Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: Vorgangsnummer 2014-09-15 D-137 - Aflibercept

Stand: März 2014

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Aflibercept
Zur Behandlung eines diabetischen Makulaödems

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	⇨ Siehe Tabelle II. Zugelassene Arzneimittel im Anwendungsgebiet
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	– Laserfotokoagulation (OPS 5-155) – Vitrektomie (OPS 5-158 und 5-159)
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	⇨ Siehe Evidenzsynopse
Bei mehreren Alternativen ist die wirtschaftlichere Therapie zu wählen, vorzugsweise eine Therapie, für die ein Festbetrag gilt.	nicht angezeigt
[…] vorzugsweise eine Therapie, […] die sich in der praktischen Anwendung bewährt hat.	nicht angezeigt

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Aflibercept (ATC-Code liegt nicht vor)	Geplantes Anwendungsgebiet: Behandlung einer Visusbeeinträchtigung aufgrund eines diabetischen Makulaödems
Ranibizumab Lucentis® S01LA04	Lucentis wird angewendet bei Erwachsenen zur: • Behandlung der neovaskulären (feuchten) altersabhängigen Makuladegeneration (AMD) • Behandlung einer Visusbeeinträchtigung infolge eines diabetischen Makulaödems (DMÖ) • Behandlung einer Visusbeeinträchtigung infolge eines Makulaödems aufgrund eines retinalen Venenverschlusses (RVV) (Venenastverschluss oder Zentralvenenverschluss) • Behandlung einer Visusbeeinträchtigung infolge einer chorioidalen Neovaskularisation (CNV) aufgrund einer pathologischen Myopie (PM)
Fluocinolonacetonid Iluvien® S01BA15	ILUVIEN ist zur Behandlung von Sehstörungen in Verbindung mit chronischem diabetischem Makulaödem indiziert, das auf verfügbare Therapien nur unzureichend anspricht.
Dexamethason Ozurdex® S01BA01	OZURDEX® wird angewendet zur Behandlung von Erwachsenen mit Makulaödem als Folge eines retinalen Venenastverschlusses (VAV) oder retinalen Zentralvenenverschlusses (ZVV) (siehe Abschnitt 5.1). OZURDEX® wird angewendet zur Behandlung von Erwachsenen mit einer Entzündung des posterioren Segments des Auges, die sich als nicht infektiöse Uveitis darstellt.
Nepafenac Nevanac® S01BC10	NEVANAC wird bei Erwachsenen angewendet bei: – Prophylaxe und Behandlung postoperativer Schmerz- und Entzündungszustände bei Kataraktoperationen – Verminderung des Risikos postoperativer Makulaödeme in Zusammenhang mit Kataraktoperationen bei Diabetikern (siehe Abschnitt 5.1).
Diclofenac Difen UD® S01BC03	Präoperative Anwendung und Behandlungsbeginn: - zur Aufrechterhaltung der Pupillenerweiterung (Mydriasis) bei operativen Eingriffen - zur Behandlung postoperativer Entzündungssymptome, z. B. nach Staroperationen oder Laserbehandlungen - zur Vorbeugung (Prophylaxe) von Veränderungen am Augenhintergrund (zystoides Makulaödem) nach Kataraktoperationen Bei allen nichtinfektiösen Entzündungen des Auges, die mit einer Erhöhung der Prostaglandinkonzentrationen im Gewebe oder Kammerwasser

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	verbunden sind, zur entzündungshemmenden, abschwellenden und schmerzhemmenden Behandlung. Bei chronisch nichtinfektiösen Entzündungen des vorderen Augenabschnittes, wie z. B. der Konjunktivitis, der Keratokonjunktivitis und der Episkleritis

Quellen: AMIS-Datenbank, Fachinformationen

Recherche und Synopse der Evidenz zur Bestimmung der zVT:

Inhalt

Indikation für die Recherche bei Wirkstoff (evtl. Markenname):

Aflibercept (Eylea®) ist indiziert zur Behandlung eines diabetischen Makulaödems

(Modifikation des AWG laut nachträglichen Angaben des pU)

„Behandlung einer Visusbeeinträchtigung aufgrund eines diabetischen Makulaödems“

Berücksichtigte Wirkstoffe/Therapien:

Für das Anwendungsgebiet zugelassenen Arzneimittel, s. Unterlage zur Beratung in AG: „Übersicht zVT, Tabelle II. Zugelassene Arzneimittel im Anwendungsgebiet“

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation ***„diabetisches Makulaödem“*** durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am ***22.11.2013*** abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (einschl. NHS CRD-Datenbanken), MEDLINE (PubMed), Leitlinien.de (ÄZQ), AWMF, GIN, NGC, TRIP, DAHTA, NIHR HSC, Clinical Evidence. Ergänzend erfolgte eine freie Internetsuche

nach aktuellen deutschen und europäischen Leitlinien. Bei der Recherche wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab ***296*** Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt wurden **14** Quellen in die synoptische Evidenz-Übersicht aufgenommen.

Abkürzungen

AE	Adverse event
ARB	Angiotensin receptor blockers
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
BCVA	Best corrected visual acuity
CMT	Central macular thickness
CoL	Conflict of Interest
CSME	Clinically significant macular edema
DAHTA	Deutsche Agentur für Health Technology Assessment
DMO/DME	Diabetic macular oedema
DR	Diabetic retinopathy
DRS	Diabetic Retinopathy Study
EbM	Evidence-based Medicine
ENSPDR	English screening programme
ETDRS	Early Treatment Diabetic Retinopathy Study
FFA	Fundud fluorescein angiography
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendation
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ICG	Indocyanine green angiography
IOP	Intraocular pressure
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IRMA	Intraretinal microvascular abnormalities
IVTA	Intravitreal triamcinolide
LL	Leitlinie
LoE	Level of Evidence
NGC	National Guideline Clearinghouse
NHMRC	National Health and Medical Research Council
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
NIHR HSC	National Institute for Health Research Horizon Scanning Centre
NPDR	Nonproliferative diabetic retinopathy
NV/NVD/NVE	New vessels
OCT	Optical coherence tomography
PDR	Proliferative diabetic retinopathy
PKC	Protein kinase C
PRP	Panretinal photocoagulation
PRP	laser treatment
RBZ	Ranibizumab
RCT	Randomized Controlled Trial
SVL	Severe visual loss
TEE	Thromboembolic events
TNF	Tumor necrosis factor
TRD	Traction retinal detachment

TRIP	Turn Research into Practice Database
UK	United Kingdom
VEGF	Vascular endothelial growth factor
VH	Vitreous hemorrhage

IQWIG Berichte/ G-BA Beschlüsse

Hinweis. Die extrahierten Informationen beziehen sich nicht auf das Anwendungsgebiet von Aflibercept. Sie beschäftigen sich mit der Frage der Definition von „Visusbeeinträchtigung“ und mit der Frage nach der Relevanz des Endpunktes „Visusverbesserung“.

IQWiG, 2013: Ocriplasmin – Nutzenbewertung gemäß § 35a SGB V (per Handsuche) (Dossierbewertung, Auftrag A: 13-20)	**Fragestellung/Ziele:** • Bewertung des Zusatznutzens von Ocriplasmin im Vergleich zur zweckmäßigen Vergleichstherapie für folgendes Anwendungsgebiet: Behandlung der vitreomakulären Traktion (VMT) bei Erwachsenen, auch im Zusammenhang mit einem Makulaloch ≤ 400 Mikrometer. **Population:** • Das durchschnittliche Niveau der Sehschärfe lag im Bereich einer leichten Sehstörung nach ICD-10 (65 Buchstaben ETDRS). **Endpunkte**: • Morbidität (Endpunkt: Besserung der Sehschärfe ≥ 2 Zeilen) **Ergebnis /Fazit:** • …

