Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

und

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

Vorgang: 2021-B-045 Faricimab

Stand: April 2021

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

Faricimab
Behandlung der neovaskulären (feuchten) altersbedingten Makuladegeneration (AMD)

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 Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	• Photodynamische Therapie (PDT), Photokoagulation mittels Laser • Protonentherapie bei altersabhängiger Makuladegeneration • photodynamische Therapie (PDT) mit Verteporfin bei altersabhängiger feuchter Makuladegeneration mit subfoveolärer klassischer choriodaler Neovaskularisation
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	• Aflibercept - Beschluss vom 6. Juni 2013 • Brolucizumab - Beschluss vom 3. September 2020 • 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 16. Oktober 2000)
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Faricimab	<u>Geplantes Anwendungsgebiet laut Beratungsanforderung</u>: Faricimab wird angewendet bei Erwachsenen zur Behandlung der neovaskulären (feuchten) altersbedingten Makuladegeneration (nAMD).
Ranibizumab S01LA04 Lucentis®	Lucentis wird angewendet bei Erwachsenen zur: […] – Behandlung der neovaskulären (feuchten) altersabhängigen Makuladegeneration (AMD) *Stand FI Juli 2020*
Aflibercept S01LA05 Eylea®	Eylea wird angewendet bei Erwachsenen zur Behandlung – der neovaskulären (feuchten) altersabhängigen Makuladegeneration (AMD) (siehe Abschnitt 5.1), *Stand FI Juni 2020*
Brolucizumab S01LA06 Beovu®	Beovu wird angewendet bei Erwachsenen zur Behandlung der neovaskulären (feuchten) altersabhängigen Makuladegeneration (AMD). *Stand FI Mai 2020*
Verteporfin S01LA01 Visudyne®	Visudyne wird angewendet für die Behandlung von […] – Erwachsenen mit exsudativer (feuchter) altersbezogener Makuladegeneration (AMD) mit vorwiegend klassischen subfovealen chorioidalen Neovaskularisationen (CNV), *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.* *Stand FI August 2019*
Pegaptanib S01LA03 Macugen®	Macugen ist indiziert zur Behandlung der neovaskulären (feuchten) altersabhängigen Makuladegeneration (AMD) bei Erwachsenen. *Stand FI August 2012*

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2021-B-045 (Faricimab)

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

Inhaltsverzeichnis

Abkürzungsverzeichnis

AMD	Altersabhängigen Makuladegeneration
AM-RL	Arzneimittel-Richtlinie
ATC	Arterial Thromboembolic
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BCVA	Best-Corrected Visual Acuity
BRVO	Branch Retinal Vein Occlusion
CMT	Central Macular Thickness
CNV	Choroidal Neovascularization
CRT	Central Retinal Thickness
CRVO	Central Retinal Vein Occlusion
DME	Diabetic Macular Edema
ETDRS	Early Treatment Diabetic Retinopathy Study
ECRI	ECRI Guidelines Trust
FA	Fluorescein Angiography
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IVR	Intravitreal Ranibizumab
KI	Konfidenzintervall
LoE	Level of Evidence
MD	Mean Difference
nAMD	Neovaskuläre Altersabhängige Makuladegeneration
NEI-VFQ	National Eye Institute Visual Function Questionnaire
NICE	National Institute for Health and Care Excellence
NMA	Network Meta-Analysis
NVAMD	Neovascular Age-related Macular Degeneration
OCT	Optical Coherence Tomography

OR	Odds Ratio
PCV	Polypoidal Choroidal Vasculopathy
PDT	Photodynamische Therapie
PRN	Pro Re Nata
RCT	Randomized Controlled Trial
RF	Reduced-Fluence
RR	Relatives Risiko
RVO	Retinal Vein Occlusion
SF	Standard-Fluence
SIGN	Scottish Intercollegiate Guidelines Network
SOAEs	Severe Ocular Adverse Events
TRIP	Turn Research into Practice Database
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organization
WMD	Weighted Mean Difference

1 Indikation

Behandlung der neovaskulären (feuchten) altersbedingten Makuladegeneration (AMD) bei Erwachsenen.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *neovaskuläre (feuchte) altersbedingte Makuladegeneration* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 01.10.2020 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 464 Quellen. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 15 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2020 [3].

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 – Brolucizumab (Neovaskuläre altersabhängige Makuladegeneration) vom 3. September 2020

Anwendungsgebiet

Beovu® wird angewendet bei Erwachsenen zur Behandlung der neovaskulären (feuchten) altersabhängigen Makuladegeneration (AMD).

Zweckmäßige Vergleichstherapie:

- Ranibizumab oder Aflibercept

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Brolucizumab gegenüber Ranibizumab oder Aflibercept:

Ein Zusatznutzen ist nicht belegt.

G-BA, 2013 [6].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 06. Juni 2013 - Aflibercept

Anwendungsgebiet

Eylea® ist angezeigt zur Behandlung von Erwachsenen mit neovaskulärer (feuchter) altersbedingter Makuladegeneration.

Zweckmäßige Vergleichstherapie

Ranibizumab

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Ranibizumab

Der Zusatznutzen im Verhältnis zur zweckmäßigen Vergleichstherapie ist nicht belegt.

Anmerkung:

Es liegen bislang keine validen Daten für Patienten vor, die mit anderen VEGF-Inhibitoren vorbehandelt wurden.

G-BA, 2010 [5].

Protonentherapie bei altersabhängiger Makuladegeneration

Abschlussbericht Beratungsverfahren nach § 137c SGB V (Krankenhausbehandlung) 13. Januar 2010

Anwendungsgebiet

altersabhängige Makuladegeneration

Fazit

Es konnten drei Fallserien und drei 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 [4].

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

Anwendungsgebiet

altersabhängige feuchte Makuladegeneration mit subfoveolärer klassischer choriodaler Neovaskularisation

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.

3.2 Cochrane Reviews

Solomon SD et al., 2019 [13].

Update von Solomon SD et al., 2014[1]

Anti-vascular endothelial growth factor for neovascular age-related macular degeneration (Review)

Fragestellung

To investigate ocular and systemic effects of, and quality of life associated with, intravitreous injection of three anti-VEGF agents (pegaptanib, ranibizumab, and bevacizumab) versus no anti-VEGF treatment for patients with neovascular AMD.

To compare the relative effects of one of these anti-VEGF agents versus another when administered in comparable dosages and regimens.

Methodik

We included only randomized controlled trials (RCTs) in this review. We included only trials in which participants were followed for at least one year. We also included outcomes at two-year follow-up when these data were available.

Population:

- We included trials in which participants had neovascular AMD as defined by study investigators.

Intervention/Komparator:

- We included studies that compared anti-VEGF treatment versus another treatment, sham treatment, or no treatment. We did not include studies that compared different doses of one anti-VEGF treatment against another, studies that included no control or comparator group, or studies that used anti-VEGF agents in combination with other treatments. We did not include studies of aflibercept (VEGF Trap-Eye/EYLEA solution) or studies that compared different treatment schedules (e.g. monthly vs as needed dosing), because other Cochrane reviews have evaluated these interventions.

Endpunkte:

Primary outcomes

- best-corrected visual acuity (BCVA) at one-year follow-up. All included RCTs randomized only one eye per participant (i.e. the study eye); therefore we defined the primary outcome for the comparison of treatments as the proportion of participants who gained 15 or more letters (three lines) of BCVA in the study eye when BCVA was measured on a visual acuity chart with a LogMAR scale.

Secondary outcomes

Visual acuity outcomes

[1] **Solomon SD, Lindsley K, Vedula SS, Krzystolik MG, Hawkins BS.** Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. Cochrane Database Syst Rev 2014(8):CD005139.

- Proportion of participants who gained 15 or more letters of BCVA in the study eye as measured at two-year follow-up
- Proportion of participants who lost fewer than 15 letters of visual acuity at one year and at two years
- Proportion of participants who lost fewer than 30 letters of visual acuity at one year and at two years
- Proportion of participants for whom blindness was avoided in the study eye, defined as eyes with visual acuity better than
- 20/200 at one year and at two years
- Proportion of participants maintaining visual acuity, defined as a gain of zero or more letters (i.e. no loss of BCVA from baseline) at one year and at two years
- Mean change in visual acuity from baseline to one year and to two years

Other secondary outcomes

- Contrast sensitivity, reading speed, or any other validated measure of visual function as measured in the included studies
- Assessment of morphologic characteristics by fluorescein angiography or optical coherence tomography (OCT), including mean change in size of CNV, mean change in size of total lesion, and mean change in central retinal
- Central retinal thickness (CRT)
- Quality of life measures, as assessed with any validated measurementscale
- Economic data, such as comparative cost analyses
- Ocular or systemic adverse outcomes

Recherche/Suchzeitraum:

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), which contains the Cochrane Eyes and Vision Trials Register (searched January 31, 2018); MEDLINE Ovid (1946 to January 31, 2018); Embase Ovid (1947 to January 31, 2018); the Latin American and Caribbean Health Sciences Literature Database (LILACS) (1982 to January 31, 2018); the International Standard Randomized Controlled Trials Number (ISRCTN) Registry (2018); ClinicalTrials.gov (searched November 28, 2018); and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (searched January 31, 2018). We did not impose any date or language restrictions in electronic searches for trials.

Qualitätsbewertung der Studien:

- risk of bias was assessed using the Cochrane Risk of Bias tool
- GRADE Working Group grades of evidence

Ergebnisse

Anzahl eingeschlossener Studien:

- We had classified one newly included study as ongoing in the 2014 version of this review. Overall, we identified and included 16 RCTs (n=6.347).
- Of six studies that compared anti-VEGF monotherapy versus control, one study evaluated three doses of pegaptanib versus sham injection (VISION 2004), three studies compared two

doses of ranibizumab versus sham injections or PDT (ANCHOR 2006; MARINA 2006; PIER 2008), and two studies compared bevacizumab with other treatments for AMD (ABC 2010; Sacu 2009). The remaining ten studies were head-to-head trials of bevacizumab versus ranibizumab (Biswas 2011; BRAMD 2016; CATT 2011; GEFAL 2013; IVAN 2013; LUCAS 2015; MANTA 2013; SAVE-AMD 2017; Scholler 2014; Subramanian 2010).

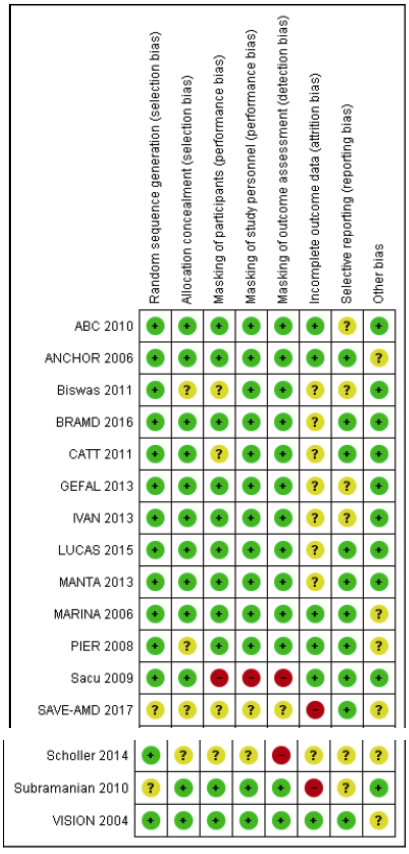
Charakteristika der Population:

- The 16 trials were similar in that all enrolled both men and women 50 years of age or older who had subfoveal CNV secondary to AMD; one study also enrolled participants with juxtafoveal or extrafoveal CNV (BRAMD 2016).
- A majority of participants in most trials were women, but one trial enrolled a greater number of men than women (Subramanian 2010).

Qualität der Studien:

- Overall, we found the included studies to be at low risk for most categories of bias.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Other potential sources of bias:

We considered various other aspects of trial design and reporting, trial sponsorship, and financial interests of investigators as other potential sources of bias. Pharmaceutical companies marketing the study drugs under investigation sponsored ANCHOR 2006, MARINA 2006, PIER 2008, and VISION 2004, and submitted data from these trials to the FDA to obtain approval for ranibizumab and pegaptanib. In addition, pharmaceutical company sponsors had important roles in trial design, analysis, and reporting. Some investigators from other trials reported that they received trial agents or financial support from pharmaceutical companies; however,

because the companies did not directly sponsor these trials, we did not judge them to be at risk of bias for this domain (CATT 2011; GEFAL 2013; IVAN 2013; Scholler 2014). We observed no other potential sources of bias for the remaining eight studies.

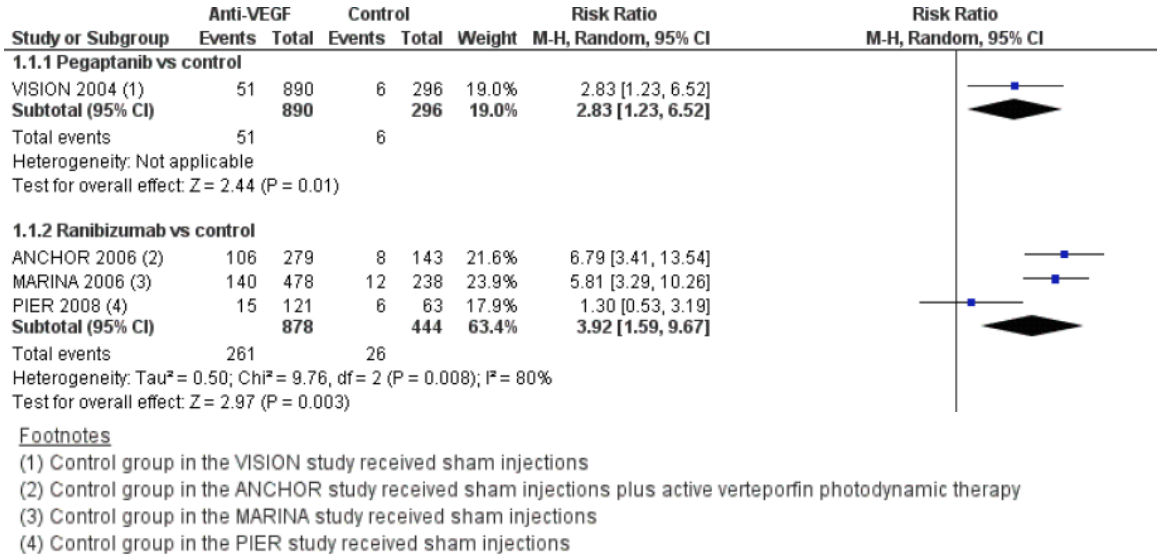
Studienergebnisse:

Der Fokus der Ergebnisdarstellung liegt auf Vergleichen zu den im AWG zugelassenen Wirkstoffen.

Primary Outcome:

Gain of 15 or more letters visual acuity

Abb.1: Comparison Anti-VEGF treatment versus control, Outcome: Gain of 15 or more letters visual acuity at 1 year



- At two years, data were available from only the three ranibizumab trials. The proportion of participants who were treated with ranibizumab and had gained 15 or more letters at two years was nearly six times the proportion of those treated with control who gained 15 or more letters (RR 5.77, 95% CI 3.38 to 9.84). We graded the certainty of evidence for the two-year outcome also as moderate, again downgrading for imprecision (-1).

Secondary Outcomes:

Loss of fewer than 15 letters of visual acuity

Abb.: Comparison Anti-VEGF treatment versus control, Loss of fewer than 15 letters visual acuity at 1 year

Study or subgroup	Anti-VEGF n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Pegaptanib vs control					
VISION 2004	612/890	164/296		21.61%	1.24[1.11,1.39]
Subtotal (95% CI)	**890**	**296**		**21.61%**	**1.24[1.11,1.39]**
Total events: 612 (Anti-VEGF), 164 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.8(P=0)					
1.3.2 Ranibizumab vs control					
ANCHOR 2006	266/279	92/143		20.27%	1.48[1.31,1.68]
MARINA 2006	452/478	148/238		22.62%	1.52[1.37,1.68]
PIER 2008	105/121	31/63		10.01%	1.76[1.36,2.29]
Subtotal (95% CI)	**878**	**444**		**52.91%**	**1.53[1.41,1.64]**
Total events: 823 (Anti-VEGF), 271 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.43, df=2(P=0.49); I^2=0%					
Test for overall effect: Z=10.99(P<0.0001)					

- At two years, the beneficial effect of ranibizumab for this outcome persisted at a similar magnitude when compared with control therapy (three ranibizumab trials). Sixty percent more participants treated with ranibizumab lost fewer than 15 letters of visual acuity at two-year follow-up as participants in control groups (RR 1.62, 95% CI 1.32 to 1.98), high certainty of evidence

Loss of fewer than 30 letters of visual acuity

Abb.: Comparison Anti-VEGF treatment versus control, Loss of fewer than 30 letters visual acuity at 1 year.

Study or subgroup	Anti-VEGF n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Pegaptanib vs control					
VISION 2004	798/890	231/296		24.17%	1.15[1.08,1.23]
Subtotal (95% CI)	**890**	**296**		**24.17%**	**1.15[1.08,1.23]**
Total events: 798 (Anti-VEGF), 231 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=4.22(P<0.0001)					
1.5.2 Ranibizumab vs control					
ANCHOR 2006	279/279	124/143		24.08%	1.15[1.08,1.23]
MARINA 2006	473/478	204/238		26.77%	1.15[1.1,1.22]
Subtotal (95% CI)	**757**	**381**		**50.85%**	**1.15[1.11,1.2]**
Total events: 752 (Anti-VEGF), 328 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=1); I^2=0%					
Test for overall effect: Z=6.89(P<0.0001)					

- When comparing ranibizumab groups versus controls, we estimated a 22% benefit of ranibizumab with respect to loss of fewer than 30 letters of visual acuity after two years (RR 1.22, 95% CI 1.15 to 1.29), (high certainty of evidence)

Prevention of blindness in the study eye (visual acuity better than 20/200)

- Treatment with pegaptanib or ranibizumab resulted in fewer blind study eyes at one year follow-up; the summary effect estimate (risk ratio) for visual acuity better than 20/200 was 1.58 (95% CI 1.34 to 1.86) for the two anti-VEGF agents compared with control (high certainty of evidence both at one year and at two years)

Mean change in visual acuity

- Participants treated with pegaptanib were able to read 7 more letters at one-year follow-up (mean difference [MD] 6.7 (95% CI 4.4 to 9.0) and participants treated with ranibizumab were

able to read 18 more (MD= 17.8, 95% CI 16.0 to 19.6) compared with participants given control treatment (moderate certainty of evidence, after downgrading for inconsistence).

- participants treated with ranibizumab were able to read 20 more letters (MD 20.1, 95% CI 18.1 to 22.2) at two years compared to control group (high certainty of evidence).

Reduction in size lesion at one year (Mean number of disc areas)

- Pegaptanib treatment resulted in smaller mean lesion size at one-year follow-up compared with sham treatment (MD 0.86 DAs, 95% CI 0.35 to 1.37), (moderate certainty of evidence, after downgrading for imprecision.
- 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 (ANCHOR and PIER study) after one year. At two years, this effect persisted in ANCHOR (MD 2.44, 95% CI 1.87 to 3.00) but not in PIER (MD 0.59, 95% CI -0.55 to 1.73), (moderate certainty of evidence, after downgrading for inconsistence).

Quality of life outcomes

- At one year, overall vision-related quality of life improved more often among participants in ranibizumab groups than among those in control groups (MD 6.7, 95% CI 3.4 to 10.0). The mean difference was greater in MARINA 2006 (MD 8.2, 95% CI 6.0 to 10.4) than in ANCHOR 2006 (MD 4.8, 95% CI 1.7 to 7.9). This difference between the two trials may have occurred because participants in the control group in ANCHOR 2006 received an active treatment (verteporfin PDT therapy).

Adverse events

- Ocular inflammation and increased intraocular pressure (IOP) after intravitreal injection were the most frequently reported serious ocular adverse events. Researchers reported endophthalmitis in less than 1% of anti-VEGF-treated participants and in no cases among control groups. The occurrence of serious systemic adverse events was comparable across anti-VEGF-treated groups and control groups; however, the numbers of events and trial participants may have been insufficient to show a meaningful difference between groups (evidence of low to moderate-certainty). Investigators rarely measured and reported data on visual function, quality of life, or economic outcomes.

Anmerkung/Fazit der Autoren

Results of this review show the effectiveness of anti-VEGF agents (pegaptanib, ranibizumab, and bevacizumab) in terms of maintaining visual acuity; studies show that ranibizumab and bevacizumab improved visual acuity in some eyes that received these agents and were equally effective. Available information on the adverse effects of each medication does not suggest a higher incidence of potentially vision- threatening complications with intravitreous injection of anti-VEGF agents compared with control interventions; however, clinical trial sample sizes were not sufficient to estimate differences in rare safety outcomes. Future Cochrane Reviews should incorporate research evaluating variable dosing regimens of anti-VEGF agents, effects of long-term use, use of combination therapies (e.g. anti-VEGF treatment plus photodynamic therapy), and other methods of delivering these agents.

Kommentare zum Review

- Kein direkter Vergleich zwischen Pegaptanib und einem anderen VEGF.
- In zwei der drei Studien zu Ranibizumab wurde gegen Scheinmedikation verglichen. Einzig die Anchor-Studie verglich Ranibizumab gegen PDT mit Verteporfin.

Sarwar S et al., 2016 [12].

Aflibercept for neovascular age-relatedmacular degeneration (Review)

Fragestellung

To assess and compare the effectiveness and safety of intravitreal injections of aflibercept versus ranibizumab, bevacizumab, or sham for treatment of patients with neovascular AMD.

Methodik

We included randomized controlled trials (RCTs) only.

Population:

- We included trials of participants with diagnosed subfoveal neovascular AMD, confirmed by fluorescein angiography, who received no previous treatment for AMD in the study eye.

Intervention/Komparator:

- We included trials in which aflibercept monotherapy was compared with ranibizumab, bevacizumab, or sham. We excluded studies in which aflibercept was evaluated as part of combination therapy versus other active treatments, such as laser photocoagulation.

Endpunkte:

Primary Outcome:

- mean change from baseline in number of letters of best-corrected visual acuity (BCVA) at one year, as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) chart or equivalent.

Secondary Outcomes:

- Mean change in number of letters of BCVA at two years.
- Proportion of participants who gained 15 or more letters of BCVA at one year and at two years.
- Proportion of participants who lost 15 or more letters of BCVA at one year and at two years.
- Proportion of participants with BCVA worse than 20/200 at one year and at two years.
- Proportion of eyes with absence of fluid on optical coherence tomography (OCT) at one year and at two years.
- Proportion of eyes with absence of leakage on fluorescein angiography at one year and at two years.
- Mean number of injections received by one year and by two years.
- Mean change in central retinal thickness from baseline to one year and to two years.

- Mean change in extent of choroidal neovascularization (CNV) from baseline at one year and at two years.

Quality-of-life outcomes

- measured by a validated scale, such as the National Eye Institute Visual Function Questionnaire (NEI-VFQ), at one year and at two years

Adverse events

- Proportion of participants with arterial thrombotic events at one year and at two years.
- Proportion of participants with serious systemic adverse events at one year and at two years.
- Proportion of eyes with serious ocular adverse events at one year and at two years.

Recherche/Suchzeitraum:

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Trials Register) (Issue 11, 2015), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to November 2015), EMBASE (January 1980 to November 2015), PubMed (1948 to November 2015), Latin American and Caribbean Health Sciences Literature Database (LILACS) (1982 to November 2015), the meta Register of Controlled Trials (mRCT) (last searched December 4, 2014), ClinicalTrials.gov, and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP). We did not use any date or language restrictions in the electronic search for trials. We last searched the electronic databases on November 30, 2015.

Qualitätsbewertung der Studien:

- risk of bias was assessed using the Cochrane Risk of Bias tool
- GRADE Working Group grades of evidence.

