COLLEGE OF PHARMACY
UNIVERSITY OF UTAH

L. S. SKAGGS PHARMACY INSTITUTE

UTAH MEDICAID P&T COMMITTEE REPORT
NOVEMBER 2023

INTRAVITREAL ANTI-VASCULAR ENDOTHELIAL GROWTH FACTORS

Ranibizumab (**Lucentis**)
Ranibizumab-eqrn (**Cimerli**)
Ranibizumab-nuna (**Byooviz**)
Ranibizumab ocular implant (**Susvimo**)
Aflibercept (**Eylea; Eylea HD**)
Faricimab-svoa (**Vabysmo**)
Brolucizumab-dbll (**Beovu**)
Bevacizumab*
**This agent is used off-label to treat ophthalmic diseases*

Report finalized: October 2023
Report presented: November 2023

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ABBREVIATIONS

AAO	American Academy of Ophthalmology
AAP	American Academy of Pediatrics
ADA	American Diabetes Association
AFI	Anterior flare intensity
AMD	Age-related macular degeneration
AOA	American Optometric Association
AREDS(2)	Age-Related Eye Disease Study (2)
ATE(s)	Arterial thromboembolic event(s)
BCVA	Best-corrected visual acuity
BLA	Biologics License Application
BRVO	Branch retinal vein occlusion
CI	Confidence interval
CI-DME	Central-involved diabetic macular edema
CMT	Central macular thickness
CRT	Central retinal thickness
CRVO	Central retinal vein occlusion
CST	Central subfield thickness
DME	Diabetic macular edema
DR	Diabetic retinopathy
DRSS	Diabetic Retinopathy Severity Scale
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein angiography
FDA	US Food and Drug Administration
H-H	Head-to-head
IOP	Intraocular pressure
ITT	Intention-to-treat population
mCNV	Myopic choroidal neovascularization
ME-RVO	Macular edema secondary to retinal vein occlusion
mL	Milliliters
nAMD	Neovascular age-related macular degeneration
NCI-DME	Non-central-involved diabetic macular edema
NOAEL	No observed adverse effect level
NPDR	Non-proliferative diabetic retinopathy
OCT	Optical coherence tomography
OCT-A	Optical coherence tomography angiography
PAHO	Pan American Health Organization
PBT	Post-baseline therapy
PDL	Preferred Drug List
PDR	Proliferative diabetic retinopathy
PDT	Photodynamic therapy
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PRN	As-needed
RCT(s)	Randomized controlled trial(s)

ROP	Retinopathy of prematurity
RVO	Retinal vein occlusion
SMD	Standardized mean difference
SR(s)	Systematic review(s)
SRF	Subretinal fluid
SRMA	Systematic review meta-analysis
T1D	Type 1 diabetes
T2D	Type 2 diabetes
US	United States
VEGF(-A)	Vascular endothelial growth factor(-A)

EXECUTIVE SUMMARY

Background:

Anti-vascular endothelial growth factor (anti-VEGF) agents are approved for treatment of a variety of ocular diseases, including diabetic retinopathy (DR), diabetic macular edema (DME), neovascular (wet) age-related macular degeneration (nAMD), macular edema secondary to retinal vein occlusion (ME-RVO), myopic choroidal neovascularization (mCNV), and retinopathy of prematurity (ROP).[1] Approved agents comprise 8 intravitreal anti-VEGF products, including two biosimilars of originator ranibizumab (Cimerli and Byooviz) that are available in the United States (US).[2-9]

Approved indications for the reviewed products are outlined as follows:

- Ranibizumab (Lucentis) and ranibizumab-eqrn (Cimerli)[4,7]: nAMD, DME, DR, ME-RVO, mCNV
- Ranibizumab-nuna (Byooviz)[8]: nAMD, ME-RVO, mCNV
- Ranibizumab ocular implant (Susvimo)[3]: nAMD
- Aflibercept (Eylea and Eylea HD)[5,6]: nAMD, DME, DR; in addition to these indications, Eylea (2 mg dosage) is also approved for ME-RVO and ROP
- Faricimab-svoa (Vabysmo) and brolucizumab-dbll (Beovu)[2,9]: nAMD, DME

Despite the agents having several overlapping indications, there are some crucial differences:

- Aflibercept (Eylea) is the only intravitreal anti-VEGF agent approved for the treatment of ROP in infants.[6] This agent is also available in a high-dose strength (Eylea HD, 8 mg).[5]
- In addition to intravitreal injection formulations, ranibizumab is also uniquely available as an ocular implant (Susvimo) with a drug reservoir holding 6 months' worth of treatment.[3]
- Newer agents (faricimab-svoa, brolucizumab-dbll) and formulations (Eylea HD, Susvimo) to market have made some advances with respect to effect durability, allowing less frequent dosing intervals, particularly for the treatment of nAMD, DME, and DR, compared to earlier approved agents/formulations.[2,3,5,9]

In addition to the aforementioned anti-VEGF products, bevacizumab, commercially available as an *intravenous* dosage form,[10] is used off-label as an intravitreal injection to treat certain ophthalmic conditions, including nAMD, DME, and ROP.[11,12] See **Table 3** for recognized ocular off-label uses compiled in the drug compendium, Micromedex.

Guideline recommendations for intravitreal anti-VEGF therapy:

Reviewed guidelines for pharmacologic treatment of nAMD, DR, DME, and ME-RVO include those from the American Academy of Ophthalmology (AAO, 2020)[13-15] and American Optometric Association (AOA, 2019).[16] In addition, a 2017 position statement by the American Diabetes Association (ADA) on the management of DR was reviewed.[17] For specific recommendations for the management of ROP, we also reviewed a 2017 guideline from the Pan American Health Organization (PAHO) and a 2018 policy statement published by the American Academy of Pediatrics (AAP).[18,19] Expert guidance statements were reviewed for the treatment of mCNV.[20,21]

Overall, reviewed treatment guidelines and expert guidance statements recommend intravitreal anti-VEGFs as a drug class, without specifying a preference for one agent over another.[13-17,19-21]

Intravitreal anti-VEGF agents are generally recommended as first-line therapy for nAMD, central-involved DME (CI-DME), branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO) in the presence of macular edema, and mCNV.[13-15,17,20,21] For severe forms of non-proliferative diabetic retinopathy (NPDR), the AOA 2019 guideline recommends either pan-retinal photocoagulation or intravitreal anti-VEGF injections as initial treatment.[16] Generally, guidelines recommend pan-retinal photocoagulation as first-line for PDR, but intravitreal anti-VEGF agents can also be considered.[14,16,17] Regarding the particular agents for use, guidelines and expert guidance statements cite evidence for the approved intravitreal agents at their time of drafting (eg, ranibizumab, aflibercept), along with evidence for the use of intravitreal bevacizumab (off-label) for the treatment of nAMD, DR, ME-RVO, and mCNV.[13-15,21]

Although laser therapy is recommended first-line by the 2017 PAHO guideline for infants meeting treatment criteria for ROP, intravitreal anti-VEGF therapy can be considered for certain infants (eg, those who failed laser therapy and/or with aggressive ROP).[19] The 2018 AAP statement on ROP specifically recommends considering intravitreal anti-VEGF agents (eg, ranibizumab, bevacizumab) for infants with zone I: stage 3+ ROP.[18] Notably, both of these aforementioned publications predated approval of aflibercept (Eylea) for the treatment of ROP.[6]

Direct comparative evidence:

We reviewed systematic reviews (SRs) of randomized controlled trials (RCTs) comparing intravitreal anti-VEGF agents addressed by this report, including the off-label use of intravitreal bevacizumab, to each other for the management of nAMD, DME, DR, ME-RVO, mCNV, and ROP. No direct head-to-head (H-H) evidence was identified for the higher dosage formulation of aflibercept (Eylea HD, 8 mg) or between any anti-VEGF products for the treatment of ROP.[22-24]

In many of the comparisons across the reviewed indications, intravitreal anti-VEGF agents were found to exhibit similarity or non-inferiority with respect to the primary efficacy endpoint, most often measured as change in best-corrected visual acuity (BCVA), and safety. The following bullets outline direct evidence showing significant differences between agents; please refer to **Section 6.0** for details regarding these comparisons in addition to comparisons with non-significant differences.