G-BA, 2013: Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Ocriplasmin (per Handsuche)	**Fazit:** Im G-BA bestehen hinsichtlich der Patientenrelevanz des Endpunktes „Verbesserung der Sehschärfe > 2 Zeilen“ unterschiedliche Auffassungen. Die Gesamtaussage zur Bewertung des Zusatznutzens bleibt jedoch hiervon unberührt. Eine dem Endpunkt maßgeblich zugrunde liegende Publikation zur Validierung der klinischen Relevanz (Koch et al. 2012[2]) wurde an einem von der Zulassung von Ocriplasmin abweichenden Patientenklientel mit dem Krankheitsbild „Altersbedingte Makula-Degeneration (*AMD*)“ und mit einer schlechteren Ausgangssehschärfe von durchschnittlich 55 Buchstaben ETDRS durchgeführt. Bei der in den Zulassungsstudien von Ocriplasmin eingeschlossenen Patientenpopulation besteht eine vitreomakuläre Traktion und eine durchschnittliche Ausgangssehschärfe von 65 Buchstaben ETDRS. Es liegen im G-BA kontroverse Auffassungen hinsichtlich eines möglichen Einflusses der Ausgangssehschärfe auf die Minimal Important Difference der klinischen Relevanz des Endpunktes „Verbesserung der Sehschärfe > 2 Zeilen“ vor. Es bleibt offen, inwieweit bei einer geringeren Ausgangssehschärfe ggf. kleine Verbesserungen der Sehschärfe von größerer Bedeutung sind. Zudem handelt es sich bei der Publikation um eine nicht randomisierte, nicht verblindete Erhebung. Durch dieses methodische Vorgehen besteht die Möglichkeit der Verzerrung der Studienergebnisse. [2] KOCH, K. R., MUETHER, P. S., HERMANN, M. M., HOERSTER, R., KIRCHHOF, B. & FAUSER, S. 2012. Subjective perception versus objective outcome after intravitreal ranibizumab for exudative AMD. Graefes Arch Clin Exp Ophthalmol, 250, 201-9.

Cochrane Reviews

Es liegen derzeit keine relevanten Dokumente vor.

Systematische Reviews

Ford AJ, et al. 2013 [1] Current treatments in diabetic macular oedema: systematic review and meta-analysis	1. Fragestellung To review the evidence for triamcinolone, dexamethasone, fluocinolone, bevacizumab, ranibizumab, pegaptanib and aflibercept in the treatment of diabetic macular oedema.
	2. Methodik **Databases**: MEDLINE, EMBASE, Web of Science with Conference Proceedings and the Cochrane Library, meeting abstracts of the Association for Research in Vision and

	Ophthalmology, the American Diabetes Association (2002–2012) and the European Association for the Study of Diabetes, web sites of the European Medicines Agency and the US Food and Drug Association searched for data on registration status and safety, Clinicaltrials.gov and the EU Clinical Trials Register searched in July 2012 for data on ongoing research **Dates searched**: From inception of each database until July 2012, meeting abstracts from 2002 to 2012 **Included study design**: RCT for clinical effectiveness, RCTs and observational studies for safety **Intervention:** Anti-VEGF drugs **Comparator:** Both laser and placebo **Inclusion criteria:** (1) use of triamcinolone, dexamethasone, fluocinolone, bevacizumab, ranibizumab, pegaptanib or aflibercept in patients with DMO (2) minimum follow-up of 6 months (3) minimum of 25 eyes per study arm **Exclusion criteria:** (1) evaluated laser only (2) assessed the effect of the aforementioned treatments in macular oedema due to other retinal diseases (instead of DMO) (3) used only a single dose (4) were combined with a surgical intervention (5) published studies in languages other than English **Included studies**: 29 studies included in the review; seven studies suitable for meta-analysis
	3. Ergebnisdarstellung **Eingeschlossene Studien zu zugelassenen Wirkstoffen und Prozeduren:** • RCTs on <u>Ranibizumab</u> (READ-2, REVEAL, RESTORE, RISE, RIDE, RESOLVE, READ-3, DRCRN) • 2 trials on fluocinolone implant for DMO (FAME, Pearson et al.) • quality of included studies in general good **Ergebnisse zu zugelassenen Wirkstoffen und Prozeduren:** <u>Ranibizumab</u>: 7 studies sponsored by industry, 2 led by independent

	investigators) • READ-2 and RESTORE were suitable for pooling through meta-analysis and, when doing so, it was found that ranibizumab statistically significantly improved mean BCVA compared with laser (SMD 0,72; 95 % CI 0,48 to 0,95; p < 0,00001). • RESTORE, READ-2 and DRCRN (12 month data used) suitable for pooling through meta-analysis to compare ranibizumab plus laser and laser alone. Ranibizumab plus laser resulted in a statistically significantly greater change in mean BCVA (SMD 0,53; 95 % CI 0,38 to 0,76), proportion of patients with more than 15 letter gain (SMD 2,76; 95 % CI 1,87 to 4,07) and CMT reduction (SMD -0,36; 95 % CI -0,69 to -0,03, high statistical heterogeneity) versus laser alone. • *Adverse events*: Conjunctival haemorrhages higher in the ranibizumab arms compared with laser (RESTORE) or no treatment (RESOLVE). In the RESOLVE, RISE and RIDE studies, a considerably higher incidence of intraocular pressure (IOP) increase was reported in the ranibizumab arm compared to control. This increase in IOP was not demonstrated in the RESTORE study. There were no consistent differences in systemic adverse events between ranibizumab and laser or placebo. <u>Fluocinolone</u>: • FAME study (n=956): At 24 months, both doses of fluocinolone showed a statistically significant improvement in mean BCVA compared to sham. There was a modest difference between fluocinolone groups. Rescue laser was given after the first 6 weeks for persistent oedema and was allowed every 3 months. A range of 35–37% of patients in the fluocinolone group and 59% in the sham injection group required rescue laser. Extended follow-up at 36 months showed that both the fluocinolone arms continued to result in a statistically significant benefit compared with sham. • Pearson et al. (n=196) compared fluocinolone (0.59 mg) with standard of care, either laser or no treatment. At 3 years, there was no statistically significant difference in the proportion of patients with 15 letter gain or more (31% fluocinolone compared with 20% standard of care) between groups and the proportion of patients losing 15 letters or more in the fluocinolone group (17% compared with 14%). Increased incidence of cataracts may have contributed to this difference. • These trials were not suitable for meta-analysis. • *Adverse events*: Pearson and colleagues reported a higher incidence of cataracts at 3 years in the fluocinolone group compared with standard of care (55.9% compared with 21.7%). In the extended report of the FAME study, there was a considerably higher incidence of cataract surgery in phakic eyes in the 0.2 and 0.5 µg/day fluocinolone groups (80% and 87.2% compared with 27.3%) and increased IOP at any point (37% and 46% compared with 12%). **Ergebnisse zum direkten Vergleich von Ranibizumab und**

	Fokal/Grid Laser (3 Studien relevant): • READ-2 (low study quality): compared ranibizumab (0.5 mg) alone, and laser alone, at 6 months, BCVA had improved significantly (p=0,0003) in the ranibizumab alone group (+7,24 letters) compared with laser alone (-0,43 letters) • RESTORE (high study quality): Ranibizumab improved (p<0,0001 vs. Laser) mean BCVA (+6,1 letters), with laser providing no additional benefit (+0,8 letters). Two-year extended follow-up suggested that these results continued. • REVEAL (study quality unclear): both ranibizumab (+5,9 letters) arms resulted in a statistically significantly (p<0,0001) better improvement in BCVA compared to laser alone (+1,4)
	4. Anmerkungen/Fazit der Autoren: *The anti-VEGFs ranibizumab and bevacizumab have consistently shown good clinical effectiveness without major unwanted side effects. Steroid results have been mixed and are usually associated with cataract formation and intraocular pressure increase. Despite the current wider spectrum of treatments for DMO, only a small proportion of patients recover good vision (≥ 20/40), and thus the search for new therapies needs to continue.* 5. Hinweise durch FB Med: • Heterogeneity assessed and discussed. • The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article. • No funding information (most probably NICE).
Abouammoh MA, et al. 2013 [2] Ranibizumab injection for diabetic macular edema: meta-analysis of systemic safety and systematic review.	1. Fragestellung The main aim of this study is to provide an evidence- based analysis of the safety profile for ranibizumab intravitreal injections in patients with DME.
	2. Methodik **Databases**: MEDLINE, EMBASE **Dates searched**: January 2000 to March 2012 **Included study design**: RCTs **Intervention:** Ranibizumab **Comparator:** Any other treatment modality for DME **Inclusion criteria:** (1) studies published in the English language and on humans (2) evaluating ranibizumab versus any other treatment modality for DME **Exclusion criteria:** (1) anti-VEGF treatment for an indication other than DME