Ergebnisse

Anzahl eingeschlossener Studien:

- 2 studies included (n=2.458). VIEW 1 included participants from 154 sites in Canada and the United States, and VIEW 2 included participants from 172 sites located elsewhere.

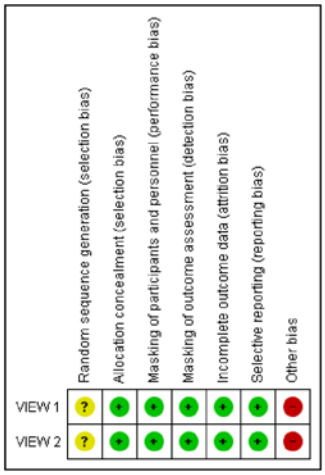
Charakteristika der Population:

- VIEW1 enrolled 1217 participants, and VIEW 2 enrolled 1240 participants.
- Criteria for participant selection common to the two RCTs included age 50 years or older, CNV lesions confirmed by fluorescein angiography, and BCVA score equivalent to 20/40 or worse.
- Both trials included one study eye per participant.

Qualität der Studien:

Risk of bias: We assessed studies at low risk of bias for most domains. However, both trials were sponsored by the manufacturer of aflibercept; therefore, we assessed these trials at high risk of bias because of the funding source.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

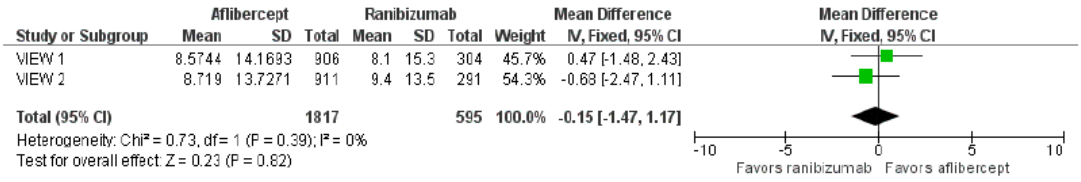


Studienergebnisse:

Primary Endpoint

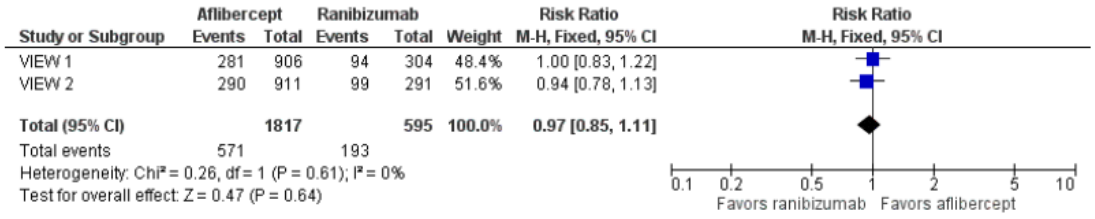
The mean difference (MD) in mean change in number of letters of BCVA from baseline to one year was less than one letter when aflibercept was compared with ranibizumab (MD -0.15, 95% CI -1.47 to 1.17). Thus, eyes treated with aflibercept and ranibizumab showed similar gains in visual acuity at one year. We graded the quality of evidence for this outcome as high.

Figure 3. Forest plot of comparison: 1 Aflibercept vs ranibizumab, outcome: 1.1 Mean change in BCVA in ETDRS letters at 1 year.



- At two years, the mean change in BCVA from baseline was 7.2 letters for the aflibercept groups versus 7.9 letters for the ranibizumab groups. Additional data regarding two-year outcomes, such as standard deviation for the mean BCVA change, were not available for further analysis of this outcome.
- At one-year follow-up, the proportion of participants who gained 15 or more letters of BCVA was 31.4% in the aflibercept groups and 32.4% in the ranibizumab groups. For this outcome, a risk ratio (RR) greater than 1 favors treatment with aflibercept. The RR for the combined aflibercept groups versus the ranibizumab groups was 0.97 (95% CI 0.85 to 1.11), which indicates that similar proportions of participants in the aflibercept and ranibizumab groups showed large visual acuity gains. We graded the quality of evidence for this outcome as high.

Figure 4. Forest plot of comparison: 1 Aflibercept vs ranibizumab, outcome: 1.2 Gain of ≥ 15 letters of BVCA at 1 year.



At two-year follow-up, 562 (30.9%) of 1,817 participants in the aflibercept groups and 188 (31.6%) of 595 participants in the ranibizumab groups gained 15 or more letters from baseline. This outcome was comparable between the two groups (RR 0.98, 95% CI 0.85 to 1.12). We graded the quality of evidence for this outcome as high.

Loss of 15 or more letters of BCVA

At one-year follow-up, the proportion of participants who lost 15 or more letters of BCVA was 5.1% in the aflibercept groups and 5.7% in the ranibizumab groups. For this outcome, an RR less than 1 favors treatment with aflibercept, as it indicates that a higher proportion of participants lost letters of visual acuity – a negative outcome - in the ranibizumab groups (RR 0.89, 95% CI 0.61 to 1.30). We graded the quality of evidence for this outcome as moderate due to imprecision.

Absence of fluid on optical coherence tomography (OCT)

- At one year, no significant difference between aflibercept and ranibizumab in the proportion of eyes who achieved dry retinas (absence of cystic intraretinal fluid and subretinal fluid on OCT) (RR = 1.06 (95% CI 0.98 to 1.14). We graded the quality of evidence for this outcome as high.
- The proportion of participants with no retinal fluid decreased in all treatment groups from one year to two years. A higher proportion of participants in the aflibercept groups (757/1520, 49.8%) showed absence of fluid on OCT compared with participants in the ranibizumab groups (231/508, 45.5%) (RR 1.10, 95% CI 0.98 1.22). We graded the quality of evidence for this outcome as high.

Mean change in central retinal thickness (CRT)

- At one-year follow-up, the MD between aflibercept and ranibizumab was -4.94 µm (95% CI -15.48 to 5.61), which is neither a clinically nor statistically important difference. We graded the quality of evidence for this outcome as high.

Vision-related quality-of-life (VRQoL)

- Similar changes in NEI-VFQ-25 composite scores from baseline to one year were reported for both aflibercept and ranibizumab (MD -0.39, 95% CI -1.71 to 0.93). We graded the quality of evidence for this outcome as high.

Adverse events

Overall, occurrence of serious systemic adverse events was similar and comparable in aflibercept- and ranibizumab-treated groups at one year (RR 0.99, 95% CI 0.79 to 1.25). Risk of any serious ocular adverse event was lower in the aflibercept group than in the ranibizumab group, but the risk estimate is imprecise (RR 0.62, 95% CI 0.36 to 1.07). As the result of imprecision, we graded the quality of evidence for all adverse events as moderate.

Anmerkung/Fazit der Autoren

Results of this review document the comparative effectiveness of aflibercept versus ranibizumab for visual acuity and morphological outcomes in eyes with neovascular AMD. Current available information on adverse effects of each medication suggests that the safety profile of aflibercept is comparable with that of ranibizumab; however, the number of participants who experienced adverse events was small, leading to imprecise estimates of absolute and relative effect sizes. The eight-week dosing regimen of aflibercept represents reduced treatment requirements in comparison with monthly dosing regimens and thus has the potential to reduce treatment burden and risks associated with frequent injections.

Kommentare zum Review

Subgroup analysis and investigation of heterogeneity: We planned to perform subgroup analysis according to the comparison intervention reported in the included trials (eg, aflibercept vs placebo or sham injections, aflibercept vs ranibizumab); however, we did not perform these subgroup analyses, as only one comparison intervention (ranibizumab) was used in trials included in this review.

3.3 Systematische Reviews

Low A et al., 2019 [8].

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

Fragestellung

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

Methodik

Population:

Adults treated with anti-VEGF agents due to one of the following conditions:

- Choroidal neovascularization secondary to age-related macular degeneration (AMD)/**neovascular AMD** (NVAMD)
- Diabetic macular edema (DME)

- Branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO) with cystoid macular edema
- Vitreous hemorrhage/proliferative diabetic retinopathy/neovascular glaucoma

Intervention:

- Aflibercept (Eylea; Trap-Eye)
- Bevacizumab (Avastin)
- Ranibizumab (Lucentis)

Komparator:

- One anti-VEGF intervention versus another anti-VEGF intervention (head-to-head)

Endpunkte:

- Mean best-corrected visual acuity (BCVA) change (minimal clinically important difference defined as five or more letters)
- ≥ 15 letter gain
- ocular adverse events
- systemic adverse events

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

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

Ergebnisse

Anzahl eingeschlossener Studien:

- 17 RCTs (8 with low risk of bias, 4 with unclear risk of bias and 5 with high risk of bias
- Eleven trials included patients with NVAMD, three with DME and three with central or branch RVO.
- NVAMD: 2 RCTs (n=2457) Aflibercept vs. Ranibizumab, 9 RCTs (n=3630) Bevacizumab vs Ranibizumab

Charakteristika der Population:

- NVAMD: The 11 trials were similar in that all enrolled both men and women; age ranged between 63.9 and 80.1 years

Qualität der Studien:

- NVAMD: risk of bias was low in six studies, unclear in three studies and high in two studies

Studienergebnisse:

Der Fokus der Ergebnisdarstellung liegt auf Vergleichen zu den im AWG zugelassenen Wirkstoffen.

- Two trials provided low-strength evidence that aflibercept and ranibizumab had similar effects in patients with NVAMD.

Table 1 Summary of the evidence on anti-VEGF agents for the treatment of NVAMD, DME or RVO

Outcome	No. studies (N=total randomised)	Summary of findings; Combined summary estimate (95% CI)	Strength of evidence*	Comments
NVAMD				
Aflibercept vs Bevacizumab: no evidence				
Aflibercept vs Ranibizumab				
Mean BCVA change†	2 RCTs (n=2457)‡ ► 2 low ROB	Mixed findings, but no clinically important differences between drugs.	Low	Attempted pooling resulted in very high statistical heterogeneity due to conflicting results.§
≥15 letter gain	2 RCTs (n=2457)‡ ► 2 low ROB	No difference.	Low	Attempted pooling resulted in very high statistical heterogeneity.¶
Ocular AEs	2 RCTs (n=2457)‡ ► 2 low ROB	Low rates of serious ocular AEs and likely no difference between drugs. Endophthalmitis: <1% per group 22 months.	Moderate	Statistical comparisons between drugs not reported.
Systemic AEs	2 RCTs (n=2457)‡ ► 2 low ROB	No significant differences reported, and no evidence of a dose-response relationship (highest exposure to aflibercept generally had lowest event rates). ATEs: 2.4% (monthly arm) vs 3.2%.	Low	Statistical comparison between drugs not reported.
Costs	2 RCTs (n=2457)‡ ► 2 low ROB	No direct data. Aflibercept required slightly less frequent injections during 10 month PRN phase (4.1 vs 4.7; P<0.001), likely representing a small savings (~$2300/year**).	Low	

Anmerkung/Fazit der Autoren

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

Nguyen CL et al., 2018 [10].

Anti-vascular endothelial growth factor for neovascular age-related macular degeneration: a meta-analysis of randomized controlled trials

Siehe auch Pham et al 2019 [11].

Fragestellung

to evaluate the relative efficacy and safety of all intravitreal anti-VEGF agents that are available compared with another treatment for neovascular age-related macular degeneration (nAMD) and in particular when compared to each other.

Methodik

Population:

- Patients with nAMD

Intervention/Komparator:

- anti-VEGF treatment (pegaptanib, ranibizumab, bevacizumab, aflibercept or conbercept)

Endpunkte:

- Efficacy: mean change in best corrected visual acuity (BCVA), central macular thickness (CMT) from baseline at 1 and 2 years of follow up.
- Safety: proportions of patients with death, arteriothrombotic and venous thrombotic events, and at least one serious systemic adverse event at 1 and 2 years of follow up.

Recherche/Suchzeitraum:

- systematic literature review with searches of CENTRAL, Ovid MEDLINE (January 1946 to June 2016), EMBASE (January 1974 to June 2016), the metaRegister of Controlled Trials (mRCT), ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP). The final search was performed on June 2016.

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- Fifteen RCTs selected for meta-analysis (8320 patients).
- Two trials compared pegaptanib, and three trials compared ranibizumab versus control. Eight trials compared bevacizumab with ranibizumab. Two trials compared aflibercept with ranibizumab.

Charakteristika der Population:

Table 1 Characteristics of included studies

Study	Location	Treatment groups	Followup, months	Number of patients	Age, years
VISION 2004 [6]	United States, Canada, Austria, Belgium, Czech Republic, Denmark, France, Germany, Hungary, Israel, Italy, the Netherlands, Poland, Portugal, Spain, Switzerland, UK, Brazil, Chile, Colombia, and Australia	Pegatanib and photocoagulation	12	904/304[a]	75/77[a]
ANCHOR 2006 [9]	United States, France, Germany, Hungary, Czech Republic, and Australia	Ranibizumab and photocoagulation	24	280/143[b]	76.7/77.8[b]
MARINA 2006 [10]	United States	Ranibizumab and photocoagulation	24	478/238[b]	77/77[b]
PIER 2008 [36]	United States	Ranibizumab and photocoagulation	24	121/63[b]	79/78[b]
ABC 2010 [34]	United Kingdom	Bevacizumab and photocoagulation	12	65/66[c]	79/81[c]
SACU 2009 [37]	Austria	Bevacizumab and photocoagulation	12	14/14[c]	78/78[c]
CATT 2011 [12]	United States	Bevacizumab and ranibizumab	24	586/599[d]	79.7/78.8[d]
IVAN 2013 [14]	United Kingdom	Bevacizumab and ranibizumab	24	296/314[d]	77.8/77.7[d]
GEFAL 2013 [35]	France	Bevacizumab and ranibizumab	12	191/183[d]	79.6/78.7[d]
MANTA 2013 [16]	Austria	Bevacizumab and ranibizumab	12	154/163[d]	76.7/77.6[d]
Subramanian 2010 [38]	United States	Bevacizumab and ranibizumab	12	15/7[d]	78/80[d]
Biswas 2011 [24]	India	Bevacizumab and ranibizumab	18	50/54[d]	64.4/63.5[d]
LUCAS 2015 [18]	Norway	Bevacizumab and ranibizumab	24	213/218[d]	62/78[d]
BRAMD 2016 [19]	Netherlands	Bevacizumab and ranibizumab	12	161/166[d]	79/78[d]
VIEW 1 [25]	United States and Canada	Aflibercept and ranibizumab	24	911/304[e]	78/78[e]
VIEW 2 [25]	Europe, the Middle East, Asia-Pacific, and Latin America	Aflibercept and ranibizumab	24	913/291[e]	74/73[e]

[a]Pegatanib group/photocoagulation group
[b]Ranibizumab group/photocoagulation group
[c]Bevacizumab group/photocoagulation group
[d]Bevacizumab group/ranibizumab group
[e]Aflibercept group/ranibizumab group

Qualität der Studien:

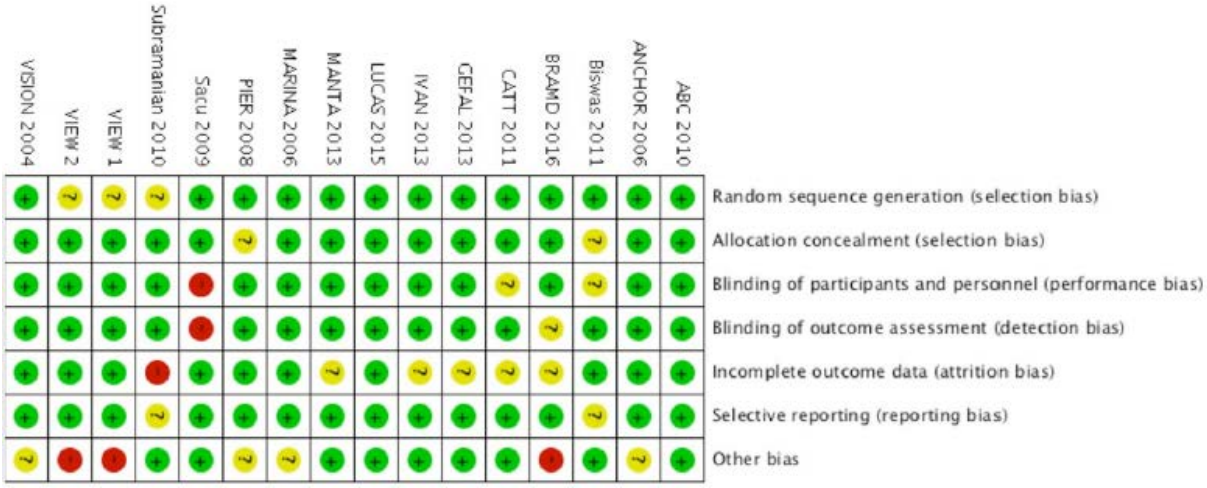


Abbildung 1: Risk of bias assessment of included studies. Low risk (+), Unclear risk (?), High risk (-)

Studienergebnisse:

Der Fokus der Ergebnisdarstellung liegt auf Vergleichen zu den im AWG zugelassenen Wirkstoffen.

Pegaptanib versus control

- The VISION 2004 study involved two RCTs. The mean difference in change in BCVA from baseline between the combined pegaptanib groups versus the control group was 6.72 letters (95% CI 4.43 to 9.01, P < 0.00001) at 1 year. Patients treated with pegaptanib lost 7 letters fewer than patients in the control group. CMT outcomes were not measured; two year outcomes were not analysed as the trial crossed over.
- Rates of systemic serious adverse events did not differ significantly between pegaptanib and control intervention at 1 year followup. Estimated relative risk ratio of at least 1 systemic serious adverse event for pegaptanib compared to control at 1 year was 1.25 (CI 0.93 to 1.70, P = 0.14).

Ranibizumab versus control

- The three trials involving 1322 patients demonstrated that patients treated with ranibizumab read 18 letters more at the 1 year follow up (weighted mean difference = 17.80, 95% CI 15.95 to 19.65, P < 0.00001, I2 = 0), and 20 letters more at the two-year follow up than patients in the control groups (weighted mean difference (WMD)= 20.11, 95% CI 18.08 to 22.15, P < 0.00001, I2 = 0). No data on CMT was available.
- Rates of death and arteriothrombotic events in ranibizumab and control groups did not differ significantly at 1 year or 2 years

Aflibercept versus ranibizumab

- Two trials comprising of 2412 patients treated with aflibercept and ranibizumab, demonstrated comparable gains in BCVA at 1 year follow up (WMD = − 0.15, 95% CI -1.47 to 1.16, P = 0.82, I^2 = 0).

- Similarly, aflibercept and ranibizumab demonstrated comparable reduction in CMT at 1 year follow up (WMD = − 4.94, 95% CI -15.48 to 5. 61, P = 0.36, I^2 = 0).
- The two-year efficacy outcomes were unable to be included in the metaanalysis as they were combined when reported. At two years the mean change in BCVA from baseline was 7.2 letters and 7.9 letters in the aflibercept and ranibizumab groups respectively, and this was not statistically significant. Data on outcomes for reduction in CMT at two years were not available.
- At 1 year follow up, there were no significant differences between aflibercept and ranibizumab in terms of rates of death, arteriothrombotic events, or venous thrombotic events. However, the numbers for these adverse events were small.
- Adverse event data from VIEW1 and VIEW2 trials were not available for analysis of two-year outcomes due to data from both studies being combined. Following two years, 3.3% (60/1824) of patients treated with aflibercept experienced an arteriothrombotic event compared to 3.2% (19/595) of patients treated with ranibizumab (RR 1.03, 95% CI 0.62 to 1.71). The risk of any serious systemic adverse event was similar between aflibercept and ranibizumab groups at two year follow-up (RR 0.98, 95% CI 0.83 to 1.15).

Anmerkung/Fazit der Autoren

The results of this review indicate effectiveness of anti- VEGF agents in terms of the stability or improvement in VA after 1 and 2 years of treatment. Bevacizumab and ranibizumab had equivalent efficacy for BCVA, while ranibizumab had greater reduction in CMT and less rate of serious systemic adverse events. Aflibercept and ranibizumab had comparable efficacy for BCVA and CMT. The available information on adverse effects with each drug does not suggest a higher incidence of vision-threatening complications with intravitreal anti-VEGF injection compared with control interventions.

Kommentare zum Review

This study conducted metaanalyses of results by anti-VEGF agent, combining different doses and regimens of the same agent evaluated in the individual trials. Studies in which different doses of one anti-VEGF agent were compared with each other, with no control or comparator were excluded. Studies in which anti-VEGF agents were used in combination with other treatments were excluded.

Gao Y et al., 2018 [2].

Anti-VEGF monotherapy versus photodynamic therapy and anti-VEGF combination treatment for neovascular age-related macular degeneration: a meta-analysis

Fragestellung

The purpose of this study was to compare the efficacy and safety of anti-VEGF monotherapy with verteporfin photodynamic therapy (PDT) and anti-VEGF combination treatment in neovascular AMD.

Methodik

Population:

- Patients with active CNV secondary to AMD

Intervention/Komparator:

- combined anti-VEGF therapy and PDT versus anti-VEGF monotherapy

Endpunkte:

- BCVA, central retinal thickness (CRT), number of anti-VEGF treatments, proportion of patients who gained ≥15 BCVA letters at end of the study

Recherche/Suchzeitraum:

- Literature published prior to July 2017 was searched in PubMed, Web of Science, and Cochrane Library databases

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias tool
- Subgroup analyses were performed based on the following factors: verteporfin PDT of different fluences in combination therapy (i.e., standard-fluence [SF] versus reduced-fluence [RF])

Ergebnisse

Anzahl eingeschlossener Studien:

- 16 studies (n=1260)

Charakteristika der Population:

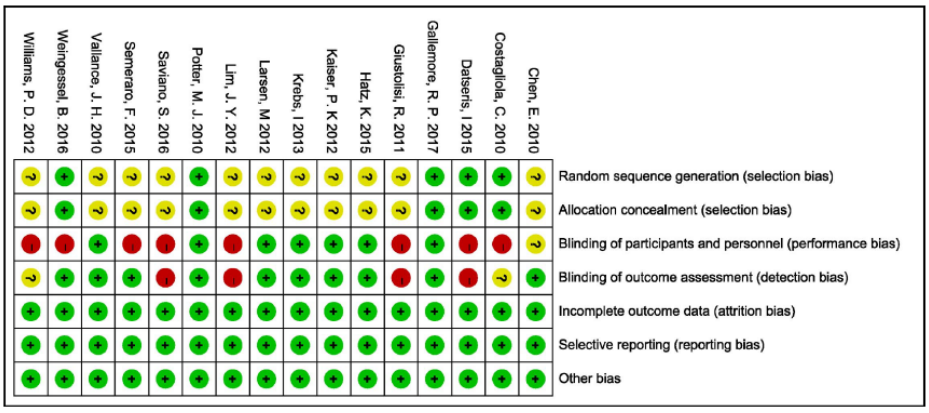
- Among the 16 studies, seven were conducted in Europe, four in the United States and three in Australia.
- The studies were divided into the anti-VEGF monotherapy group (587 patients) and PDT and anti-VEGF combination therapy group (673 patients).
- Thirteen trials were followed-up for 12 months, one trial was followed-up for 24 months, and two trials were followed-up for 6 months.
- Eleven studies compared ranibizumab monotherapy with ranibizumab + PDT combination treatment. Five studies compared bevacizumab monotherapy with bevacizumab + PDT combination therapy.

