Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2015-B-051 Brolucizumab

Stand: Juni 2015

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

Brolucizumab
Neovaskuläre (feuchte) altersbedingte Makuladegeneration

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 zugelassene Arzneimittel
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Aufzählung, wenn dies in Betracht gezogen wird, sonst „nicht angezeigt“
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Aflibercept (Beschluss vom 6. Juni 2013) **Zugelassenes Anwendungsgebiet:** Eylea® ist angezeigt zur Behandlung von Erwachsenen mit neovaskulärer (feuchter) altersbdingter Makuladegeneration **Zweckmäßige Vergleichstherapie:** Ranibizumab **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Ranibizumab:** Der Zusatznutzen im Verhältnis zur zweckmäßigen Vergleichstherapie ist nicht belegt. nicht-medikamentösen Behandlungen • Photodynamische Therapie (PDT), Photokoagulation mittels Laser • Protonentherapie bei altersabhängiger Makuladegeneration (Beschluss vom 17. September 2009) • photodynamische Therapie (PDT) mit Verteporfin bei altersabhängiger feuchter Makuladegeneration mit subfoveolärer klassischer choriodaler Neovaskularisation (Beschluss vom 21. Februar 2006)
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	
Brolucizumab S01LA06 Beovu®	Zugelassenes Anwendungsgebiet : Brolucizumab wird angewendet bei Erwachsenen zur Behandlung der neovaskulären (feuchten) altersbedingten Makuladegeneration (AMD)
Ranibizumab S01LA04 (Lucentis®)	Behandlung der neovaskularen (feuchten) altersabhangigen Makuladegeneration (AMD)
Aflibercept S01LA05 (Eylea®)	Behandlung der neovaskulären (feuchten) altersabhängigen Makuladegeneration (AMD)
Verteporfin S01LA01 (Visudyne®)	Behandlung von Erwachsenen mit exsudativer (feuchter) altersbezogener Makuladegeneration (AMD) mit vorwiegend klassischen subfovealen chorioidalen Neovaskularisationen. *Der erste Schritt besteht in einer 10-minutigen intravenösen Infusion von Visudyne. Der zweite Schritt besteht in der Lichtaktivierung von Visudyne 15 Minuten nach Beginn der Infusion.*
Pegaptanib S01LA03 (Macugen®)	Behandlung der neovaskulären (feuchten) altersabhängigen Makuladegeneration (AMD) ➔ Außer Vertrieb (Stand Lauer-Taxe 1.5.2015)

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2015-B-051 Brolucizumab

Auftrag von:	Abt. AM
bearbeitet von:	Abt. FB Med
Datum:	22.05.2015

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

Inhalt

Indikation für die Recherche bei Brolucizumab:

Geplantes Anwendungsgebiet lt. Beratungsanforderung: Patienten mit neovaskulärer (feuchter) altersbedingter Makuladegeneration (AMD)

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 ***„neovaskuläre altersbedingte Makuladegeneration“*** durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am ***08.05.2015*** abgeschlossen. Die

Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database), MEDLINE (PubMed), arztbibliothek.de (ÄZQ), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP. 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 **341** Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Davon wurden **80** Quellen eingeschlossen. Insgesamt ergab dies **11** Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Abkürzungen

AMD	Altersbedingte Makuladegeneration
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CNV	Choroidale Neovaskularisation
DAHTA	Deutsche Agentur für Health Technology Assessment
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
NEI-VFQ	National Eye Institute Visual Functioning Questionnaire
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
PDT	Photodynamische Therapie
TRIP	Turn Research into Practice Database
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organization

IQWiG Berichte/ G-BA Beschlüsse

IQWiG, 2013: [6] **Aflibercept (Eylea) – Nutzenbewertung gemäß § 35a SGB V** (Dossierbewertung Nr. 156)	**Fragestellung/Ziele:** Bewertung des Zusatznutzens von Aflibercept im Vergleich zu Ranibizumab als zweckmäßige Vergleichstherapie bei erwachsenen Patienten mit altersabhängiger feuchter Makuladegeneration (AMD). **Population/Studien** Keine geeignete Studie mit entsprechender zVT vorgelegt. Zulassungsstudien, VIEW 1 und VIEW 2, mit Komarator Ranibizumab nicht entsprechend der Zulassung. Zusätzlich wurde vom pU eine mathematische Simulation zur zulassungskonformen Anwendung von Ranibizumab und daraus resultierenden okularen Schadensereignisses am Beispiel der Endophthalmitis eingereicht. **Ergebnis /Fazit:** Eine valide Bewertung des Zusatznutzens von Aflibercept auf Basis der in Modul 4 des Dossiers vorgelegten Evidenz im Vergleich zu Ranibizumab nicht möglich, da keine relevanten Studien verfügbar. Insgesamt sind die zur Verfügung gestellten Daten für eine Nutzenbewertung nicht verwertbar. Aus den vorliegenden Daten ergibt sich kein Beleg für einen Zusatznutzen von Aflibercept im Vergleich zu der vom G-BA festgelegten zweckmäßigen Vergleichstherapie. Demzufolge gibt es keine Patientengruppen, für die sich ein therapeutisch bedeutsamer Zusatznutzen ableiten lässt.
G-BA, 2013: [5] **Zusammenfassende Dokumentation über die Änderung der Arzneimittel-Richtlinie (AM-RL) zu Aflibercept** **Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V**	**Fazit:** Der Zusatznutzen von Aflibercept im Verhältnis zur zweckmäßigen Vergleichstherapie (Ranibizumab) ist nicht belegt. Der pharmazeutische Unternehmer schließt sich der zweckmäßigen Vergleichstherapie des G-BA an, jedoch legt er keine Daten entsprechend des zugelassenen Behandlungsschemas vor. Im Dossier sind keine direkt vergleichenden Studien mit Aflibercept versus der zweckmäßigen Vergleichstherapie entsprechend der Zulassung eingeschlossen. In den im Dossier dargestellten RCTs (VIEW 1 und VIEW 2) wurde Ranibizumab nicht gemäß aktuellem Zulassungsstatus eingesetzt, sondern monatlich, unabhängig davon, ob der Visus bei 3 aufeinanderfolgenden monatlichen Kontrollen stabil war und laut Zulassung die Medikation ausgesetzt werden muss.