	(2) controlled trials that used nonrandom allocation (3) uncontrolled studies and case series **Included studies**: 5 studies (READ-2, DRCR.net, RESOLVE, RESTORE, RISE, RIDE, n = 2 072)
	3. Ergebnisdarstellung • Pooled RR for TEEs after ranibizumab intravitreal injection was 0.74 (95%CI 0.52–1.06) • no clinical heterogeneity detected • no statistical heterogeneity detected • quality of trials assessed by Jadad score
	4. Anmerkungen/Fazit der Autoren: *Intravitreal ranibizumab for the treatment of diabetic macular edema did not increase the risk for TEEs as shown by this meta-analysis of 5 randomized, controlled clinical trials.* 5. Hinweise durch FB Med: • The author has no proprietary or commercial interest in any materials discussed in this article. • No funding information • publication bias not mentioned • study quality not discussed • relevance of outcome (TEE) unclear
Evoy KE, et al. 2013 [3] Ranibizumab: The First Vascular Endothelial Growth Factor Inhibitor Approved for the Treatment of Diabetic Macular Edema	1. Fragestellung This article reviews the pharmacology, efficacy, and safety data available for ranibizumab and compares the drug to other therapeutic options for DME to determine its likely role in therapy.
	2. Methodik **Databases**: MEDLINE **Dates searched**: Conducted in February 2013 **Included study design**: RCTs **Intervention:** Ranibizumab alone or in combination **Comparator:** Focal/grid laser photocoagulation or sham **Exclusion criteria:** (1) Animal studies and those written in a language other than English **Included studies**: 6 Phase II or III RCTs (READ-2, RESOLVE, RESTORE, DRCR.net, RISE/RIDE, more than 2 000 eyes)
	3. Ergebnisdarstellung • Ranibizumab consistently produced significantly greater gains in mean best corrected visual acuity than focal/grid laser

	photocoagulation or sham (7,4 to 12,5 letter improvement with ranibizumab vs 0,5 to 3 letters following focal/grid laser photocoagulation monotherapy) with a favorable safety and tolerability profile. • Ranibizumab was also studied in combination with focal/grid laser photocoagulation, showing no additional gains in vision versus ranibizumab monotherapy.
	4. Anmerkungen/Fazit der Autoren: *The identified trials provide support for the safety and efficacy of ranibizumab in the treatment of vision loss due to DME and present a strong case for the shift to first-line treatment with vascular endothelial growth factor inhibitors from focal/grid laser photocoagulation, the standard of care since the Early Treatment Diabetic Retinopathy Study of 1985.* 5. Hinweise durch FB Med: • Conflict of interest: Authors reported none • No funding information • Study quality not mentioned
Wang H, et al. 2012 [4] Intravitreal Ranibizumab (Lucentis) for the Treatment of Diabetic Macular Edema: A Systematic Review and Meta-Analysis of Randomized Clinical Control Trials.	1. Fragestellung To evaluate the therapeutic effect and safety of intravitreal ranibizumab (RBZ) or RBZ combined with focal/grid laser in diabetic macular edema
	2. Methodik **Databases:** Cochrane Central Register of Controlled Trials, PUBMED, EMBASE, the metaRegister of Controlled Trials, and ClinicalTrials.gov **Population:** Patients with diabetic macular edema (DME) **Intervention:** Intravitreal ranibizumab (RBZ) **Komparator:** RBZ combined with focal/grid laser **Endpunkt:** Best corrected visual acuity (BCVA), or central macular thickness (CMT), mean Number of Intravitreal Injections, systemic and ocular adverse events (AEs) **Suchzeitraum (Aktualität der Recherche):** 2000 to 2011 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** Four studies with a total of 1 313 DME patients were included.
	3. Ergebnisdarstellung • The included studies had a low risk of bias. **<u>Comparing RBZ to Non-Drug Control:</u>** • **Best-Corrected Visual Acuity**: The mean difference in BCVA at 12 months (7.50) was statistically significant

	(95% CI = 3.43–11.58; p = 0.0003) in support of RBZ treatment but with substantial heterogeneity (p = 0.13, I2 = 55%) possibly due to the small sample size in the study by Massin et al., so the random effects was used. Only Nguyen et al. analyzed the results at 24 months, so the meta-analysis could not be performed; therefore we pooled data of the two arms as seen in the 24 months subgroup and the direction of the effect was favorable to RBZ but no statistically significant difference could be demonstrated. • **Central Macular Thickness**: At 12 months, a more obvious reduction of CMT in the RBZ group was observed compared to the non-drug group, and the mean difference in CMT was statistically significant (−94.42 μm; 95% CI = −174.22 to −14.62 μm; p = 0.02); however, the corresponding I2 value was 82%. • **Adverse Events:** o Ocular AEs: The available case data analysis showed that lower incidence of eye pain was observed in RBZ arm (0.95) and exhibited no heterogeneity (p = 0.74, I2 = 0%); however, the results were not statistically significant (95% CI = 0.50–1.80; p = 0.88). o Systemic AEs: The available case data analysis showed that lower incidence of hypertension was observed in the RBZ arm (0.95) with no heterogeneity (p = 1.00, I2 = 0%), while there was no statistical difference presented in the analysis (95% CI = 0.44–2.07; p = 0.91). o Fewer patients treated with non-drug intervention developed arterial thromboembolic incidence. The mean difference was not statistically significant (2.99; 95% CI = 0.79–11.28; p = 0.11) and lacked heterogeneity (p = 0.32, I2 = 0%). **Comparing RBZ+Laser to Laser:** • Best-Corrected Visual Acuity: At 12 months, the analysis showed more obvious improvement in BCVA from baseline in the RBZ combined with laser arm. The mean difference was statistically significant (5.83; 95% CI = 4.07–7.59; p < 0.00001) and has no heterogeneity (p = 0.79, I2 = 0%). Patients treated with RBZ combined with laser had a greater change in BCVA at the end of 24 months compared with those treated with laser alone. The mean difference was statistically significant (3.77; 95% CI = 0.63–6.90; p = 0.02) and exhibited no heterogeneity (p = 0.32, I2 = 0%). • Central Macular Thickness: At 12 months, there was a more significant reduction of CMT in the RBZ plus laser group compared to the laser arm. The mean difference in CMT was statistically significant (−46.82 μm; 95% CI = −83.98 to −9.65 μm; p = 0.01) but had heterogeneity (p = 0.07, I2 = 69%). • Adverse Events: The AEs were abstracted from two studies. The data were inadequate, thus limiting the meta-

	analysis assessment. In the study by Elman et al., there was no obvious difference in ocular AEs such as increased intraocular pressure (IOP), vitreous hemorrhage, and incidence of glaucoma surgery between the two interventions. There was one serious adverse event reported in the study by Nguyen et al.: a patient in RBZ combined with focal/ grid laser group died of a cerebral vascular accident 6 weeks after his first injection of RBZ. But, in light of the long period between its occurrence and the prior injection as well as the patient's high risk for cerebral vascular accident because of a preexisting cardiovascular disease, the event was judged to be unrelated to RBZ. **Comparing RBZ to RBZ+Laser:** • Best-Corrected Visual Acuity and Central Macular Thickness: Due to the inadequate data of BCVA and CMT, only the description was performed instead of meta-analysis. Better improvement in BCVA was observed in RBZ compared with RBZ plus laser arm at the end of 12 and 24 months in the studies by Mitchell et al. and Nguyen et al. (12 months, 0.40; 24 months, 0.90). But, there was no statistically significant difference between the two arms in both studies (12 months, 95% CI = −2.21 to 3.01; p = 0.76; 24 months, 95% CI = −4.39 to 6.19; p = 0.74). In the study by Mitchell et al., the mean change from baseline to 12 month in reduction of CMT was greater in RBZ combined with laser group but with no statistically significant difference (−9.60; 95% CI = −39.06 to 19.86; p = 0.52). The 24-month data of the study by Nguyen et al. supported RBZ plus laser therapy with significant difference (−82.00; 95% CI = −144.98 to −19.02; p = 0.01). • The Mean Number of Intravitreal Injections: The mean number of intravitreal injections was analyzed in the two studies. Without impairment of visual acuity, the mean number at the end of 24-month followup was 9.3 and 2.9 in RBZ and RBZ plus laser arms, respectively. In the study by Mitchell et al., the mean number of RBZ injections received was similar for the two treatment groups. Between months 3 and 11, 4.1 and 3.8 RBZ intravitreal injections were performed in RBZ and RBZ plus laser arms, respectively. • Adverse Events: Data about complications were abstracted from the two studies. Because of the insufficiency, the meta-analysis assessment could not be performed. In the study by Mitchell et al., there was no obvious difference in ocular and systemic AEs such as increased IOP, conjunctival hemorrhage, eye pain, blurred vision, hypertension, and arterial thromboembolic events.
	4. Anmerkungen/Fazit der Autoren: *Our analysis shows that RBZ and RBZ combined with focal/grid laser is more advantageous than non-drug treatment or focal/grid laser in reducing CMT and improving BCVA in DME during 12 and 24 months follow-up period and can be well tolerated based on the safety*