TABLE 1. The Characteristics of the Included Studies

First Author	Publication Year	Location	Previous CNV Treatment	Design	Follow-up, mo	Groups	Sample Size	Average Age, y
Larsen, M.	2012	Europe	Naive	Double-masked RCT	12	IVR(3+PRN)+sham PDT	133	75.5 ± 7.4
						IVR(3+PRN)+SF PDT	122	76.8 ± 7.7
Kaiser, P.K.	2012	USA	Naive	Double-masked RCT	12	IVR(3+PRN)+sham PDT	112	NR
						IVR(3+PRN)+SF PDT	104	NR
						IVR(3+PRN)+RF PDT	105	NR
Krebs, I.	2013	Austria	Naive	RCT	12	IVR(3+PRN)	24	77.71 ± 8.87
						IVR(3+PRN)+SF PDT	20	80.25 ± 6.32
Vallance, J.H.	2010	UK	Naive	Double-masked RCT	12	IVR(3+PRN)+sham PDT	9	NR
						IVR(3+PRN)+SF PDT	9	NR
Chen, E.	2010	USA	Naive	RCT	12	IVR(3+PRN)+sham PDT	2	76 ± 4.62
						IVR(3+PRN)+20% PDT	2	
						IVR(3+PRN)+40% PDT	3	
Williams, P.D.	2012	USA	Naive	RCT	12	IVR(3+PRN)	27	79.1
						IVR(3+PRN)+RF PDT	29	79.3
Gallemore, R.P.	2017	USA	Naive	RCT	24	IVR(3+PRN)	41	NR
						IVR(3+PRN)+RF PDT	43	NR
Hatz, K.	2015	Austria	No laser, intravitreal steroids or PDT within 30 d before enrollment	Double-masked RCT	12	IVR(3+PRN)	21	78
						IVR(3+PRN)+SF PDT	19	79
Lim, J.Y.	2012	Korea	No intravitreal triamcinolone or PDT within 90 d before enrollment	RCT	12	IVB(3+PRN)	13	NR
						IVB(3+PRN)+SF PDT	18	NR
Costagliola, C.	2010	Italy	Naive	RCT	12	IVB(1+PRN)	45	65.3 ± 15
						IVB(1+PRN)+RF PDT	40	63.2 ± 12
Datseris, I.	2015	Greece	Naive	RCT	12	IVB(1+PRN)	46	74 ± 10.3
						IVB(1+PRN)+RF PDT	49	73 ± 8.5
Saviano, S.	2016	Italy	No intravitreal anti-VEGF or PDT within 6 mo before enrollment	RCT	12	IVB(3+PRN)	31	79 ± 7.3
						IVB(1+PRN)+RF PDT	31	77 ± 7.8
Weingessel, B.	2016	Austria	Naive	RCT	12	IVR(3+PRN)	16	81.1 ± 7.9
						IVR(3+PRN)+SF PDT	14	83.3 ± 6.1
Semeraro, F.	2015	Italy	Naive	RCT	12	IVR(3+PRN)	25	77.2 ± 8.3
						IVR(3+PRN)+RF PDT	25	76.6 ± 6.2
Giustolisi, R.	2011	Italy	Naive	RCT	6	IVR(3+PRN)	30	70.57
						IVR(3+PRN)+SF PDT	17	71.24
Potter, M.J.	2010	Canada	Naive	Double-masked RCT	6	IVB(1+PRN)+sham PDT	12	80.6 ± 7.9
						IVB(1+PRN)+RF PDT	11	83.4 ± 6.9
						IVB(1+PRN)+25% PDT	12	78.3 ± 8.6

Monotherapy, group that received anti-VEGF treatment only; PDT (SF), PDT with SF; PDT (RF), PDT with RF; IVR, intravitreal ranibizumab; IVB, intravitreal bevacizumab; PRN, as needed; NR: not recorded.

Qualität der Studien:



Studienergebnisse:

Best Corrected Visual Acuity

- Seven studies reported the BCVA at baseline: The pooled result showed no statistical difference between the baseline BCVA of the two groups (WMD=-1.672, 95% CI: -3.959 to 0.735, P=0.178)

- Nine studies reported the BCVA at the end of the study: no statistical difference between the end-of-study BCVA of the two groups (WMD=1.928, 95% CI: -1.495 to 5.352, P=0.270).
- Monotherapy was associated with a higher ratio of patients who gained ≥15 BCVA letters as compared to combination treatment. However, the pooled result revealed no statistical difference between the two groups (RR =0.948, 95% CI: 0.890~1.009, P=0.095).

Central Retinal Thickness

- Twelve studies reported CRT at baseline: no statistical difference between the two groups (WMD=-5.209, 95% CI: -18.979 to 8.560, P=0.458)
- Thirteen studies reported the CRT at the end of the study: no significant difference between the end-of-study CRT of the two groups (WMD=2.906, 95% CI: -6.205 to 12.017, P = 0.532)

Number of Anti-VEGF Treatments

- The combination therapy group required fewer anti-VEGF treatments than the monotherapy group (WMD: 1.254; 95% CI: 0.111~2.397; P= 0.032).

Adverse Events

- Six studies reported adverse events at the end of the study. Overall, the incidence of serious adverse events (endophthalmitis, macular hole) was very low. Comparison of the number of ocular and nonocular adverse events revealed no significant difference between the two treatment groups.

Subgroup analyses

- In the combination therapy group, the intervention was 50 J/cm^2 standard-fluence (SF) PDT and anti-VEGF treatment in seven studies and was 25 J/cm^2 reduced-fluence (RF) PDT and anti-VEGF treatment in six studies. There was no obvious trend in the effects on BCVA at the end of the study based on fluence (SD PDT: WMD: 0.947, 95% CI: -3.855 to 5.749, P=0.699; RF PDT: WMD: 3.305, 95% CI: -11.390 to 18.000, P=0.659).
- CRT at end of the study was thinner in the SF PDT combination therapy group than in the monotherapy group (WMD: 17.229; 95% CI: 5.378~29.080; P = 0.004). The RF PDT combination therapy group required fewer anti-VEGF injections than the monotherapy group (WMD: 3.157; 95% CI: 1.275~5.041; P = 0.001), while the number of anti-VEGF treatments between the SF PDT combination therapy and monotherapy groups was not statistically different (WMD: 0.23; 95% CI: -0.016~0.475; P = 0.067).

Anmerkung/Fazit der Autoren

In conclusion, combination therapy with verteporfin PDT and anti-VEGF therapy is effective for achieving BCVA gain and CRT reduction compared with anti-VEGF monotherapy. Combination therapy with RF PDT has the potential to decrease the number of anti-VEGF injections, thereby reducing the overall treatment burden and serious adverse events associated with intravitreal injection. However, monotherapy is associated with a higher ratio of patients who gain ≥ 15 BCVA letters than does combination therapy, despite the lack of statistical difference.

Su Yet al., 2018 [14].

Photodynamic therapy in combination with ranibizumab versus ranibizumab monotherapy for wet age-related macular degeneration: a systematic review and meta-analysis

Fragestellung

To evaluate the efficacy and safety becween photodynamic therapy (PDT] combined with intravitreal ranibizumab (IVR) and ranibizumab monotherapy in treating wet age-related macular degeneration (AMD).

Methodik

Population:

- Patients with AMD diagnosed by professional ophthalmic examinations

Intervention/ Komperator:

- Photodynamic therapy in combination with ranibizumab versus ranibizumab monotherapy

Endpunkte:

primary outcomes

- BCVA, number of ranibizumab injections and central retinal thickness (CRT)

secondary outcomes

- lesion size of CNV, proportion of patients gaining ≥ 15 letters, proportion of patients losing ≥ 15 letters and ocular adverse events.

Recherche/Suchzeitraum:

- search was performed in the PubMed, Embase, Web of Science and the Cochrane Library databases through December 31, 2017.

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 RCTs included (n=922)

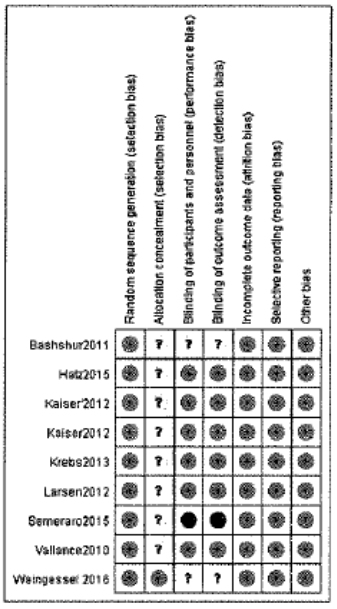
Charakteristika der Population:

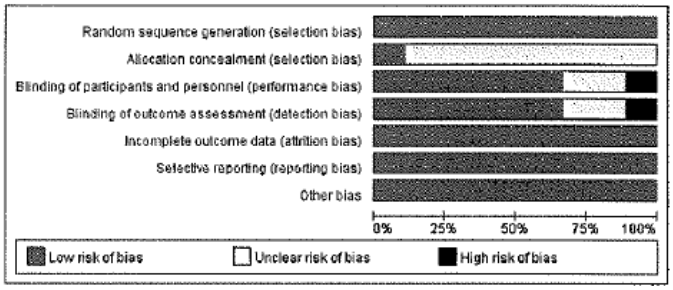
Characteristics of included studies.

Author	Publication year	Location	Eyes		Age(mean ± SD)		OCT	Major inclusion criteria	Major Exclusion criteria
			Combination therapy	Monotherapy	Combination therapy	Monotherapy			
Weingessel	2016	Austria	14	16	81.1 ± 7.9	83.3 ± 6.1	Spectralis OCT(Heidelberg Engineering, Heidelberg,Germany)	BCVA letter score of 73–24 letters; Lesion size of ≤ 5400 μm	Patients had received any prior treatment for AMD
Semeraro	2015	Multicenter(2 hospitals in Italy)	25;25	25	76.6 ± 6.2	77.2 ± 8.3	Spectralis OCT(Heidelberg Engineering, Heidelberg,Germany)	Presence of treatment-naïve neovascular AMD	Any previous intravitreal treatment or laser treatment
Hatz	2015	Austria	19	21	>50		Stratus OCT(Zeiss Meditec, Dublin, CA)	CNV occupying >50% of total lesion; BCVA score 23-73 leters	Laser photocoagulaton, intravitreal steroidsor verteporfin PDT in 30 days; History of intravitreal ant-VEGF treatment
Krebs	2013	Multicenter(3 hospitals in Austria)	24	24	80.25 ± 6.32	77.71 ± 8.87	Cirrus OCT(Zeiss, Dublin, CA,USA); Spectralis OCT(Heidelberger Ing, Heidelberg, Germany); Stratus OCT(Zeiss)	Area of CNV occupy at least 50% of the total lesion	BCVA < 33 letters (about 20 /200) in both eyes;History of eye surgery or drugs or eye treatment
Larsen	2012	Multicenter(45 centers in 12 European countries)	122	133	≥50		Stratus OCT(Carl Zeiss Meditec, Jena, Germany)	CNV occupying ≥50% of the total lesion; BCVA letter score of 73-24 letters	Patients had received prior treatment for neovascular AMD; Other pathological changes except CNV occupying ≤50% of the total lesion
Kaiser	2012	The United States,Canada	103;105	110	≥50		NA	BCVA letter score of 73-24 letters; Lesion size of ≤ 5400 μm; CNV occupying ≥50% of the total lesion	Prior treatmentfor neovascular AMD;
Bashshur	2011	Lebanon	20	20	71 ± 7.99	75.59 ± 6.25	Stratus OCT(Carl Zeiss Meditec, Dublin, CA)	BCVA of 20/50 to 20/400(Snellen equivalent); Lesion size of ≤ 5400 μm; CNV occupying ≥50% of the total lesion	Previous treatment for CNV Anti-VEGF treatment, or Verteporfin PDT
Vallance	2010	UK	9	9	NA		Stratus OCT(Zeiss Meditech, Jena, Germany)	BCVA letter score of 73-24 letters	Any previous CNV treatment

Qualität der Studien:

- The quality of five RCTs were high, of two RCTs moderate and of one low.
- The overall risk of bias is low

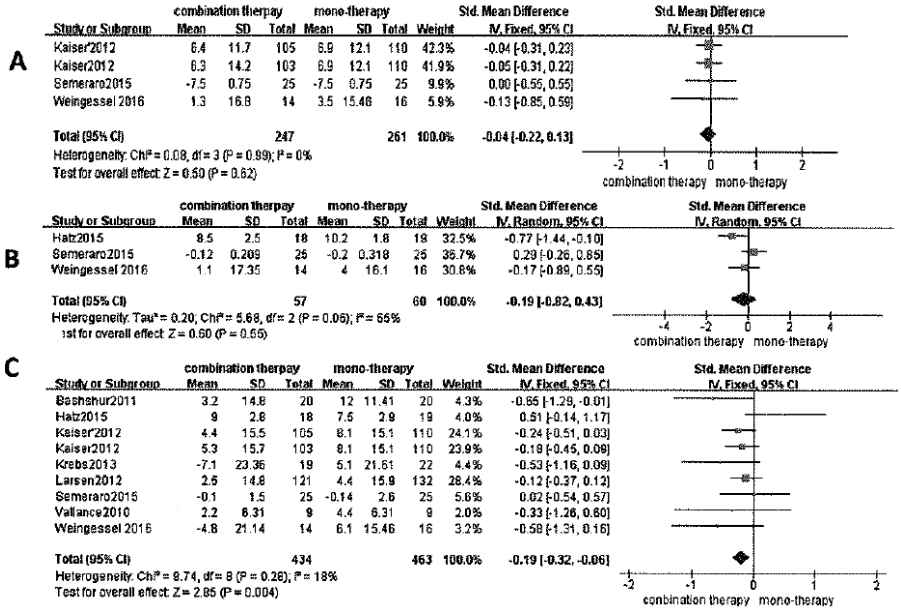




Studienergebnisse:

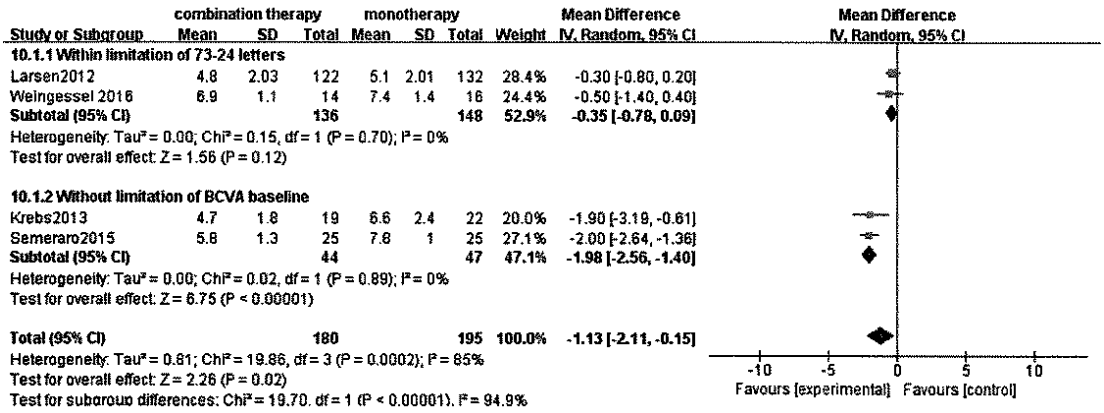
- No significant difference between combination therapy and monotherapy at month 3 and 6, but significant difference at month 12 (siehe Abbildung 1). This result suggested that ranibizumab monotherapy achieved better BCVA improvement than combination therapy as an AMD treatment.

Abbildung 1: Forest plot of standard mean difference in BCVA (logMAR was used in Semararo's study and ETDRS letters in the others). A: BCVA at month 3; B: BCVA at month 6; C: BCVA at month 12.



- The analysis showed a significant difference between the two groups in the proportion of patients gaining ≥ 15 letters (RR = 0.70, 95% CI: 0. 56-0.87; P = 0.001), showing that the proportion of patients gaining ≥ 15 letters in combination therapy was statistically smaller than those in the monotherapy group after 12 months.
- no significant difference between the two groups in proportion of patients loosing ≥ 15 letters (RR = 1.35, 95% CI: 0. 89-2.04, P= 0.16).
- no significant difference between the two groups in CRT (MD = 4.80, 95% CI: -6.28 to15.89, P = 0.40).
- The analysis showed no significant difference between the two groups in adverse events (RR = 1.12, 95% CI: 0.94-1.33, P=0. 22)
- significant difference between the two groups in the number of ranibizumab injections (MD= -1.13, 95% CI: -2.11 to -0.15, P = 0. 0002, I^2 = 85%). Subgroup analysis was conducted according to BCVA baseline (siehe Abbildung 2)

Abbildung 2: Forest plot of number of ranibizumab at month 12



Anmerkung/Fazit der Autoren

Although BCVA improvement in the combination group was inferior to that with ranibizumab alone at month 12 and the proportion of patients gaining more than 15 letters was less than that of the monogroup, PDT combined with ranibizumab could decrease the number of injections of ranibizumab, thus reducing the financla! burden and making it more convenient for patienis who could not be regularly followed up. We should consider individualized treatments according to patients specific conditions and different needs. There was no difference in adverse effects between the groups.

Kommentare zum Review

Our meta-analysis also had the following limitations 1) most studies failed to mention the method of allocation concealment, so the quality of these studies was moderate; 2) some studies did not mention the proportion of each type of CNV, and PDT was more suitable for the classical type, while anti-VEGF drugs were fit for all types; 3) no funnel plots could be drawn for the meta-analysis because there were only eight studies; 4) because there were only three RCTs measuring mean BCVA changes at month 6, we were not able to perform the subgroup analysis; 5) it would be better to include data for more years because wet AMD is a chronic disease, and therefore a longtherm perspective is needed; and 6) the types of OCT differed in the 8 RCTs, so there might be statistical errors in the CRT data.

Li S et al., 2017 [7].

Combinatorial treatment with topical NSAIDs and anti-VEGF for age-related macular degeneration, a meta-analysis

Fragestellung

In this study, we systematically reviewed clinical trials comparing combined treatment versus anti-VEGF alone in AMD patients.

Methodik

Population:

Patients: treated or naive wet AMD requiring anti-VEGF therapy

Intervention/Komparator:

- combined treatment with topical non-steroidal anti-inflammatory drugs (NSAIDs) and anti-VEGF versus anti-VEGF alone

Endpunkte:

- injection number of anti-VEGF, best corrected visual acuity (BCVA) at the end point, central retinal thickness (CRT) at the end point, adverse effects

Recherche/Suchzeitraum:

- A systematic literature review was performed to identify relevant articles comparing anti-VEGF agents combined with topical NSAIDS and anti-VEGF alone for the treatment of nAMD from inception to December 2016. Two independent reviewers searched electronic data-bases including PubMed, EMBASE and the Cochrane Central Register of Controlled Trials.

Qualitätsbewertung der Studien:

- Risk of bias of each included study was evaluated using the Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- six studies (n=278 patients), including two quasi-RCTs and four RCTs, were included in this meta-analysis.
- Follow up duration for all studies were between 6 months to 12 months.

Charakteristika der Population:

- n=142 in study group and n=136 in control group
- Of the 278 eyes, 172 (62%) in four trials received ranibizumab as the anti-VEGF agent, 54 eyes (19%) in one trial received aflibercept, and 52 eyes (19%) in another trial received bevacizumab as anti-VEGF agent.
- Bromfenac was used in four studies, including 89 eyes (63%). Ketorolac was employed in two trials, including 53 eyes (37%).

Table 1. Baseline characteristics of the included studies.

Study	Design	Country	Patients	No. of patients	Mean age	Anti-VEGF	NSAIDs	Follow-up	Outcomes
Flaxel et al., 2012 [10]	RCT	United States	New or recurrent exudative or neovascular AMD	20/10	85.5/ 77.5	Ranibizumab (4 +PRN)	Bromfenac (1 drop twice daily for 12 months)	12	BCVA, CRT
Gomi et al., 2012[8]	RCT	Japan	nAMD with lesions smaller than 2 disk diameters	16/22	75/ 74.4	Ranibizumab (1 +PRN)	Bromfenac (1 drop twice daily for 6 months)	6	CVA, CRT, No.of injection
Russo et al., 2013 [11]	RCT	Italy	New neovascular AMD	28/26	76/ 77.8	Ranibizumab (3 +PRN)	Ketorolac (1 drop three times a day for 6 months)	6	CVA, CRT, No.of injection
Wyględowska-Promieńska et al., 2014[12]	Quasi-RCT	Poland	Exudative AMD	26/26	72.4/ 72.3	Bevacizumab (3+PRN)	Bromfenac (1 drop twice daily for 3 months)	8	CVA, CRT, No.of injection
Semeraro et al., 2015[13]	RCT	Italy	Naïve eyes affected by neovascular AMD	25/25	76.3/ 77.2	Ranibizumab (3 +PRN)	Ketorolac (1 drop three times a day for 12 months)	12	CVA, CRT, No.of injection
Wyględowska-Promieńska et al., 2015[14]	Quasi-RCT	Poland	Exudative AMD	27/27	72.3/ 72.8	Aflibercept (4 +PRN)	Bromfenac (1 drop twice daily for 3 months)	8	BCVA, CRT

Qualität der Studien:

Table 2. Assessment of risk of bias of the included studies.

Domain	Flaxel et al. 2012	Gomi et al. 2012	Russo et al. 2013	Wyględowska-Promieńska et al., 2014	Semeraro et al. 2015	Wyględowska-Promieńska et al. 2015
Random sequence generation	Low risk	Low risk	Low risk	High risk	Low risk	High risk
Allocation concealment	Unclear	Unclear	Unclear	High risk	Unclear	High risk
Blinding for visual acuity						
Participants and personnel	High risk	Low risk	High risk	High risk	High risk	High risk
Outcome assessment	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Blinding for other outcomes						
Participants and personnel	High risk	Low risk	High risk	High risk	High risk	High risk
Outcome assessment	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Incomplete outcome data	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Selective reporting	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Other bias	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Studienergebnisse:

- Four studies compared the mean injection numbers between treatment and control group. Pooling results showed that combined topical NSAIDs with anti-VEGF was associated with fewer anti-VEGF injections (Fig 2A).
- Subgroup studies were assessed according to type of topical NSAID, anti-VEGF, and duration of follow-up (Fig 2B). Regardless of anti-VEGF agent used, combined treatment decreased the number of anti-VEGF treatments required. This trend is more significant with follow-up duration greater than 6 months. However, only bromfenec demonstrated a statistically-significant reduction of anti-VEGF injection number.

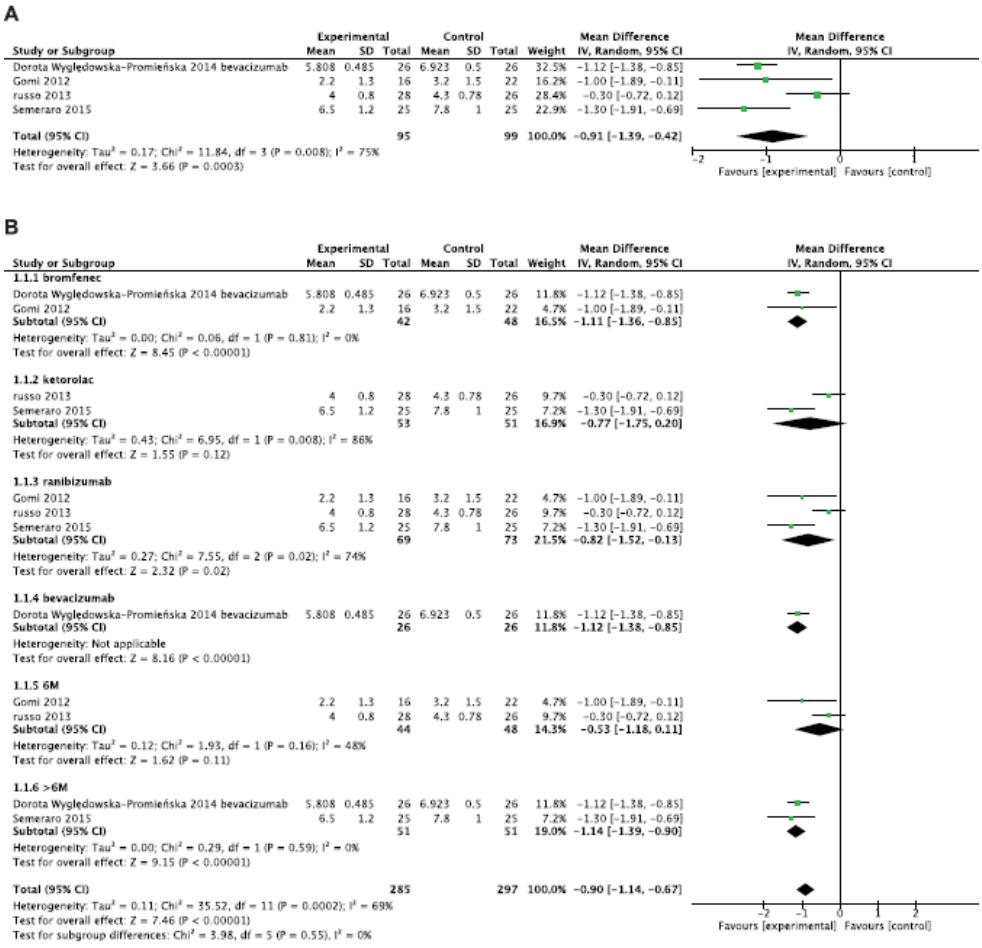


Fig 2. Forest plot showing the weighted mean difference of required anti-VEGF injections, comparing combined treatment and anti-VEGF alone. A. Pooled data computed using the random effects model. B. Data was grouped by type of NSAIDs (bromfenac and ketorolac), type of anti-VEGF (ranibizumab and bevacizumab) and follow-up duration (6 months and greater than 6 months).