G-BA, 2010: [4] Protonentherapie bei altersabhängiger Makuladegenration **Abschlussbericht Beratungsverfahren nach § 137c SGB V (Krankenhausbehandlung) 13. Januar 2010**	**Fazit:** Es konnten 3 Fallserien und 3 randomisierte klinische Studien identifiziert werden, die zur Nutzenbewertung herangezogen wurden. Die Anwendung der Strahlentherapie mit Photonen und Protonen bei der Indikation AMD wurde zudem in einem Cochrane-Review, einem HTA-Bericht und einer systematischen Übersichtsarbeit bewertet. Zusammenfassend ergeben sich aus den vorliegenden Daten keine belastbaren Hinweise auf einen Nutzen der Protonentherapie bei der altersabhängigen Makuladegeneration.
G-BA, 2001: [2] Photodynamische Therapie (PDT) mit Verteporfin bei altersabhängiger feuchter Makuladegeneration mit subfoveolären klassischen choriodalen Neovaskularisationen **Zusammenfassender Bericht des Arbeitsausschusses "Ärztliche Behandlung" des Bundesausschusses der Ärzte und Krankenkassen über die Beratungen gemäß §135 Abs.1 SGB V**	**Fazit:** Die Analyse und Bewertung aller Stellungnahmen, der aktuellen wissenschaftlichen Literatur und sonstigen Fundstellen ergab im Ergebnis, dass die Wirksamkeit und medizinische Notwendigkeit der PDT bei der Indikation der neovaskulären AMD mit subfoveolären klassischen Neovaskularisationen in soweit belegt ist, dass durch (ggf. wiederholte) Anwendung dieser Therapie die Progredienz einer drohenden Erblindung aufgehalten oder verzögert werden kann. Dieser Effekt ist durch eine Studie für den Zeitraum eines Jahres belegt, nach derzeit noch unveröffentlichten Studiendaten, die dem Ausschuss bereits vorliegen, ist die Wirksamkeit auch über eine Beobachtungszeitraum von zwei Jahren gegeben.
G-BA, 2007: [3] Photodynamische Therapie (PDT) mit Verteporfin bei **• chorioidaler Neovaskularisation (CNV) aufgrund hoher Myopie** **• rein okkulter subfoveolärer CNV bei altersabhängiger Makulopathie** **• juxtafoveolärer CNV** **• sekundärer CNV nach Chorioretinitis unklarer Genese** **Zusammenfassender Bericht des Unterausschusses "Ärztliche Behandlung" des Gemeinsamen Bundesausschusses über die Bewertung gemäß § 135 Abs. 1 SGB V**	Beschlussfassung des Gemeinsamen Bundesausschusses Der Gemeinsame Bundesausschuss nimmt die Photodynamische Therapie (PDT) mit Verteporfin auch bei folgenden zusätzlichen Indikationen in die vertragsärztliche Versorgung in die Anlage A (Anerkannte Untersuchungs- und Behandlungsmethoden) der BUB-Richtlinien unter der Nr. 11 auf: Photodynamische Therapie (PDT) mit Verteporfin bei 1. subfovealer chorioidaler Neovaskularisation (CNV) aufgrund von pathologischer Myopie mit bestkorrigiertem Visus von mindestens 0,2 bei der ersten Indikationsstellung und einer Läsionsgröße von max. 5400 µm. 2. subfovealer okkulter CNV ohne klassischen Anteil aufgrund von altersabhängiger feuchter Makuladegeneration (AMD) mit bestkorrigiertem Visus von mindestens 0,2 bei der ersten Indikationsstellung und einer Läsi-onsgröße von max. 5400 µm sowie - mit Verschlechterung durch Hämorrhagie bei CNV oder - Verschlechterung innerhalb der letzten 3 Monate mit entweder a) visuell: Verlust von mindestens 5 Buchstaben bzw. einer Zeile auf der ETDRS-Tafel

	oder b) anatomisch: Zunahme der Läsion um mindestens 10%. Auszuschließen von der Therapie mit PDT sind Patienten mit einem Krankheitsbild gemäß Nr. 2, bei denen eine Läsionsgröße größer vier Papillenflächen und ein Visus größer oder gleich 0,4 vorliegen. Die Anerkennung erfolgt auf Grundlage von Studienergebnissen der Evidenzklasse Ib gemäß BUB-Richtlinie. Der Gemeinsame Bundesausschuss hält es für erforderlich, die PDT bei diesen Indikationen in spätestens drei Jahren erneut gemäß § 135 Abs. 1 SGB V zu überprüfen.