	assessment. Intravitreal RBZ may be equivalent to RBZ combined with focal/grid laser. 5. Hinweise durch FB Med: • Qualität der eingeschlossenen Studien untersucht anhand Cochrane Handbook for Systematic Reviews of Interventions • Pooling of studies unclear (non-drug controls = laser?) • work supported by National Program on Key Basic Research Project (973 Program, Grant No. 2011CB707506) • The research review boards of the Shanghai Jiao tong University approved this study • No information about CoI.
Mohamed QA, et al. 2011 [5] Diabetic retinopathy (treatment).	1. Fragestellung What are the effects of laser treatments in people with diabetic retinopathy? What are the effects of drug treatments for diabetic retinopathy? What are the effects of treatments for vitreous haemorrhage?
	2. Methodik Clinical Evidence is neither a textbook of medicine nor a set of guidelines - orientiert an den 5 Schritten der EbM - keine formalen Konsensusprozesse - Anwendung von GRADE - Categories of effektiveres (siehe Anhang) **Population:** People with clinically significant macular oedema **Intervention:** Siehe Ergebnisteil **Komparator:** Siehe Ergebnisteil **Endpunkt:** Visual acuity, Clinically important loss of vision, Regression, Adverse effects of treatment **Suchzeitraum (Aktualität der Recherche):** Bis Juni 2010 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 58 systematic reviews, RCTs, observational studies
	3. Ergebnisdarstellung **Eingeschlossene Studien zur lokalen Laserkoagulation:** 2 RCTs (n = 2 300 Augen) **Verwendete Verfahren:** photocoagulation, focal laser treatment using an argon laser **Ergebnisse zur lokalen Laserkoagulation:** • Im Vergleich zu keiner Behandlung ist die lokale Laserkoagulation effektiv in der Reduktion des Visusverlustes nach 2-3 Jahren bei Menschen mit einem klinisch signifikanten DMO und milder bis moderater nichtproliferativer Retinopathie (hochqualitative Evidenz).

	• Erste (nicht entsprechend gepowerte Studie) fand keinen stat. sign. Unterschied nach 2 Jahren (RR 0,54, 95% KI: 0,25 bis 1,16) - Blankenship GW (1979) Ophthalmology • Die zweite größere Studie berichtet einen stat. signifikanten Unterschied in der Reduktion des moderaten Visusverlusts (RR 0,50, 95% KI: 0,47 bis 0,53; NNT=8 Augen, 95% KI: 7 bis 12 Augen). Die Subgruppenanalyse zeigt, dass der Therapievorteil größer ist bei Augen mit einem klinisch signifikanten DMO, insbesondere bei Menschen mit der vorliegenden oder anstehenden Betroffenheit des Zentrums der Makula - Early Treatment Diabetic Retinopathy Study Research Group (1985) Arch Ophthalmol **Adverse events** • Uncontrolled studies reported that loss of contrast sensitivity and visual acuity occurred after direct application of the laser to the centre of the fovea.We found no accurate estimates of the frequency of adverse effects. • The RCT found no significant differences in the frequency of immediate visual loss, visual field, or colour vision scores (reported as not significant; further data not reported) **Eingeschlossene Studien zu Laser + VEGF-Inhibitor:** 1 RCT (84 people) compared intravitreal ranibizumab 0.5 mg at the time of focal macular laser photocoagulation and 3 months later and laser alone (moderate quality evidence) - READ-2 study (2009) Ophthalmology **Ergebnisse:** • Compared with photocoagulation alone Macular photocoagulation plus vascular endothelial growth factor inhibitor injection may improve visual acuity at 6 months in people with diabetic macular oedema (p = 0,07) **Eingeschlossene Studien zur medikamentösen Therapie:** 1 subsequent RCT (126 people [126 eyes]) compared ranibizumab 0,5 mg, focal/grid laser photocoagulation, and ranibizumab 0,5 mg plus laser photocoagulation (moderate Quality of Evidence) - READ-2 study (2009) Ophthalmology **Ergebnisse zur medikamentösen Therapie:** • ranibizumab versus laser photocoagulation: ranibizumab significantly improved visual acuity compared with laser treatment at 6 months (BCVA changes from baseline: +7.24 with ranibizumab v –0.43 with laser treatment; p = 0,0001) • ranibizumab plus laser photocoagulation versus ranibizumab alone: no significant difference between groups in BCVA at 6 months (BCVA changes from baseline: 3.8 with combination treatment v 7.24 with ranibizumab alone; p = 0,08)

	4. Anmerkungen/Fazit der Autoren: *Die lokale Laserkoagulation vermindert signifikant den moderaten Visusverlust und wird empfohlen bei Augen mit einem klinisch signifikanten DMO (…), insbesondere wenn das Zentrum der Makula betroffen oder bevorstehend betroffen ist. Eine Überlegenheit im Vergleich der verschiedenen VEGF Inhibitoren ist nicht bekannt. Es bleibt unklar, ob die Kombination von VEGF Inhibitor plus Laser effektiv ist, da nur eine Studie mit Ranibizumab in Kombinationen gefunden wurde.* 6. Hinweise durch FB Med: • Competing interests: QAM has received honoraria and travel reimbursements and has served on advisory boards for Novartis, Allergan, Bay, and Pfizer. QAM was an investigator in the Resolve Study, and is the author of one systematic review referenced in this review. AR and CJC declare that they have no competing interests. • No funding information • Study quality assessed using GRADE
Boscia F, et al. 2010 [6] Current Approaches to the Management of Diabetic Retinopathy and Diabetic Macular Oedema	1. Fragestellung This article provides a brief overview of the present state of knowledge of the epidemiology, pathophysiology and approaches to the prevention and treatment of DR and diabetic macular oedema (DME), with a focus on those that are the most relevant to current clinical practice.
	2. Methodik **Databases**: MEDLINE, ClinicalTrials.gov registry was reviewed for ongoing initiatives, meeting abstracts, in particular the Association for Research in Vision and Ophthalmology (www.arvo.org/eweb/startpage.aspx?site=arvo2) and investigative Ophthalmology and Visual Science (www.iovs.org), obtained from relevant websites **Dates searched**: January 2006 through September 2010 **Included study design**: primary focus on reports that included a comparative arm with RCT of particular interest **(relevant) Intervention/Comparator:** Laser photocoagulation, Vitrectomy, Ranibizumab **Inclusion criteria:** (1) English-language articles **Included studies**: just over 600 articles obtained
	3. Ergebnisdarstellung **Eingeschlossene Studien zu „Laser Photocoagulation“:** 22