Direct comparative evidence with significant differences for nAMD:

- The 2 phase III RCTs (HAWK and HARRIER) comparing **aflibercept 2 mg** (every 8 weeks, after 3 initial monthly loading doses) to **brolucizumab 6 mg** (every 8 or 12 weeks depending on disease activity, after 3 initial monthly injections) showed no significant differences for the primary endpoint, BCVA improvement at week 48.[25] After 96 weeks of treatment, brolucizumab 6 mg continued to perform similarly to aflibercept with respect to BCVA improvement in the two studies.[26] However, some significant differences occurred in favor of brolucizumab 6 mg for the following secondary outcomes: a) proportion of treated eyes with disease activity at week 16, b) improvement in central subfield thickness (CST) at weeks 16 and 48, and c) resolution of retinal fluid at 16 and 48 weeks.[25] In both trials, brolucizumab 6 mg continued to outperform aflibercept for reduction in CST and resolution of retinal fluid at 96 weeks.[26] A recent SR meta-analysis (SRMA), including the 48-week

results from HAWK and HARRIER and a phase II RCT, also showed brolucizumab (3 mg and 6 mg) had significantly greater reductions in CST at month 12 compared to aflibercept 2 mg.[27]

- A single-dose (phase I/II) RCT found the median duration to receiving post-baseline therapy (predefined by protocol criteria and determined by investigators' discretion) was significantly longer with **brolucizumab 6 mg** compared to **ranibizumab 0.5 mg** (75 days vs 45 days, respectively).[28] However, longer duration studies are needed to more fully describe how these agents compare to one another over multiple doses.
- In the VIEW RCTs, a significantly higher proportion of participants had no retinal fluid at week 96 (a secondary endpoint) with monthly **aflibercept 2 mg** (54.4%) versus monthly **ranibizumab 0.5 mg** (45.5%).[29] Additionally, participants treated with aflibercept had significantly fewer number of mean injections compared to participants treated with ranibizumab during weeks 52 through 96. No significant difference between aflibercept and ranibizumab was shown for the primary endpoint (BCVA improvement at week 52).[29]
- Based on 7 RCTs, a direct SRMA (2022) reported a significant difference favoring **ranibizumab** over **bevacizumab**[*] for the change in central macular thickness (CMT) after 12 months; however, no significant difference was found after 24 months of treatment.[30] Another SRMA, which included all of the same studies as the previous SRMA plus an additional study, showed a significant pooled-effect difference in favor of monthly ranibizumab versus bevacizumab as-needed (PRN) for improvement in BCVA and reduction in central retinal thickness (CRT) from baseline to 12 months.[31,32] In addition, when both ranibizumab and bevacizumab were administered on a fixed monthly regimen, there was a significantly greater reduction in CRT with ranibizumab from baseline to 12 months.[31,32]

Direct comparative evidence with significant findings for DME:

- A recently published SRMA of 8 trials showed **aflibercept 2 mg** appears comparable to **ranibizumab (0.3 mg and 0.5 mg)** for the change in BCVA and CMT reduction at 6 and 12 months; most included studies used a PRN dosing interval[†].[33] Aflibercept-treated participants had a significantly lower mean number of injections compared to ranibizumab-treated participants.[33] An additional short-term RCT (with up to 2 treatment doses per arm over 3 months) favored **aflibercept 2 mg** over **ranibizumab 0.5 mg** for the improvement in CRT at day 90 in a pooled population with phakic and pseudophakic eyes.[34]
- Two-year results from the RCT Protocol T comparing **aflibercept 2 mg** to **ranibizumab 0.3 mg** and **bevacizumab 1.25 mg** (all PRN dosing intervals), showed aflibercept was superior to bevacizumab at 2 years for improving visual acuity among the subgroup of participants with worse baseline visual acuity (20/50 to 20/320).[35] Aflibercept demonstrated superiority to ranibizumab among participants with worse visual acuity at 1 year[36]; however, no significant difference was observed at year 2.[35] In the entire study population, ranibizumab and aflibercept performed similarly to each other regarding changes in visual acuity and CST reduction, but both significantly outperformed bevacizumab for reducing mean CST from baseline to year 2. A higher rate of any vascular events

[*] Most of the included RCTs used ranibizumab 0.5 mg and bevacizumab 1.25 mg, administered on a PRN or monthly regimen after 3 initial monthly injections.
[†] Some of the included studies by Chen et al (2023) had full-text non-English publications; therefore the dosing and dosing interval was unable to be ascertained for all included studies.

including non-fatal stroke and vascular death occurred with ranibizumab (12%) versus aflibercept (5%) and bevacizumab (8%), according to the Antiplatelet Trialists' Collaboration definition.[35]

- A phase II RCT (BOULEVARD) showed monthly **faricimab 6 mg** was superior to monthly **ranibizumab 0.3 mg** for improving baseline BCVA at week 24 among *treatment-naïve* adults with CI-DME.[37] Furthermore, faricimab 6 mg resulted in a greater reduction in mean CST from baseline to week 24 compared to ranibizumab in treatment-naïve and treatment-experienced participants.[37]
- In a phase III RCT (KITE), **brolucizumab 6 mg** (every 12 weeks, with the option of every 8 week dosing based on disease activity) was significantly favored over **aflibercept 2 mg** (every 8 weeks) for the average change from baseline in CMT from week 40 through week 52.[38] Nonetheless, this RCT in addition to a second phase III RCT (KESTREL) showed no significant difference between brolucizumab 6 mg and aflibercept 2 mg for the primary endpoint of mean change in BCVA at week 52.[38]
- Three RCTs evaluated **bevacizumab (1.25 mg or 1.5 mg)** compared to **ranibizumab 0.5 mg**.[39-41] In the first RCT, ranibizumab 0.5 mg (PRN) produced a significantly greater improvement in mean BCVA from baseline to weeks 8 and 32 compared to bevacizumab 1.5 mg (PRN).[39] Notably, a significantly higher proportion of eyes treated with ranibizumab achieved a CST ≤275 µm at weeks 4, 28, 36, and 44 compared to bevacizumab. Overall, the mean number of injections was significantly higher with bevacizumab versus ranibizumab (9.84 vs 7.67, respectively).[39] Yet, the second RCT, also using PRN dosing intervals, found participants treated with bevacizumab 1.25 mg had a significantly lower number of mean injections at the end of the 12-month period compared to treatment with ranibizumab 0.5 mg (5.1 vs 6.5, respectively).[40] The third RCT found monthly ranibizumab 0.5 mg significantly outperformed monthly bevacizumab 1.25 mg for improving BCVA from baseline to 6 months and for reducing central area thickness at 6 months.[41]