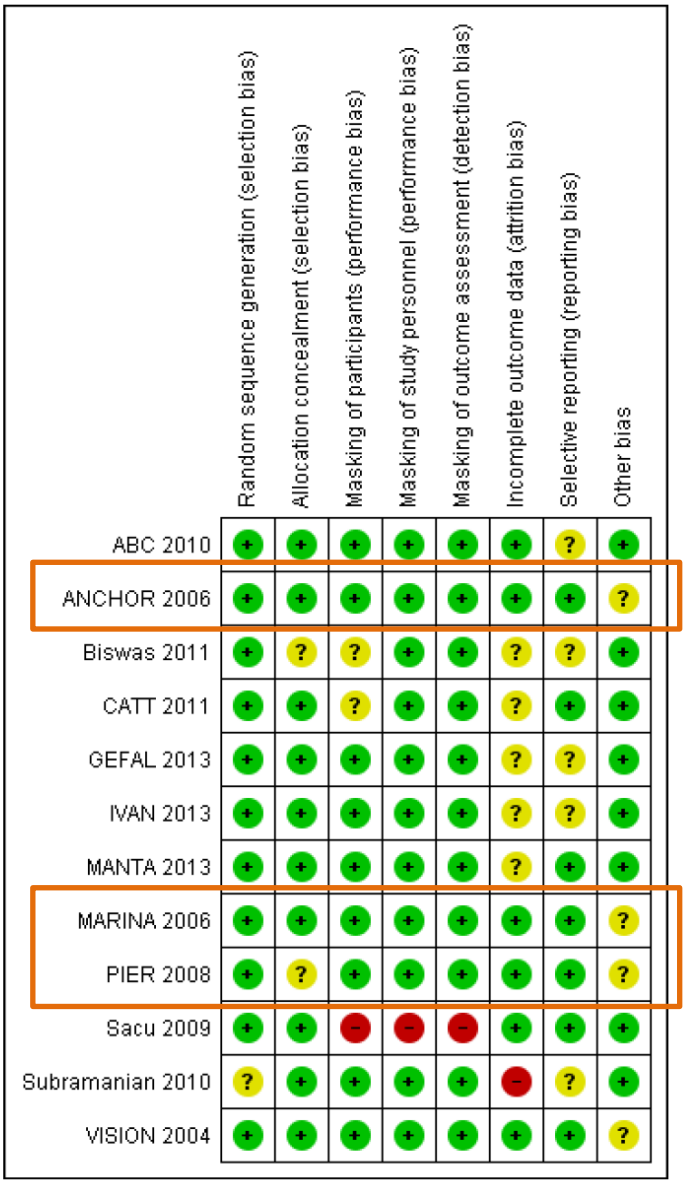
Cochrane Reviews

Solomon SD, 2014: [10] **Anti-vascular endothelial growth factor for neovascular agerelated macular degeneration (Review)**	1. Fragestellung To investigate: (1) the ocular and systemic effects of, and quality of life associated with, intravitreally injected anti-VEGF agents (pegaptanib, ranibizumab, and bevacizumab) for the treatment of neovascular AMD compared with no anti-VEGF treatment; and (2) the relative effects of one anti-VEGF agent compared with another when administered in comparable dosages and regimens.
	Methodik Population: participants had neovascular AMD as defined by study investigators. Intervention: ranibizumab (injections administered monthly over study period in ANCHOR and MARINA study – two doses: 0.3 or 0.5 mg, monthly administration of 0.3 mg for first 3 month and then every three months in PIER study) Komparator: sham treatment, photodynamic therapy (injections administered monthly over study period in ANCHOR and MARINA study, monthly administration for first 3 month and then every three months in PIER study) Endpunkt: Primary: • best-corrected visual acuity (BCVA) at one year of follow up Secondary: • Visual acuity outcomes o Proportion of participants who gained 15 letters or more of BCVA in the study eye at two years of follow up o Proportion of participants who lost fewer than 15 letters of visual acuity o Proportion of participants who lost fewer than 30 letters of visual acuity o Proportion of participants in whom blindness was prevented in the study eye, defined as those eyes with visual acuity better than 20/200 o Proportion of participants maintaining visual acuity, defined as gain of 0 letters or more (i.e. no loss of BCVA from baseline) o Mean change in visual acuity • Contrast sensitivity, reading speed, or any other validated measure of visual function as measured in the included studies • Assessment of morphological characteristics by fluorescein angiography or OCT, including mean change in size of CNV,

	mean change in size of total lesion, and mean change in central retinal thickness (CRT) • Quality-of-life measures, as assessed with any validated measurement scale • Economic data, such as comparative cost analyses • Ocular or systemic adverse outcomes This review is restricted to: (1) primary RCTs of anti-VEGF agents versus no anti-VEGF treatment; and (2) head-to-head (comparative effectiveness) RCTs of one anti-VEGF agent versus another. Studies of dosage, different treatment strategies, and the combination of anti-VEGF agents with other treatments are outside the scope of this review. Suchzeitraum (Aktualität der Recherche): Cochrane Central Register of Controlled Trials (CENTRAL), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, OvidOLDMEDLINE, EMBASE, LatinAmerican and CaribbeanHealth Sciences LiteratureDatabase (LILACS), themetaRegister of Controlled Trials (mRCT), ClinicalTrials.gov, theWorldHealthOrganization (WHO) International Clinical Trials Registry Platform (ICTRP) until 27 March 2014 Anzahl eingeschlossene Studien/Patienten (Gesamt): 12 RCTs including a total of 5496 participants with neovascular AMD (davon aber nur 3 RCTs zu Ranibizumab n=1.322) Qualitätsbewertung der Studien: Cochrane risk of bias tool Einschluss von RCTs mit mind. 1 Jahr Follow-up
	2. Ergebnisdarstellung 3 RCTs zu Ranibizumab vs. Kontrolle, n=1.322 Treatment: Control therapy: ANCHOR-Study: sham injections plus active verteporfin photodynamic therapy MARINA-study: sham injections PIER-study: sham injections **Gain of 15 letters or more visual acuity** • Large heterogeneity for first year of follow-up • After 2 years of follow-up much less heterogeneity, statistically significant higher proportion of patients treated with ranibizumab gained 15 letters or more (RR=5,77, 95% CI 3,38-

	9,84) **Loss of fewer than 15 letters visual acuity** • Participants were 1.53 times more likely to not lose 15 letters or more of visual acuity when treated with ranibizumab compared with sham or control therapy (RR 1.53; 95%CI 1.41 to 1.64) • Similar magnitude for two years of follow-up • Significant heterogeneity due to active treatment in ANCHOR-study **Loss of fewer than 30 letters visual acuity** • Only ANCHOR and MARINA-study provided data • Comparing both ranibizumab groups combined with controls, we observed a 15% benefit of ranibizumab with respect to the loss of fewer than 30 letters of visual acuity (RR 1.15; 95% CI 1.11 to 1.20) • Similar magnitude for two years of follow-up **Visual acuity better than 20/200 (prevention of blindness)** • comparing the combined ranibizumab groups with the control intervention groups, a greater proportion of participants in the ranibizumab groups had visual acuity better than 20/ 200 than participants in the control group at one year (RR 1.69; 95%CI 1.41 to 2.03) and two years (RR 1.73; 95% CI 1.52 to 1.98) **Mean change in visual acuity at one year (number of letters)** • Participants treated with ranibizumab were able to read 18 letters more at the one-year follow up (MD 17.80, 95%CI 15.95 to 19.65) and 20 letters more at the two-year follow up (MD 20.11, 95% CI 18.08 to 22.15) **Reduction in size lesion at one year (Mean number of disc areas)** • Results based on ANCHOR and PIER study • The mean reduction in the size of the lesion was greater by 2.34 disc areas (95% CI 1.88 to 2.81) among participants treated with ranibizumab compared with participants treated with control interventions after one year • Effect of similar magnitude after two years of follow-up **Change in quality of life scores (interviewer-administered NEI-VFQ questionnaire)** • Results based on ANCHOR and PIER study • At one year, overall vision-related quality of life improved more often among participants in ranibizumab groups compared with participants in control groups (MD 6.69; 95% CI 3.38 to 9.99). • Effect greater in MARINA than in ANCHOR due to active treatment with verteporfin and PDT in ANCHOR • Subscale domains of the NEI-VFQ questionnaire in which

	participants in ranibizumab groups showed greater improvement at one-year of follow up than participants in control groups included: o near-vision activities, o distance-vision activities, o vision-related dependency, o driving ability, o general health, o role difficulties, o mental health, o general vision, o social functioning, o color vision, and o peripheral vision. • Results for two years of follow-up were consistent and of similar magnitude • **Assessment of risk of bias**



Hohe Studienqualität: geringes Verzerrungspotential

3. Anmerkungen/Fazit der Autoren

The results of this review indicate the effectiveness of ranibizumab in terms of maintaining and improving visual acuity. The information available on the adverse effects do not suggest a higher incidence of potentially vision-threatening complications with intravitreal injection compared with control interventions; however, clinical trial sample sizes may not have been sufficient to detect rare safety outcomes.

Systematische Reviews

Jiang S, 2014: [7]

Ranibizumab for age-related macular degeneration: a meta-analysis of dose effects and comparison with no anti-VEGF treatment and bevacizumab

1. Fragestellung

The objectives of this study are to: (i) evaluate the comparative effectiveness of as-needed/quarterly versus monthly treatments; and (ii) compare the efficacy of ranibizumab with no-anti-VEGF (sham injection or PDT); and the efficacy of ranibizumab 0,5 mg treatment with: (a) ranibizumab 0,3 mg and (b) bevacizumab.