	sources cited, no further information **Ergebnisse zu „Laser Photocoagulation“:** • Laser-based therapies remain the cornerstone of treatment, with panretinal photocoagulation indicated for proliferative and severe nonproliferative DR and focal photocoagulation indicated for treatment of DME. **Eingeschlossene Studien zu „Pars Plana Vitrectomy“:** 32 sources cited, no further information **Ergebnisse zu „Pars Plana Vitrectomy“:** • For patients who do not benefit from these approaches (photocoagulation), vitrectomy may provide therapeutic benefits. **Eingeschlossene Studien zu „ Ranibizumab“:** 7 sources cited, no further information **Ergebnisse zu „Ranibizumab“:** • With respect to molecular targets, evidence has been adduced for the roles of vascular endothelial growth factor (VEGF), tumour necrosis factor (TNF)-C (and protein kinase C (PKC)-ß2 in the pathogenesis of DR, and agents targeting these factors around their intense investigation. The role of VEGF in mediating pathological angiogenesis and vascular hyperpermeability has been best defined. Preliminary efficacy of pegaptanib and ranibizumab in the treatment of DME is being confirmed in additional clinical trials with these agents.
	Anmerkungen/Fazit der Autoren: *Treatment options including laser photocoagulation, corticosteroids and anti-VEGF agents have demonstrated efficacy for treatment of DME and in some cases PDR; while anti-VEGF agents are not approved for this indication, they are currently under investigation. Moreover, anti-inflammatory agents such as corticosteroids, which have a wider spectrum of action, as well as drugs directed against other specific molecular targets, including TNF<X and PKC-ß2, also hold much promise.* 4. Hinweise durch FB Med: • Qualität der eingeschlossenen Studien nicht bewertet • Ein- und Ausschlusskriterien unklar • Editorial support provided by Lauren Swenarchuk, PhD. of Zola Associates and was funded by Pfizer Inc. • Dr Boscia reports no conflicts of interests that are directly relevant to the content of this review.
O'Doherty M, et al. 2008 [7] Interventions for	1. Fragestellung In this review, we discuss the evolution of the treatment of diabetic macular oedema and give helpful guidelines in the treatment of diabetic macular oedema based on available evidence to date.

diabetic macular oedema: a systematic review of the literature	2. Methodik **Databases:** Medline and Cochrane database, RCTs in humans in the English language **Population:** People with Diabetic macular oedema (DMO) **Intervention:** Siehe Ergebnisteil **Komparator:** Siehe Ergebnisteil **Endpunkt:** Not previously stated **Suchzeitraum (Aktualität der Recherche):** From 1979 to 2007 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 31 articles corresponded to subject matter
	3. Ergebnisdarstellung **Eingeschlossene Studien zur Laserkoagulation:** 11 RCTs (n = 3 646 Augen), different laser types (argon, diode, dye, krypton) and methods **Ergebnisse zur Laserkoagulation:** • Es liegt gute Evidenz vor, dass die lokale Laserkoagulation das Sehvermögen beim DMO erhält (ETDRS-Studie). **Adverse events** • include inadvertent foveal burn, central visualfield defect, colour vision abnormalities, retinal fibrosis and spread of laser scars. • Lovestain-Adrian et al reported the long-term outcome (5.5 years) of macular laser in 2000. This study showed that 51% of patients did not suffer any complication postlaser. However, 21% developed either subretinal fibrosis or atrophic creep within 1/3 of a disc diameter from the fovea with extension into the fovea in 22%. They also found that photocoagulation for DMO with hard exudates was more often associated with subretinal fibrosis or atrophic creep than photocoagulation of oedema without exudates. Hard exudates as well as complications after photocoagulation were more common in type 2 diabetes, resulting in a poorer outcome.14 **Eingeschlossene Studien zur Vitrektomie:** 8 RCTs (n = 261 Augen) **Ergebnisse zur Vitrektomie:** • RCTs have small numbers (poor statistical power) and inconsistent results • Most show significant improvement in macular thickness and volume postvitrectomy, but this does not consistently correlate with improvement in vision **Eingeschlossene Studien zur medikamentösen Therapie:** 2 RCTs, 2 ongoing studies

	Ergebnisse zur medikamentösen Therapie: • Ranibizumab (Lucentis; Genentech, South San Francisco, California) may also be useful for DR and DMO
	4. Anmerkungen/Fazit der Autoren: *Although laser treatment remains the cornerstone of treatment in diabetic macular oedema, the literature is beginning to support combination therapy. Using one or two intravitreal injections to reduce central macular thickness followed by focal or grid laser to give a sustained response may offer an alternative to treatment in DMO.* 5. Hinweise durch FB Med: • Qualität der eingeschlossenen Studien nicht bewertet • Competing interests: None. • No information about funding source

Leitlinien

Hooper P, et al. 2012 [8] **Canadian Ophthalmological Society (COS)** Canadian Ophthalmological Society evidence-based clinical practice guidelines for the management of diabetic retinopathy	Fragestellung: The objective of this document is to provide guidance to Canadian ophthalmologists regarding screening and diagnosis of diabetic retinopathy (DR), management of diabetes as it pertains specifically to DR, and surgical and nonsurgical approaches to the treatment of DR.
	Methodik: • These guidelines were systematically developed and based on a thorough consideration of the medical literature and clinical experience. • Where possible, the content of this document was developed in accordance with the Canadian Medical Association Handbook on Clinical Practice Guidelines and the criteria specified in the 6 domains of the Appraisal of Guidelines Research and Evaluation II (AGREE II) Instrument. Suchzeitraum: An English-language literature search for the years 1997–2010 was conducted using PubMed, EMBASE, the Cochrane Library, the National Guideline Clearing House, and the United States Preventative Services Task Force databases. LoE (siehe Anhang dieser Synopse) GoR nicht angegeben
	Treatment of macular edema: <u>Key messages:</u> • There is increasing evidence that intraocular injections of VEGF inhibitors are an effective treatment for DME and produce a larger gain in vision than focal or grid laser alone. • Intraocular injection of steroid results in rapid resolution of DME; however, the improvement is not sustained and is associated with a significant increase in the incidence of

	raised IOP and cataract. For pseudophakic patients, visual acuity improvements may approach those of anti-VEGF therapies. <u>Recommendations:</u> • Eyes that demonstrate clinically significant macular edema by ETDRS criteria without central macular thickening should receive focal laser [*Level 1*]; however, eyes with central macular thickening should be considered for treatment with a VEGF inhibitor alone or in conjunction with focal laser [*Level 1 for ranibizumab; Level 2 for bevacizumab*]. • Eyes that demonstrate evidence of vitreomacular traction and macular edema should be considered for vitrectomy [*Level1*].
Scottish Intercollegiate Guidelines Network (SIGN), 2010 [10] Management of diabetes. A national clinical guideline	Fragestellung(en) … 7. What is the optimal laser treatment for: a) proliferative diabetic retinopathy and b) diabetic macular oedema? 8. What pharmacological agents reduce the development or progression of diabetic retinopathy, and are independent of blood pressure and glucose effects: a) statins b) fibrates (fenofibrate) c) ACE Inhibitors d) angiotensin receptor blockers (ARB) e) PKC Inhibitors f) VEGF aptamers g) intraocular steroids h) somatostatin analogues and pegvisomant? …
	Methodik: systematische Evidenzaufbereitung mit formalem Konsensusprozess (considered judgement) - eigene Checklisten - eigenes Graduierungssystem (siehe Anhang) Grundlage der Leitlinie: Aktualisierung der SIGN 55: Management of Diabetes, siehe Ergebnisteil Suchzeitraum: 2003 - 2009 *Weitere Kriterien für die Qualität einer LL:* • *Empfehlungen sind mit Literaturstellen verknüpft* • *Öffentliche Konsultation und Expertenbegutachtung durchgeführt* Sonstige methodische Hinweise