Contraindications, and safety warnings and precautions:

All of the reviewed FDA-approved intravitreal anti-VEGF agents are contraindicated in patients who have previously exhibited hypersensitivity reactions (eg, intraocular inflammation, rash, urticaria, pruritus) to the active ingredient or any excipient(s), and those with an active periocular or ocular infection.[2-9] Except for ranibizumab and its biosimilars (Cimerli and Byooviz), the remaining products are also contraindicated in patients with active intraocular inflammation.[2,3,5,6,9]

All of the reviewed FDA-approved intravitreal anti-VEGF injectable agents carry warnings for the potential of endophthalmitis, retinal detachment(s), elevated intraocular pressure (IOP), and arterial thromboembolic events (ATEs).[2,4-9] Certain agents also carry unique labeled warnings and precautions, as outlined below:

- Ranibizumab (Lucentis) and ranibizumab-eqrn (Cimerli)[4,7]: A higher frequency of fatalities was observed in patients with DME and DR at baseline receiving monthly injections compared to control.
- Aflibercept (Eylea)[6]: Long-term ROP monitoring is required in treated infants in order to identify possible need (ie, with reactivation of disease) for retreatment or additional treatment with other options.
- Brolucizumab (Beovu)[9]: Patients may be at risk of developing retinal vascular occlusion and/or retinal vasculitis after receiving the injection; patients should be advised to promptly report any visional changes.

Susvimo also carries a risk of endophthalmitis and retinal detachment, in addition to implant- or procedure-related warnings (eg, implant dislocation, conjunctival reactions, vitreous hemorrhage, postoperative reduction in visual acuity).[3]

Utah Medicaid Preferred Drug List (PDL) considerations:

The Utah Medicaid Pharmacy and Therapeutics Committee may consider recommending the following for the PDL.

A. At least 1 FDA-approved *injectable* (ie, non-implant) intravitreal anti-VEGF agent as preferred on the PDL.
    I. In general, intravitreal anti-VEGF agents, as a drug class (including intravitreal bevacizumab), are recommended as first-line therapy for most reviewed ocular diseases (nAMD, CI-DME, ME-RVO, mCNV), without preference of one agent over another specified among guidelines or guidance statements.[13-17,19-21] Intravitreal anti-VEGF agents are generally not considered first-line for DR and ROP in reviewed guidelines, but may be a subsequent-line treatment option.[14,16-19]
    II. Off-label use of intravitreal bevacizumab for nAMD, DME, DR, ME-RVO, mCNV, and ROP can be an acceptable alternative to PDL-preferred, FDA-approved intravitreal anti-VEGF agents, and may be permitted via prior authorization[‡].
        i. Bevacizumab administered intravitreally has recognized off-label uses for all of the reviewed indications (nAMD, DME, DR, ME-RVO, mCNV, and ROP) in Micromedex, each rated as *Evidence Favors Efficacy*.[11] However, unlike the other anti-VEGF agents that are formulated for intravitreal administration, bevacizumab must be compounded for intravitreal use.[1,42]
        ii. Of note, *intravenous* bevacizumab has on-label uses for many oncology indications[10]; its intravenous use will be addressed in a future report.
    III. Because the ocular implant of ranibizumab is approved only for the treatment of nAMD in patients who have previously responded to ≥2 anti-VEGF intravitreal injections, it may be reserved (via non-preferred status/prior-authorization) for patients who have limitations using other agents.

[‡] A non-preferred intravitreal anti-VEGF agent should be accessible by prior authorization for reasonable requests (eg, for a unique indication not shared with the preferred anti-VEGF agent[s] or good-quality evidence supporting the preference).

1.0 INTRODUCTION

Anti-vascular endothelial growth factor (anti-VEGF) agents are used to treat a variety of ocular diseases including diabetic retinopathy (DR), diabetic macular edema (DME), neovascular age-related macular degeneration (nAMD), macular edema secondary to retinal vein occlusion (ME-RVO), myopic choroidal neovascularization (mCNV),[1] and more recently, retinopathy of prematurity (ROP),[6] previously referred to as retrolental fibroplasia.[43] These agents target VEGF, a protein that stimulates angiogenesis and vascular permeability.[1,42,44] While VEGF is fundamental in regulating vascular homeostasis throughout the body, pathogenic mechanisms resulting from over-production of VEGF in the eye can lead to retinal damage and ultimately permanent vision loss.[44-46] These mechanisms are as follows[44-46]:

- Edema due to exudate leaking from new, fragile capillaries, existing capillaries, or both
- Formation of new, aberrant blood vessels outside of the retina in the pre-retinal space
    - Vascular leakage can result in vitreous hemorrhaging or macular scarring

Eight intravitreal anti-VEGF products (including 2 biosimilars of originator ranibizumab) are available in the United States (US) and are approved by the Food and Drug Administration (FDA) to treat ≥1 ophthalmic indication. These products are aflibercept (Eylea and Eylea HD)[5,6]; faricimab-svoa (Vabysmo)[2]; brolucizumab-dbll (Beovu)[9]; ranibizumab (Lucentis)[4]; 2 biosimilars of ranibizumab, ranibizumab-eqrn (Cimerli)[7] and ranibizumab-nuna (Byooviz)[8]; and the ranibizumab ocular implant (Susvimo)[§].[3] **Table 1** summarizes the labeled indications for the ocular anti-VEGF agents.

Despite the overlap in indications among these agents, there are some crucial differences:

- Unlike the other intravitreal agents, aflibercept as the brand Eylea has a unique pediatric-only indication for the treatment of retinopathy in preterm infants[6]; this is the first and only FDA-approved pharmacotherapy for this indication.[47] Additionally, aflibercept is available in two dosage strengths: 8 mg (Eylea HD) and 2 mg (Eylea); both are approved for nAMD, DME, and DR, while Eylea (2 mg dose) is additionally approved for ME-RVO and ROP.[5,6]
- Unlike the other FDA-approved intravitreal anti-VEGF agents, originator ranibizumab (Lucentis) and its biosimilars (Cimerli and Byooviz) are uniquely approved for mCNV.[4,7,8] Of the ranibizumab biosimilars, Cimerli is approved for all of the indications of Lucentis, whereas Byooviz is approved for all but DME and DR.[4,7,8]
- The ocular implant of ranibizumab (Susvimo) is only approved for nAMD in patients who previously responded to ≥2 anti-VEGF intravitreal injections.[3]

Newer formulations to market have made some advances with respect to effect durability and dosing intervals, particularly for the treatment of nAMD, DME, and DR. Newer formulations of aflibercept, faricimab-svoa, brolucizumab-dbll, and ranibizumab generally maintain their efficacy with longer dosing intervals after the initial loading dose phase. High-dose aflibercept (8 mg) can be extended to every 2−4 months for nAMD/DME or every 2−3 months for DR;[5] faricimab-svoa can employ intervals as long as every 4 months for nAMD, or every 2 months for DME;[2] brolucizumab-dbll dosing can extend to every 2−3 months for nAMD and DME[9]; and ranibizumab ocular implant for the treatment of nAMD lasts for 6

[§] The earliest intravitreal anti-VEGF drug approved by the FDA (2004), pegaptanib (Macugen), has been discontinued in the US, and therefore, is not reviewed in this report.

