil der den Zulassungen zugrundeliegenden Studien Einschränkungen in Bezug auf den Visus und genaue Bedingungen zu Art und dem Ausmaß der zentralen Beteiligung enthielten.
Folgende Faktoren sollten in der Entscheidung berücksichtigt werden:

- **Foveale Beteiligung**

Die Beteiligung der zentralen Netzhaut kann mit Hilfe der optischen Kohärenztomographie (OCT) (Bereiche: central subfield: Durchmesser ca. 1 m, innerer Ring: Durchmesser: ca. 3 mm) oder der Fluoreszeinangiographie beurteilt werden [1]. In den Zulassungsstudien wurde eine Beteiligung der Netzhautmitte über die zentrale Netzhautdicke geprüft.
Fehlende Wirksamkeitsdaten und die Wirtschaftlichkeit sprechen gegen eine Ausweitung der IVOM-Therapie auf Patienten ohne foveale Beteiligung. Die fokale Laserkoagulation kann dann eine sinnvolle Therapieoption darstellen [3].
Für Patienten mit fovealer Beteiligung ist die Wahl der Therapie abhängig vom Ausmaß der Visusbeeinträchtigung und dem morphologischen Befund.

- **Visusbeeinträchtigung**

Eine Visusbeeinträchtigung kann bei Patienten mit Diabetes durch diabetesbedingte Schäden, aber auch durch andere Augenerkrankungen bedingt sein. Dabei ist es nicht immer einfach, den Anteil unterschiedlicher Ursachen für eine Sehverschlechterung zu bewerten. Während in den meisten Zulassungsstudien und Wirksamkeitsstudien andere Erkrankungen des Auges ausgeschlossen waren, werden im klinischen Alltag auch Patienten behandelt, die z.B. Linsentrübung, Oberflächen-Benetzungsstörung oder Glaskörperblutung aufweisen können.
Eine IVOM-Therapie sollte nach den Empfehlungen der augenärztlichen Fachgesellschaften nicht bereits bei sehr gutem Visus erfolgen, aber auch dann nicht, wenn eine positive Beeinflussung des funktionellen (und morphologischen) Befundes aufgrund des Befundes nicht mehr erwartet werden kann, also z.B. die Visusprognose unter 0.05 liegt [1].
Infolge einer ausgeprägten und irreversiblen Schädigung der zentralen Makula ist für Betroffene auch nach einer Abnahme des diabetischen Makulaödems keine relevante Sehverbesserung profitieren. Ein wichtiges Instrument, um die Vorschädigung der zentralen Netzhaut zu bewerten, ist auch hier die OCT-Untersuchung [4-7]. Eine starke Verdünnung der zentralen Netzhaut, eine Disorganisation der inneren Netzhautschichten, eine strukturelle Schädigung der äußeren Netzhaut (Photorezeptoren) [8] oder eine besonders ausgeprägte pathologische Ansammlung sub- und intraretinaler Flüssigkeit über längere Zeit können Hinweise auf die eingeschränkte Prognose geben. Die alleinige Betrachtung der Netzhautdicke im individuellen Fall hat jedoch einen nur geringen Vorhersagewert [9]. Es gibt Hinweise darauf, dass jede Form von Flüssigkeit (intra- und subretinal) mit einer reduzierten Sehfunktion verbunden sind [10,11]:
Ohne Behandlung können 24% der Augen mit klinisch signifikantem diabetischen Makulaödem innerhalb eines Zeitraums von 3 Jahren einen Sehverlust von ≥15 Buchstaben (Halbierung der Sehschärfe) haben [12]. Dazu hatten unbehandelte Patienten in den Kontrollgruppen mit intraretinaler oder subretinaler Flüssigkeit eine mehr als 4x so hohe Wahrscheinlichkeit, eine entsprechende Halbierung des Visus (Verlust um ≥15 Buchstaben gegenüber dem Ausgangsvisus) zu erleiden,

verglichen mit Patienten ohne diese (*odds ratio* 4,26 für intraretinale Flüssigkeit, *odds ratio* 4,29 für subretinale Flüssigkeit) [13].
Im Rahmen einer prospektiven Studie (NCT01909791) wurden Lasertherapie, IVOM-Therapie mit Aflibercept und abwartendes Vorgehen über einen Zeitraum von 2 Jahren miteinander für solche Patienten verglichen, die trotz einer fovealen Beteiligung (central subfield mindestens 290 µm bzw. 305 µm) eine gute Sehfunktion (Visus 0.8 oder besser) aufwiesen [14]. Nach zwei Jahren unterschied sich der Anteil mit einer leichten Sehverschlechterung (Verlust um 5 Buchstaben) nicht zwischen den drei Gruppen (16%, 17%, 19%). In den beiden Gruppen ohne initiale IVOM-Behandlung wurde diese begonnen, wenn der Visus um mindestens 10 Buchstaben (oder um 5 Buchstaben an zwei aufeinanderfolgenden Visiten) fiel. Dieses Ereignis trat in der Lasergruppe (25%) und unter alleiniger Beobachtung (34%) nicht so häufig auf, sodass für den Fall einer - trotz Ödems mit zentraler Beteiligung – noch guten Sehfunktion nur ein geringes Risiko einer starken Sehverschlechterung besteht. Ein abwartendes Vorgehen mit Verlaufskontrollen ist daher bei dieser Konstellation eine sinnvolle Option.