	Aus öffentlichen Mitteln finaziert, CoI nicht deklariert
	Freitext/Empfehlungen/Hinweise: **LASER PHOTOCOAGULATION** Macular laser using the Early Treatment Diabetic Retinopathy Study (ETDRS) modified grid can slow visual impairment in people with diabetes and macular oedema affecting the fovea in the absence of predominant macular ischaemia (LoE 1++, 3) Recommendation: Modified ETDRS grid laser photocoagulation should be used for patients with clinically significant macular oedema in the absence of significant macular ischaemia (GoR A). Anmerkung FBMed: *Sonstige Empfehlungen beziehen sich auf die Laser-Photokoagulation bei diabetischer Retinopathie. Für die Vitrektomie bei DMO gibt es keine Empfehlung.* **PHARMACOLOGICAL THERAPY** Insufficient evidence was identified to warrant routine usage of antivascular endothelial growth factor (VEGF) therapies (pegaptanib, bevacizumab) for the treatment of proliferative diabetic retinopathy or diabetic macular oedema either as stand-alone therapy or as an adjuvant to laser therapy. Phase II trials show a beneficial effect when used in combination with laser (LoE 1+, 1-). Although a number of treatments for diabetic retinopathy are of interest, there is no compelling evidence for their routine use. Anmerkung FBMed: *Beide Wirkstoffe haben keine Zulassung im Anwendungsgebiet.*
American Optometric Association (AOA), 2013 [11] Eye care of the patient with diabetes mellitus.	Fragestellung: This guideline will assist optometrists in achieving different objectives with respect to eye care of a patient with diabetes mellitus.
	Methodik: systematische Evidenzaufbereitung mit formalem Konsensusprozess (14 Schritte zur Entwicklung der evidenz-basierten LL) Graduierungssystem (siehe Anhang dieser Synopse)
	Laser photocoagulation: Diabetic Macular Edema: • The management of patients with DME has evolved substantually in recent years. The ETDRS established the efficacy of focal/grid photocoagulation of the treatment of CDME **(LoE/SoE: A/A)** → *basierend auf der ETDRS. 'In this randomized clinical trial, which was supported by the National*

	Eye Institute, 754 eyes that had macular edema and mild to moderate diabetic retinopathy were randomly assigned to focal argon laser photocoagulation, while 1,490 such eyes were randomly assigned to deferral of photocoagulation.' • Patients with center-involved diabetic macular edema (DME) should be referred to an ophthalmologist experienced in the management of diabetic retinal disease for possible treatment with a regimen of anti-VEGF injection, with prompt or deferred focal/grid laser photocoagulation ***(SoE: A / Recommendation: A)*** → *basierend auf ETDRS (1985), DRCRN (2010): →, The DRCRN demonstrated that center-involved DME, with vision reduced to 20/32 or worse, is best treated with anti-VEGF followed by promt or deferred laser.* • Recent data demonstrated that a regimen of repeated intravitreal anti-VEGF injections is more effective than focal/grid laser alone in the treatment of center-involved DME **(LoE/SoE: A/B)** → *basierend auf Ngyen et al. 2012: Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE which compare Ranibizumab vs. Ranibizumab (different dosing schedules) or sham. Center involvement not reported in this study.* • Patients with diabetic macular edema (DEME), but without clinically significant macular edema (CSME), should be re-examined at 4- to 6 month intervals. Once clinically significant macular edema develops treatment with focal laser photocoagulation or intravitreal anti-VEGF injection is indicated. ***(SoE: A / Recommendation: A)*** → *basierend auf Mohamed QA(2011) Clincal Evidence (siehe Abschnitt "systematische Reviews" in dieser Synopse)* **Vitrectomy:** • Eyes with vitreous hemorrhage (VH), traction retinal detachment (TRD), macular traction, or an epiretinal membrane should be referred to an ophthalmologist experienced in the management of diabetic retinal disease for evaluation for possible vitrectomy ***(No level of evidence available).*** **Vascular Endothelial Growth Factor Inhibitors:** • The current standard of care for treatment of center-involved diabetic macular edema (DME) is anti-VEGF injections ***(SoE: A / Recommendations: A)*** → *basierend auf 2 Quellen. Davon eine Quelle zur Gabe von Ranibizumab: Diabetic retinopathy clinical research network, 2010: Randomized trial evaluating ranibizumab plus prompt or deferred laser or traminolone plus prompt laser for diabetic macular edema. Center involvement*

	not reported in this studies.
The Royal College of Ophthalmologists (RCO), 2012 [12] Diabetic Retinopathy Guidelines	Fragestellung: The aim of the guidelines is to provide evidence-based, clinical guidance for the best management of different aspects of diabetic eye disease. Methodik: • Systematische Evidenzaufbereitung mit formalem Konsensusprozess. • The guidelines described recommendation levels as follows: Level A: where strength of evidence was universally agreed; Level B: where the probability of benefit to the patient outweighed the risks; Level C: where it was recognized that there was difference of opinion as to the likely benefit to the patient and decision to treat would be based after discussion with the patient. **EVIDENCE BASE FOR THE TREATMENT OF DIABETIC MACULAR OEDEMA** **Photocoagulation treatment** • Recommendation: Patients with non centre-involving clinically significant macular oedema (CSMO; defined as: retinal thickening that involves or threatens the center of the macula (even if visual acuity is not yet reduced)) may be treated with laser photocoagulation according to modified ETDRS criteria (**Level A**) Evidenz: There is **level 1**evidence for benefit of photocoagulation using the modified ETDRS protocol vs no treatment, or compared to mild modified grid laser (basierend auf ETDRS: *The Early Treatment Diabetic Retinopathy Study (ETDRS) was a landmark trial that firmly established laser photocoagulation as a treatment for diabetic maculopathy. 2244 patients were randomly assigned to receive either early treatment with focal and grid photocoagulation or deferral of photocoagulation*). • Overall, while photocoagulation treatment reduces the risk of visual loss, and works over a long timescale, it is clear that recovery of vision is much harder to achieve with laser alone. Current treatments using intravitreal antiVEGF agents with prompt or delayed focal laser photocoagulation are most effective in preserving vision and restoring vision when centre-involved macular oedema is present and acuity is reduced to 20/32 or less (**Level 1**). **Ranibizumab:**

	• Recommendation: Patients with centre-involving macular oedema and reduced vision would benefit most from anti-VEGF (Ranibizumab as licenced) treatment (with or without combination laser treatment at the outset) (**Level 1, Level A**) Evidenz**: READ-2 study** *(compared the effect of 0.5mg intravitreal ranibizumab versus laser photocoagulation versus combined ranibizumab and laser photocoagulation in 126 treatment naive eyes.);* **RESOLVE** *(a randomised controlled double-masked, multicentre phase II study evaluating the safety and efficacy of ranibizumab in the treatment of DMO at 12 months. Patients were randomised to 3 treatment arms: 0.3mg ranibizumab, 0.5mg ranibizumab or sham injection and received 3 initial monthly injections);* **RESTORE** *(phase III study evaluating the efficacy and safety of ranibizumab in patients with visual impairment due to DMO (RESTORE) was a randomised, double-masked, multicentre trial with 3 treatment arms: Ranibizumab 0.5mg in addition to sham laser, ranibizumab in addition to active laser, and sham injection in addition to active laser); landmark* **DRCR.net study** *(comparing 0.5mg intravitreal ranibizumab with prompt focal/grid laser photocoagulation, 0.5 mg ranibizumab with deferred laser photocoagulation (at least 24 weeks later), 4mg intravitreal triamcinolone with prompt laser, or a sham injection with prompt laser).* Auch genannt wurden die RISE und RIDE Studien aus den USA (keine detaillierte Ausführungen). **Vitrectomy in diabetic eye disease:** • Similarly, DMO not responsive to treatment, especially cases with taut hyaloid face and those with vitreomacular traction can benefit from vitrectomy **(Level B).** • Newer techniques of using anti-VEGF injection concurrent with vitrectomy and use of microplasmin for chemical vitreolysis seem promising but need further evaluation **(Level B).** • Early intervention with vitrectomy has been suggested to be of benefit in diabetic patients **(Level B).**