months before requiring surgical refill of the medication reservoir.[3] In contrast, based on prescribing information, early-approved formulations of ranibizumab and aflibercept intravitreal injections entail monthly or bimonthly (for aflibercept) maintenance dosing for nAMD, DME, and DR; an extended interval of every 3 months can be used for nAMD, but the extension can lessen efficacy.[4,6] **Table 2** summarizes the dosing recommendations for the labeled indication(s) and available formulations of the FDA-approved anti-VEGF intravitreal agents. Of note, alternative, more flexible, dosing strategies (ie, treat-and-extend, as-needed [PRN]) may be used in clinical practice to reduce injection burden.[14]

Table 1. FDA-approved Indications for Intravitreal Anti-VEGF Agents[2-9,48]

Generic Name (Brand)	Labeled Indications					
	nAMD	DME	DR	ME-RVO	mCNV	ROP
Ranibizumab (**Lucentis**)	✓	✓	✓	✓	✓	
Ranibizumab-eqrn (**Cimerli**)[a]	✓	✓	✓	✓	✓	
Ranibizumab-nuna (**Byooviz**)[a]	✓			✓	✓	
Aflibercept (**Eylea**)	✓	✓	✓	✓		✓
Aflibercept (**Eylea HD**)	✓	✓	✓			
Faricimab-svoa (**Vabysmo**)	✓	✓				
Brolucizumab-dbll (**Beovu**)	✓	✓				
Ranibizumab ocular implant (**Susvimo**)	✓					

[a] *FDA-approved biosimilar of originator ranibizumab*

Abbreviations: DME, diabetic macular edema; DR, diabetic retinopathy; FDA, Food and Drug Administration; mCNV, myopic choroidal neovascularization; ME-RVO, macular edema secondary to retinal vein occlusion; nAMD, neovascular (wet) age-related macular degeneration; ROP, retinopathy of prematurity; VEGF, vascular endothelial growth factor

Anti-VEGF agents for intravitreal injection are available as either a single-dose pre-filled syringe, a single-dose glass vial, or both, depending on the product.[2,4-9] Each syringe or vial is recommended for single-use in one eye. If the other eye needs to be treated, a new syringe or vial should be used. Intravitreal anti-VEGF agents are required to be administered by a qualified practitioner[2,5,6,9] such as an ophthalmologist or retina specialist.[44] With respect to Susvimo, a qualified practitioner in *vitreoretinal surgery* should perform the implantation procedure, initial filling of the implant, and removal of the implant (when needed), whereas a specialized practitioner in *ophthalmic surgery* should perform the refill-exchange procedure. See **Appendix A** for additional details on the preparation, administration, and proper storage of these products.

Table 2. FDA-approved Intravitreal Anti-VEGF Agents: Dosing Recommendations, and Product Formulation and Strength

Generic Name **Brand** (approval year)	Formulation and Strength	Dosing Recommendations per Labeled Indication(s)[a]
Ranibizumab **Lucentis** (2006)[4]	Single-dose prefilled syringe (0.05 mL) • 10 mg/mL (0.5 mg) • 6 mg/mL (0.3 mg)	• **nAMD:** intravitreally inject 0.5 mg into the affected eye once a month (**recommended regimen**). While not as effective as the recommended regimen, the following alternative dosing regimen(s) may be used: ▪ Intravitreally inject 0.5 mg into the affected eye once a month for the *first 3 months*, then reduce the dosing frequency ▪ Intravitreally inject 0.5 mg into the affected eye once a month for the *first 4 months*, then inject 0.5 mg once every 3 months ○ If an alternative regimen is used, patients should have regular ocular assessments • **DME and DR:** intravitreally inject 0.3 mg into the affected eye once a month • **ME-RVO:** intravitreally inject 0.5 mg into the affected eye once a month • **mCNV:** intravitreally inject 0.5 mg into the affected eye once a month for ≤3 months. If needed, patients may be retreated
Ranibizumab-eqrn **Cimerli** (2022)[7]	Single-dose glass vial (0.05 mL) • 10 mg/mL (0.5 mg) • 6 mg/mL (0.3 mg)	
Ranibizumab-nuna **Byooviz** (2021)[8]	Single-dose glass vial (0.05 mL) • 10 mg/mL (0.5 mg)	• **nAMD:** intravitreally inject 0.5 mg into the affected eye once a month (**recommended regimen**). While not as effective as the recommended regimen, the following alternative dosing regimen(s) may be used: ▪ Intravitreally inject 0.5 mg into the affected eye once a month for the *first 3 months*, then reduce the dosing frequency ▪ Intravitreally inject 0.5 mg into the affected eye once a month for the *first 4 months*, then inject 0.5 mg once every 3 months ○ If an alternative regimen is used, patients should have regular ocular assessments • **ME-RVO:** intravitreally inject 0.5 mg into the affected eye once a month • **mCNV:** intravitreally inject 0.5 mg into the affected eye once a month for ≤3 months. If needed, patients may be retreated
Ranibizumab ocular implant **Susvimo** (2021)[3,49]	Single-dose glass vial 100 mg/mL	• **nAMD:** ocular implant provides continuous intravitreal delivery of ranibizumab 2 mg (0.02 mL of 100 mg/mL) over a 6-month period; refill-exchange procedures should be conducted every 24 weeks (about 6 months) ○ Indicated for patients who previously responded to ≥2 anti-VEGF intravitreal injections ○ Supplemental treatment: an intravitreal injection of ranibizumab 0.5 mg (0.05 mL of 10 mg/mL) can be considered if needed; the injection can be administered while the implant is inserted
Aflibercept **Eylea** (2011)[6]	Single-dose pre-filled syringe or glass vial (0.05 mL) • 2 mg/0.05 mL	• **nAMD:** intravitreally inject 2 mg into the affected eye once a month for the *first 3 months*, then inject 2 mg once every 2 months (8 weeks; **recommended regimen**)[b]. While not as effective as the recommended regimen, the following alternative dosing regimen(s) may be used: ▪ After a patient has been effectively treated for 1 year, an intravitreal injection of 2 mg into the affected eye can be administered once every 12 weeks ○ If an alternative regimen is used, patients should have regular ocular assessments • **DME and DR:** intravitreally inject 2 mg into the affected eye once a month for the first 5 injections, then inject 2 mg once every 2 months (8 weeks)[b] • **ME-RVO:** intravitreally inject 2 mg into the affected eye once a month (around 25 days) • **ROP:** intravitreally inject 0.4 mg (0.01 mL) into the affected eye using medication from a glass vial (not pre-filled syringe); can also be administered bilaterally on the same day. Repeat injections into the same eye can be given, but should be at least 10 days apart
Aflibercept **Eylea HD** (2023)[5,50]	Single-dose glass vial (0.07 mL) • 114.3 mg/mL (8 mg)	• **nAMD and DME:** intravitreally inject 8 mg into the affected eye once a month for the *first 3 months*, then inject 8 mg once every 8 to 16 weeks • **DR:** intravitreally inject 8 mg into the affected eye once a month for the *first 3 months*, then inject 8 mg once every 8 to 12 weeks
Faricimab-svoa **Vabysmo** (2022)[2]	Single-dose glass vial (0.05 mL) • 120 mg/mL (6 mg)	• **nAMD:** intravitreally inject 6 mg into the affected eye once a month for the first 4 injections[c]. Based on assessments of visual acuity and optical coherence tomography, one of the following dosing regimens should be given after the initial 4 injections: ▪ At week 28 and week 44; ▪ At week 24, week 36, and week 48; or ▪ At week 20, week 28, week 36, and week 44 ○ Patients should have regular ocular assessments • **DME:** one of the following recommended regimens may be used[c]:

[a] *Unless specified otherwise, intravitreal injections that are given on a monthly basis around every 28 days.*

[b] *Compared to an 8-week dosing interval, a more frequent dosing regimen of every 4 weeks (around 25 days) was not shown to have greater efficacy in the majority of aflibercept-treated patients; however, some patients may require monthly dosing after the initial 3 months (12 weeks) of treatment for nAMD, or after the initial 5 months (20 weeks) of treatment for DME or DR.*[6]

[c] *Compared to an 8-week dosing interval, a more frequent dosing regimen of every 4 weeks (monthly) was not shown to have greater efficacy in the majority of patients treated with faricimab-svoa; however, some patients may require monthly dosing after the initial 4 injections of treatment for nAMD or DME.*[2]

Abbreviations: CST, central subfield thickness; DME, diabetic macular edema; DR, diabetic retinopathy; FDA, Food and Drug Administration; mCNV, myopic choroidal neovascularization; ME-RVO, macular edema secondary to retinal vein occlusion; mg, milligram; ml, milliliter; nAMD, neovascular (wet) age-related macular degeneration; ROP, retinopathy of prematurity; VEGF, vascular endothelial growth factor

Table 2. FDA-approved Intravitreal Anti-VEGF Agents: Dosing Recommendations, and Product Formulation and Strength

Generic Name **Brand** (approval year)	**Formulation and Strength**	**Dosing Recommendations per Labeled Indication(s)**[a]
		▪ Intravitreally inject 6 mg into the affected eye once a month for at least 4 injections. If after injecting at least 4 doses, the edema has resolved based on optical coherence tomography of the macula CST, then the dosing interval may be extended up to 4 weeks or decreased up to 8 weeks, with respect to visual acuity and CST assessments ▪ Intravitreally inject 6 mg into the affected eye once a month *for the first 6 injections*, then inject 6 mg once every 2 months (8 weeks) ○ Patients should have regular ocular assessments
Brolucizumab-dbll **Beovu** (2019)[9]	Single-dose pre-filled syringe or glass vial (0.05 mL) • 6 mg/0.05 mL	• **nAMD:** intravitreally inject 6 mg into the affected eye once a month (around every 25 to 31 days) for the *first 3 injections*, then inject 6 mg once every 8 to 12 weeks • **DME:** intravitreally inject 6 mg into the affected eye once every 6 weeks (around every 39 to 45 days) for the *first 5 injections*, then inject 6 mg once every 8 to 12 weeks

[a] *Unless specified otherwise, intravitreal injections that are given on a monthly basis around every 28 days.*

[b] *Compared to an 8-week dosing interval, a more frequent dosing regimen of every 4 weeks (around 25 days) was not shown to have greater efficacy in the majority of aflibercept-treated patients; however, some patients may require monthly dosing after the initial 3 months (12 weeks) of treatment for nAMD, or after the initial 5 months (20 weeks) of treatment for DME or DR.*[6]

[c] *Compared to an 8-week dosing interval, a more frequent dosing regimen of every 4 weeks (monthly) was not shown to have greater efficacy in the majority of patients treated with faricimab-svoa; however, some patients may require monthly dosing after the initial 4 injections of treatment for nAMD or DME.*[2]

Abbreviations: CST, central subfield thickness; DME, diabetic macular edema; DR, diabetic retinopathy; FDA, Food and Drug Administration; mCNV, myopic choroidal neovascularization; ME-RVO, macular edema secondary to retinal vein occlusion; mg, milligram; ml, milliliter; nAMD, neovascular (wet) age-related macular degeneration; ROP, retinopathy of prematurity; VEGF, vascular endothelial growth factor

Bevacizumab, an *intravenous* anti-VEGF agent approved by the FDA for the treatment of certain oncological diseases,[10] is used off-label as an intravitreal injection to treat certain ophthalmic conditions (eg, nAMD, DME, ROP).[11,12] Because the marketed dosage of bevacizumab is not designed for use in the eye, the appropriate dosage for intravitreal injection must be compounded,[1,42] which raises potential concerns for inconsistent potency between compounded injections and risk of contamination.[51] **Table 3** provides off-label dosing of bevacizumab based on the pharmacy compendium, Micromedex.

Bevacizumab-vikg (ONS-5010/Lytenava), an ophthalmic formulation, is currently under clinical investigation for the treatment of nAMD[51,52]; information from the phase III, active comparator trial (NORSE TWO) is reviewed in **Section 6.1.10** of this report.

Table 3. Off-label Use of Bevacizumab for Ocular Indications: Dosing Recommendations[a]

Off-Label Indications (Strength of Recommendation and Level of Evidence) and Dosing[11]
Adult off-label indications
• **nAMD - CNV** (Class IIa, Category B): ○ Continuous regimen(s): ▪ Intravitreally inject 1.25 mg into the affected eye once every 4 weeks, 6 weeks, or 8 weeks for 1 year, irrespective of changes in visual acuity ○ As-needed regimen(s): ▪ Intravitreally inject 1.25 mg into the affected eye once every 6 weeks for the first 3 doses, then on an as-needed basis ▪ Intravitreally inject 1.25 mg into the affected eye once every 4 weeks for a total of 3 doses, or until subretinal fluid, macular edema, pigment epithelial detachment, or all of these conditions have resolved ▪ Intravitreally inject 2.5 mg into the affected eye once every 4 weeks for a total of 3 doses • **DME** (Class IIb, Category B)**:** intravitreally inject 1.25 mg into the affected eye at baseline, 6 weeks, and 12 weeks. Repeated injections once every 6 weeks can be considered (maximum number of injections during the first year, 9) • **DR** (Class IIa, Category B): No dosing regimen is provided • **ME-RVO** (Class IIb, Category B)**:** ○ Branch RVO regimen(s): intravitreally inject 1.25 mg into the affected eye as a one-time dose. Repeated injections can be administered on a 1 to 3 month basis for patients who have: ▪ Foveal thickness ≥250 µm; or ▪ Recurring or persisting macular edema ○ Central RVO regimen(s): intravitreally inject 1.25 mg into the affected eye once every 6 weeks for a total of 24 weeks (4 total doses) • **mCNV** (Class IIb, Category B)**:** intravitreally inject 1.25 mg into the affected eye as a one-time dose. Repeated monthly injections can be administered on an as-needed basis
Pediatric off-label indications
• **ROP** (Class IIb, Category B): ○ Intravitreally inject 0.625 mg into the affected eye as a one-time dose ○ Intravitreally inject 0.625 mg into the affected eye as a one-time dose, followed by a vitrectomy after 7 days ○ Intravitreally inject 0.25 mg into the affected eye as a one-time dose, followed by laser treatment (ie, deferred laser or sparing laser therapy) ○ As a one-time dose, intravitreally inject 0.016 mg, 0.008 mg, or 0.004 mg

*Strength of recommendation: Class I, recommended; Class IIa, recommended in **most** cases; Class IIb, recommended in **some** cases*

Level of Evidence: Category A, based on well-conducted, RCTs with a large sample size, or meta-analyses of RCTs demonstrating homogeneous results; Category B, based on non-randomized studies, RCTs with a small sample size or methodological limitations, or meta-analyses of RCTs with conflicting results

[a] *Note that other off-label dosing regimens may be used in the treatment of the listed ophthalmic conditions; the dosing regimens provided in this table are reported according to the information presented by the drug compendium, Micromedex.*

Abbreviations: CNV, choroidal neovascularization; DME, diabetic macular edema; DR, diabetic retinopathy; mCNV, myopic choroidal neovascularization; ME-RVO, macular edema secondary to retinal vein occlusion; nAMD, neovascular (wet) age-related macular degeneration; ROP, retinopathy of prematurity; RVO, retinal vein occlusion

2.0 METHODS

2.1 Systematic literature search

Search strategies for systematic reviews (SRs) of randomized controlled trials (RCTs) were developed using keyword phrases and controlled vocabulary (eg, Medical Subject Headings [MeSH]) in Ovid-Medline and Epistemonikos. Methodological filters, either independently derived, website-embedded, or from McMaster University,[53] were used in the bibliographic databases to identify SRs. Databases were searched from 2020 to current; if no SRs were identified within that timeframe for a particular indication, a supplemental SR search was performed for the earliest proceeding year (ie, 2019). **Appendix B** lists the complete search strategy, including search terms, for each database.