2. Methodik

Population: patients with AMD
Intervention: ranibizumab vs. non-anti-VEGF, ranibizumab, 0,5 mg vs. ranibizumab 0,3 mg

Komparator: non-anti-VEGF (Placebo injection (Sham) and tradition treatment (PDT) are grouped together as non-anti-VEGF), ranibizumab 0,3 mg

Endpunkt: visual acuity outcome, which was defined as either the effect size of letters gained (continuous) or whether or not a patient gained ≥ 15 letters in visual acuity (dichotomous)

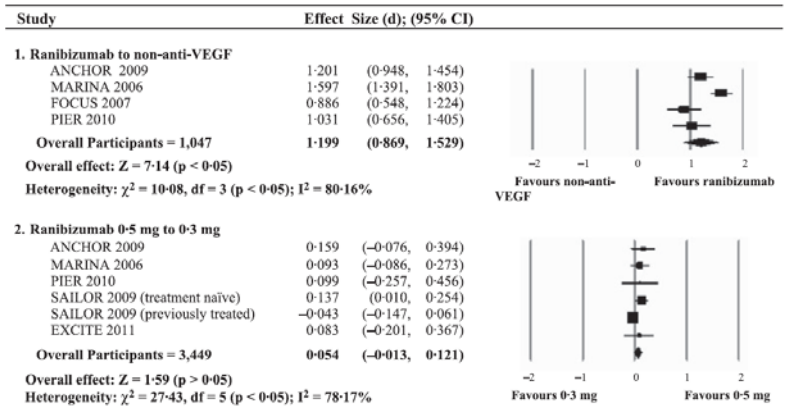
Suchzeitraum (Aktualität der Recherche): PubMed, Web of Science and Google Scholar from Jan 2004 to March 2013.
Anzahl eingeschlossene Studien/Patienten (Gesamt): 8 RCTs davon 6 RCTs relevant mit n=3,449

Qualitätsbewertung der Studien: Jadad Scaled Criteria (JSC)

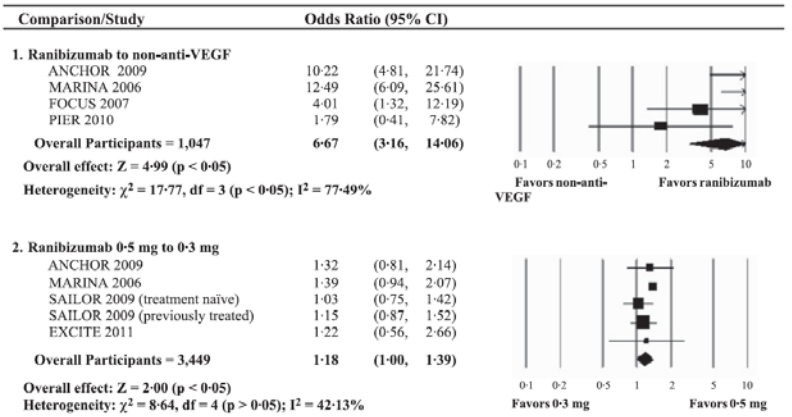
3. Ergebnisdarstellung

Study	Treatment regimen	Comparison	Follow-up months	Treated patients (N)	Control patients (N)	Jadad score[a]
ANCHOR 2009[14]	Monthly	PDT/0·3 ranibizumab	24	140	283	3
MARINA 2006[15]	Monthly	Sham/0·3 ranibizumab	24	240	476	4
FOCUS 2007[26]	Monthly	PDT	24	106	56	3
PIER 2010[16]	Monthly for 3 months then quarterly	Sham/0·3 ranibizumab	24	61	123	4
CATT 2012[10]	Monthly/ PRN	Bevacizumab	24	398	380	4
SUBRAMANIAN 2010[12]	Monthly for 3 months then PRN	Bevacizumab	12	7	15	5
SAILOR 2009[17]	Monthly for 3 months then PRN	0·3 ranibizumab	12	1169	1209	4
EXCITE 2011[8]	Quarterly	0·3 ranibizumab	12	88	104	4

- The quality of the articles was fairly high with a mean JSC of 3,9 ± 0,7.



- ranibizumab had greater improvements in visual acuity letters gained compared with the non-anti-VEGF (sham injection/PDT) (d = 1,20, z = 7,14, P < 0,05)
- substantial heterogeneity was found in this comparison (P<0,05, I² = 80,16%)
- No significant difference was found between ranibizumab 0,5 mg and 0,3 mg and letters gained



- a higher proportion of ranibizumab-treated patients gained ≥15 letters when compared to sham injection and PDT (OR: 6,67; 95% CI 3,16–14,06; P < 0,05). A substantial amount of heterogeneity was present in this comparison (P < 0,05, I2 = 77,49%).
- No significant difference was found between ranibizumab 0,5 mg and 0,3 mg and proportion of patients who gained ≥ 15 letters (OR: 1,18; 95% CI 1,00–1,39; P > 0,05).

4. Anmerkungen/Fazit der Autoren

Ranibizumab 0,3 or 0,5 mg monthly treatment was more effective for neovascular AMD than non-anti-VEGF treatments

5. Hinweise durch FB Med)

Heterognenität wahrscheindlich durch Kombination von unterschiedlicher Behandlungen in der Kontrollgruppe

Schmid MK, 2015: [8] **Efficacy and adverse events of aflibercept, ranibizumab and bevacizumab in age-related macular degeneration: a trade-off analysis**	1. Fragestellung To quantify the gain in visual acuity and serious side effects of ranibizumab, bevacizumab and aflibercept in age-related macular degeneration (AMD).
	2. Methodik Population: patients with age-related macular degeneration (AMD) Intervention: ranibizumab 0.3 mg 0.5 mg; aflibercept 0.5 mg and 2 mg Komparator: Placebo Endpunkt: efficacy (increase in letters gained), severe side effects Suchzeitraum (Aktualität der Recherche): Medline, Premedline, EMBASE, SCOPUS and the Cochrane Library until June 2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): 11 (n=4.405) Qualitätsbewertung der Studien: In duplicate, we extracted salient methodological features (description of generation of random sequence and concealment of random allocation, blinding of patients and caregivers, whether the analysis was based on the intention to treat principle and the proportion of patient lost during follow-up)
	3. Ergebnisdarstellung ranibizumab 0.3 mg was assessed in 1782 patients and ranibizumab 0.5 mg in 3566 patients; aflibercept 0.5 mg in 597 patients and aflibercept 2 mg in 1220 patients