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

Deutsche Ophthalmologische Gesellschaft (DGO), 2013: Stellungnahme	Therapiemodalitäten und Strategie: a) Diabetisches Makulaödem mit fovealer Beteiligung: • Besteht eine foveale Beteiligung eines Makulaödems,

der deutschen Opthalmologischen Gesellschaft der Retinologischen Gesellschaft und des Berufsverbandes der Augenärzte Deutschlands: Therapie der diabetischen Makulopathie.	kommen verschiedene Thera-piemodalitäten sowie deren Kombination in Betracht, über die der Patient mit den entsprechenden Behandlungsfrequenzen und Komplikationshäufigkeiten informiert werden sollte: • Die Anti-VEGF-Monotherapie besitzt die beste Wirksamkeit ein Makulaödem zu-rückzubilden und die bestmögliche Visusentwicklung zu ermöglichen. Allerdings sind viele Behandlungen - zumindest während der ersten Monate und gegebenenfalls auch über Jahre - mit den entsprechenden Konsequenzen erforderlich, d.h. häufigen Arztbesuchen und kumulativem Endophthalmitis-Risiko. Studien mit monatlicher Medikamenteneingabe haben gute Ergebnisse gezeigt; die (nach Upload mit mindes-tens drei Medikamenteneingaben) bedarfsabhängige Gabe nach morphologischen Kriterien zeigte in Studien eine im Mittel deutlich abnehmende Behandlungsnotwen-digkeit über die Zeit (erstes Jahr: ca. 7-8, zweites Jahr: unter 4, drittes Jahr: unter 3). Langzeitentwicklung und Sicherheitsprofil der Anti-VEGF-Therapie können noch nicht endgültig beurteilt werden. Eine Evidenz aus Phase III-Studien gibt es nur zu Ranibizumab (RESTORE, RIDE, RISE, DRCR). Größere Vergleichsstudien mit Bevacizumab - entsprechend CATT für die AMD - oder große Bevacizumab-Studien wurden bisher nicht publiziert. Nach positiven Daten über sechs Monate ist für Aflibercept eine Phase III-Studie (VIVID-DME) begonnen worden. • Die Laserbehandlung zeigt in Vergleichsstudien schlechtere Visusergebnisse als die intravitreale Anti-VEGF-Therapie, aber einen klaren Nutzen gegenüber dem un-behandelten Spontanverlauf. Das Therapieziel der Lasertherapie ist vor allem eine Visus-Stabilisierung. Vorteile der Lasertherapie sind die erheblich niedrigere Behand-lungsfrequenz und das Fehlen der potentiellen Komplikationen der intravitrealen Medikamentengabe, Nachteile sind die schlechteren Visusergebnisse und die durch die Lasereffekte verursachten Schädigungen der Sehzellen und des retinalen Pig-mentepithels, selbst wenn bei einer Lasertherapie schonende 'energiearme' Einstel-lungen, die in Studien etabliert wurden (DRCR), verwendet werden. Eine fokal/grid-Laserkoagulation sollte frühestens nach drei Monaten wiederholt werden. Bisher gibt es keine eindeutigen Daten, die einen zusätzlichen Nutzen der gleichzeitigen Kombination von VEGF-Inhibition und Lasertherapie nach morphologischen Kriterien belegen. Insbesondere gibt es bei der Kombinationstherapie nach bisheri-gen Daten während des ersten Behandlungsjahres keinen Hinweis auf eine Reduktion der erforderlichen

	Injektionsfrequenz. Eine sinnvolle Abfolge kann aber auch in der sequentiellen Anwendung von Anti-VEGF-Therapie und Lasertherapie oder umge-kehrt bestehen. • Die intravitreale Gabe von Steroid-Präparaten ist trotz eines positiven Effektes auf den Visus und einer im Vergleich mit den VEGF-Inhibitoren geringeren Injektionsfre-quenz eine Reserveoption, vor allem weil relativ häufig Nebenwirkungen wie Druck-erhöhung und Katarakt-Induktion bzw. -Progression zu beachten sind. Pseudophake Patienten zeigen ein günstigeres Nutzen-Risiko-Profil. Klare Kriterien, wann eine Ste-roidgabe als „second-line"-Therapie nach oder statt Anti-VEGF-Gabe sinnvoll sein kann, sind bisher noch nicht etabliert. Regelmäßige Kontrollen des Augendrucks sind bei dieser therapeutischen Option notwendig. Angesichts des Nebenwirkungsprofils von Fluocinolon sollten die therapeutischen Alternativen ausreichend erprobt und dokumentiert worden sein. Für eine Kombinationstherapie aus VEGF-Inhibitoren und Kortikoiden liegen bisher noch keine ausreichenden Daten vor. a. <u>Diabetisches Makulaödem ohne foveale Beteiligung:</u> • Die „fokal/grid"-Laserkoagulation ist alleiniger Standard für klinisch signifikante Ödeme (ETDRS-Kriterien) ohne foveale Beteiligung.

Primärstudien

Da ausreichend Information aus aggregierter Evidenz vorliegt, wurde eine Recherche nach Primärstudien nicht durchgeführt.

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library am 21.11.2013

Suchschritt	Suchfrage
#1	MeSH descriptor: [Macular Edema] explode all trees
#2	((macular or retinal) and (oedema or edema)):ti,ab
#3	macular dystroph*:ti,ab
#4	irvine gass syndrome*:ti,ab
#5	maculopath*:ti,ab
#6	MeSH descriptor: [Diabetes Mellitus] explode all trees
#7	(diabetes or diabetic):ti,ab
#8	#1 or #2 or #3 or #4 or #5
#9	#6 or #7
#10	#8 and #9
#11	MeSH descriptor: [Diabetic Retinopathy] explode all trees
#12	diabetic retinopath*:ti,ab
#13	#10 or #11 or #12 from 2008 to 2013

MEDLINE (PubMed) am 21.11.2013

Suchschritt	Suchfrage
#1	macular edema[MeSH Terms]
#2	(((macular[Title/Abstract]) OR retinal[Title/Abstract])) AND ((edema[Title/Abstract]) OR oedema[Title/Abstract])
#3	(macular[Title/Abstract]) AND dystroph*[Title/Abstract]
#4	((irvine[Title/Abstract]) AND gass[Title/Abstract]) AND syndrome*[Title/Abstract]
#5	maculopath*[Title/Abstract]
#6	((((#1) OR #2) OR #3) OR #4) OR #5
#7	diabetes mellitus[MeSH Terms]
#8	(diabetes[Title/Abstract]) OR diabetic[Title/Abstract]
#9	(#7) OR #8
#10	(#6) AND #9
#11	diabetic retinopathy[MeSH Terms]
#12	(diabetic[Title/Abstract]) AND retinopath*[Title/Abstract]
#13	((#10) OR #11) OR #12
#14	(#13) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])
#15	((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR

Suchschritt	Suchfrage
	publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
#16	(#13) AND #15
#17	(#14) OR #16
#18	(#17) AND ("2008/11/01"[PDAT] : "2013/11/21"[PDAT])

MEDLINE (PubMed) nach Leitlinien am 21.11.2013

Suchschritt	Suchfrage
#1	macular edema[MeSH Terms]
#2	(((macular[Title/Abstract]) OR retinal[Title/Abstract])) AND ((edema[Title/Abstract]) OR oedema[Title/Abstract])
#3	(macular[Title/Abstract]) AND dystroph*[Title/Abstract]
#4	((irvine[Title/Abstract]) AND gass[Title/Abstract]) AND syndrome*[Title/Abstract]
#5	maculopath*[Title/Abstract]
#6	((((#1) OR #2) OR #3) OR #4) OR #5
#7	diabetes mellitus[MeSH Terms]
#8	(diabetes[Title/Abstract]) OR diabetic[Title/Abstract]
#9	(#7) OR #8
#10	(#6) AND #9
#11	diabetic retinopathy[MeSH Terms]
#12	(diabetic[Title/Abstract]) AND retinopath*[Title/Abstract]
#13	((#10) OR #11) OR #12
#14	((((Guideline[Publication Type]) OR Practice Guideline[Publication Type]) OR Consensus Development Conference[Publication Type]) OR Consensus Development Conference, NIH[Publication Type]) OR guideline*[Title]
#15	(#13) AND #14
#16	(#15) AND ("2008/11/01"[PDAT] : "2013/11/21"[PDAT])

Literatur:

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4. **Wang H, Sun X, Liu K, Xu X**. Intravitreal ranibizumab (lucentis) for the treatment of diabetic macular edema: a systematic review and meta-analysis of randomized clinical control trials. Curr Eye Res 2012; 37 (8): 661-70.

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7. **O'Doherty M, Dooley I, Hickey-Dwyer M**. Interventions for diabetic macular oedema: a systematic review of the literature. Br J Ophthalmol 2008; 92 (12): 1581-90.