- The mean BCVA (logMAR) at final followup in the combined treatment group and anti-VEGF alone group were not statistically significant.
- subgroup analysis: The BCVAs from two quasi-RCTs were strongly different from other studies in the forest plot. Therefore, the two quasi-RCTs were excluded from the analysis owing to differences in study design. After removing quasi-RCTs, the heterogeneity decreased but yet failed to detect significant change.
- A grouping was also examined with respect to follow-up duration. This also failed to show any difference between the two groups.
- Combining topical NSAIDs with anti-VEGF may reduce the CRT significantly (followed up from 6 months to 12 months), with WMD of -22.9, 95% CI: -41.20 to -4.59, P = 0.01 (Fig 4).

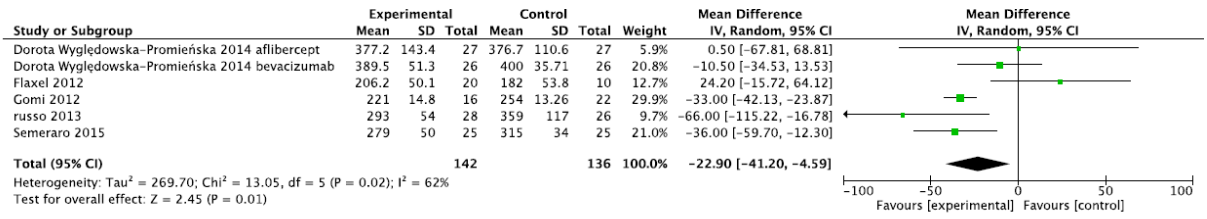


Fig 4. Forest plot showing weighted mean difference of CRT comparing combined treatment and anti-VEGF alone using the random effects model.

- Adverse events (3 RCTs on ranibizumab): only foreign body sensation significantly increased with topical NSAIDs (odds ratio [OR] =2.63, 95%CI: 1.06 to 6.52, P = 0.76, I^2 = 0%).

Anmerkung/Fazit der Autoren

Combining topical NSAIDs with intravitreal anti-VEGF results in a small but statistically significant reduction in required anti-VEGF injections and central retinal thickness. BCVA was not improved significantly. No additional side effects were observed apart from foreign body sensation. Combining topical NSAIDs and anti-VEGF agents may serve as a new strategy in AMD treatment.

Kommentare zum Review

- all included studies have **small number of participants**, lowering the power of the analysis.
- Two of the included studies are **quasi-RCTs**, which do not have a trusted randomization process. In this analysis, we used a sensitivity test and found that excluding any study did not affect the final result.

Ye L et al., 2020 [15].

Comparative efficacy and safety of anti-vascular endothelial growth factor regimens for neovascular age-related macular degeneration: systematic review and Bayesian network meta-analysis

Fragestellung

To provide substantial evidence for clinical nAMD treatment, this study ranks the priority of anti-VEGF regimens via Bayesian network meta-analysis (NMA), comparing data collected from randomized controlled trials (RCTs).

Methodik

Population:

- Adults (≥50 years) were treatment-naive patients with a primary diagnosis of nAMD, whose baseline BCVA was generally better than 20/500 (Snellen equivalent) assessed using Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity charts

Intervention:

- Pegaptanib every 6 weeks, ranibizumab monthly, ranibizumab quarterly, ranibizumab pro re nata (PRN), ranibizumab treat-and- extend regimen, bevacizumab monthly, bevacizumab PRN, bevacizumab treat-and-extend regimen, aflibercept monthly, aflibercept bimonthly, aflibercept treat-and-extend regimen, conbercept monthly, conbercept PRN, conbercept quarterly, brolucizumab bimonthly, brolucizumab quarterly, and PDT monotherapy.

Komparator:

- Sham or active comparator

Endpunkte:

- proportion of patients gaining 15 (three ETDRS lines or 0.3 logMAR) or more letters, and the incidence of arterial thromboembolic (ATC) events as our primary efficacy and safety outcomes, respectively, from baseline to month 12. ATC events involve non-fatal myocardial infarction, non-fatal stroke, or death from a vascular cause and including any death from an unknown cause because most deaths in high-risk patients are likely to be due to vascular causes
- Secondary efficacy outcomes comprised mean change in BCVA from baseline to 12 months, the change in anatomical measurements from baseline to 12 months, including reductions in central retinal thickness (CRT) measured using optical coherence tomography (OCT) and mean change in area of CNV based on fluorescein angiography (FA).
- In addition, secondary safety outcomes represented by the incidence of severe ocular adverse events (SOAEs) such as endophthalmitis, traumatic cataract, retinal detachment, and vitreous hemorrhage, from baseline to 12 months were recorded.
- The end point for evaluation of the previously mentioned outcomes was 54 weeks after first treatment.

Recherche/Suchzeitraum:

- PubMed Central, MEDLINE Ovid, Embase Ovid, ISRCTN, ICTRP and ClinicalTrials. gov from a database established until 1 April 2019

Qualitätsbewertung der Studien:

- Cochranes risk of bias tool
- Inconsistency between direct and indirect sources of evidence was statistically assessed by globally and locally (by computing difference between direct and indirect estimates in each closed loop in the network).

Ergebnisse

Anzahl eingeschlossener Studien:

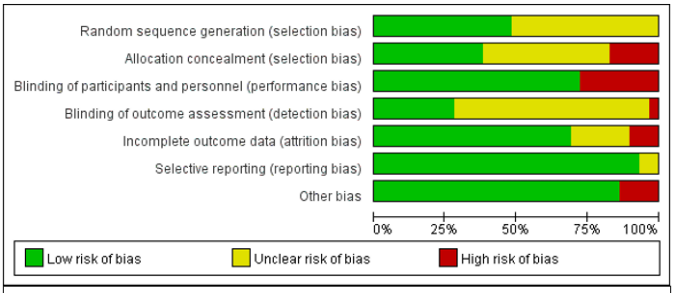
- 29 RCTs including 13,596 participants

Charakteristika der Population:

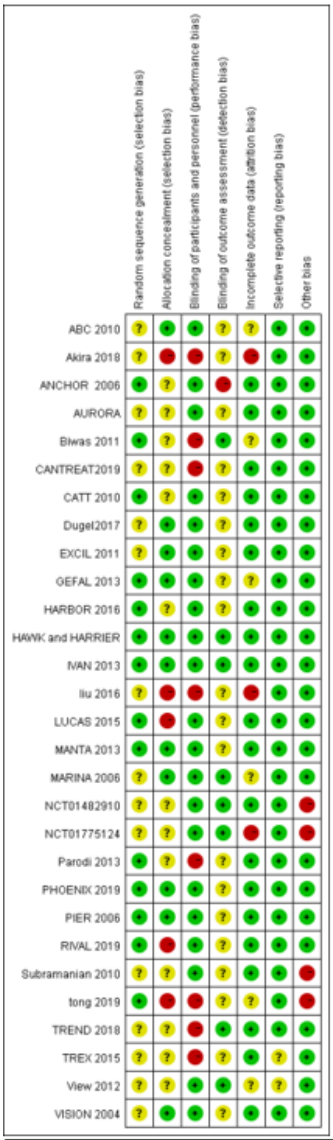
- A total of 18 multicenter RCTs recruited patients from the US or Europe. Six studies (20%) contained participants of predominantly Mongolian race, whereas the rest had mostly Caucasian patients.
- Regarding participants, the included records recruited 13,596 patients (mean age 74 years) and 56% (n = 7679) were female.
- The median baseline BCVA across studies was 56.7 letters [interquartile range (IQR) = 52.5–60.6]. Female proportion (p = 0.99), baseline BCVA (p = 0.98), and mean age (p = 0.99) were similar across included trials.
- Participants with polypoidal choroidal vasculopathy (PCV) were involved in 17 trials.
- These studies covered PDT and 15 different regimens for six anti-VEGF drugs.
- Of 153 possible comparisons between included treatments, 24 were compared directly in the identified studies.

Qualität der Studien:

- As for overall risk of bias, 86% of these trials were rated as low risk or uncertain risk bias.
- The percentage of studies with high risk of bias for each individual domain was: 17.2% for allocation concealment, 27% for blinding of participants and personnel, 10.7% for blinding of outcome assessment, and 7% for missing information.



Risk of bias graph: it is a plot of the distribution of judgments (Yes, No, Unclear) across studies for each risk of bias entry



Risk of bias summary: it is a summary table of review authors' judgments for each risk of bias entriy for each study

Studienergebnisse:

Pairwise meta-analysis:

- No significant differences were found between aflibercept and ranibizumab or aflibercept and brolucizumab in terms of primary efficacy outcome (proportions of patients with gain of three or more BCVA lines)

Tabelle 1: Pairwise meta–analysis of primary outcomes

a. sham VS active		15letters						ATC events					
comparisons		I^2	τ^2	OR	LL	UL	p	I^2	τ^2	OR	LL	UL	p
sham	PDT	-	-	0.77	0.04	13.41	0.85	-	-	-	-	-	-
sham	pegaq6w	0.00	0.00	**2.67**	**1.17**	**6.09**	**0.02**	-	-	1.00	0.50	2.01	1.00
sham	raniM	-	-	**5.81**	**3.16**	**10.69**	**0.00**	-	-	1.20	0.56	2.54	0.64
sham	raniQ	-	-	1.30	0.48	3.52	0.60	-	-	-	-	-	-
sham	conberQ	-	-	1.44	0.56	3.70	0.45	-	-	0.53	0.03	8.70	0.66
b.active VS active		**15letters**						**15letters**					
PDT	pegaq6w	-	-	0.90	0.08	10.55	0.93	-	-	-	-	-	-
PDT	raniM	-	-	**6.79**	**3.22**	**14.33**	**0.00**	-	-	-	-	-	-
PDT	bevaP	-	-	5.58	0.70	44.48	0.11	-	-	-	-	-	-
PDT	aflibB	-	-	-	-	-	-	-	-	0.33	0.05	2.41	0.28
pegaq6w	bevaP	-	-	**6.23**	**1.38**	**28.08**	**0.02**	-	-	1.19	0.21	6.79	0.85
raniM	raniQ	-	-	**0.56**	**0.33**	**0.93**	**0.03**	-	-	0.73	0.12	4.40	0.73
raniM	raniP	0.00	0.00	1.19	0.98	1.45	0.08	0.00	0.00	1.20	0.70	2.06	0.51
raniM	raniTE	0.00	0.00	1.08	0.84	1.39	0.54	0.00	0.00	0.78	0.29	2.06	0.61
raniM	bevaM	0.24	0.01	1.23	0.94	1.61	0.14	-	-	1.19	0.21	6.79	0.85
raniM	bevaP	-	-	1.22	0.86	1.72	0.26	-	-	0.73	0.12	4.40	0.73
raniM	aflibM	-	-	0.94	0.77	1.14	0.52	0.00	0.00	1.20	0.70	2.06	0.51
raniM	aflibB	-	-	0.96	0.77	1.21	0.75	0.00	0.00	0.78	0.29	2.06	0.61
raniP	bevaM	-	-	0.80	0.56	1.14	0.21	-	-	0.93	0.30	2.92	0.90
raniP	bevaP	0.00	0.00	0.95	0.75	1.20	0.67	0.00	0.00	0.86	0.44	1.70	0.67
raniP	conberP	-	-	-	-	-	-	-	-	-	-	-	-
raniTE	bevaTE	-	-	0.94	0.61	1.47	0.79	-	-	0.30	0.08	1.11	0.07
raniTE	aflibTE	-	-	1.10	0.61	1.97	0.76	-	-	0.98	0.24	3.99	0.98
bevaM	bevaP	-	-	1.12	0.78	1.59	0.54	-	-	0.77	0.26	2.24	0.63
aflibM	aflibB	-	-	1.02	0.83	1.24	0.86	-	-	0.61	0.36	1.01	0.05
aflibB	aflibTE	-	-	0.95	0.31	2.89	0.93	-	-	-	-	-	-
aflibB	broliB	-	-	-	-	-	-	-	-	0.40	0.07	2.17	0.29
aflibB	broliQ	-	-	1.10	0.88	1.36	0.40	-	-	1.59	0.86	2.94	0.14

Note. Effect-sizes pooled using a random-effects model. Pegaq6w= pegaptanib every 6 weeks. raniM=ranibizumab Monthly. raniQ=ranibizumab Quarterly. raniP=ranibizumab PRN. raniTE=ranibizumab treat-and-extend regimen. bevaM=bevacizumab Monthly. bevaP=bevacizumab PRN. bevaTE=bevacizumab treat-and-extend regimen. aflibM=aflibercept Monthly. afflibB=aflibercept Bimonthly. aflibTE=aflibercept treat-and-extend regimen. conberM=conbercept Monthly. conberP=conbercept PRN. conberQ=conbercept Quarterly. broliB=brolucizumab Bimonthly broliQ=brolucizumab Quarterly

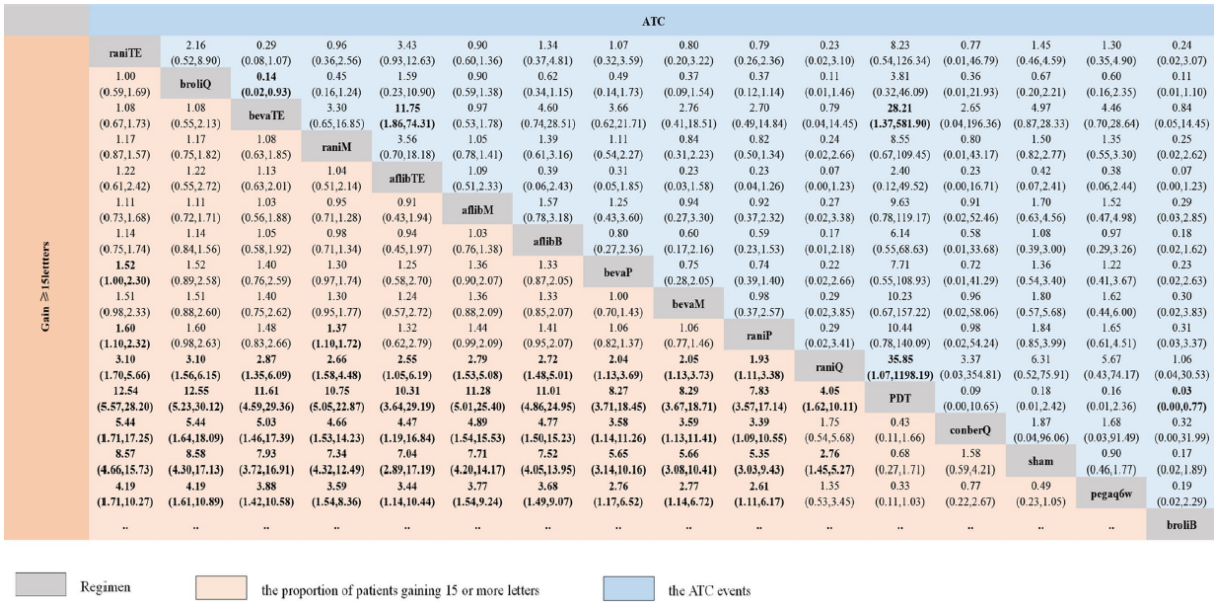
Tabelle 2: Pairwise meta–analysis of secondary outcomes

a. sham VS active		BCVA change						CRT change						CNV change						SOAE events					
comparisons		I^2	τ^2	SMD	LL	UL	p	I^2	τ^2	SMD	LL	UL	p	I^2	τ^2	SMD	LL	UL	p	I^2	τ^2	OR	LL	UL	p
sham	PDT	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
sham	pegaq6w	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	15.34	0.94	#####	0.06
sham	raniM	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1.65	0.46	5.93	0.45
sham	raniQ	-	-	**0.82**	**0.45**	**1.19**	**0.00**	-	-	-	-	-	-	-	-	**0.79**	**0.48**	**1.11**	**0.00**	-	-	-	-	-	-
sham	conberQ	-	-	0.09	-0.28	0.46	0.65	-	-	-	-	-	-	-	-	**0.44**	**0.07**	**0.81**	**0.02**	-	-	0.54	0.03	8.79	0.66
b.active VS active		**15letters**						**15letters**						**15letters**						**15letters**					
PDT	pegaq6w	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PDT	raniM	-	-	**1.25**	**0.99**	**1.50**	**0.00**	-	-	-	-	-	-	-	-	**0.86**	**1.07**	**0.65**	**0.00**	-	-	2.05	0.23	18.51	0.52
PDT	bevaP	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PDT	aflibB	-	-	**0.79**	**0.52**	**1.06**	**0.00**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1.00	0.04	24.91	1.00
pegaq6w	bevaP	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.40	0.06	2.48	0.32
raniM	raniQ	-	-	**0.31**	**0.09**	**0.54**	**0.01**	-	-	0.04	-0.18	0.26	0.72	-	-	-0.06	-0.28	0.16	0.60	-	-	3.39	0.17	66.18	0.66
raniM	raniP	0.00	0.00	**0.12**	**0.03**	**0.21**	**0.01**	0.05	0.00	-0.06	-0.15	0.03	0.20	0.00	0.00	**-0.19**	**-0.29**	**-0.10**	**0.00**	0.00	0.00	3.67	0.60	22.36	0.16
raniM	raniTE	0.64	0.02	0.78	0.29	2.06	0.61	-	-	-0.01	-0.16	0.15	0.92	-	-	-	-	-	-	-	-	0.61	0.14	2.56	0.50
raniM	bevaM	-	-	0.03	-0.13	0.20	0.70	-	-	**-0.18**	**-0.35**	**-0.01**	**0.04**	-	-	-0.05	-0.22	0.12	0.55	-	-	0.47	0.09	2.57	0.38
raniM	bevaP	-	-	**0.17**	**0.01**	**0.34**	**0.04**	-	-	**-0.25**	**-0.42**	**-0.08**	**0.00**	-	-	-0.22	-0.38	-0.05	0.01	-	-	4.77	0.23	99.84	0.31
raniM	aflibM	-	-	0.02	-0.07	0.12	0.63	-	-	0.03	-0.07	0.13	0.52	-	-	0.05	-0.04	0.15	0.28	-	-	3.46	0.18	67.07	0.41
raniM	aflibB	-	-	0.00	-0.10	0.10	1.00	-	-	0.00	-0.11	0.12	0.96	-	-	0.02	-0.09	0.13	0.75	-	-	6.92	0.36	#####	0.20
raniP	bevaM	-	-	-	-	-	-	-	-	-0.02	-0.19	0.15	0.80	-	-	0.05	-0.12	0.21	0.60	-	-	-	-	-	-
raniP	bevaP	0.02	0.00	-0.02	-0.13	0.09	0.68	0.19	0.00	-0.10	-0.20	0.01	0.07	0.00	0.00	-0.07	-0.20	0.06	0.28	0.00	0.00	1.49	0.24	9.19	0.67
raniP	conberP	-	-	-0.02	-0.41	0.38	0.94	0.60	0.11	-0.39	-0.98	0.19	0.19	-	-	-	-	-	-	-	-	-	-	-	-
raniTE	bevaTE	-	-	-0.02	-0.23	0.18	0.82	-	-	0.09	-0.15	0.32	0.47	-	-	-	-	-	-	-	-	7.03	0.36	#####	0.20
raniTE	aflibTE	-	-	0.14	-0.10	0.37	0.25	-	-	-0.08	-0.28	0.12	0.45	-	-	-	-	-	-	-	-	0.98	0.24	3.99	0.98
bevaM	bevaP	-	-	0.13	-0.04	0.30	0.14	-	-	-0.07	-0.24	0.10	0.44	-	-	-0.18	-0.3‹	-0.01	0.04	-	-	4.11	0.46	36.97	0.21
aflibM	aflibB	-	-	0.02	-0.07	0.12	0.63	-	-	0.03	-0.07	0.13	0.56	-	-	-0.03	-0.13	0.07	0.54	-	-	0.50	0.10	2.48	0.39
aflibB	aflibTE	-	-	-	-	-	-	-	-	-0.04	-0.65	0.58	0.91	-	-	-	-	-	-	-	-	-	-	-	-
aflibB	broliB	-	-	0.05	-0.36	0.46	0.81	-	-	-0.06	-0.47	0.35	0.78	-	-	-	-	-	-	-	-	0.47	0.10	2.35	0.36
aflibB	broliQ	-	-	0.02	-0.09	0.12	0.78	-	-	**0.31**	**0.41**	**0.20**	**0.00**	-	-	-	-	-	-	-	-	**-0.01**	**0.00**	**-0.04**	**0.00**

Note. Effect-sizes pooled using a random-effects model. Pegaq6w= pegaptanib every 6 weeks. raniM=ranibizumab Monthly. raniQ=ranibizumab Quarterly. raniP=ranibizumab PRN. raniTE=ranibizumab treat-and-extend regimen. bevaM=bevacizumab Monthly. bevaP=bevacizumab PRN. bevaTE=bevacizumab treat-and-extend regimen. aflibM=aflibercept Monthly. afflibB=aflibercept Bimonthly. aflibTE=aflibercept treat-and-extend regimen. conberM=conbercept Monthly. conberP=conbercept PRN. conberQ=conbercept Quarterly. broliB=brolucizumab Bimonthly broliQ=brolucizumab Quarterly

Network meta-analysis

- Figure 2 presents the results of the NMA for the primary outcome of efficacy (the proportion of patients gaining 15 or more BCVA letters) and safety (incidence of ATC events).