Table 1 Summary of included studies and treatments assessed

Author	Year	Study name	Treatment (0=placebo, 1=Ranibizumab, 2=bevacizumab, 3=aflibercept, 4=verteporfin/PDT, 5=ranibizumab+PDT)	Dosage (mg)	Mean age (years)	Mean age SD	Female (n)	Male (n)	Total patients	Random allocation (0=no, 1=yes, 2=not reported)	Concealment of allocation (0=no, 1=yes, 2=not reported)	Blinding patients (0=no, 1=yes, 2=not reported)	Blinding outcome assessors (0=no, 1=yes, 2=not reported)	Intention to treat (0=no, 1=yes, 2=not reported)	Drop-outs reported (0=no, 1=yes, 2=not reported)	Withdrawals reported (0=no, 1=yes, 2=not reported)
Boyer	2009	SAILOR	1	0.3	79	7.6	700	469	1169	1	2	1	0	1	1	1
			1	0.5	79	8.6	702	507	1209	1	2	1	0	1	1	1
Brown	2006	ANCHOR	4	–	78	7.8	79	64	143	1	2	1	1	1	1	1
			1	0.3	77	7.5	67	73	140	1	2	1	1	1	1	1
			1	0.5	76	8.6	65	75	140	1	2	1	1	1	1	1
Heier	2006	FOCUS	0	–	73	8.7	26	30	56	1	2	1	0	1	1	1
			1	0.5	75	7.2	60	46	106	1	2	1	0	1	1	1
Rosenfeld	2006	MARINA	0	0	77	7.0	159	79	238	1	2	1	1	1	1	1
			1	0.3	77	8.0	153	85	238	1	2	1	1	1	1	1
			1	0.5	77	8.0	152	88	240	1	2	1	1	1	1	1
Chakravarthy	2012	IVAN	1	0.5	78	7.8	185	129	314	1	2	1	1	1	1	1
			2	1.25	78	7.6	181	115	296	1	2	1	1	1	1	1
Heier	2012	VIEW 1	1	0.5	78	7.6	172	132	304	1	2	1	1	1	1	1
			3	2	78	8.1	372	233	605	1	2	1	1	1	1	1
			3	0.5	78	8.1	167	134	301	1	2	1	1	1	1	1
Heier	2012	VIEW 2	1	0.5	73	9.0	169	122	291	1	2	1	1	1	1	1
			3	2	74	8.5	351	264	615	1	2	1	1	1	1	1
			3	0.5	75	8.6	147	149	296	1	2	1	1	1	1	1
Schmid-Erfurth	2011	EXCITE	1	0.3	75	7.8	136	99	235	1	2	1	1	1	1	1
Larsen*	2012	MONT BLANC	1	0.5	76	7.0	73	45	118	1	2	1	1	1	1	1
			5	0.5	77	7.7	78	44	122	1	2	1	1	1	1	1
Kaiser*	2012	DENALI	1	0.5	76	7.4	74	59	133	1	2	1	1	1	1	1
			5	0.5	77	8.5	117	92	209	1	2	1	1	1	1	1
			1	0.5	77	8.0	75	37	112	1	2	1	1	1	1	1
Martin	2011	CATT	1	0.5	79	7.6	368	231	599	1	2	1	0	1	1	1
			2	1.25	80	7.5	364	222	586	1	2	1	0	1	1	1

*Studies with PDT treatment arm were used for indirect comparisons; reporting is restricted to anti-VEGF treatments.
anti-VEGF, antivascular endothelial growth factor; PDT, photodynamic therapy.

Generally low potential for risk of bias

Efficacy:

Compared with placebo, significantly higher percentage of letters gained:

- ranibizumab 0.3 mg 2.39% (95% CI 1.59 to 3.19; p<0.001)
- ranibizumab 0.5 mg 3.56% (95% CI 2.58 to 4.13; p<0.001)
- Aflibercept 0.5 mg 2.91% (95% CI 0.99 to 4.82; p=0.003)

- Aflibercept 2 mg 3.44% (95% CI 1.73 to 5.14; p<0.001)

Serious side effects:

Compared with placebo, serious side effects were higher in all treatments:

- ranibizumab 0.3 mg 4.41% (95% CI 3.42 to 5.40; p<0.001),
- ranibizumab 0.5 mg 5.33% (95% CI 4.37 to 6.30; p<0.001),
- aflibercept 0.5 mg 5.65% (95% CI 3.28 to 8.02; p<0.001)
- aflibercept 2 mg 5.29% (95% CI 3.18 to 7.39; p<0.001)

Trade off analysis:

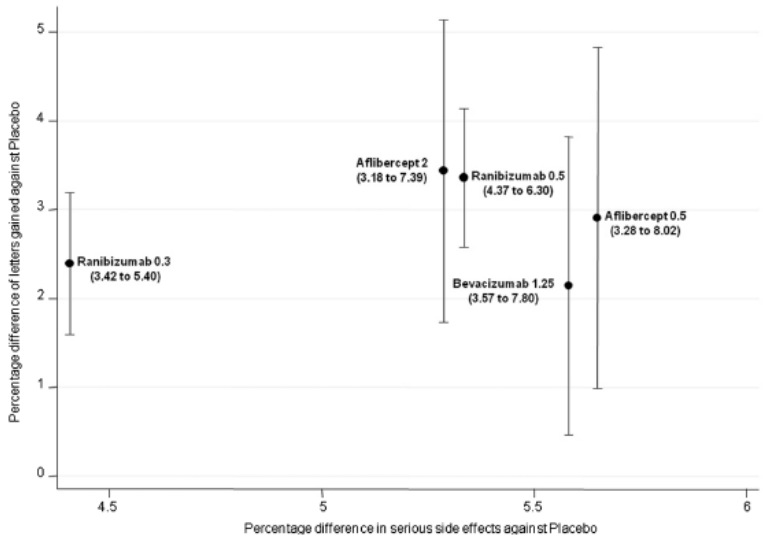


Figure 2 A trade-off chart of the relationship between letters gained and serious side effects (vascular death, any death, stroke, myocardial infarction, transient ischaemic attack) of various antivascular endothelial growth factor (anti-VEGF) treatments. Compared with placebo, all treatments show higher percentages of serious side effects. Aflibercept 2 mg and ranibizumab 0.5 mg show similar profiles. Values in parenthesis indicate 95% CIs for serious side effects.

- the two higher dosages of ranibizumab and aflibercept show slightly higher efficacy than ranibizumab 0.3 mg at the cost of higher percentages of serious side effects
- aflibercept 0.5 mg is slightly more efficient than ranibizumab 0.3 mg

4. Anmerkungen/Fazit der Autoren

there is no treatment clearly standing out. Differences between the various treatments are rather small. The study revealed only a modest superiority of aflibercept 2 mg and ranibizumab 0.5 mg against other formulations and dosages.