For treatment guidelines addressing intravitreal injections of anti-VEGF therapy for the 6 FDA-approved ocular indications (ie, nAMD, DR, DME, ME-RVO, mCNV, and ROP), we primarily focused on recently published (within the past 6 years) US-based guidelines, or if unavailable, international guidelines. If no US- or international-based guidelines were found, we included expert guidance statements. Although guidelines may have included additional recommendations about screening or non-pharmacologic interventions, these recommendations were not extracted. The following organizational websites were searched for relevant guidelines pertaining to the pharmacologic management of the aforementioned indications:

- American Optometric Association (AOA; https://www.aoa.org/)
- American Academy of Ophthalmology (AAO; https://www.aao.org/)
- American Diabetes Association (ADA; https://www.diabetes.org/)
- American Academy of Pediatrics (AAP; https://www.aap.org/): this website was searched specifically for guidelines on ROP
- Pan American Health Organization (PAHO; https://www.paho.org/en); this website was searched specifically for guidelines on ROP

Additionally, the following information was obtained from the listed websites:

- Package inserts (ie, prescribing information): drug sponsors' websites; Drugs@FDA website (https://www.accessdata.fda.gov/scripts/cder/daf/)
- Evidence-based drug information: Micromedex (https://www.micromedexsolutions.com/home/dispatch); DynaMed (https://www.dynamed.com/); UpToDate (https://www.uptodate.com/contents/search)

2.2 Screening

Publication titles and abstracts were independently screened by one reviewer to determine eligibility for inclusion. Full text articles were retrieved for publications that were voted for inclusion. The final determination for publication inclusion was made by the lead author after reviewing the full text article. See **Appendix C** for the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart, which displays the literature review process.

2.3 Inclusion and exclusion criteria

SRs of RCTs that included direct head-to-head (H-H) comparative efficacy or safety outcomes among the FDA-approved intravitreal anti-VEGF agents (see **Table 2**), as well as intravitreal bevacizumab, for the treatment of nAMD, DR, DME, ME-RVO, mCNV, and ROP were included. Excluded references met one or more of the following criteria:

- An SR methodology was not used in the review
- RCTs with a comparison to placebo, an agent not of interest, or to the same active drug ingredient with a different dosage strength
- Network meta-analyses (NMAs) with only indirect comparative outcome results
- SRs or RCTs that solely compared differing injection regimens (eg, treat-and-extend vs. monthly) between the same intravitreal anti-VEGF agent, an agent not of interest, or in general without specifying particular agents
- Pharmacokinetic, observational, or extension studies
- RCTs of non-parallel design (eg, crossover)
- Studies addressing use for non-ophthalmic-related indications

SRs were also excluded if a more recent SR identified all of the H-H RCT comparisons of interest for a particular agent or indication. Notably, comparative outcome information was not extracted from SRs if the authors did not provide appropriate citations to identify the corresponding primary study. It is possible that more recent H-H RCTs (eg, published in 2023) are available but not mentioned in this report because an additional RCT search was not performed to supplement the SR search.

A list of included and excluded references is provided in **Appendix D**.

3.0 DISEASE OVERVIEW AND TREATMENT GUIDELINES

For pharmacologic recommendations on the use of intravitreal anti-VEGF agents, we reviewed guidelines from the American Academy of Ophthalmology (AAO, 2020),[13-15] and American Optometric Association (AOA, 2019),[16] along with a 2017 position statement by the American Diabetes Association (ADA) on the management of DR.[17] For specific recommendations for the management of ROP, we also reviewed a 2017 guideline from the Pan American Health Organization (PAHO) and a 2018 policy statement published by the American Academy of Pediatrics (AAP).[18,19] Expert guidance statements were reviewed for the treatment of mCNV.[20,21]

Overall, treatment guidelines and expert guidance statements for the management of nAMD, DME, DR, ME-RVO, mCNV, and ROP recommend anti-VEGFs as a drug class, without specifying preference for one agent over another.[13-17,19-21] Some guidelines and expert guidance statements cited evidence from SRs and/or RCTs demonstrating that anti-VEGF agents tend to have comparable efficacy and/or safety.[13-17] Although reviewed guidelines and expert guidance statements do not recommend a particular anti-VEGF dosing interval for nAMD, DME, DR, or ME-RVO, 3 dosing interval approaches may be used: fixed (on a consistent scheduled basis), treat-and-extend, or as-needed (PRN).[14,15,54] Treat-and-extend and

PRN regimens involve timing additional doses based on response to therapy**.[15,54] Such individualized dosing schedules reduce injection burden, compared to fixed regimens.[14] Generally, intravitreal anti-VEGF agents are recommended as first-line for most reviewed indications, with an exception being ROP. The 2017 PAHO guideline and 2018 AAP policy statement predate FDA approval of aflibercept (Eylea) for the treatment of ROP,[6,18,19] therefore at the time these documents were published, anti-VEGF agents were used off-label for the treatment of this condition.

The following subsections provide an overview of disease states and summarize guideline recommendations for each of the FDA-approved ocular indications (nAMD, DME, DR, ME-RVO, mCNV, ROP) of the reviewed intravitreal anti-VEGF products. *All reviewed guidelines predated FDA-approval of the higher dosage form of aflibercept (Eylea HD, 8 mg), and therefore "aflibercept" will be used to refer to the 2 mg dosage form (Eylea) in the following subsections*.

3.1 Neovascular (wet) age-related macular degeneration (nAMD)

Age-related macular degeneration (AMD) consists of two subtypes: neovascular, often referred to as "wet" AMD (nAMD); or non-neovascular or atrophic, often called "dry" AMD.[15,55-58] Damage to the macula occurs from age-related changes, including drusen deposits in the retina (in dry AMD) or from choroidal neovascularization (in nAMD).[59] Both wet and dry subtypes cause impaired central vision (eg, distortion, blurring) but unchanged peripheral vision.[55] Although nAMD is less common (10% to 15% of AMD cases) than dry AMD (85% to 90% of AMD cases), nAMD is more progressive than dry AMD and leads to severe visual acuity loss if untreated.[15,56-58] Notably, individuals with any severity of dry AMD (ie, early, intermediate, advanced) have the potential to progress to nAMD during the course of the disease.[58,60] Eye examinations can be used to detect nAMD using optical coherence tomography (OCT), OCT angiography (OCT-A), or fluorescein angiography (FA).[15,58] Screening for AMD helps ensure prompt treatment, thereby improving disease prognosis.[15,58] **Table 4** summarizes the severity of AMD subtypes according to the American Academy of Ophthalmology (AAO) guideline.