Gain ≥15letters \ ATC	raniTE	broliQ	bevaTE	raniM	aflibTE	aflibM	aflibB	bevaP	bevaM	raniP	raniQ	PDT	conberQ	sham	pegaq6w	broliB
raniTE		2.16 (0.52,8.90)	0.29 (0.08,1.07)	0.96 (0.36,2.56)	3.43 (0.93,12.63)	0.90 (0.60,1.36)	1.34 (0.37,4.81)	1.07 (0.32,3.59)	0.80 (0.20,3.22)	0.79 (0.26,2.36)	0.23 (0.02,3.10)	8.23 (0.54,126.34)	0.77 (0.01,46.79)	1.45 (0.46,4.59)	1.30 (0.35,4.90)	0.24 (0.02,3.07)
broliQ	1.00 (0.59,1.69)		**0.14 (0.02,0.93)**	0.45 (0.16,1.24)	1.59 (0.23,10.90)	0.90 (0.59,1.38)	0.62 (0.34,1.15)	0.49 (0.14,1.73)	0.37 (0.09,1.54)	0.37 (0.12,1.14)	0.11 (0.01,1.46)	3.81 (0.32,46.09)	0.36 (0.01,21.93)	0.67 (0.20,2.21)	0.60 (0.16,2.35)	0.11 (0.01,1.10)
bevaTE	1.08 (0.67,1.73)	1.08 (0.55,2.13)		3.30 (0.65,16.85)	**11.75 (1.86,74.31)**	0.97 (0.53,1.78)	4.60 (0.74,28.51)	3.66 (0.62,21.71)	2.76 (0.41,18.51)	2.70 (0.49,14.84)	0.79 (0.04,14.45)	**28.21 (1.37,581.90)**	2.65 (0.04,196.36)	4.97 (0.87,28.33)	4.46 (0.70,28.64)	0.84 (0.05,14.45)
raniM	1.17 (0.87,1.57)	1.17 (0.75,1.82)	1.08 (0.63,1.85)		3.56 (0.70,18.18)	1.05 (0.78,1.41)	1.39 (0.61,3.16)	1.11 (0.54,2.27)	0.84 (0.31,2.23)	0.82 (0.50,1.34)	0.24 (0.02,2.66)	8.55 (0.67,109.45)	0.80 (0.01,43.17)	1.50 (0.82,2.77)	1.35 (0.55,3.30)	0.25 (0.02,2.62)
aflibTE	1.22 (0.61,2.42)	1.22 (0.55,2.72)	1.13 (0.63,2.01)	1.04 (0.51,2.14)		1.09 (0.51,2.33)	0.39 (0.06,2.43)	0.31 (0.05,1.85)	0.23 (0.03,1.58)	0.23 (0.04,1.26)	0.07 (0.00,1.23)	2.40 (0.12,49.52)	0.23 (0.00,16.71)	0.42 (0.07,2.41)	0.38 (0.06,2.44)	0.07 (0.00,1.23)
aflibM	1.11 (0.73,1.68)	1.11 (0.72,1.71)	1.03 (0.56,1.88)	0.95 (0.71,1.28)	0.91 (0.43,1.94)		1.57 (0.78,3.18)	1.25 (0.43,3.60)	0.94 (0.27,3.30)	0.92 (0.37,2.32)	0.27 (0.02,3.38)	9.63 (0.78,119.17)	0.91 (0.02,52.46)	1.70 (0.63,4.56)	1.52 (0.47,4.98)	0.29 (0.03,2.85)
aflibB	1.14 (0.75,1.74)	1.14 (0.84,1.56)	1.05 (0.58,1.92)	0.98 (0.71,1.34)	0.94 (0.45,1.97)	1.03 (0.76,1.38)		0.80 (0.27,2.36)	0.60 (0.17,2.16)	0.59 (0.23,1.53)	0.17 (0.01,2.18)	6.14 (0.55,68.63)	0.58 (0.01,33.68)	1.08 (0.39,3.00)	0.97 (0.29,3.26)	0.18 (0.02,1.62)
bevaP	**1.52 (1.00,2.30)**	1.52 (0.89,2.58)	1.40 (0.76,2.59)	1.30 (0.97,1.74)	1.25 (0.58,2.70)	1.36 (0.90,2.07)	1.33 (0.87,2.05)		0.75 (0.28,2.05)	0.74 (0.39,1.40)	0.22 (0.02,2.66)	7.71 (0.55,108.93)	0.72 (0.01,41.29)	1.36 (0.54,3.40)	1.22 (0.41,3.67)	0.23 (0.02,2.63)
bevaM	1.51 (0.98,2.33)	1.51 (0.88,2.60)	1.40 (0.75,2.62)	1.30 (0.95,1.77)	1.24 (0.57,2.72)	1.36 (0.88,2.09)	1.33 (0.85,2.07)	1.00 (0.70,1.43)		0.98 (0.37,2.57)	0.29 (0.02,3.85)	10.23 (0.67,157.22)	0.96 (0.02,58.06)	1.80 (0.57,5.68)	1.62 (0.44,6.00)	0.30 (0.02,3.83)
raniP	**1.60 (1.10,2.32)**	1.60 (0.98,2.63)	1.48 (0.83,2.66)	**1.37 (1.10,1.72)**	1.32 (0.62,2.79)	1.44 (0.99,2.09)	1.41 (0.95,2.07)	1.06 (0.82,1.37)	1.06 (0.77,1.46)		0.29 (0.02,3.41)	10.44 (0.78,140.09)	0.98 (0.02,54.24)	1.84 (0.85,3.99)	1.65 (0.61,4.51)	0.31 (0.03,3.37)
raniQ	**3.10 (1.70,5.66)**	**3.10 (1.56,6.15)**	**2.87 (1.35,6.09)**	**2.66 (1.58,4.48)**	**2.55 (1.05,6.19)**	**2.79 (1.53,5.08)**	**2.72 (1.48,5.01)**	**2.04 (1.13,3.69)**	**2.05 (1.13,3.73)**	**1.93 (1.11,3.38)**		**35.85 (1.07,1198.19)**	3.37 (0.03,354.81)	6.31 (0.52,75.91)	5.67 (0.43,74.17)	1.06 (0.04,30.53)
PDT	**12.54 (5.57,28.20)**	**12.55 (5.23,30.12)**	**11.61 (4.59,29.36)**	**10.75 (5.05,22.87)**	**10.31 (3.64,29.19)**	**11.28 (5.01,25.40)**	**11.01 (4.86,24.95)**	**8.27 (3.71,18.45)**	**8.29 (3.67,18.71)**	**7.83 (3.57,17.14)**	**4.05 (1.62,10.11)**		0.09 (0.00,10.65)	0.18 (0.01,2.42)	0.16 (0.01,2.36)	**0.03 (0.00,0.77)**
conberQ	**5.44 (1.71,17.25)**	**5.44 (1.64,18.09)**	**5.03 (1.46,17.39)**	**4.66 (1.53,14.23)**	**4.47 (1.19,16.84)**	**4.89 (1.54,15.53)**	**4.77 (1.50,15.23)**	**3.58 (1.14,11.26)**	**3.59 (1.13,11.41)**	**3.39 (1.09,10.55)**	1.75 (0.54,5.68)	0.43 (0.11,1.66)		1.87 (0.04,96.06)	1.68 (0.03,91.49)	0.32 (0.00,31.99)
sham	**8.57 (4.66,15.73)**	**8.58 (4.30,17.13)**	**7.93 (3.72,16.91)**	**7.34 (4.32,12.49)**	**7.04 (2.89,17.19)**	**7.71 (4.20,14.17)**	**7.52 (4.05,13.95)**	**5.65 (3.14,10.16)**	**5.66 (3.08,10.41)**	**5.35 (3.03,9.43)**	**2.76 (1.45,5.27)**	0.68 (0.27,1.71)	1.58 (0.59,4.21)		0.90 (0.46,1.77)	0.17 (0.02,1.89)
pegaq6w	**4.19 (1.71,10.27)**	**4.19 (1.61,10.89)**	**3.88 (1.42,10.58)**	**3.59 (1.54,8.36)**	**3.44 (1.14,10.44)**	**3.77 (1.54,9.24)**	**3.68 (1.49,9.07)**	**2.76 (1.17,6.52)**	**2.77 (1.14,6.72)**	**2.61 (1.11,6.17)**	1.35 (0.53,3.45)	0.33 (0.11,1.03)	0.77 (0.22,2.67)	0.49 (0.23,1.05)		0.19 (0.02,2.29)
broliB	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	

Figure 2. Network meta-analysis of primary efficacy and safety outcomes.
Regimens are reported in order of patients' proportion gaining 15 or more letters ranking according to SUCRAs. Summary OR and 95% CrI for categorical outcomes to estimate the treatment effect size.
afflibB, aflibercept Bimonthly; aflibM, aflibercept Monthly; aflibTE, aflibercept treat-and-extend regimen; ATC, arterial thromboembolic; bevaM, bevacizumab Monthly; bevaP, bevacizumab PRN; bevaTE, bevacizumab treat-and-extend regimen; broliB, brolucizumab Bimonthly; broliQ, brolucizumab Quarterly; conberM, conbercept Monthly; conberP, conbercept PRN; conberQ, conbercept Quarterly; CrI, credible intervals; OR, odds ratio; Pegaq6w, pegaptanib every 6 weeks; raniM, ranibizumab Monthly; raniP, ranibizumab PRN; raniQ, ranibizumab Quarterly; raniTE, ranibizumab treat-and-extend regimen; SUCRA, surface under the cumulative ranking curve.

- The primary outcome of efficacy results contains 105 treatment arms made up of 51 data points (Figure 3).

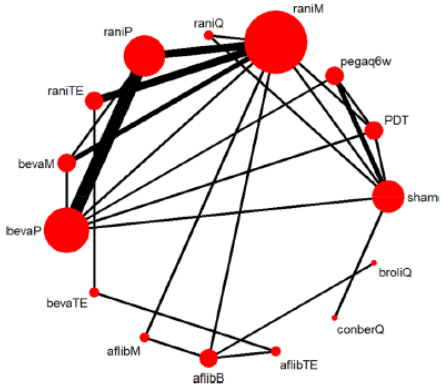


Figure 3. Network plot of available treatment comparisons for primary efficacy outcome.
Size of node represent the number of patients randomized to each regimen. Line width represent the number of RCTs comparing each pair of regimens directly.
afflibB, aflibercept Bimonthly; aflibM, aflibercept Monthly; aflibTE, aflibercept treat-and-extend regimen; bevaM, bevacizumab Monthly; bevaP, bevacizumab PRN; bevaTE, bevacizumab treat-and-extend regimen; broliQ, brolucizumab Quarterly; conberQ, conbercept Quarterly; Pegaq6w, pegaptanib every 6 weeks; raniM, ranibizumab Monthly; raniP, ranibizumab PRN; raniQ, ranibizumab Quarterly; raniTE, ranibizumab treat-and-extend regimen; RCT, randomized controlled trial.

- The highest probability of being most efficacious in terms of primary efficacy outcome was the ranibizumab treat-and-extend regimen (SUCRA 86.7%), whereas pegaptanib every 6 weeks (SUCRA 3.2%) was lowest (s.Tab. 3).

Tabelle 3: The proportion of patients gaining 15 or more letters

treatments	SUCRA(%)	meanrank
sham	6.7	14.1
PDT	19.7	12.2
pegaq6w	3.2	14.6
raniM	74.3	4.6
raniQ	26.7	11.3
raniP	44.8	8.7
raniTE	86.7	2.9
bevaM	51.7	7.8
bevaP	51.9	7.7
bevaTE	77.4	4.2
aflibM	70.9	5.1
aflibB	68.1	5.5
aflibTE	71.2	5
conberQ	17.5	12.6
broliQ	79.5	3.9

* Larger SUCRAs denote more effective regimens.

- A total of 18 studies with 11,500 participants reported usable data concerning the primary outcome of safety results (incidence of ATC events), with 120 treatment arms containing 16 regimens available (Figure 3).
- With respect to ranking probabilities, the bevacizumab treat-andextend regimen (SUCRA 87.5%) had the highest mean ranks (lowest incidence of ATC) (s. Tab.4).

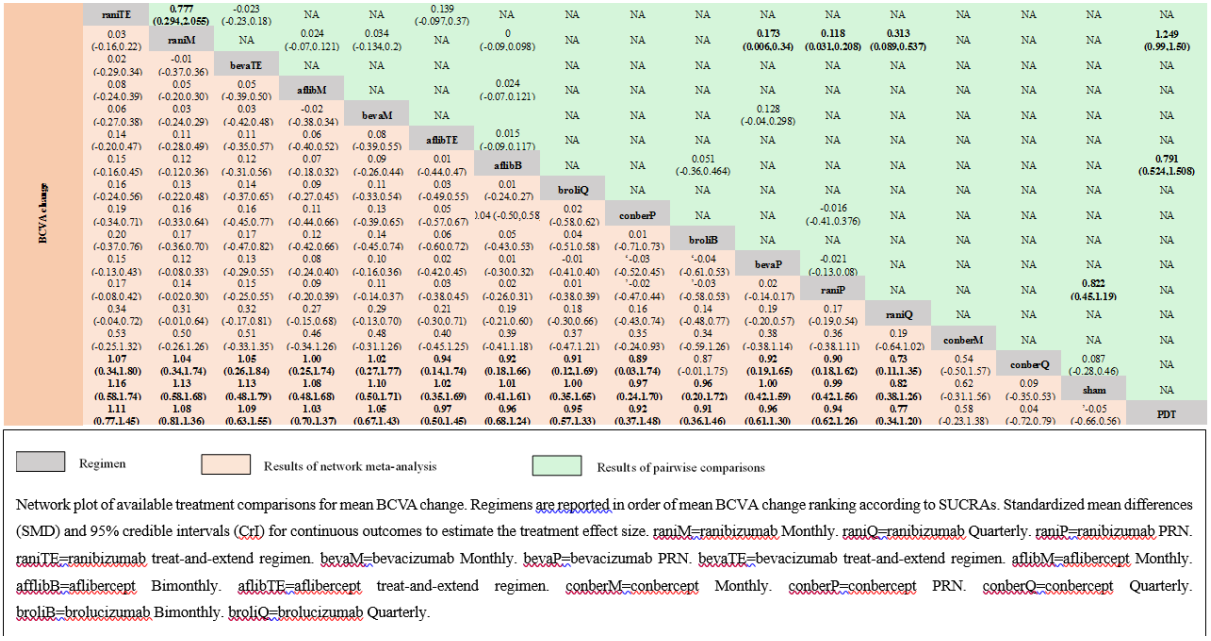
The results of network meta-analysis for secondary outcomes

Tabelle 4: The incidence of Arterial thromboembolic events

treatments	SUCRA(%)	meanrank
sham	59	7.2
PDT	11.3	14.3
pegaq6w	58	7.3
raniM	45.1	9.2
raniQ	55.6	7.7
raniP	61.5	6.8
raniTE	47.4	8.9
bevaM	39.7	10
bevaP	51.6	8.3
bevaTE	87.5	2.9
aflibM	64.8	6.3
aflibB	23.9	12.4
aflibTE	47.1	8.9
conberQ	68.4	5.7
broliB	66.3	6.1
broliQ	12.7	14.1

* Larger SUCRAs denote safer regimens.

- A total of 10,588 participants from 22 studies presented usable mean BCVA change data.
- Compared with sham injection, the SMDs for 13 regimens were associated with significant BCVA improvement.



Network plot of available treatment comparisons for mean BCVA change. Regimens are reported in order of mean BCVA change ranking according to SUCRAs. Standardized mean differences (SMD) and 95% credible intervals (CrI) for continuous outcomes to estimate the treatment effect size. raniM=ranibizumab Monthly. raniQ=ranibizumab Quarterly. raniP=ranibizumab PRN. raniTE=ranibizumab treat-and-extend regimen. bevaM=bevacizumab Monthly. bevaP=bevacizumab PRN. bevaTE=bevacizumab treat-and-extend regimen. aflibM=aflibercept Monthly. afflibB=aflibercept Bimonthly. aflibTE=aflibercept treat-and-extend regimen. conberM=conbercept Monthly. conberP=conbercept PRN. conberQ=conbercept Quarterly. broliB=brolucizumab Bimonthly. broliQ=brolucizumab Quarterly.

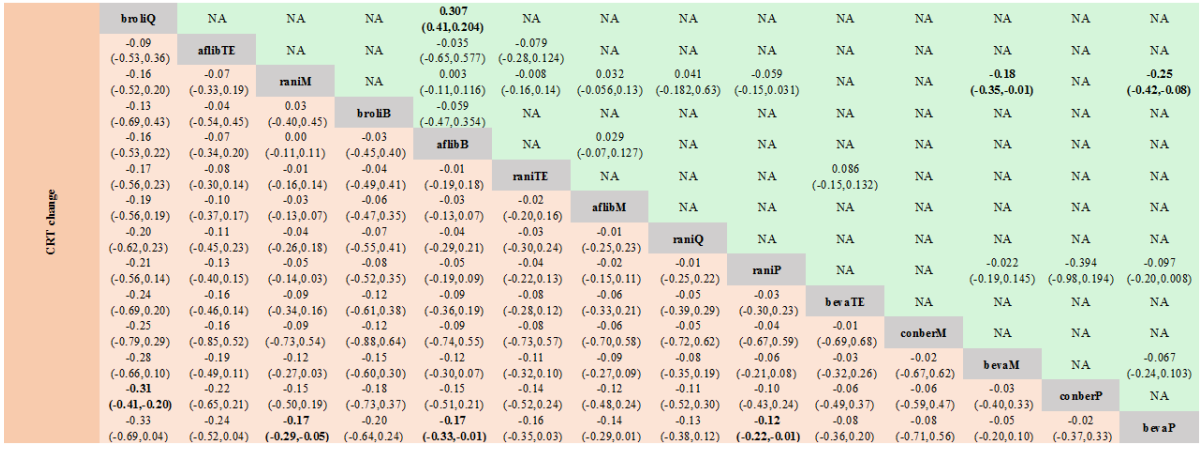
- Based on SUCRA plots, the ranibizumab treat-and-extend regimen (SUCRA 77.7%) had the highest mean ranks, whereas the conbercept quarterly regimen (SUCRA 11.8%) and PDT (SUCRA 5.3%) had the lowest ranks (s. Tab.5).

Tabelle 5: mean change in BCVA

treatments	SUCRA(%)	meanrank
sham	7.7	15.8
PDT	5.3	16.1
raniM	77.7	4.6
raniQ	47.3	9.4
raniP	50.7	8.9
raniTE	80.7	4.1
bevaM	66.3	6.4
bevaP	51.9	8.7
bevaTE	73.3	5.3
aflibM	68.4	6.1
aflibB	57.2	7.9
aflibTE	59.4	7.5
conberQ	11.8	15.1
conberM	29.6	12.3
conberP	53.6	8.4
broliB	53.4	8.5
broliQ	56	8

* Larger SUCRAs denote more BCVA change regimens.

- A total of 18 studies with 9223 participants presented data of mean CRT change. A brolucizumab quarterly regimen significantly reduced CRT compared with a conbercept PRN regimen (SMD –0.31, 95% CrI –0.41 to –0.20).



Network plot of available treatment comparisons for mean CRT change. Regimens are reported in order of mean CRT change ranking according to SUCRAs. Standardized mean differences (SMD) and 95% credible intervals (CrI) for continuous outcomes to estimate the treatment effect size. raniM=ranibizumab Monthly. raniQ=ranibizumab Quarterly. raniP=ranibizumab PRN. raniTE=ranibizumab treat-and-extend regimen. bevaM=bevacizumab Monthly. bevaP=bevacizumab PRN. bevaTE=bevacizumab treat-and-extend regimen. aflibM=aflibercept Monthly. afflibB=aflibercept Bimonthly. aflibTE=aflibercept treat-and-extend regimen. conberM=conbercept Monthly. conberP=conbercept PRN. conberQ=conbercept Quarterly. broliB=brolucizumab Bimonthly. broliQ=brolucizumab Quarterly.

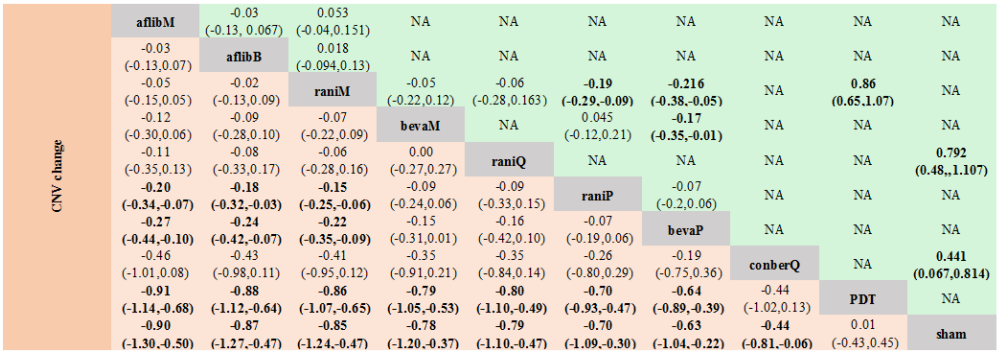
- Brolucizumab quarterly (SUCRA 75.1%) had the highest mean ranks (s. Tab. 5).

Tabelle 6: mean change in CRT

treatments	SUCRA(%)	meanrank
raniM	63.2	5.8
raniQ	51.8	7.3
raniP	47.9	7.8
raniTE	57.3	6.6
bevaM	33	9.7
bevaP	20.5	11.3
bevaTE	40.6	8.7
aflibM	53.4	7.1
aflibB	61.1	6.1
aflibTE	70	4.9
conberM	39.8	8.8
conberP	25	10.8
broliB	61.2	6
broliQ	75.1	4.2

* Larger SUCRAs denote more CRT change regimens.

- Only 8 studies with 6117 participants reported usable result for mean change in CNV area. The SMDs for the eight (80%) anti-VEGF regimens that significantly reduced CNV area ranged from –0.90 (95% CrI –1.30 to –0.50) for aflibercept monthly to –0.44 (–0.81 to –0.06) to a conbercept quarterly regimen.



Network plot of available treatment comparisons for mean CNV change. Regimens are reported in order of mean CNV change ranking according to SUCRAs. Standardized mean differences (SMD) and 95% credible intervals (CrI) for continuous outcomes to estimate the treatment effect size. raniM=ranibizumab Monthly. raniQ=ranibizumab Quarterly. raniP=ranibizumab PRN. bevaM=bevacizumab Monthly. bevaP=bevacizumab PRN. aflibM=aflibercept Monthly. afflibB=aflibercept Bimonthly. conberQ=conbercept Quarterly.

- Aflibercept monthly regimen (SUCRA 81.6%) had the highest mean ranks, whereas conbercept quarterly regimen (SUCRA 34%) and PDT (SUCRA 8.9%) had the lowest ranks (s. Tab 6).

Tabelle 7: mean change in CNV

treatments	SUCRA(%)	meanrank
sham	74.5	3.3
PDT	9	9.2
raniM	9	9.2
raniQ	63	4.3
raniP	48.3	5.7
bevaM	64.2	4.2
bevaP	40.5	6.4
aflibM	80.9	2.7
aflibB	75.5	3.2
conbetrQ	35	6.8

* Larger SUCRAs denote more CRT change regimens.

- A total of 11,500 participants from 17 trials reported usable result for the rates of SOAEs. No significant difference was found between active regimens or sham injection.
- The findings of SUCRA for the SOAEs are presented in Tab. 8.

Tabelle 8: incidence of SOAEs

treatments	SUCRA(%)	meanrank
sham	76.2	4.6
PDT	75.1	4.7
pegaq6w	40.4	9.9
raniM	57.6	7.4
raniQ	58.6	7.2
raniP	54.9	7.8
raniTE	66.4	6
bevaM	33.7	11
bevaP	69.1	5.6
bevaTE	33.4	11
aflibM	32.8	11.1
aflibB	23.7	12.4
aflibTE	64.4	6.3
conbetrQ	73.2	5
broliB	30.1	11.5
broliQ	10.4	14.4

* Larger SUCRAs denote more CRT change regimens.

Efficacy versus safety in network analysis

- A clustered ranking plot for both primary efficacy and safety results indicated that the higher frequency injection regimens were better for efficacy and worse for safety, as most of them lay in the lower right corner. Among included anti-VEGF regimens, the bevacizumab treat-and-extend regimen was the most efficacious and safest regimen in this analysis (Figure 4).