Schmucker C, 2012: [9] **A Safety Review and Meta-Analyses of Bevacizumab and Ranibizumab: Off-Label versus Goldstandard**	1. Fragestellung to address the crucial question whether the available information allow us to judge that unlicensed therapy with bevacizumab is as safe as licensed therapy with ranibizumab, and whether clinicians are justified in offering it to their patients with AMD as a medication with no additional risk. Besides comparing both drugs, we also evaluated whether adverse effects are dose related
	2. Methodik Population: patients with neovascular AMD Intervention: Ranibizumab • ANCHOR trial: comparison monthly ranibizumab injections with photodynamic therapy (PDT) • MARINA study: comparison monthly intravitreal ranibizumab with sham injections • PIER study: comparison sham with ranibizumab injections once monthly for three consecutive months, followed by a dose administered once every three months. • SAILOR study: compared three consecutive monthly injections of 0.3 mg or 0.5 mg ranibizumab. After three months, patients were followed by a pro re nata schedule. • EXCITE study: compared 0.3 mg quarterly, 0.5 mg quarterly, or 0.3 mg monthly doses of ranibizumab Treatment comprised a loading phase (three consecutive monthly injections) followed by a nine month maintenance phase (with monthly or quarterly injections) Komparator: Placebo, sham therapy, PDT with verteporfin Endpunkt: adverse events Suchzeitraum (Aktualität der Recherche): Medline, Premedline, Embase and the Cochrane library from inception until May 2011 Anzahl eingeschlossene Studien/Patienten (Gesamt): 11 RCTs (Ranibizumab versus any control (5 trials, 4054 patients)) Qualitätsbewertung der Studien: quality assessment was carried out after a modified evaluation tool of the Center for Reviews and Dissemination (Chapter 4, Systematic

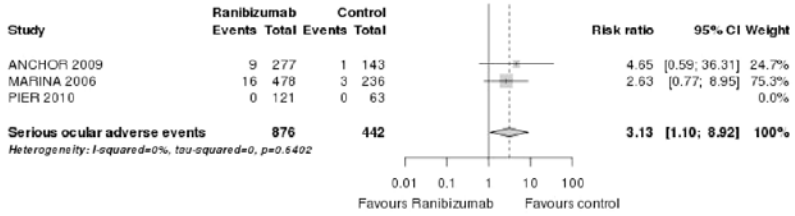
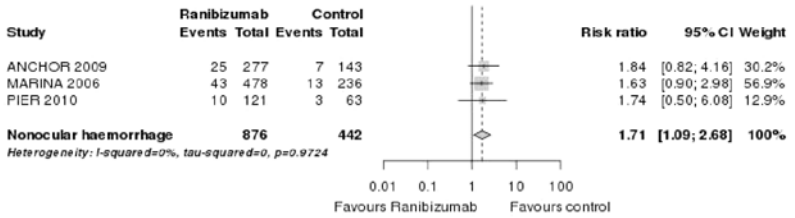
	Reviews of Adverse Effects)
	3. Ergebnisdarstellung **Ocular Adverse Effects**  • A pooled analysis of the ANCHOR, MARINA and PIER studies showed low absolute rates of serious ocular adverse effects • relative harm was significantly raised compared to controls (RR = 3.1; 95% CI 1.1–8.9) • risk did not appear to be increased with higher doses of ranibizumab as compared to the lower dose (RR= 0.9; 95% CI 0.5–1.6). **Nonocular Adverse Effects**  • sign. higher risk of non-ocular haemorrhage (such as gastrointestinal haemorrhage, traumatic subdural haematoma and duodenal ulcer haemorrhage) with RR = 1.7; 95% CI 1.1–2.7 in patients with ranibizumab as compared to patients receiving control treatment **Summary of Methodological Quality and Risk of Bias** • Three of the ranibizumab trials were of high methodological quality • remaining two studies (SAILOR and EXCITE) showed deficiencies in the definition and method used to collect expected adverse effects data

Table 11. Methodological quality of RCTs evaluating ranibizumab for indirect comparison.

Study	Comparability of groups	Adequate blinding	Definition of expected AE	Definition of method used to collect AE data	Transparency of patient flow	Validity safety
ANCHOR 2009 [21]	yes	double blind	yes	yes	yes	high
MARINA 2006 [22]	yes	double blind	yes	yes	yes	high
PIER 2008 [23]	yes	double blind	yes	yes	yes	high
SAILOR 2009 [24]	yes	single (patient)	in part	no	yes	moderate
EXCITE 2011 [25]	in part	double blind	in part	no	yes*	moderate/low

AE: Adverse effects.

*It was outstanding that in the 0.5 mg group 10.2% of patients discontinued because of adverse effects, in the 0.3 mg quarterly group 3.3% and in the 0.3 mg monthly group 4.3%, respectively.

doi:10.1371/journal.pone.0042701.t011

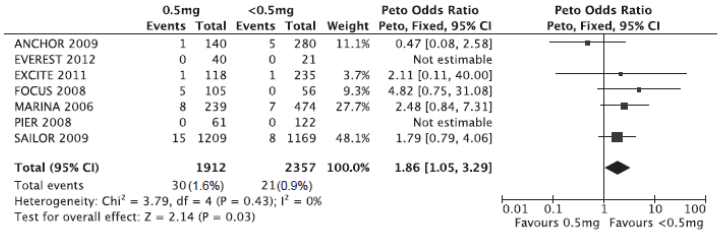
Moderate to low risk of bias

4. Anmerkungen/Fazit der Autoren

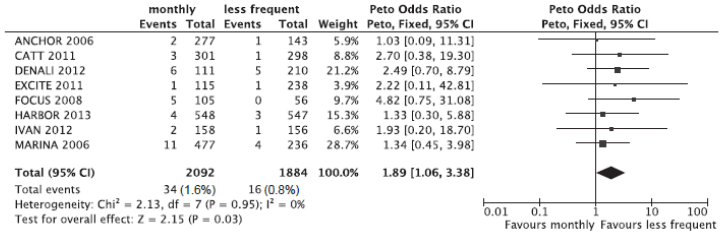
Ranibizumab associated with higher risk of AE both ocular and non-occular as compared to placebo.

Ueta T, 2014: [11] **Systemic Vascular Safety of Ranibizumab for Age-Related Macular Degeneration**	1. Fragestellung to address the systemic risks associated with ranibizumab administration for patients with AMD
	2. Methodik Population: patients with AMD Intervention: different intensities of Ranibizumab (in terms of dose per injection (0.0, 0.3, or 0.5 mg) as well as retreatment frequency: Monthly, less frequent (i.e., pro re nata [PRN] or quarterly), and no active ranibizumab treatment) Komparator: possible comparisons between the different regimen categories, as long as there were ≥2 trials for which meta-analysis could be applied Endpunkt: incidence of cerebrovascular accidencts CVAs, myocardial infarction (MI), nonocular hemorrhage, overall arterial thromboembolic events (ATEs), and/or all-cause mortality Suchzeitraum (Aktualität der Recherche): MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials databases until March 2014 Anzahl eingeschlossene Studien/Patienten (Gesamt): 11 studies with 13 published articles Qualitätsbewertung der Studien: according criteria recommended by the Cochrane Collaboration
	3. Ergebnisdarstellung **Cerebrovascular accidents:** • No statistically significant results for increase of CVAs for any regimens of ranibizumab (0.5 versus 0.0 mg; 0.5 versus 0.3 mg; monthly treatment compared with PRN treatment)

0.5 mg vs 0.3 / 0.0 mg



Monthly vs PRN / cotrol



- Influence of 0.5 mg compared with the combination of 0.3 mg and no ranibizumab groups was significant (OR, 1.86; 95% CI, 1.05-3.29; P = 0.03).
- when the monthly treatment group was compared with the combined PRN and no ranibizumab groups: significant increase in the number of CVAs (OR, 1.89; 95% CI, 1.06-3.38; P = 0.03).