The estimated prevalence of AMD in Americans 40 years and older is 12.6% (19.8 million), based on 2019 data.[61] The risk of developing AMD is greater for older adults (>50 years of age).[55] The estimated prevalence of early- and late-stage AMD among adults (50 years or older) is between 9.9% and 19.5%, 1.1% and 3.9%, respectively.[62] Other predisposing risk factors for AMD include northern European descent, genetics (eg, complement factor H gene), current cigarette smoking, a family history of AMD, and hyperlipidemia.[15,55,58,59] Although genetic factors play a role in developing AMD, routine genetic testing is currently not recommended by the 2020 AAO guideline.[15] The risk of developing AMD does not appear to be associated with aspirin use; therefore, the AAO guideline recommends that patients with AMD taking practitioner-recommended aspirin should continue using it as instructed.[15]

** A PRN regimen usually includes monthly monitoring, with intravitreal injections administered only upon detecting disease activity (eg, presence of subretinal fluid).[15,54] A treat-and-extend regimen extends or reduces the dosing interval based on the physician's judgement, considering changes in visual acuity and/or anatomical findings, after receiving the initial loading doses; an intravitreal injection is administered at every clinic visit, regardless of the disease measurement findings taken on that specific day.[54]

Table 4. Age-related Macular Degeneration Disease Severity Scale, According to Subtype[15] [a]

Dry AMD			nAMD
Early AMD	**Intermediate AMD**	**Advanced AMD[a] (any of the following)**	
Present in either one or both eye(s)[b]		Present in at least one eye	
• Presence of several small drusen, a couple medium-sized drusen (63 to 124 µm in diameter); and/or • Mild RPE changes (eg, hyper- or hypo-pigmentation)	Any of the following: • Several medium-sized drusen (63 to 124 µm in diameter) • ≥1 large-sized drusen (≥125 µm in diameter) • Geographic atrophy of the RPE (*excludes the center of the fovea*)	• Geographic atrophy of the RPE (*includes the center of the fovea*)	Neovascular maculopathy as indicated by the following: • Choroidal neovascularization • Hemorrhagic and/or serous retinal or RPE detachment • Hard retinal exudates • Sub-RPE and subretinal fibrovascular proliferation • Disciform scar

[a] To classify the disease severity of AMD, the 2020 AAO guideline on AMD uses the Age-Related Eye Disease Study (AREDS), and a proposed clinical classification system from a 2013 publication.[15]

[a] Caused in the absence of other etiologies

[b] Based on the guideline, ambiguity exists regarding the potential presence of early AMD symptoms in either one or both eyes[15]; nonetheless, the AREDS classification highlights that symptoms may manifest in either a single eye or both eyes during the early stage of AMD.[63]

Abbreviations: AAO, American Academy of Ophthalmology; AMD, age-related macular degeneration; nAMD, neovascular (wet) age-related macular degeneration; RPE, retinal pigment epithelium

3.1.1 Guideline treatment recommendations for nAMD

To reduce disease progression, a certain combination of antioxidant vitamins and minerals (based on the formula used in the Age-Related Eye Disease Study 2 [AREDS2]) are recommended for patients with intermediate or advanced AMD; there is no supportive evidence for the use of this supplementation in patients with lower severity disease (early AMD), or as prophylaxis in family members absent of AMD signs or symptoms.[15] Additionally, all active smokers presenting with AMD or who may be at-risk should be encouraged to quit smoking.[15]

Until 2023 there were no effective treatments for dry AMD.[15,56,64] Pegcetacoplan (Syfovre), an intravitreal complement inhibitor, is the first and only approved treatment for geographic atrophy, a type of dry AMD.[64] Treatment options for nAMD include photodynamic therapy (PDT), laser photocoagulation, and anti-VEGF agents (eg, ranibizumab, aflibercept, off-label bevacizumab).[15] Of these treatment options, anti-VEGF agents are recommended as first-line for nAMD. The 2020 AAO guideline does not specify preference of one anti-VEGF agent over another; instead the guideline encourages an individualized, shard-decision approach between the patient and practitioner to determine the optimal agent.[15] Based on evidence from two cited Cochrane SRs,[65,66] the AAO guideline states the safety differences between ranibizumab, off-label bevacizumab, and aflibercept are likely minimal, if a difference exists at all.[15]

The 2020 AAO guideline predates FDA approval of newer formulations approved for nAMD: the 2 biosimilars of originator ranibizumab (Cimerli and Byooviz), the ranibizumab ocular implant (Susvimo), the higher dosage formulation of aflibercept (Eylea HD), and faricimab-svoa (Vabysmo).[15] The guideline briefly mentions brolucizumab-dbll (Beovu) regarding the results from 2 phase III trials (HAWK and HARRIER), but does not comment on its use.[15]

Table 5 summaries the guideline recommendations for the treatment of nAMD.

Table 5. Guideline Recommendations for the Treatment of nAMD[15]

Age-related macular degeneration preferred practice pattern (American Academy of Ophthalmology; 2020)[15] Target age group/population for recommendations: adults aged ≥50 years
General recommendations for neovascular age-related macular degeneration (nAMD) or dry age-related macular degeneration (AMD) (Strength; LOE, if available)[a]:
• Patients who are at risk or have AMD are recommended to quit smoking (**ungraded statement**) • Currently, routine genetic testing is not recommended (**ungraded statement**) • Patients taking practitioner-recommended aspirin should continue using it as instructed; aspirin use is not correlated with an increased risk of acquiring AMD (**ungraded statement**) • Patients with *intermediate* or *advanced* AMD should be offered the following antioxidant vitamins and minerals (AREDS2 formula; **ungraded statement**):   ○ Vitamin C 500 mg; Vitamin E 400 IU; Lutein/zeaxanthin 10 mg/2 mg; Zinc oxide 80 mg or 25 mg; Cupric oxide 2 mg
Neovascular age-related macular degeneration (nAMD) (Strength; LOE, if available)[a]:

• **First-line treatment**: **intravitreal injection of anti-VEGF agents**
  ○ **Ranibizumab, aflibercept** (dosed at 2 mg), and **bevacizumab** have been shown to effectively maintain visual acuity, fostering the use of anti-VEGF treatment as first-line (**Strong recommendation; good quality, I+**)
  ○ Safety differences between **ranibizumab, aflibercept** (dosed at 2 mg), and **bevacizumab** are likely minimal, if a difference exists at all (**Strong recommendation; good quality, I+**)
  ○ Symptoms of retinal detachment or endophthalmitis that occur after an intravitreal injection should be quickly evaluated (**ungraded statement**)

[a] *Refer to **Appendix E** for a description of the level of evidence (LOE) and recommendation strength.*

Abbreviations: AMD, age-related macular degeneration; LOE, level of evidence; nAMD, neovascular (wet) age-related macular degeneration; VEGF, vascular endothelial growth factor

3.2 Diabetic retinopathy (DR) and diabetic macular edema (DME)

Patients with diabetes mellitus (type 1 or type 2) may suffer from microvascular complications (ie, neuropathy, nephropathy, retinopathy) as a result of chronic hyperglycemia.[67,68] Microvascular complications of the retina commonly manifest as diabetic retinopathy (DR).[16,67,69] Diabetic macular edema (DME) is a severe complication of DR.[16,67,69] Therefore, guidelines recommended that all individuals with diabetes have annual dilated ophthalmic examinations.[14,16,17] Examinations may occur more frequently depending on visual changes, disease severity or progression, pregnancy status, or comorbidities.[14,16,17,69] It is recommended that retinal imaging or fundus photography be used to detect

DR lesions, and OCT be used to evaluate DME,[16] provided no other etiologies exist for cystoid macular edmea.[14] Other ocular, non-retinal complications (eg, refractive shifts, papillopathy, cataracts) can develop as a result of diabetes mellitus,[16] but the management of these conditions are considered outside the scope of this report.