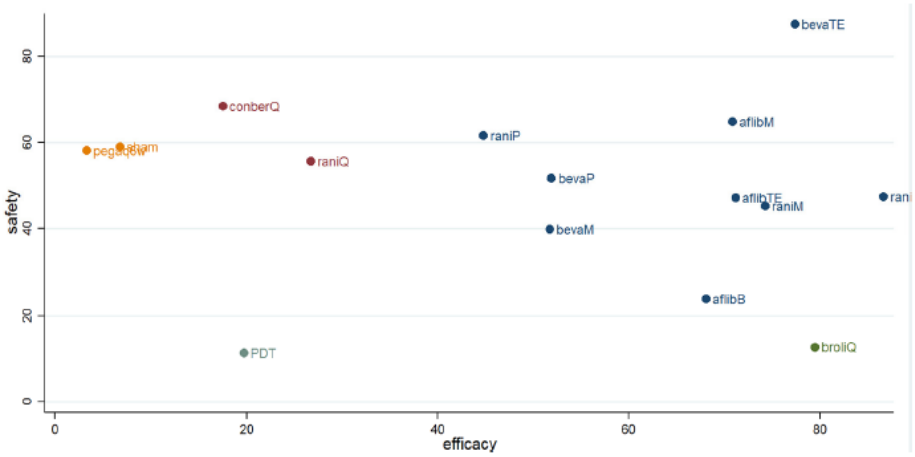


Figure 4. Clustered ranking plot of nAMD regimens network based on primary efficacy and safety outcomes. Each color represents a group of regimens that belong to the same cluster. Regimens lying in the upper right corner are more effective and acceptable than the other regimens.
afflibB, aflibercept Bimonthly; aflibM, aflibercept Monthly; aflibTE, aflibercept treat-and-extend regimen; bevaM, bevacizumab Monthly; bevaP, bevacizumab PRN; bevaTE, bevacizumab treat-and-extend regimen; broliQ, brolucizumab Quarterly; conberQ, conbercept Quarterly; nAMD, neovascular age-related macular degeneration; Pegaq6w, pegaptanib every 6weeks; raniM, ranibizumab Monthly; raniP, ranibizumab PRN; raniQ, ranibizumab Quarterly; raniTE, ranibizumab treat-and-extend regimen.

- Results for the primary outcome did not substantially change in sensitivity analyses after removing studies at high risk of bias and small sample size (n < 100), respectively.

Inconsistency

- The test of global inconsistency did not detect any evidence of statistically significant inconsistency for primary and secondary outcomes (global inconsistency: p = 0.2–0.63).
- No publication bias was found in comparison adjusted funnel plots of the NMA for any outcome

Anmerkung/Fazit der Autoren

This comprehensive Bayesian NMA provides substantial evidence for the clinical application of anti-VEGF drug regimens for nAMD. The treat-and- extend regimen of ranibizumab and aflibercept are the preferred anti-VEGF regimens for nAMD. The bevacizumab treat-and-extend regimen needs more head-to-head comparisons with other regimens or sham injection for advanced application. The treat-and-extend regimen proved to be the most effective for all the anti-VEGF drugs in this NMA. Pegaptanib every 6 weeks and Conbercept quarterly are unable to satisfy the BCVA improvement required by nAMD patients.

Kommentare zum Review

NMA: Annahme der Transitivität wurde nicht überprüft und diskutiert.

3.4 Leitlinien

National Institute for Health and Care Excellence, 2018 [9].

NICE Guideline NG82

Methods, evidence and recommendations

January 2018

Age-related macular degeneration: diagnosis and management

Leitlinienorganisation/Fragestellung

1) What is the effectiveness of different antiangiogenic therapies (including photodynamic therapy) for the treatment of late AMD (wet active)?
2) What is the effectiveness of adjunctive therapies for the treatment of late AMD (wet active)?

Methodik

Grundlage der Leitlinie

This guideline covers diagnosing and managing age-related macular degeneration (AMD) in adults. It aims to improve the speed at which people are diagnosed and treated to prevent loss of sight. This guidance replaces NICE technology appraisal guidance on the use of photodynamic therapy for age-related macular degeneration (TA68).

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

Recherche/Suchzeitraum:

- The search undertaken by the Cochrane group on photodynamic therapy (PDT) for AMD up to 2005. We also conducted an additional update search on PDT. The search undertaken by the Cochrane group on anti-vascular endothelial growth factor (anti-VEGF) treatment for neovascular AMD up to 2015. An update search carried out near the end of guideline development identified 2 further studies including.

LoE/GoR

- The risk of bias of included RCTs was assessed using the **Cochrane risk of bias tool**.
- **GRADE** was used to assess the quality of evidence for the selected outcomes as specified in 'Developing NICE guidelines' (2014). A modified version of the standard GRADE approach for pairwise interventions was used to assess the quality of evidence across the network meta-analyses undertaken.

Table 2: Rationale for downgrading evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	The quality of the evidence was downgraded if there were concerns about factors including the design or execution of the study, including concealment of allocation, blinding and loss to follow up. This was based on intervention checklists in the NICE guidelines manual (2012).
Inconsistency	The quality of the evidence was downgraded if there were concerns about inconsistency of effects across studies: occurring when there is variability in the treatment effect demonstrated across studies (heterogeneity). This was assessed using visual inspection and the statistic, I^2 where; $I^2 < 50\%$ was categorised as no inconsistency, $I^2 \geq 50\%$ was categorised as serious inconsistency, and $I^2 \geq 50\%$ plus obvious additional heterogeneity on visual inspection categorised as very serious inconsistency.
Indirectness	The quality of the evidence was downgraded if there were concerns about the population, intervention, comparator and outcome in the included studies and how directly these variables could address the specific review question.
Imprecision	If MIDs (one corresponding to meaningful benefit; one corresponding to meaningful harm) were defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one MID, and twice if it crosses both MIDs. If an MID was not defined for the outcomes, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant).

Strength of recommendation

Interventions that must (or must not) be used

We usually use ‘must’ or ‘must not’ only if there is a legal duty to apply the recommendation. Occasionally we use ‘must’ (or ‘must not’) if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions that should (or should not) be used – a ‘strong’ recommendation

We use ‘offer’ (and similar words such as ‘refer’ or ‘advise’) when we are confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. We use similar forms of words (for example, ‘Do not offer…’) when we are confident that an intervention will not be of benefit for most patients.

Interventions that could be used

We use ‘consider’ when we are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient’s values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Zu Fragestellung 1:

Four studies on photodynamic therapy (PDT) for AMD, one study comparing PDT and anti-vascular endothelial growth factor, twelve studies on bevacizumab and/or ranibizumab and two studies for aflibercept met the study inclusion criteria and were included in the review. The update search identified two further studies: one RCT compared the effectiveness of bevacizumab and ranibizumab treatment and one study compared vision-related function between people who received aflibercept and ranibizumab injection.

Siehe Anhang: Abbildung 1

Zu Fragestellung 2:

A total of 17 RCTs were included in the review – twelve with ranibizumab as the anti-VEGF used and five with bevacizumab. Fourteen studies compared anti-VEGF monotherapy with anti-VEGF + PDT, two compared anti-VEGF monotherapy with anti-VEGF + steroids and one compared anti-VEGF + PDT with anti-VEGF + PDT + steroids. An update search carried out near the end of guideline development identified further one study.

Siehe Anhang: Abbildung 2

Zu Fragestellung 1:

Empfehlungen Antiangiogenic therapies

Empfehlung 21:

Offer intravitreal anti-vascular endothelial growth factor (VEGF) treatment[2] for late AMD (wet active) for eyes with visual acuity within the range specified in recommendation 26.

Empfehlung 22:

Be aware that no clinically significant differences in effectiveness and safety between the different anti-VEGF treatments[3] have been seen in the trials considered by the guideline committee.

Empfehlung 23:

In eyes with visual acuity of 6/96 or worse, consider anti-VEGF treatment for late AMD (wet active) only if a benefit in the person's overall visual function is expected (for example, if the affected eye is the person's better-seeing eye).

Empfehlung 24:

Be aware that anti-VEGF treatment for eyes with late AMD (wet active) and visual acuity better than 6/12 is clinically effective and may be cost effective depending on the regimen used.[4,5]

Empfehlung 25:

Do not offer photodynamic therapy alone for late AMD (wet active). Recommendations from NICE technology appraisals

[2] At the time of publication (January 2018), bevacizumab did not have a UK marketing authorisation for, and is considered by the Medicines and Healthcare products Regulatory Agency (MHRA) to be an unlicensed medication in, this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the prescribing decision. Informed consent would need to be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines, and the MHRA's guidance on the supply of unlicensed medicinal products ("specials"), for further information. The guideline may inform any decision on the use of bevacizumab outside its UK marketing authorisation but does not amount to an approval of or a recommendation for such use.

[3] Given the guideline committee's view that there is equivalent clinical effectiveness and safety of different anti-VEGF agents (aflibercept, bevacizumab and ranibizumab), comparable regimens will be more cost effective if the agent has lower net acquisition, administration and monitoring costs.

[4] At the time of publication (January 2018), bevacizumab did not have a UK marketing authorisation for, and is considered by the Medicines and Healthcare products Regulatory Agency (MHRA) to be an unlicensed medication in, this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the prescribing decision. Informed consent would need to be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines,, and the MHRA's guidance on the supply of unlicensed medicinal products ("specials"), for further information. The guideline may inform any decision on the use of bevacizumab outside its UK marketing authorisation but does not amount to an approval of or a recommendation for such use.

[5] Given the guideline committee's view that there is equivalent clinical effectiveness and safety of different anti-VEGF agents (aflibercept, bevacizumab and ranibizumab), comparable regimens will be more cost effective if the agent has lower net acquisition, administration and monitoring costs.

Empfehlung 26:

Ranibizumab, within its marketing authorisation, is recommended as an option for the treatment of wet age-related macular degeneration if:

- all of the following circumstances apply in the eye to be treated:
  - the best-corrected visual acuity is between 6/12 and 6/96
  - there is no permanent structural damage to the central fovea
  - the lesion size is less than or equal to 12 disc areas in greatest linear dimension
  - there is evidence of recent presumed disease progression (blood vessel growth, as indicated by fluorescein angiography, or recent visual acuity changes)

and

- the manufacturer provides ranibizumab with the discount agreed in the patient access scheme (as revised in 2012). [This recommendation is from Ranibizumab and pegaptanib for the treatment of age-related macular degeneration (NICE technology appraisal guidance 155).]

Empfehlung 27:

Pegaptanib is not recommended for the treatment of wet age-related macular degeneration.

Empfehlung 28:

People who are currently receiving pegaptanib for any lesion type should have the option to continue therapy until they and their clinicians consider it appropriate to stop. [This recommendation is from Ranibizumab and pegaptanib for the treatment of age-related macular degeneration (NICE technology appraisal guidance 155).]

Empfehlung 29.:

Aflibercept solution for injection is recommended as an option for treating wet age−related macular degeneration only if:

- it is used in accordance with the recommendations for ranibizumab NICE technology appraisal guidance 155 (re−issued in May 2012 [see recommendation 26]) and
- the manufacturer provides aflibercept solution for injection with the discount agreed in the patient access scheme. [This recommendation is from Aflibercept solution for injection for treating wet age−related macular degeneration (NICE technology appraisal guidance 294).]

Empfehlung 30:

People currently receiving aflibercept solution for injection whose disease does not meet the criteria in recommendation 29 should be able to continue treatment until they and their clinician consider it appropriate to stop. [This recommendation is from Aflibercept solution for injection for treating wet age−related macular degeneration (NICE technology appraisal guidance 294).]

Hintergrundinfos:

Siehe Anhang: Abbildung 3, Abbildung 4, Abbildung 5, Abbildung 6

Zu Fragestellung 2:

Empfehlungen Adjunctive therapies

Empfehlung 31:

Do not offer photodynamic therapy as an adjunct to anti-VEGF as first-line treatment for late AMD (wet active).

Empfehlung 32:

Only offer photodynamic therapy as an adjunct to anti-VEGF as second-line treatment for late AMD (wet active) in the context of a randomised controlled trial.

Empfehlung 33:

Do not offer intravitreal corticosteroids as an adjunct to anti-VEGF for late AMD (wet active).

Hintergrundinfos:
siehe Anhang: Abbildung 7, Abbildung 8, Abbildung 9

Anmerkung:

There are currently licensed treatments for wet AMD and a treatment **(bevacizumab**) which has been used to treat AMD despite not having a marketing authorisation for such use. It is clear that, without authorisation in the product's SPC, **the use of bevacizumab in AMD is off-label**. NICE has previously performed technology appraisals, which are incorporated in this guideline, on the licensed anti-VEGF agents. These recommend **aflibercept and ranibizumab** for late AMD (wet active), and commissioners in England and Wales are bound to fund them as a result. **For this guideline**, the committee has considered the published evidence on clinical effectiveness and cost effectiveness of **all treatments for late AMD (wet active), regardless of license status.**

American Academy of Ophthalmology, 2019 [1].

Age-Related Macular Degeneration

Leitlinienorganisation/Fragestellung

American Academy of Ophthalmology entwickelte eine "Preferred Practice Pattern Guideline"

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

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium unklar, kein Patientenvertreter;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Keine Informationen zu formale Konsensusprozesse;

- Externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Literature searches to update the PPP were undertaken in March 2018 and June 2019 in PubMed and the Cochrane Library

LoE/GoR

- 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

- All studies used to form a recommendation for care are graded for strength of evidence individually, and that grade is listed with the study citation.
- 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)

- 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

Empfehlungen

Neovaskuläre AMD (nAMD)

Anti-VEGF therapies have become first-line therapy for treating and stabilizing most cases of neovascular AMD and a Cochrane systematic review demonstrates the effectiveness of these agents to maintain visual acuity.[167] *(I+, Good quality, Strong recommendation)*

Hintergrundinformation:

With the introduction of the VEGF inhibitors pegaptanib sodium (Macugen®, Eyetech, Inc., Cedar Knolls, NJ) in 2004, off-label bevacizumab (Avastin®, Genentech, Inc., South San Francisco, CA) in 2005, ranibizumab (Lucentis®, Genentech, Inc., South San Francisco, CA) in 2006, and aflibercept (Eylea™, Regeneron Pharmaceuticals, Inc., Tarrytown, NY) in

2011, more effective treatments for neovascular AMD exist. The VEGF inhibitors have demonstrated improved visual and anatomic outcomes compared with other therapies.

Aflibercept is a pan–VEGF-A and placental growth factor (PGF) blocker approved by the US Food and Drug Administration (FDA) that has been documented to be of similar efficacy to ranibizumab in the head-to-head phase III VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW) trials.[168] In these pivotal studies, the currently approved 2-mg dose of aflibercept was administered by intravitreal injection every 4 weeks and every 8 weeks after three monthly loading doses. In the first year, both study arms were similar to 0.5- mg ranibizumab dosed every 4 weeks.

Bevacizumab is a full-length monoclonal antibody that binds all isoforms of VEGF. It is FDA approved for intravenous use in the treatment of metastatic colorectal, metastatic breast, and non-small cell lung cancer. Bevacizumab was investigated first as a systemic intravenous treatment for AMD and then as an intravitreal injection (1.25 mg) before the FDA approved ranibizumab.[169,170] Because preliminary reports appeared favorable, ophthalmologists began to use intravitreal bevacizumab off-label to treat CNV. Comparative trials and uncontrolled case series reported improvements in VA and decreased retinal thickness by optical coherence tomography (OCT) following intravitreal bevacizumab treatment.[171-177] Informed consent information is available on the benefits and risks of intravitreal bevacizumab and its off-label status.[178]

Intravitreal **ranibizumab** (0.5 mg) is FDA approved for the treatment of all subtypes of neovascular AMD, based on results from three double-masked, randomized controlled trials.[179,180] (siehe Anhang Abbildung 10.) Ranibizumab is a recombinant, humanized immunoglobulin G1 kappa isotype therapeutic antibody fragment developed for intraocular use. Ranibizumab binds to and inhibits the biologic activity of all isoforms of human VEGF-A.

The Comparison of AMD Treatment Trials (CATT) was a multicenter clinical trial that compared the safety and effectiveness of bevacizumab with ranibizumab and an individualized dosing regimen (as needed, or PRN) with monthly injections. At 1 year, the CATT study found that ranibizumab and bevacizumab had comparable equivalence VA improvements for monthly dosing.[174] Ranibizumab PRN had similar VA improvements compared with a fixed schedule of monthly injections. Further follow-up at 2 years showed that the two drugs remained comparable in both efficacy and safety, but the PRN arms together did not perform as well in terms of maintaining the visual gains at the end of year 1 compared with the two monthly arms, especially in the bevacizumab PRN group.[183] The CATT 5-year follow-up study demonstrated vision gains during the first 2 years that were not maintained at 5 years. However, 50% of eyes had VA of 20/40 or better, confirming anti- VEGF therapy as a major long-term therapeutic advance for neovascular AMD.[184] Similar results were seen in the 2-year Inhibition of VEGF in Age-related choroidal Neovascularization (IVAN) trial conducted in the United Kingdom.[185,186] (See Glossary.)

Presently, there does not appear to be a significant difference in efficacy between ranibizumab and bevacizumab.[184] A meta-analysis by Nguyen in 2018 of over 8,000 eyes comparing all three drugs concluded that bevacizumab and ranibizumab had equivalent efficacy for bestcorrected visual acuity (BCVA), whereas ranibizumab had greater reduction in central macular thickness, and aflibercept and ranibizumab had comparable efficacy for BCVA and central macular thickness.[187] The review by Chen in 2015 also elicited similar results.[188] The systemic safety data in the CATT and IVAN studies are inconclusive and two Cochrane systematic reviews have also concluded that if a difference in safety between these anti-VEGF drugs exists, it is minimal.[189,190] (I+, Good quality, Strong recommendation) A real world analysis of 13,859 patients found that all three agents improved visual acuity similarly over 1 year.[191]

Pegaptanib sodium is a selective VEGF antagonist that binds to the 165 isoform of VEGF-A. It was the first anti-VEGF agent available for treating neovascular AMD. Pegaptanib sodium injection is FDA approved for the treatment of all subtypes of neovascular AMD, with a recommended dosage of 0.3 mg injected every 6 weeks into the vitreous. These recommendations were based on results from two double-masked, randomized controlled trials.[181] (See Table 3.) Unlike the other anti-VEGF agents that are currently available (ranibizumab, aflibercept, and bevacizumab), pegaptanib treatment does not improve VA on average in patients with new-onset neovascular AMD and is rarely used in current clinical practice.

Randomized clinical trials have been performed to study the adjunct use of intravitreal corticosteroids and/or anti-VEGF agents in various drug combinations or with verteporfin PDT, following the publication of results from uncontrolled case series.[192-195] However, the data do not currently support the use of combination therapy with steroids, especially given the long-term side effects of glaucoma and cataract that are associated with corticosteroid use.

The DENALI and MONT BLANC studies (ranibizumab and verteporfin PDT compared with ranibizumab alone) did not show a significant benefit of adding PDT to anti-VEGF therapy in new-onset neovascular AMD.[196,197] (See Glossary.) However, the EVEREST study demonstrated that fewer anti-VEGF injections were needed in combination therapy compared with anti-VEGF monotherapy in eyes with the PCV variant of neovascular AMD.[198] A 2017 meta-analysis and systematic review also concluded that treatment of PCV by PDT combined with ranibizumab is valuable in improving VA and maintaining long-term effectiveness but recommended further study.[199,200] A randomized trial of 310 subjects has shown aflibercept to effectively treat PCV in 85% of patients; 15% required PDT for control.[200] A 2018 metaanalysis of 16 studies by Gao et al compared 587 patients in the monotherapy group with various anti-VEGF agents against 673 patients in the combination group and found no statistically significant difference between groups in mean BCVA, the proportion of patients who gained 15 or more letters, or central retinal thickness at the end of the study.[201] However, combination therapy did require fewer anti-VEGF injections, as noted in other studies with reduced-fluence PDT demonstrating this reduction in number of injections at a statistically significant level as opposed to the standard fluence group.[201]

Subfoveal Choroidal Neovascularization

In addition to intravitreal injections of VEGF inhibitors, verteporfin PDT and thermal laser photocoagulation surgery remain approved options for the treatment of subfoveal lesions. Current practice patterns support the use of anti-VEGF monotherapy for patients with newly diagnosed neovascular AMD and suggest that these other therapies are rarely needed. Photodynamic therapy with verteporfin has FDA approval for the treatment of AMD-related, predominantly classic, subfoveal CNV; treatment trial results are described in Table 3. The efficacy of thermal laser photocoagulation surgery for

CNV was studied in the MPS (early 1990s) in a randomized, controlled, multicenter trial.[148-151] The MPS directly treated eyes that had subfoveal lesions using thermal laser surgery,[150] but the outcomes were poor and do not compare with the positive VA benefits found with current anti-VEGF therapy. Thus, thermal laser photocoagulation surgery is no longer recommended for subfoveal CNV treatment.

Table 3 (at the end of this section) summarizes the findings from randomized controlled trials of verteporfin PDT and VEGF inhibitors for the treatment of subfoveal CNV. The entry criteria varied among these studies and may have contributed to the differences among treatment cohorts.

Juxtafoveal Choroidal Neovascularization

Although randomized, controlled clinical trials have not routinely included patients with juxtafoveal CNV, many clinicians extrapolated the data from current trials to consider intravitreal injections of anti-VEGF agent as the primary therapy for juxtafoveal lesions. In the MPS, treatment of well-demarcated juxtafoveal CNV lesions resulted in a small overall treatment benefit.151 The rates of “persistence” (CNV leakage within 6 weeks of laser photocoagulation surgery) and “recurrence” (CNV leakage more than 6 weeks after laser photocoagulation surgery) were high (80%) at 5 years. After 5 years of follow-up, 52% of eyes treated for juxtafoveal lesions progressed to visual loss of 30 or more letters (quadrupling of the visual angle) compared with 61% of untreated eyes.[151]

Extrafoveal Choroidal Neovascularization

There still remains a possible role for thermal laser surgery treatment in eyes with extrafoveal and peripapillary CNV lesions as defined by the MPS.[148,202] Although photocoagulation of well-demarcated extrafoveal CNV lesions resulted in a substantial reduction in the risk of severe visual loss for the first 2 years, recurrence or persistence occurs in approximately 50% of cases, thus reducing this benefit over the subsequent 3 years of follow-up.[148] After 5 years of follow-up, 48% of eyes treated for extrafoveal lesions progressed to VA loss of 30 or more letters when compared with 62% of untreated eyes.148 The historical data are important to recognize in current practice patterns, as none of the anti-VEGF or PDT trials included extrafoveal lesions. Practitioners have extrapolated and applied data from the dramatic improvements seen in the treatment of subfoveal lesions to extrafoveal lesions. The current trend is to use anti- VEGF agents in preference to laser photocoagulation surgery. Laser surgery for extrafoveal lesions remains a less commonly used, yet reasonable, therapy. Current therapies that have insufficient data to demonstrate clinical efficacy include radiation therapy, acupuncture, electrical stimulation, macular translocation surgery, and adjunctive use of intravitreal corticosteroids with verteporfin PDT. Therefore, at this time, these therapies are not recommended.