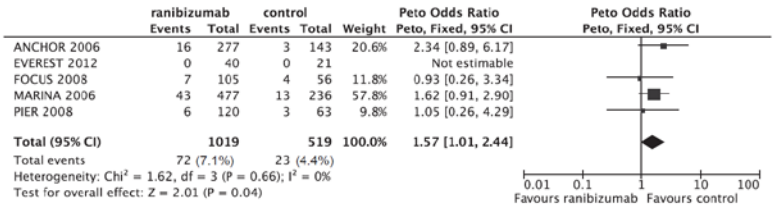
Myocardial infarction

- No statistically significant results for increase of MI for any regimens of ranibizumab

Nonocular Haemorrhage

- No statistically significant results for increase of nonocular haemorrhage for any regimens of ranibizumab

0.3 / 0.5 mg vs 0.0 mg



- the combined categories significant difference for the comparison of 0.3/0.5 mg with no ranibizumab (OR, 1.57; 95% CI, 1.01-2.44; P= 0.04)

Overall Arterial Thromboembolic Event

- No statistically significant results for increase of overall arterial thromboembolic events for any regimens of ranibizumab

All-cause Mortality

- Ranibizumab has no effect on all cause mortality

Table 2. Risk of Bias Assessment

	Random Sequence Generation (selection bias)	Allocation Concealment (selection bias)	Blinding of Participants and Personnel (performance bias)	Blinding of Outcome Assessment (detection bias)	Incomplete Outcome Data (attrition bias)	Selective Reporting (reporting bias)	Other bias
MARINA 2006[2]	L	L	L	L	L	L	L
FOCUS 2008[36,37]	U	H	H	L	L	L	L
PIER 2008[38]	L	L	L	L	L	L	L
ANCHOR 2006, 2009[3,35]	U	U	L	L	L	L	L
SAILOR 2009[39]	U	U	H	H	L	L	L
CATT 2011[41]	L	L	L	H	L	L	L
EXCITE 2011[40]	U	U	L	L	L	L	L
IVAN 2012[43]	L	L	H	H	L	L	L
DENALI 2012[42]	U	U	L	L	L	L	L
EVEREST 2012[34]	U	U	L	L	L	L	L
HARBOR 2013[44]	L	L	H	L	L	L	L

H = high risk; L = low risk; U = unclear risk.

- Two studies with a low risk of bias in all assessment categories.
- 9 studies were considered to have some risk of bias

4. Anmerkungen/Fazit der Autoren

In ranibizumab treatment for patients with AMD, a possible

	relationship of more intensive treatment to more systemic vascular adverse events was identified, but no relationship with mortality was identified. 5. Hinweise durch FB Med) Follow-up Zeit max. 24 Monate, Aussagen zur Mortalität nur begrenzt möglich

Leitlinien

American Academy of Ophthalmology, 2015: [1]

Age-Related Macular Degeneration

American Academy of Ophthalmology entwickelte eine “Peferred Practice Pattern Guideline”

Ziel der LL: to provide guidance for the pattern of practice, not for the case of a particular individual

Methodik:

systematische Recherche: PubMed, Cochrane Library until June2013

Application of methods from SIGN and GRADE to grade strength of the total body of evidence and all studies used to form a recommendation are graded for strength of evidence individually

LoE

- To rate individual studies, a scale based on SIGN[1] is used. The definitions and levels of evidence to rate individual studies are as follows:

I++	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
I+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
I-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
II++	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
II+	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
II-	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
III	Nonanalytic studies (e.g., case reports, case series)

GoR

- Recommendations for care are formed based on the body of the evidence. The body of evidence quality ratings are defined by GRADE[2] as follows:

Good quality	Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Insufficient quality	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 Any estimate of effect is very uncertain

- Key recommendations for care are defined by GRADE[2] as follows:

Strong recommendation	Used when the desirable effects of an intervention clearly outweigh the undesirable effects or clearly do not
Discretionary recommendation	Used when the trade-offs are less certain—either because of low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced

Keine Informationen zur Konsensfindung

Empfehlungen

Page 5: Intravitreal injection therapy using pan-vascular endothelial growth factor (VEGF) inhibiting agents (e.g., aflibercept, bevacizumab, and ranibizumab) is the most effective way to manage neovascular AMD, and it represents the first line of treatment: I++; Good; Strong

Page 12: Anti-VEGF therapies have become first-line therapy for treatment and stabilizing most cases of neovascular AMD: I++; Good; Strong

Begründung der Empfehlungen:

- Pivotal study: Aflibercept in 2 mg dose was administered by intraviteal injection every 4 weeks and every 8 weeks after three monthly loading doses. During first year of follow-up both study arms were noninferior to 0.5 ranibizumab dosed every 4 weeks
- Individualized discontinuous treatment regimen using ranibizumab and aflibercept appear to have comparable efficacy and safety to fixed continuous regimens over 1 year, but do not maintain the initial visual gains with longer follow-up.
- RCTs studying the adjunct use of intravitreal anti-VEGF agents in various drug combinations or with verteporfin PDT do not support the use of combination therapy.
- No beneficial effect of using ranibizumanb and verteporfin PDT compared with ranibizumab alone in new-onset neovascular AMD

Weitere Empfehlungen zu Subtypen der AMD:

Page 14: Most juxtafoveal lesions that may have been previously treated with laser photocoagulation surgery are currently managed with the anti-VEGF agents: III; Good; Strong

Page 14: Patients with juxtafoveal lesions may also be considered eligible for the off-label use of PDT with verteporfin: III; Good; Discretionary

Page 14: The current trend is to use anti-VEGF agents in preference to laser photocoagulation for extrafoveal lesions: III; Good; Strong

Page 14: Laser surgery for extrafoveal lesions remains a less-commonly used, yet reasonable, therapy: III; Moderate; Discretionary

Highlighted finding regarding adverse events:

Intravitreal anti-VEGF therapy is generally well tolerated and rarely associated with serious adverse events such as infectious endophthalmitis or retinal detachment. Symptoms suggestive of postinjection endophthalmitis or retinal detachment require prompt evaluation.