8. **Hooper P, Boucher MC, Cruess A, Dawson KG, Delpero W, Greve M, Kozousek V, Lam WC, Maberley DA**. Canadian Ophthalmological Society evidence-based clinical practice guidelines for the management of diabetic retinopathy. Can J Ophthalmol 2012; 47 (2 Suppl): S1-54.

9. **Boyd S, Advani A, Altomare F, Stockl F**. Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Retinopathy. Can J Diabetes 2013; 37 (Suppl 1): S137-S141.http://download.journals.elsevierhealth.com/pdfs/journals/1499-2671/PIIS1499267113000397.pdf, Zugriff am 24.09.2013.

10. **Scottish Intercollegiate Guidelines Network (SIGN)**. Management of diabetes. A national clinical guideline. Stand: März 2010. Edinburgh: SIGN, 2010 http://www.sign.ac.uk/pdf/sign116.pdf, Zugriff am 24.09.2013.

11. **American Optometric Association**. Evidence-Based Clinical Practice Guideline Eye Care of the patient with diabetes mellitus (draft version for peer/public review and comment November 2013, final version available in January 2014). St Louis (MO): American Optometric Association, 2013 http://www.aoa.org/documents/optometrists/QI/Clinical%20Practices%20Guidelines-%20FINAL-%20103113-%20SECURE.pdf, Zugriff am 21.11.2013.

12. **Royal College of Ophthalmologists**. Diabetic Retinopathy Guidelines. London: RCO, 2012 http://www.rcophth.ac.uk/core/core_picker/download.asp?id=1789&filetitle=Diabetic+Retinopathy+Guidelines+2012+%28minor+update+July+2013%29, Zugriff am 24.09.2013.

Anhang:

Intervention	Icon	Description
Beneficial	↑↑	For which effectiveness has been demonstrated by clear evidence from systematic reviews, RCTs, or the best alternative source of information, and for which expectation of harms is small compared with the benefits.
Likely to be beneficial	↑?	For which effectiveness is less well established than for those listed under "beneficial".
Trade off between benefits and harms	↑↓	For which clinicians and patients should weigh up the beneficial and harmful effects according to individual circumstances and priorities.
Unknown effectiveness	??	For which there are currently insufficient data or data of inadequate quality.
Unlikely to be beneficial	?↓	For which lack of effectiveness is less well established than for those listed under "likely to be ineffective or harmful".
Likely to be ineffective or harmful	↓↓	For which ineffectiveness or associated harm has been demonstrated by clear evidence.

Abbildung 1: Categorisation of interventions – Clinical Evidence (http://clinicalevidence.bmj.com/x/set/static/cms/nuts-and-bolts.html)

Table 1. Criteria for assigning levels of evidence to the published studies	
Level	***Criteria***
Studies of diagnosis	
Level 1	a) Independent interpretation of test results (without knowledge of the result of the diagnostic or gold standard) b) Independent interpretation of the diagnostic standard (without knowledge of the test result) c) Selection of people suspected (but not known) to have the disorder d) Reproducible description of both the test and diagnostic standard e) At least 50 patients with and 50 patients without the disorder
Level 2	Meets 4 of the Level 1 criteria
Level 3	Meets 3 of the Level 1 criteria
Level 4	Meets 1 or 2 of the Level 1 criteria
Studies of treatment and prevention	
Level 1A	Systematic overview or meta-analysis of high-quality RCTs a) Comprehensive search for evidence b) Authors avoided bias in selecting articles for inclusion c) Authors assessed each article for validity d) Reports clear conclusions that are supported by the data and appropriate analyses OR Appropriately designed RCT with adequate power to answer the question posed by the investigators a) Patients were randomly allocated to treatment groups b) Follow-up at least 80% complete c) Patients and investigators were blinded to the treatment* d) Patients were analyzed in the treatment groups to which they were assigned e) The sample size was large enough to detect the outcome of interest
Level 1B	Nonrandomized clinical trial or cohort study with indisputable results
Level 2	RCT or systematic overview that does not meet Level 1 criteria
Level 3	Nonrandomized clinical trial or cohort study
Level 4	Other
Studies of prognosis	
Level 1	a) Inception cohort of patients with the condition of interest, but free of the outcome of interest b) Reproducible inclusion/exclusion criteria c) Follow-up of at least 80% of subjects d) Statistical adjustment for extraneous prognostic factors (confounders) e) Reproducible description of outcome measures
Level 2	Meets criterion a) above, plus 3 of the other 4 criteria
Level 3	Meets criterion a) above, plus 2 of the other criteria
Level 4	Meets criterion a) above, plus 1 of the other criteria

*In cases where such blinding was not possible or was impractical (e.g. intensive vs. conventional insulin therapy), the blinding of individuals who assessed and adjudicated study outcomes was felt to be sufficient

Abbildung 2: aus Hooper P, et al. 2012 [8]

Evidence dimensions

Type of evidence	*Definition*
Strength of the evidence	
Levels of evidence	The study design was used as an indicator of the degree to which bias has been eliminated by design
Quality	The methods used by the investigators to minimise bias within a study design
Statistical precision	The *p*-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect.
Size of the effect	The distance of the study estimate from the "null" value and the inclusion of only clinically important effects in the confidence interval
Relevance of the evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used

Level of evidence	*Study Design for Interventions*
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case-series, either post-test or pre-test/post-test

Source: NHMRC (1999)

Abbildung 3: aus Mitchell P, 2008. Canberra ACT: National Health and Medical Research Council (NHMRC) Guidelines for the Management of Diabetic Retinopathy

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS	
LEVELS OF EVIDENCE	
1^{++}	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1^{+}	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2^{++}	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2^{+}	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2^{-}	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion
GRADES OF RECOMMENDATION	
Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.	
A	At least one meta-analysis, systematic review, or RCT rated as 1^{++}, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1^{+}, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2^{++}, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1^{++} or 1^{+}
C	A body of evidence including studies rated as 2^{+}, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2^{++}
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2^{+}
GOOD PRACTICE POINTS	
☑	Recommended best practice based on the clinical experience of the guideline development group

Abbildung 4: aus 2010 Scottish Intercollegiate Guidelines Network (SIGN) Management of diabetes. A national clinical guideline

Key to Strength of Evidence and Clinical Recommendation Grading	
GRADE	**STRENGTH OF EVIDENCE**
A	Data derived from well-designed, multiple randomized clinical trials, meta-analyses (Systematic Review), or diagnostic studies on relevant populations. Randomized Control Studies (RCT), Systematic Reviews with meta-analysis when available, Diagnostic Studies
B	RCTs or diagnostic studies with minor limitations - overwhelmingly consistent evidence from observational studies. Weaker RCT (weak design but multiple studies confirm) Cohort Study (this may include retrospective and prospective studies)
C	Studies of strong design, but with substantial uncertainty about conclusions, or serious doubts about generalization, bias, research design, or sample size; or retrospective or prospective studies with small sample size.
D	Expert opinion, case reports, reasoning from principles. No evidence is available that directly supports or refutes the conclusion Cross-sectional study, case series/ case report, opinion or principle reasoning.
GRADE	**CLINICAL RECOMMENDATION**
A	Clinicians should follow this recommendation unless clear and compelling rationale for an alternative approach is present. There is a *clinically important outcome* and the **study population is representative** of the focus population in the recommendation. The quality of evidence may not be excellent, but there is clear reason to make a recommendation.
B	Clinicians should generally follow this recommendation, but should remain alert for new information. There is a *clinically important outcome* but it may be a **validated surrogate outcome or endpoint.** The benefits exceed the harm or vice versa, but the quality of evidence is not as strong.
C	Clinicians should be aware of this recommendation, and remain alert for new information. The **evidence quality that exists is suspect** or not that well-designed; **Well conducted studies have demonstrated little clear advantage of one approach versus another.**
D	Clinicians should be aware of this recommendation. The **outcome is an invalid surrogate** for clinically important population, or the **applicability of the study is irrelevant.** There is **both lack of pertinent evidence and an unclear balance between benefits and harms.**

Abbildung 5: aus AOA, 2013: Eye care of the patient with diabetes mellitus.