Indications for Treatment for Choroidal Neovascularization

Assessment and treatment plans for non-neovascular and neovascular AMD are listed in Table 4. The criteria for treatment of AMD and the techniques of therapy are described in the aflibercept, bevacizumab, ranibizumab, pegaptanib, MPS, and AREDS literature. Aflibercept, ranibizumab, and pegaptanib-injection product labeling and other literature discuss techniques of intravitreal injection.[181,207,239-241] Recently, conbercept has shown promising results in the management of wet AMD,[242] although it has yet to receive FDA approval for its use. Similarly, abicipar has completed phase II clinical trials and has shown an extended duration of effect with a good safety profile; however, it has not received FDA approval. [243,244] Recently reported results from the HAWK and HARRIER phase III clinical trials showed that **brolucizumab** achieved its primary endpoint of noninferiority of BCVA change compared with aflibercept at week 48. Patients treated with brolucizumab achieved superior reductions in central subfield thickness compared with aflibercept. Fewer patients treated with brolucizumab had sub-retinal fluid, inter-retinal fluid, and sub-RPE fluid. Brolucizumab received FDA approval in October 2019.[245]

As is the case with most clinical trials, these treatment trials do not provide clear guidance for the management of all patients encountered in clinical practice. To date, the major prospective randomized anti-VEGF treatment trials (Anti-VEGF Antibody for the Treatment of Predominantly Classic CNV in AMD [ANCHOR], Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD [MARINA], VIEW, CATT, IVAN, HARBOR) used either a fixed continuous treatment regimen (approximately every 4 or 8 weeks) or an individualized discontinuous treatment regimen (PRN).[168,174,179,180,183,185,186,246]

The PRN regimens using ranibizumab appear to have efficacy and safety comparable to fixed monthly regimens over 1 year of treatment, but they do not maintain the initial visual gains with longer follow-up.[183,255] Caution should be used when dosing PRN bevacizumab, as it may be slightly less effective than other monthly anti-VEGF regimens and other PRN anti-VEGF regimens.[183] Vision gains during the first 2 years of the CATT clinical trials were not maintained at the 5-year follow-up visit, but 50% of the patients maintained a VA of 20/40.[184]

A continuous, variable dosing regimen that attempts to individualize therapy, commonly referred to as “treat and extend,” is frequently used in clinical practice as an alternative to the two treatment approaches above.248-251 Prospective studies such as Lucentis Compared to Avastin Study (LUCAS) have shown similar efficacy between monthly and treat-and-extend for bevacizumab and ranibizumab.[256]

Subretinal hemorrhages are relatively common in neovascular AMD. Small subretinal hemorrhages are a sign of active CNV or PCV and may be managed with anti-VEGF therapy. For the management of larger submacular hemorrhages, the SST study was inconclusive. Pneumatic displacement procedures, the use of tPA, and/or pars plana vitrectomy have been proposed. The data on management of these larger hemorrhages are inadequate to make a recommendation at this time.[257]

The risks, benefits, and complications of the treatment and the alternatives to it should be discussed with the patient and informed should be consent obtained.[146,258]

TABLE 4 TREATMENT RECOMMENDATIONS AND FOLLOW-UP FOR AGE-RELATED MACULAR DEGENERATION

Recommended Treatment	Diagnoses Eligible for Treatment	Follow-up Recommendations
Neovascular AMD		
Aflibercept intravitreal injection 2.0 mg as described in published reports[168]	Macular CNV	• Patients should be instructed to promptly report symptoms suggestive of endophthalmitis, including eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, increased sensitivity to light, or increased number of floaters • Return examination approximately 4 weeks after treatment initially; subsequent follow-up and treatment depends on the clinical findings and judgment of the treating ophthalmologist. A maintenance treatment regimen of every 8 weeks has been shown to have results comparable to every 4 weeks in the first year of therapy. • Monitoring of monocular near vision (reading/Amsler grid)
Bevacizumab intravitreal injection 1.25 mg as described in published reports[172-177,183,185,240,248] The ophthalmologist should provide appropriate informed consent with respect to the off-label status.[176]	Macular CNV	• Patients should be instructed to promptly report symptoms suggestive of endophthalmitis, including eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, increased sensitivity to light, or an increased number of floaters. • Return examination approximately 4 weeks after treatment initially; subsequent follow-up and treatment depends on the clinical findings and judgment of the treating ophthalmologist • Monitoring of monocular near vision (reading/Amsler grid)
Brolucizumab intravitreal injection 6.0 mg as described in FDA labeling[245]	Macular CNV	• Patients should be instructed to promptly report symptoms suggestive of endophthalmitis, including eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, increased sensitivity to light, or an increased number of floaters • Return examination approximately 4 weeks after treatment initially; subsequent follow-up and treatment depends on clinical findings and judgment of the treating ophthalmologist • Monitoring of monocular near vision (reading/Amsler grid)
Ranibizumab intravitreal injection 0.5 mg as recommended in literature[174,179,180,183,185,207,246,249-251]	Macular CNV	• Patients should be instructed to promptly report symptoms suggestive of endophthalmitis, including eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, increased sensitivity to light, or an increased number of floaters.[207] • Return examination approximately 4 weeks after treatment initially; subsequent follow-up and treatment depends on the clinical findings and judgment of the treating ophthalmologist • Monitoring of monocular near vision (reading/Amsler grid)
Less Commonly Used Treatments for Neovascular AMD		
PDT with verteporfin as recommended in the TAP and VIP reports[182,252-254]*	• Macular CNV, new or recurrent, where the classic component is >50% of the lesion and the entire lesion is ≤5400 µm in greatest linear diameter • Occult CNV may be considered for PDT with vision <20/50 or if the CNV is <4 MPS disc areas in size when the vision is >20/50 • Juxtafoveal CNV is an off-label indication for PDT but may be considered in select cases	• Return examination approximately every 3 months until stable, with retreatments as indicated • Monitoring of monocular near vision (reading/Amsler grid)
Thermal laser photocoagulation surgery as recommended in the MPS reports is rarely used[148,151,247]	• May be considered for extrafoveal classic CNV, new or recurrent • May be considered for juxtapapillary CNV	• Return examination with fluorescein angiography approximately 2–4 weeks after treatment, and then at 4–6 weeks and thereafter depending on the clinical and angiographic findings • Retreatments as indicated • Monitoring of monocular near vision (reading/Amsler grid)

AMD = Age-Related Macular Degeneration; AREDS = Age-Related Eye Disease Study; CNV = choroidal neovascularization; MPS = Macular Photocoagulation Study; OCT = optical coherence tomography; OCTA = optical coherence tomography angiography; PDT = photodynamic therapy; TAP = Treatment of Age-Related Macular Degeneration with Photodynamic Therapy; VIP = Verteporfin in Photodynamic Therapy

* Contraindicated in patients with porphyria or known allergy.

Complications of Treatment

Possible complications of the four main modalities of treatment for AMD are listed below. Retinal pigment epithelium rips (tears) may occur with or without these treatment modalities, yet this is not a contraindication to continued anti-VEGF therapy.

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.[259-262] A recent review of the literature concluded that anti- VEGF therapy is safe and effective for neovascular AMD.[263] The risks of intravitreal anti-VEGF agents in pregnant or lactating women have not been studied.[264,265] Intravitreal pharmacotherapy can result in endophthalmitis, noninfectious inflammation, retinal tear, or detachment.

Aflibercept injection

- Endophthalmitis (cumulative ≤1.0% over 1 year in VIEW studies)[168]

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.[168,266]

Bevacizumab injection

- Reported safety data are limited by relatively short and variable follow-up periods and by differences in reporting criteria.[267,268]

- Reported ocular adverse events include bacterial endophthalmitis per injection (0.16%), tractional retinal detachments (0.16%), uveitis (0.09%), rhegmatogenous retinal detachment (0.02%), and vitreous hemorrhage (0.16%).[240,269]

The CATT study had limited statistical power to identify any differences in treatmentrelated adverse events between bevacizumab and ranibizumab. At 1 year, there were no statistically significant differences in rates of death, arteriothrombotic events, or venous thrombotic events for the two drugs. There was a higher rate of serious systemic events (e.g., arteriothrombotic events, venous thrombosis, or gastrointestinal disorders such as hemorrhage) among patients treated with bevacizumab compared with ranibizumab (24% vs. 19%; P=0.04), and this statistically significant difference was persistent at 2 years of follow-up.[174,183] The IVAN trial showed greater serum VEGF suppression with bevacizumab but did not show any statistically significant difference in serious systemic adverse events.[185]

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)[179,180]

Pegaptanib sodium injection270

- Endophthalmitis (1.3% of treated cases during the first year of treatment)
- Traumatic injury to the lens (0.6% of treated cases during the first year of treatment)
- Retinal detachment (0.7% of treated cases during the first year of treatment)
- Anaphylaxis/anaphylactoid reactions including angioedema (rare; these were reported following FDA approval)

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[182,252,253]

- Infusion site extravasation
- Idiosyncratic back pain during infusion of the drug (1%–2% of patients)[182,252,25]
- Photosensitivity reaction (<3% of patients).[182,252,253] The stated, current recommendations are to avoid direct sunlight for the first 5 days 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, breastfeeding, 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 subfoveal or juxtafoveal CNV

Thermal laser is no longer recommended for subfoveal CNV. Introduction or enlargement of a pre-existing scotoma, with or without VA loss, is not a complication of thermal laser photocoagulation surgery; 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.

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 9 of 12, September 2020) am 29.09.2020

#	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
4	((age OR wet OR exudative OR neovascular) AND maculopath*):ti,ab,kw
5	((AMD OR wAMD OR nAMD OR ARMD OR wARMD OR nARMD) AND macular):ti,ab,kw
6	#1 OR #2 OR #3 OR #4 OR #5
7	#6 with Cochrane Library publication date from Sep 2015 to present, in Cochrane Reviews

Systematic Reviews in Medline (PubMed) am 29.09.2020

#	Suchfrage
1	Macular Degeneration[mh:noexp]
2	Wet Macular Degeneration[mh]
3	(macular[tiab]) AND ((degeneration*[tiab]) OR dystroph*[tiab])
4	((((((age[tiab]) OR wet[tiab]) OR exudative[tiab]) OR neovascular[tiab])) AND maculopath*[tiab]
5	((AMD[tiab] OR wAMD[tiab] OR nAMD[tiab] OR ARMD[tiab] OR wARMD[tiab] OR nARMD[tiab]) AND macular[tiab])
6	#1 OR #2 OR #3 OR #4 OR #5
7	(#6) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR

#	Suchfrage
	studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
8	(#7) AND ("2015/09/01"[PDAT] : "3000"[PDAT])
9	(#8) NOT "The Cochrane database of systematic reviews"[Journal]
10	(#9) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
11	(#10) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 29.09.2020

#	Suchfrage
1	Macular Degeneration[mh:noexp]
2	Wet Macular Degeneration[mh]
3	(macular[tiab]) AND ((degeneration*[tiab]) OR dystroph*[tiab])
4	(((((age[tiab]) OR wet[tiab]) OR exudative[tiab]) OR neovascular[tiab])) AND maculopath*[tiab]
5	((AMD[tiab] OR wAMD[tiab] OR nAMD[tiab] OR ARMD[tiab] OR wARMD[tiab] OR nARMD[tiab]) AND macular[tiab])
6	#1 OR #2 OR #3 OR #4 OR #5
7	(#6) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
8	(#7) AND ("2015/09/01"[PDAT] : "3000"[PDAT])
9	(#8) NOT (retracted publication [pt] OR retraction of publication [pt])

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Anhang

National Institute for Health and Care Excellence, 2018 [9].

Antiangiogenic therapies

Table 37: Photodynamic therapy vs control

Study	Population	Intervention	Comparator	Outcome
TAP 1999	People with subfoveal CNV lesions caused by AMD (n=609 people)	Photodynamic therapy following verteporfin injection	Photodynamic therapy following intravenous 5% dextrose	Visual acuity at 12 and 24 months

Study	Population	Intervention	Comparator	Outcome
VIM 2005	People with minimally classic CNV due to AMD (n=117 people)	Photodynamic therapy following verteporfin injection	Photodynamic therapy following intravenous 5% dextrose	Visual acuity at 12 and 24 months
VIO 2007	People with occult but no classic CNV due to AMD (n=364 people)	Photodynamic therapy (verteporfin)	Placebo (5% dextrose in water for injection)	Loss of fewer than 15 letters
VIP 2001	People with subfoveal CNV cause by AMD (n=339 people)	Photodynamic therapy following verteporfin injection	Photodynamic therapy following intravenous 5% dextrose	Visual acuity

Table 38: Anti-vascular endothelial growth factor for late AMD (wet active)

Study	Population	Intervention	Comparator	Outcome
Bevacizumab vs control				
ABC 2010	People with CNV lesion in study eye due to AMD (n=131 people)	Bevacizumab	Standard treatment (including pegaptanib, verteporfin PDT, sham injection)	Proportion of people gaining 15 letter or more at 1 year
Sacu 2009	People with late AMD (wet active) (n=28 people)	Bevacizumab	Verteporfin PDT plus intravitreal triamcinolone	Change in mean visual acuity
Ranibizumab vs control				
ANCHOR 2006	People with CNV due to AMD (n=423 people)	Ranibizumab	Sham injection	Proportion of people losing fewer than 15 letter at 12 months
MARINA 2006	People with active primary or recurrent subfoveal lesions with CNV secondary to AMD (n=716 people)	Ranibizumab	Sham injection	Proportion of people losing fewer than 15 letter at 12 months
PIER 2008	People with primary or recurrent subfoveal CNV secondary to AMD(n=184 people)	Ranibizumab	Sham injection	Changes in VA at 1 year
LAPTOP 2013	People with treatment naïve PCV (n=93 people)	Ranibizumab	Photodynamic therapy (verteporfin)	Proportion of people losing of more than 0.2logMAR at 24 weeks
Bevacizumab vs ranibizumab				
Biswas 2011	People with presence of subfoveal or juxtafoveal CNV (n=120 people)	Bevacizumab	Ranibizumab	Changes in BCVA

CATT 2011	People with untreated active CNV due to AMD (n=1,208 people)	Bevacizumab	Ranibizumab	Change in visual acuity
GEFAL 2013	People with active foveal neovascular AMD (n=501 people)	Bevacizumab	Ranibizumab	Change in BCVA at 1 year
IVAN 2013	People with untreated neovascular AMD (n=628 people)	Bevacizumab	Ranibizumab	Change in BCVA at 2 years
LUCAS 2015	People with untreated active neovascular AMD in study eye (n=441 people)	Bevacizumab	Ranibizumab	Change in BCVA at 2 years
MANTA 2013	People with active primary or recurrent subfoveal lesion with CNV (n=321 people)	Bevacizumab	Ranibizumab	Change in BCVA at 1 year
Schauwvlieghe 2016	People with primary or recurrent sub- or juxtafoveal CNV due to AMD (n=327 people)	Bevacizumab	Ranibizumab	Change in BCVA at 1 year
Subramanian 2010	People with presence of symptomatic CNV (n=28 people)	Bevacizumab	Ranibizumab	Visual acuity
Aflibercept vs Ranibizumab				
VIEW 1	People diagnosed with neovascular AMD in the study eye (n=1,217 people)	Aflibercept	Ranibizumab	Proportion of people maintaining vision at week 52
VIEW 2	People diagnosed with neovascular AMD in the study eye (n=1,240 people)	Aflibercept	Ranibizumab	Proportion of people maintaining vision at week 52
Yuzawa 2015	People diagnosed with neovascular AMD in the study eye (VIEW 1 and VIEW2) (n=2,419 people)	Aflibercept	Ranibizumab	NEI-VFQ score

Abbildung 1: Brief summary of included studies antiangiogenic therapies

Adjunctive therapies

Study [country]	Study population	Intervention	Comparator	Outcomes
PDT combined with anti-VEGF				
Bashshur Z F et al 2011 [Lebanon]	Patients with neovascular AMD (n=30 people, 40 eyes)	Verteporfin photodynamic therapy combined with as-needed ranibizumab treatment	Ranibizumab monotherapy	Proportion of patients who lost <15 letters in best-corrected visual acuity; Mean change in BCVA
Datseris I et al 2015 [Greece]	Patients with predominantly classic and occult choroidal neovascularisation in one or both eyes (n=100 people)	Photodynamic therapy combined with intravitreal bevacizumab	Bevacizumab monotherapy	Mean number of re-injection; Corrected distance visual acuity
Gomi F et al 2015 [Japan]	Patients with treatment-naïve polypoidal choroidal vasculopathy (n=72 people, 72 eyes)	Photodynamic Therapy in combination with ranibizumab	Ranibizumab monotherapy	Change in best corrected visual acuity
Hatz K et al 2015	Patients with subfoveal choroidal neovascularisation secondary to AMD (n=40 people)	Verteporfin photodynamic therapy plus ranibizumab	Ranibizumab monotherapy	Number of ranibizumab retreatment; Best-corrected visual acuity
Kaiser P K, et al 2012	Patients had subfoveal choroidal neovascularisation secondary to neovascular age-related degeneration (n=321 people)	Verteporfin plus ranibizumab	Ranibizumab monotherapy	Best-corrected visual acuity
Koh A et al 2012 [Hong Kong, Singapore, South Korean, Taiwan, Thailand]	Treatment naïve patients with symptomatic macular polypoidal choroidal vasculopathy (n=61 people)	Verteporfin photodynamic therapy in combination with ranibizumab	Ranibizumab monotherapy	The proportion of patients in achieving complete regression of polyps; Mean best-corrected visual acuity
Krebs I et al 2013 [Austria]	Patients with subfoveal choroidal neovascularisation secondary to neovascular age-related degeneration; patients with predominantly classic lesions;	Combination of photodynamic therapy with ranibizumab	Ranibizumab monotherapy	The number of Ranibizumab injections; Mean changes in best-corrected visual acuity

Study [country]	Study population	Intervention	Comparator	Outcomes
	Evidence that CNV extends under the geometric centre of the foveal avascular zone (n=48 people)			
Larsen M, et al 2012 [12 European countries]	Patients with a diagnosis of AMD related active subfoveal choroidal neovascularisation (n=255 people)	Verteporfin plus ranibizumab	Ranibizumab monotherapy	Mean change in best-corrected visual acuity
Lazic R. et al 2007	Patients with minimally classic or occult choroidal neovascularisation due to AMD in one or both eyes (n=156 people)	Verteporfin therapy and intravitreal bevacizumab combined	Bevacizumab monotherapy	Best-corrected visual acuity; Central foveal thickness
Lim J Y et al 2012. [Korean]	Patients with neovascular AMD or polypoidal choroidal vasculopathy (n=47 people)	Photodynamic therapy combination with intravitreal bevacizumab	Bevacizumab monotherapy	Best corrected visual acuity; Central foveal thickness
Semeraro F, et al 2015	Naïve eyes affected by neovascular AMD (n=75 people)	Photodynamic Therapy combined ranibizumab	Ranibizumab monotherapy	Best corrected visual acuity
Vallance J H et al 2010.	FFA demonstrating choroidal neovascularisation secondary to AMD (n=18 people)	Combination photodynamic treatment and intravitreal ranibizumab	Ranibizumab monotherapy	Best corrected visual acuity
Weingessel 2016 [Austria]	People with new onset CNV due to CNV (n=34 people)	Combination photodynamic treatment and intravitreal ranibizumab	Ranibizumab monotherapy	Best corrected visual acuity
Williams P D et al. 2012	Patients with untreated subfoveal neovascular AMD (n=60 people)	Combined and photodynamic therapy and intravitreal ranibizumab	Ranibizumab monotherapy	Visual acuity
Anti-VEGF combined with steroids				
Ahmadieh H. et al 2011 [Iran]	Patients with subfoveal choroidal neovascularisation (n=120 people)	Combined intravitreal bevacizumab and triamcinolone	Bevacizumab monotherapy	Change in best-corrected visual acuity
Kuppermann Baruch D et al 2015	Patients with choroidal neovascularisation secondary to AMD (n=310 people)	Dexamethasone intravitreal implant as adjunctive therapy to ranibizumab	Ranibizumab monotherapy	The ranibizumab injection free interval; Best-corrected visual acuity
Ranchod T M, et al 2013.	Patients with neovascular AMD (n=40 people)	Ranibizumab plus dexamethasone combination	Ranibizumab monotherapy	Best corrected visual acuity
PDT combined with anti-VEGF and steroids				
Piri Niloofar, et al 2014 [Iran]	Patients with subfoveal choroidal neovascularisation of all types (predominantly classic, minimally classic, occult and retinal angiomatous proliferation) secondary to AMD and no history of treatment (n=84 people)	Photodynamic therapy and intravitreal bevacizumab with triamcinolone	Photodynamic therapy and intravitreal bevacizumab without triamcinolone	Change in best corrected visual acuity

Abbildung 2: Brief summary of included studies adjunctive therapies

Antiangiogenic therapies

GRADE tables and meta-analysis results

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect	No of Participants	Quality of the evidence
	Corresponding risk	Assumed risk	(95% CI)	(studies)	(GRADE)
	Intervention (photodynamic therapy with verteporfin)	Control (photodynamic therapy with 5% dextrose in water)			
Loss of 3 or more lines (15 or more letter) visual acuity ETDRS at 24 months	487 per 1000 (445 to 536)	609 per 1000	RR 0.8, 0.73 to 0.89	1381 (4 studies)	⊕⊕⊕⊖ Moderate[1]
Loss of 6 or more lines (30 or more letter) visual acuity ETDRS at 24 months	220 per 1000 (176 to 276)	333 per 1000	RR 0.66, 0.55 to 0.78	1381 (4 studies)	⊕⊕⊕⊕ High
Gain of 3 or more lines (15 or more letter) visual acuity ETDRS at 24 months	80 per 1000 (43 to 151)	36 per 1000	RR 2.59, 1.33 to 5.06	941 (3 studies)	⊕⊕⊕⊕ High
Adverse effects: acute severe visual acuity decrease (follow-up: 7 days)	11 per 1000 (3 to 48)	3 per 1000	RR 3.75 0.87 to 16.12	1075 (3 studies)	⊕⊕⊕⊖ Moderate[1]
Adverse effects: visual disturbance	270 per 1000	170 per 1000	RR 1.56 1.21 to 2.01	1075 (3 studies)	⊕⊕⊕⊖ Moderate[1]
Adverse effects: injection site	120 per 1000	60 per 1000	RR 1.36 0.50 to 3.71	1075 (3 studies)	⊕⊖⊖⊖ Very low[2]
Adverse effects: infusion-related back pain	20 per 1000 (6 to 70)	2 per 1000	RR 9.93 (2.82 to 35.02)	1439 (4 studies)	⊕⊕⊕⊕ High[3]
Adverse effects: allergic reactions	17 per 1000	19 per 1000	RR 0.94 (0.35 to 2.51)	948 (2 studies)	⊕⊕⊖⊖ Low[4]
Adverse effects: photosensitivity reactions	24 per 1000	3 per 1000	RR 2.73 (0.08 to 97.96)	948 (2 studies)	⊕⊖⊖⊖ Very low[2]

*The basis for the assumed risk is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI)
1. Downgrade one level of imprecision: 95%CI of the estimated effect across 1 line of defined minimal important difference.
2. Downgrade one level of heterogeneity (i2>=50%), and downgrade two levels of imprecision (wide confidence interval)
3. Not downgraded for imprecision: confidence interval wide however do not include 1 (no effect)
4. Downgrade two levels of serious imprecision.