Begründung:

Intravitreal Pharmacotherapy

All anti-VEGF treatments may carry theoretical risks for systemic arterial thromboembolic events and increased intraocular pressure, although the results of clinical trials studying these risks remain inconclusive.[211-214] The risks of intravitreal anti-VEGF agents in pregnant or lactating women have not been studied.[215,216]

- Aflibercept injection
  - Endophthalmitis (cumulative ≤1.0% over 1 year in VIEW studies)[146]

  At 1 year, there were no statistically significant differences in rates of serious systemic adverse events such as death, arteriothrombotic events, or venous thrombotic events between ranibizumab and aflibercept.[146]
- Ranibizumab injection
  - Endophthalmitis (cumulative ≤1.0% over 2 years in MARINA study; <1.0% over 1 year in ANCHOR study)
  - Retinal detachment or traumatic injury to the lens (<0.1% of treated cases during the first year of treatment)[157,158]

Verteporfin Photodynamic Therapy

- A severe decrease in central vision occurred within 1 week following treatment in 1% to 4% of patients, and may be permanent[174,207,208]
- Infusion site extravasation
- Idiosyncratic back pain during infusion of the drug (1% to 2% of patients)[174,207,208]
- Photosensitivity reaction (<3% of patients).[174,207,208] The stated, current recommendations are to avoid direct sunlight for the first 5days after a treatment.

Verteporfin is contraindicated in patients with porphyria or a known allergy or sensitivity to the drug. Careful consideration should be given to patients with liver dysfunction and to patients who are pregnant, breast-feeding, or of pediatric age, because these patients were not studied in published reports.

Thermal Laser Photocoagulation Surgery

- Severe vision loss following treatment, which may be permanent
- Rupture of Bruch's membrane with subretinal or vitreous hemorrhage
- Effects on the fovea in juxtafoveal CNV

Introduction or enlargement of a pre-existing scotoma, with or without visual acuity loss, is not a complication of thermal laser photocoagulation; rather, it is an anticipated side effect of the treatment. Similarly, recurrence or persistence of CNV, or the development of new CNV and further visual deterioration after adequate thermal laser surgery, is usually a result of the disease process and is not a complication. These realities must be emphasized to the patient and family before treatment.

Ausgewählte Referenzen:

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157. Rosenfeld PJ, Brown DM, Heier JS, et al, MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419-31.

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Detaillierte Darstellung der Recherchestrategie:

Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database) **am 08.05.2015**

#	Suchfrage
#1	MeSH descriptor: [Macular Degeneration] this term only
#2	MeSH descriptor: [Wet Macular Degeneration] explode all trees
#3	macular and (degeneration* or dystroph*):ti,ab,kw (Word variations have been searched)
#4	(age or wet or neovascular or exudative) and maculopath*:ti,ab,kw (Word variations have been searched)
#5	amd:ti,ab,kw (Word variations have been searched)
#6	#1 or #2 or #3 or #4 or #5
#6	#1 or #2 or #3 or #4 or #5 Publication Year from 2010 to 2015, in Cochrane Reviews (Reviews only), Other Reviews and Technology Assessments

SR, HTAs in Medline (PubMed) am 08.05.2015

#	Suchfrage
#1	"Macular Degeneration"[Mesh:NoExp]
#2	wet macular degeneration[MeSH Terms]
#3	(macular[Title/Abstract]) AND ((degeneration*[Title/Abstract]) OR dystroph*[Title/Abstract])
#4	(((((age[Title/Abstract]) OR wet[Title/Abstract]) OR exudative[Title/Abstract]) OR neovascular[Title/Abstract])) AND maculopath*[Title/Abstract]
#5	amd[Title/Abstract]
#6	((((#1) OR #2) OR #3) OR #4) OR #5
#7	(#6) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])
#8	(#6) AND (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR 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]))))
#9	(#7) OR #8
#10	(#9) AND ("2010/05/01"[PDAT] : "2015/05/08"[PDAT])

Leitlinien in Medline (PubMed) am 08.05.2015

#	Suchfrage
#1	"Macular Degeneration"[Mesh:NoExp]
#2	wet macular degeneration[MeSH Terms]
#3	(macular[Title/Abstract]) AND ((degeneration*[Title/Abstract]) OR dystroph*[Title/Abstract])
#4	(((((age[Title/Abstract]) OR wet[Title/Abstract]) OR exudative[Title/Abstract]) OR neovascular[Title/Abstract])) AND maculopath*[Title/Abstract]
#5	amd[Title/Abstract]
#6	((((#1) OR #2) OR #3) OR #4) OR #5
#7	(#6) AND (((((Guideline[Publication Type]) OR Practice Guideline[Publication Type]) OR Consensus Development Conference[Publication Type]) OR Consensus Development Conference, NIH[Publication Type]) OR guideline*[Title])
#8	(#7) AND ("2010/05/01"[PDAT] : "2015/05/08"[PDAT])

Literatur:

1. **American Academy of Ophthalmology (AAO)**. Age-related macular degeneration: preferred practice pattern. San Francisco (USA): AAO 2015; www.aao.org/Assets/db935a77-1997-4d60-b850-71b7602f46e2/635582143853270000/age-related-macular-degeneration-ppp-pdf, Zugriff am 08.05.2015.

2. **Gemeinsamer Bundesausschuss (G-BA)**. Photodynamische Therapie (PDT) mit Verteporfin bei altersabhängiger feuchter Makuladegeneration mit subfoveolären klassischen choriodalen Neovaskularisationen. Zusammenfassender Bericht des Arbeitsausschusses "Ärztliche Behandlung" des Bundesausschusses der Ärzte und Krankenkassen über die Beratungen gemäß §135 Abs.1 SGB V vom 22. Januar 2001. Berlin (GER): G-BA 2001; https://www.g-ba.de/downloads/40-268-249/HTA-Photodynamische_Therapie_.pdf, Zugriff am 08.05.2015.

3. **Gemeinsamer Bundesausschuss (G-BA)**. Photodynamische Therapie (PDT) mit Verteporfin bei chorioidaler Neovaskularisation (CNV) aufgrund hoher Myopie, rein okkulter subfoveolärer CNV bei altersabhängiger Makulopathie, juxtafoveolärer CNV, sekundärer CNV nach Chorioretinitis unklarer Genese. Zusammenfassender Bericht des Unterausschusses "Ärztliche Behandlung" des Gemeinsamen Bundesausschusses über die Bewertung gemäß §135 Abs.1 SGB V vom 22. Februar 2007. Berlin (GER): G-BA 2007; https://www.g-ba.de/downloads/40-268-301/2007-02-22-Abschluss-PDT.pdf, Zugriff am 08.05.2015.

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