- **Linsenstatus und Alter**
Der Zustand der Linse und das Alter haben einen Einfluss auf die mögliche Naheinstellungsreaktion (Akkomodation). Weil intraokulare Steroide ein Fortschreiten bzw. das Auftreten einer relevanten Katarakt bewirken, sollten diese Präparate zurückhaltend für junge Menschen mit erhaltener Akkommodation bzw. eigener Linse gewählt werden, da es durch eine Katarakt-Operation zum Verlust der Akkommodation kommt [1]. Daher sind entsprechende Hinweise auch den Fachinformationen von Ozurdex und Iluvien erhalten.

- **Glaukom**
Nach der Gabe von Steroiden in den Glaskörperraum kam es teilweise zu einer Erhöhung des Augeninnendruckes, sodass Patienten mit augendrucksenkenden Augentropfen oder in seltenen Fällen mit einer Glaukom-Operation behandelt werden mussten, um einen irreversiblen Glaukomschaden zu verhindern. Die Wahrscheinlichkeit für erhöhte Druckwerte nach der Gabe von Steroiden wird zusätzlich durch eine schon vorbekannte Glaukom-Erkrankung erhöht. Daher müssen Hinweise auf erhöhte Druckwerte oder ein vorbestehendes Glaukom beachtet werden, um die Patienten über das Nebenwirkungsprofil ausreichend aufklären zu können [1].

- Begleiterkrankungen und systemische Therapie
Systemische Risikofaktoren wie ein erhöhter Blutdruck oder Wirkstoffe, die eine Progression der diabetischen Retinopathie fördern können, sollten beachtet werden [15-17]. In Deutschland dürfte die Versorgungspraxis aufgrund einer unterschiedlichen Umsetzung von Selektivverträgen regionale Unterschiede für den Einsatz der intravitrealen Medikamente aufweisen [18]. Einzelne nicht interventionelle Studien deuten darauf hin, dass die Wahrscheinlichkeit einer Unterbehandlung besteht [19-21] und auf die Adhärenz der behandelten Patienten geachtet werden muss [22].

Nach den Kriterien gemäß 5. Kapitel § 6 VerfO sind – ähnlich wie im Rahmen der Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V Vorgang: Vorgangsnummer 2014-09-15 D-137 – Aflibercept im März 2014 [23] vor allem die zugelassenen Arzneimittel zu berücksichtigen. Obwohl nicht-medikamentöse Behandlungen diskutiert werden müssen, muss die Einordnung im Rahmen der aktuellen Stellungnahme berücksichtigt werden [1]. Die Laserfotokoagulation (OPS 5-155) kommt, insbesondere für den Fall der fovealen Beteiligung meist verzögert oder unterstützend zur Anwendung. Der Einsatz der Vitrektomie (OPS 5-158 und 5-159) beschränkt sich auf die Situationen mit ausgeprägten

komplikativen Veränderungen der proliferativen diabetischen Retinopathie (Neovaskularisationen und/oder Gefäßbindegewebsproliferationen mit Blutungen und/oder traktiven Membranen).

Die Fachinformation von Eylea [24] weist auf folgende Einschränkungen hin:
• Es gibt nur begrenzte Erfahrung bei der Behandlung von Patienten mit DMÖ aufgrund eines Typ-I-Diabetes.
• Es gibt nur begrenzte Erfahrungen für Menschen mit sehr hohen mittleren Blutzuckerwerten (HbA1c über 12%).
• Es gibt nur begrenzte Erfahrungen für Menschen mit einer fortgeschrittenen diabetischen Augenerkrankung, auch proliferative diabetische Retinopathie genannt.
• Es gibt keine Erfahrung bei der Behandlung von Menschen mit Diabetes und einem nicht eingestelltem Bluthochdruck.

Die Fachinformation von Iluvien [25] weist auf folgende Besonderheiten hin:
• ILUVIEN ist zur Behandlung von Sehstörungen in Verbindung mit chronischem diabetischem Makulaödem indiziert, das auf verfügbare Therapien nur unzureichend anspricht.
• Die Injektion von ILUVIEN in beide Augen wurde nicht untersucht und wird nicht empfohlen.

Die Fachinformation von Ozurdex [26] weist auf folgende Besonderheiten hin:
• Ozurdex ist zur Behandlung erwachsener Menschen mit einer Sehbeeinträchtigung aufgrund eines diabetischen Makulaödems (DMÖ) vorgesehen, die pseudophak sind oder auf Therapie mit Nicht-Kortikosteroiden unzureichend ansprechen.

Aktuelle Studien systemischer Medikamente lassen keine abschließende Bewertung zu, weil die Erhebung der Retinopathie und die Untersuchung des Augenhintergrunds oft unzureichend standardisiert ist. Daher ergeben sich vorerst aus Studien mit kardiovaskulären Endpunkten keine oder nur eingeschränkte Erkenntnisse möglicher Wechselwirkungen in Bezug auf die diabetische Retinopathie [27].

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