Abbildung 3: Photodynamic therapy versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect	No of Participants	Quality of the evidence	Comments
	Corresponding risk	Assumed risk	(95% CI)	(studies)	(GRADE)	
	Ranibizumab	Control				
Gain of 15 letters or more visual acuity at one year	230 per 1000 (93 to 566)	59 per 1000	RR 3.25 (1.44 to 7.33)	1415 (4 studies)	⊕⊕⊕⊖ Moderate[1]	
Loss of fewer than 15 letters visual acuity at one year	934 per 1000 (861 to 1000)	610 per 1000	RR 1.51 (1.41 to 1.63)	1415 (4 studies)	⊕⊕⊕⊕ High	
Mean change in visual acuity at one year (number of letters)	The mean change in visual acuity in the ranibizumab groups was on average 17.80 more letters gained (95%CI 15.95 to 19.65 letters)	The mean change across control groups ranged from a loss 10 to 16 letter	MD 17.81 (15.94 to 19.67)	1322 (3 studies)	⊕⊕⊕⊕ High	
Mean change in vision-related quality of life	The mean change in vision related quality of life in the ranibizumab groups ranged from 5 to 7 points	The mean change across control groups in vision-related quality of life scores ranged from -3 to 2 points	MD 6.69 (3.38 to 9.99)	1134 (2 studies)	⊕⊕⊕⊕ High	Using the NEI-VFQ questionnaire with a 10-point difference considered as being clinically meaningful.
Serious systemic adverse events at one year	Range of 0 to 55 per 1000	Range of 5 to 83 per 1000 for various systematic adverse events	Range of RR 0.17 (0.01 to 4.24) to 2.08 (0.23 to 18.45)	603 (2 studies)		
Myocardial infarction	10 per 1000	< 10 per 1000	RR 2.08 (0.23, 18.45)	603 (2 studies)	⊕⊕⊖⊖ Low[2]	
Stroke or cerebral infarction	< 10 per 1000	< 10 per 1000	RR 1.04 (0.09, 11.38)	603 (2 studies)	⊕⊕⊖⊖ Low[2]	
Treatment-emergent hypertension	60 per 1000	80 per 1000	RR 0.67 (0.36, 1.24)	603 (2 studies)	⊕⊕⊕⊖ Moderate[3]	
Non-ocular hemorrhage	60 per 1000	30 per 1000	RR 1.90 (0.78, 4.62)	603 (2 studies)	⊕⊕⊖⊖ Low[2]	
Serious ocular adverse events at one year	Range of 3 to 118 per 1000	Range of 0 to 68 per 1000 for various systematic adverse events	Range of RR 0.52 (0.03 to 8.25) to 2.71 (1.36 to 5.42)	603 (2 studies)		
Ocular inflammation	120 per 1000	40 per 1000	RR 2.71 (1.36 to 5.42)	603 (2 studies)	⊕⊕⊕⊕ High	
Elevated intraocular pressure (30 mmHg or more increase)	80 per 1000	30 per 1000	RR 2.22 (0.99, 4.98)	603 (2 studies)	⊕⊕⊕⊖ Moderate[3]	
Cataract	100 per 1000	70 per 1000	RR 1.48 (0.83, 2.66)		⊕⊕⊕⊖ Moderate[3]	

*The basis for the assumed risk is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI)
1. Downgrade one level for inconsistency due to heterogeneity (i2>=50%).
2. Downgrade two levels for serious imprecision.
3. Downgrade one level for imprecision.

Abbildung 4: Ranibizumab vs control (sham injection or PDT)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect	No of Participants	Quality of the evidence	Comments
	Corresponding risk	Assumed risk	(95% CI)	(studies)	(GRADE)	
	Alfibercept	Ranibizumab				
Mean change in BCVA in ETDRS letters at 1 year	Mean change in visual acuity in aflibercept groups was on average 0.15 fewer letters gained (95% CI 1.47 fewer letters to 1.17 more letters)	Mean change in visual acuity across ranibizumab groups ranged from gains of 8.57 letters to 8.71 letters	MD -0.15 (-1.47 to 1.17)	2412 (2 studies)	⊕⊕⊕⊕ High	
Gain of 15 of BCVA at one year	314 per 1000 (275 to 360)	324 per 1000	RR 0.97 (0.85 to 1.11)	2412 (2 studies)	⊕⊕⊕⊕ High	
Quality of life measures at 1 year (national eye institute-visual function questionnaire)	Mean improvement in composite NEI-VQF score in intervention groups was on average 0.39 points lower (95% CI 1.71 points lower to 0.93 points higher)	Mean improvement in composite NEI-VQF score ranged across control groups from 4.9 to 6.3 points	MD -0.39 (-1.71 to 0.93)	2412 (2 studies)	⊕⊕⊕⊕High	
Adverse events (serious systemic events at 1 year)	138 per 1000 (110 to 174)	139 per 1000	RR 0.99 (0.79 to 1.25)	2419 (2 studies)	⊕⊕⊕⊖ Moderate[1]	
Adverse events (serious ocular events at 1 year)	20 per 1000 (12 to 34)	32 per 1000	RR 0.62 (0.36 to 1.07)	2419 (2 studies)	⊕⊕⊕⊖ Moderate[1]	

*The basis for the assumed risk is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI)
1. Adverse vent outcome downgrade to moderate quality as the numbers of events were small (wide confidence intervals), and 95%CI of estimated effect under the possibility of significant and non-significant values

Abbildung 5: Aflibercept vs. Ranibizumab

The data presented in the GRADE table below were identified by update searches undertaken after the search date of the Cochrane systematic reviews used above

Aflibercept vs ranibizumab: NEI-VFQ 25

Number of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
Proportion of people gaining more than 5 ETDRS letters and having clinical improvement (more than 6-points) in the NEI-VFQ25 at 52-weeks follow –up							
2 (VIEW 1, VIEW2)	Not serious	Serious[1]	Not serious	Not serious	1193	RR 0.97 (0.86, 1.10)	MODERATE
NEI-VFQ-25 subscale score changes from baseline to week 52 (higher scores indicate better QoL)							
General vision	Not serious	Not serious	Not serious	Not serious	1193	MD 0.06 (-2.00, 2.13)	HIGH
Near activities	Not serious	Not serious	Not serious	Not serious	1193	MD -0.62 (-3.09, 1.86)	HIGH
Distance activities	Not serious	Not serious	Not serious	Serious[2]	1193	MD 0.08 (-2.43, 2.58)	MODERATE
Mental health	Not serious	Not serious	Not serious	Serious[2]	1193	MD 0.14 (-2.41, 2.70)	MODERATE
Role difficulities	Not serious	Not serious	Not serious	Serious[2]	1193	MD 1.09 (-2.04, 4.23)	MODERATE
Dependency	Not serious	Not serious	Not serious	Serious[2]	1193	MD -1.29 (-4.00, 1.43)	MODERATE
Social funictioning	Not serious	Not serious	Not serious	Serious[2]	1193	MD 0.18 (-2.35, 2.70)	MODERATE
Driving	Not serious	Not serious	Not serious	Serious[2]	1193	MD 1.51 (-1.15, 4.17)	MODERATE
Colour vision	Not serious	Not serious	Not serious	Not serious	1193	MD -2.04 (-4.33, 0.26)	HIGH
Ocular pain	Not serious	Not serious	Not serious	Not serious	1193	MD -0.94 (-3.21, 1.32)	HIGH
Peripheral vision	Not serious	Not serious	Not serious	Not serious	1193	MD 0.86 (-3.73, 2.00)	HIGH
General health	Not serious	Not serious	Not serious	Not serious	1193	MD -0.23 (-2.56, 2.10)	HIGH

1. Downgraded one level for inconsistency due to heterogeniety (i2>50%)
2. Downgraded one level for imprecision due to 95%CI of estimated effect crossing 1 line of a defined minimal important difference (2.3 point)

Abbildung 6: Aflibercept vs. Ranibizumab: NEI-VFQ 25

Adjunctive therapies

GRADE tables and meta-analysis results

Number of RCTs	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
Anti-VEGF + PDR vs anti-VEGF								
BCVA (ETDRS letters ≤3 months) - positive values favour combination								
1 (Lazic)*	RCT	Serious[1]	Not serious	Not serious	Serious[2]	106	MD -7.25 (-19.82, 5.31)	LOW
BCVA (ETDRS letters >3 months) - positive values favour combination								
11 (Datseris; Bashshur; Hatz; Kaiser; Krebs; Larsen; Semeraro*; Weingessel; Williams: Gomi; Koh)	RCT	Not serious[3]	Not serious	Not serious	Not serious	1025	MD -0.54 (-1.29, 0.21)	HIGH
BCVA (proportion gain ≥15 letters, >3 months) - values greater than 1 favour combination								
9 (Datseris; Bashshur; Hatz; Kaiser; Larsen; Vallance; Williams: Gomi; Koh)	RCT	Not serious[3]	Not serious	Not serious	Serious[2]	923	RR 0.76 (0.63, 0.92)	MODERATE
Reinjections (>3 months) - positive values favour monotherapy								
5 (Datseris; Bashshur; Larsen; Gomi; Koh)	RCT	Serious[4]	Serious[5]	Not serious	Not serious	488	MD -1.43 (-2.42, -0.45)	LOW
Total number of injections (>3 months) - positive values favour monotherapy								
6 (Lim; Krebs;	RCT	Serious[4]	Serious[5]	Not serious	Not serious	474	MD -0.94	LOW
Larsen; Semeraro; Weignessel, Williams)							(-1.76, -0.12)	
Proportion needing retreatment (>3 months) - values greater than 1 favour combination								
1 (Hatz)	RCT	Serious[6]	N/A	Not serious	Serious[2]	40	RR 0.69 (0.42, 1.13)	LOW
Proportion having ocular adverse events - values greater than 1 favour combination								
5 (Lazic; Bashshur; Hatz; Kaiser; Larsen)	RCT	Not serious[3]	Not serious	Not serious	Not serious	762	RR 1.03 (0.88, 1.21)	HIGH
Proportion having non-ocular adverse events - values greater than 1 favour combination								
1 (Larsen)	RCT	Not serious	N/A	Not serious	Serious[2]	255	RR 1.03 (0.82, 1.29)	MODERATE

1. Downgraded one level for study design (open label, single blinded)
2. Downgraded one level for confidence interval crossing 1 line of a defined minimal important difference.
3. Some individual studies at high-risk of bias, but overall risk of bias rated low due to consistency of effect size estimates between high and low quality studies.
4. Downgraded one level for includes open label studies; lack of appropriate assessor masking.
5. Downgraded one level for heterogeneity (I^2>50%).
6. Downgraded one level for selection bias (differences in baseline characteristics between treatment groups)

*visual acuity outcome reported in the study used logMAR, and was converted to number of letters (logMAR=no. of letters x -0.02).

Abbildung 7: Anti-VEGF +PDT vs anti-VEGF

Number of RCTs	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
Anti-VEGF vs anti-VEGF steroids								
BCVA (ETDRS letters >3 months) - postive values favour combination								
3 (Ahmadieh; Kuppermann; Ranchod)	RCT	Not serious[1]	Not serious	Serious[2]	Not serious	267	MD 0.82 (-1.91, 3.55)	MODERATE
BCVA (proportion gain ≥15 letter, >3 months) - values greater than 1 favour combination								
2 (Kuppermann; Ranchod)	RCT	Serious[3]	Not serious	Serious[2]	Very serious[4]	152	RR 1.20 (0.53, 2.70)	VERY LOW
Total number of injections (>3 months) - positive values favour combination								
1 (Ranchod)	RCT	Serious[3]	N/A	Serious[2]	Serious[5]	37	MD -0.50 (-1.30, 0.30)	VERY LOW
Proportion needing retreatment (>3 months) - values greater than 1 favour combination								
1 (Ahmadieh)	RCT	Serious[3]	N/A	Serious[2]	Serious[6]	115	RR 0.65 (0.42, 1.00)	VERY LOW
Proportion having ocular adverse events - values greater than 1 favour combination								
1 (Kuppermann)	RCT	Serious[3]	N/A	Serious[2]	Serious[6]	333	RR 1.20 (0.91, 1.59)	VERY LOW

1. Some individual studies at high-risk of bias, but overall risk of bias rated low due to consistency of effect size estimates between high and low quality studies.
2. Downgraded one level for unclear about cataract status of study population.
3. Downgraded one level for study design (open label, single blinded)
4. Downgraded one level for confidence interval crossing 2 lines of a defined minimal important difference.
5. Downgraded one level for non-significant effect.
6. Downgraded one level for confidence interval crossing 1 line of a defined minimal important difference.

*visual acuity outcome reported in the study used logMAR, and was converted to number of letters (logMAR=no. of letters × -0.02).

Abbildung 8: Anti-VEGF + steroids vs anti-VEGF

Number of RCTs	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
Anti-VEGF + PDT vs anti-VEGF steroids + PDT								
BCVA (ETDRS letters >3 months) – positive values favour triple therapy								
1 (Piri)*	RCT	Not serious	Not serious	Serious[1]	Serious[2]	84	MD 0.50 (-6.04, 7.04)	LOW
Reinjections (>3 months) – positive values favour triple therapy								
1 (Piri)	RCT	Not serious	Not serious	Serious[1]	Serious[2]	84	MD -0.40 (-0.83, 0.03)	LOW
Proportion needing retreatment (>3 months) – values greater than 1 favour triple therapy								
1 (Piri)	RCT	Not serious	Not serious	Serious[1]	Serious[2]	84	RR 0.84 (0.71, 0.98)	LOW

1. Downgraded one level for unclear about cataract status of study population
2. Downgraded one level for confidence interval crossing 1 line of a defined minimal important difference.

*visual acuity outcome reported in the study used logMAR, and was converted to number of letters (logMAR=no. of letters × -0.02).

Abbildung 9: Anti-VEGF +PDT vs anti-VEGF steroid + PDT

American Academy of Ophthalmology, 2019 [1].

TABLE 3 Effects of Treatment on Vision in Randomized Controlled Trials of Subfoveal Choroidal Neovascularization

Study	No. of Patients	Patient Characteristics	Duration and Frequency of Treatment	Treated Eyes		Untreated Eyes		Years after Enrollment
				Visual Loss of 15 Letters or More*	Visual Gain of 15 Letters or More*	Visual Loss of 15 Letters or More*	Visual Gain of 15 Letters or More*	
ANCHOR (2006; ranibizumab injection)[160]	423	Mean age 77 years; BCVA 20/40 to 20/320; total lesion size ≤5400 µm; no previous treatment (including verteporfin therapy) that might compromise an assessment of the study treatment; predominantly classic CNV lesions	Monthly ranibizumab injections for 2 years	10% (0.5 mg)	41% (0.5 mg)	N/A (All patients received treatment)		2
			Verteporfin PDT on day 0 and then PRN following FA at months 3, 6, 9, or 12	66%	6%			
MARINA (2006; ranibizumab injection)[179]	716	Mean age 77 years; BCVA 20/40 to 20/320; primary or recurrent CNV; minimally classic or occult with no classic CNV lesions; presumed recent progression of disease	Monthly ranibizumab injections for 2 years	10% (0.5 mg)	33% (0.5 mg)	47%	4%	2
VIEW 1 and 2 (2012; aflibercept injection)[168]	2419	Mean age 76 years; BCVA 20/40 to 20/320; primary, active subfoveal (or juxtafoveal) CNV, with the total CNV area (classic plus occult CNV) ≥50% of total lesion size; any lesion subtype	Aflibercept 0.5 mg q 4 weeks 4	4%	30%	NA (All patients received treatment)		1
				5%	34%			
			Aflibercept 2.0 mg q 4 weeks	4%	31%			
			Aflibercept 2.0 mg q 4 weeks x 3, then q 8 weeks	6%	33%			
			Ranibizumab 0.5 mg q 4 weeks					

TABLE 3 Effects of Treatment on Vision in Randomized Controlled Trials of Subfoveal CNV (continued)

Study	No. of Patients	Patient Characteristics	Duration and Frequency of Treatment	Treated Eyes		Untreated Eyes		Years after Enrollment
				Visual Loss of 15 Letters or More*	Visual Gain of 15 Letters or More*	Visual Loss of 15 Letters or More*	Visual Gain of 15 Letters or More*	
CATT (2011; bevacizumab vs ranibizumab injection)[174]	1208	Mean age 79 years; BCVA 20/25 to 20/320; untreated, active CNV, with CNV, fluid, or hemorrhage under the fovea	Ranibizumab 0.5 mg q 4 weeks	6%	34%	NA (All patients received treatment)	1	CATT (bevacizumab vs. ranibizumab injection)[174]
			Bevacizumab 1.25 mg q 4 weeks	6%	31%			
			Ranibizumab 0.5 mg PRN	5%	25%			
			Bevacizumab 1.25 mg PRN	9%	28%			
VISION (2006; pegaptanib sodium injection)[181†]	590	Age ≥50 years; BCVA 20/40 to 20/320; subfoveal CNV with total lesion size ≤12 disc areas; IOP ≤23 mmHg	Injection every 6 weeks for 54 weeks (9 total treatments); then rerandomized and injection every 6 weeks through week 96 (8 total treatments)	45%	10%	59%	4%	2
TAP (2001; verteporfin PDT)[182]	609	Mean age 75 years; BCVA 20/40 to 20/200; classic CNV or occult CNV if >50% of total lesion size	Following first treatment, retreatment was considered every 3 months per FA findings through 21 months of follow-up	47%	8%	62%	4%	2
				41%‡		69%‡		

ANCHOR = Anti-VEGF Antibody for the Treatment of Predominantly Classic CNV in AMD; BCVA = best-corrected visual acuity; CNV = choroidal neovascularization; FA = fluorescein angiography; CATT = Comparison of Age-Related Macular Degeneration Treatment Trials; IOP = intraocular pressure; MARINA = Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD; NA = not applicable; PRN = as needed; PDT = photodynamic therapy; TAP = Treatment of Age-Related Macular Degeneration with Photodynamic Therapy; VIEW = VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD; VISION = VEGF Inhibition Study in Ocular Neovascularization

* Defined as doubling of the visual angle.

† Pegaptanib sodium injection was administered to patients who were allowed both prior and on-study PDT.

‡ Predominantly classic.

Abbildung 10: Effects of Treatment on vision in RCTs of subfoveal choroidal neovascularization

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

2021-B-045

Kontaktdaten

Deutsche Ophthalmologische Gesellschaft (DOG)

Unterstützt von:

Deutschsprachige Gesellschaft für Intraokularlinsen-Implantation (DGII), Berufsverband der Augenärzte (BVA), Retinologische Gesellschaft (RG)

DGf Allgemein- und Familienmedizin (DEGAM)

Indikation gemäß Beratungsantrag

…wird angewendet bei Erwachsenen zur Behandlung der neovaskulären (feuchten) altersabhängigen Makuladegeneration (nAMD).

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

Die Behandlung der neovaskulären altersabhängigen Makuladegeneration (nAMD) wurde zuletzt in einer Stellungnahme der ophthalmologischen Fachgesellschaften ausführlich dargestellt [1].
Nach Sicherung der Diagnose hat bisher eine Therapie mit Hemmstoffen des *vascular endothelial growth factor* (VEGF) zu erfolgen. Für die intravitreale operative Medikamentenapplikation (IVOM) ist nach der initialen Therapie eine Festlegung der Wiederbehandlungsstrategie gemäß individueller Kriterien angeraten. Obwohl in den meisten Zulassungsstudien eine Wiederbehandlung mit festen Intervallen zur Kontrolle und Behandlung erfolgte, gibt es auch zunehmend Evidenz für die Alternative einer Anpassung der Behandlungsintervalle in Abhängigkeit von der Aktivität der zugrundeliegenden Gefäßmembran. Einerseits geht eine Unterbehandlung mit schlechteren funktionellen Ergebnissen einher; andererseits gehen die Behandlungsrisiken, insbesondere die Gefahr einer infektiösen Entzündung, mit dem Risiko eines irreversiblen Sehverlusts, auf die Verabreichungsprozedur zurück. Daher ist der Grundsatz „so viel wie nötig, so wenig wie möglich“ zielführend.
In früheren Verfahren der frühen Nutzenbewertung (Aflibercept: A12-19 / BAnz AT 27.06.2013 B3, Brolucizumab: A20-23 / BAnz AT 01.10.2020 B6) hatten pharmazeutische Unternehmer keine Studiendaten vorlegen können, in denen die zweckmäßige Vergleichstherapie (Ranibizumab oder Aflibercept) gemäß deren Zulassung oder der jeweils aktuellen medizinischen Fachinformation eingesetzt worden war. Allerdings sehen die Fachinformationen unterschiedliche Wiederbehandlungsstrategien vor und lassen der ärztlichen Therapiefreiheit ausdrücklich Spielraum [2,3]. In die Beurteilung, ob eine Wiederbehandlung erfolgen soll, gehen sinnvollerweise viele Parameter wie die Funktion des Partnerauges, der Allgemeinzustand, Begleiterkrankungen und die Prognose von Sehfunktion und Lebenserwartung ein [1].

Zu berücksichtigen ist, dass vergleichende Studien bisher zumeist die Frage einer Nicht-Unterlegenheit („non-inferiority“) bewerten sollten. Statistische Signifikanz ist hier nicht gleichbedeutend mit einem klinisch relevanten Unterschied [4]. Zudem müssen Verzerrungspotential und Sensitivität (Fallzahlplanung, Studiendesign) berücksichtigt werden. Ein Beispiel für Studien mit geringer Aussagekraft ist die TREX-AMD Studie, in der anfangs nur 60 Patienten randomisiert wurden, zwei identisch behandelte Gruppen (‚treat & extend‘ vs. ‚treat & extend to PRN‘) einen signifikanten Unterschied bei Monat 24 zeigten, die

Retention allerdings nur bei 77% lag [5]. Eine Abnahme der notwendigen Wiederbehandlungen um 30 bis 50% bei vergleichbarer Wirksamkeit wäre durchaus ein relevanter Vorteil. Weil bisher eine Phase mit regelmäßigen Behandlungen für den Therapiestart vorgesehen ist, ist damit zu rechnen, dass die relevanten Unterschiede erst mit zunehmender Behandlungsdauer, als auch Studien mit mehrjähriger Nachverfolgung sichtbar werden.

Unterschiede auf seltene sicherheitsrelevante Ereignisse durch Wirkstoffe oder unterschiedlichen Behandlungshäufigkeiten sind nur mit sehr großen Fallzahlen zu belegen. Für die wirtschaftlichen Auswirkungen müssen neben der Prozedur und dem Medikament die Kosten der Kontrolluntersuchungen berücksichtigt werden.

Es gibt Hinweise auf eine jährliche Zunahme der zu behandelnden Patienten mit nAMD [6]. Diese Zunahme wird mit einer früheren Diagnose und dem demographischen Wandel erklärt. In der deutschen Versorgungspraxis findet die IVOM-Therapie im Rahmen der gesetzlichen Krankenversorgung statt. Es gibt zudem Selektivverträge, die von Maßnahmen der Qualitätskontrolle und Anreizen zu einem wirtschaftlichen Medikamenteneinsatz getragen werden [7,8]. In Deutschland wird mit einem wesentlichen Anteil auch der nicht zugelassene Wirkstoff Bevacizumab eingesetzt [9,10], für den eine vergleichbare Wirksamkeit und Sicherheit in randomisierten kontrollierten Studien nachgewiesen wurde [11,12].
Der Charakter der chronischen Erkrankung bedeutet für die nAMD, dass der Adhärenz eine wesentliche Bedeutung zukommt [13,14]. Registerdaten und nicht-interventionelle Studien belegen, dass im klinischen Alltag eine Unterbehandlung mit schlechteren funktionellen Ergebnissen assoziiert ist [15,16].

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung von „neovaskulärer (feuchter) altersabhängiger Makuladegeneration“, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

Basis der Entscheidung über die Behandlungsindikation ist die klinische Untersuchung mit Erhebung der bestkorrigierten Sehschärfe, Untersuchung von vorderem und hinterem Augenabschnitt und die optische Kohärenztomographie (OCT) [1]. Für die Bestätigung einer behandlungsbedürftigen Läsion ist initial außerdem eine Fluoreszenz-Angiographie gefordert.
Insbesondere die Untersuchung mit Hilfe der OCT (BAnz AT 22.03.2019 B2) liefert hochaufgelöste Bilder der zentralen Netzhaut, in denen nicht nur über die Detektion von Flüssigkeit in und unter der Netzhaut und Veränderungen der entsprechenden Netzhautschichten die Aktivität der nAMD-Läsionen beurteilt werden kann, sondern auch Hinweise auf eine limitierte Visusprognose und einen sinnvollen Therapie-Abbruch gefunden werden können. Neu aufgetretene Blutungen und eine Sehverschlechterung sind weitere Aktivitätskriterien, die auf eine notwendige Wiederbehandlung hinweisen können.
Bisher gibt es keine Belege dafür, dass unterschiedliche Strategien der Wiederbehandlung (PRN: Kontrolle und Wiederbehandlung bei Aktivität, Behandlungsserien, Treat & Extend: Verkürzung oder Verlängerung der Behandlungsintervalle) für individuelle Entscheidungen oder Subgruppen der Erkrankung Vorteile bieten. Daher sind verschiedene Behandlungsstrategien als zusätzliche Optionen in die Fachinformationen aufgenommen worden (Flexibilisierung ohne Priorisierung) [3].

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