DR is classified as either non-proliferative (absence of neovascularization) or proliferative (presence of neovascularization).[16] Comparatively, proliferative diabetic retinopathy (PDR) is more severe than non-proliferative diabetic retinopathy (NPDR) due to the potential to cause severe vision loss from retinal detachment or vitreous hemorrhages.[16] Patients with DR may be asymptomatic, especially during the early stages of the disease.[16,70] However, patients with severe or very severe NPDR have a greater risk (50% or 75%, respectively) of developing PDR within a year.[16] **Table 6** outlines disease severity categories among these 2 DR classifications.

Table 6. Stages of Diabetic Retinopathy[14,16,17] [a]

Diabetic retinopathy classification	Stages

Non-proliferative diabetic retinopathy (NPDR)	• **Mild:**
	  ○ Presence of ≥1 microaneurysms, which may leak fluid
	• **Moderate:**
	  ○ Greater degree of microaneurysms or hemorrhages are present in 1 to 3 retinal quadrants
	  ▪ Minor intraretinal microvascular abnormalities and vascular beading may be present
	• **Severe (any of the following):**
	  ○ Serious microaneurysms or hemorrhages are present in each of the 4 quadrants
	  ○ Definite vascular beading in ≥2 retinal quadrants
	  ○ Prominent intraretinal microvascular abnormalities in ≥1 quadrant
	• **Very Severe[b]:**
	  ○ No obvious signs of neovascularization are present, but ≥2 criteria for severe NPDR are fulfilled

Proliferative diabetic retinopathy (PDR)	Neovascularization at any location in the eye, including near or on the optic disc
	• **High-risk (presence of ≥3 of the following):**
	  ○ Neovascularization at any location in the eye
	  ○ Neovascularization near or on the optic disc
	  ○ At least moderate neovascularization, defined according to blood vessel size and location
	  ○ Vitreous or pre-retinal hemorrhage

[a] The reported stages are a summation of the information presented in the 2017 ADA statement on diabetic retinopathy,[17] and the diabetic retinopathy guidelines by the AOA (2019)[16] and AAO (2020, updated 2022).[14]

[b] The category of "very severe NPDR" is listed only in the 2019 AOA guideline on diabetic retinopathy[16]; other reviewed guidelines on diabetic retinopathy do not include this category.[14,17]

Abbreviations: AAO, American Academy of Ophthalmology; ADA, American Diabetes Association; AOA, American Optometric Association; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy

DME is defined as fluid accumulation in the macular space of the retina from vascular damage, including destruction of the blood-retinal barrier.[69] DME causes retinal thickening and can be present with or without cystoids or lipid exudates.[16] DME is classified based on whether the center subfield zone of the macula is involved: non-central-involved (NCI-DME), or central-involved (CI-DME).[16] Typically, CI-DME is associated with greater degree of visual loss than NCI-DME.[16] Although the risk of developing DME increases with DR severity, DME can present at any stage of DR.[16,71,72]

Common risk factors for both DME and DR include having diabetes mellitus for a longer duration, sustained periods of hyperglycemia, hypertension, dyslipidemia, or diabetic nephropathy.[17,67,72] Pregnancy can also transiently increase the risk of developing DME or DR for patients who have pregestational diabetes.[14,71,72] Among adults aged ≥40 years living with diabetes in the US, approximately 40.3% have some stage of DR, 8.2% have vision-threatening DR (PDR or severe NPDR and/or DME), and 3.8% have DME.[16] It is projected that the number of adults in the US affected with DR will increase to 16 million by 2050, from 5.5 million in 2005.[16] Additionally, it is expected the number of adults in the US affected with vision-threatening DR will increase to 3.4 million by 2050, from 1.2 million in 2005.[16]

Visual impairment secondary to DR tends to affect a larger proportion of individuals with type 2 diabetes (T2D) than those with type 1 diabetes (T1D).[14] Notably, at the time of diagnosis, up to 40% of T2D patients have some degree of retinopathy; whereas, DR tends to be rare among recently diagnosed T1D patients.[68] Guidelines recommend screening annually for DR in patients with T1D or T2D, but the recommended time at which to start screening differs according to the type of diabetes: for T1D, annual eye examinations should start 5 years after diagnosis whereas annual eye examinations for T2D should start immediately at the time of diagnosis.[14,17]

3.2.1 Guideline treatment recommendations for DR and DME

Treatment goals for DR include preserving or improving visual acuity, improving quality of life with respect to vision-related aspects, and ensuing optimal control of risk factors.[14] As a part of diabetes management, patients should be educated on the potential long-term benefits of adequately controlling modifiable risk factors (eg, glycemic values, blood pressure, lipids) in order to minimize the risk of DR onset or progression.[14,16,17] Referral to an experienced ophthalmologist in the management of diabetic retinal conditions is recommended for patients with severe or very severe NPDR, PDR, or any degree of macular edema, especially CI-DME.[16,17]

Treatment options for DR and DME include laser photocoagulation (pan-retinal or focal/grid), intravitreal anti-VEGF injections (for CI-DME), and vitrectomy.[14,16,17] Anti-VEGF therapy has not been established for NCI-DME.[73] Vitrectomy is often reserved for patients who have severe ocular complications (eg, non-clearing vitreous hemorrhaging, macular traction, presence of fibrous tissue, traction retinal detachment),[16] or those with disease refractory to anti-VEGF agents or pan-retinal photocoagulation.[14]

Intravitreous anti-VEGF agents (without preference of one agent over another) tend to be the recommended first-line treatment for CI-DME,[14,17] especially in patients with reduced visual acuity (20/30 or worse).[14] It may be reasonable to defer treatment until visual acuity has worsened, but this approach should not be used for patients with medical conditions that may exacerbate macular edema

(eg, hypertension, kidney failure, fluid retention secondary to heart failure).[14] If the patient is unresponsive or cannot tolerate anti-VEGF injections, laser therapy may be considered.[16] An advantage of using anti-VEGF agents for the treatment of CI-DME is that they are able to improve visual acuity, whereas laser photocoagulation typically is not as effective for this outcome; however, both treatment modalities reduce the risk of subsequent vision loss.[16] Anti-VEGF treatment for CI-DME requires patients to have near-monthly injections during the initial months to year after starting treatment; however, the number of injections required to maintain remission generally decreases over time.[16,17]

Guideline treatment recommendations for DR vary based on the stage of disease, whether DME is present or absent, and the type of DME, if present. In the absence of DME, typically, individuals with mild or moderate NPDR should have treatment deferred, and should be re-evaluated at 6 to 12 month intervals depending on the severity.[14,16,17] For the treatment of severe or very severe NPDR, early PDR that is likely to progress, or high-risk PDR, the AOA 2019 guideline recommends either pan-retinal photocoagulation or intravitreal anti-VEGF injections as initial treatment.[16] A key consideration for deciding which modality to use depends on patient reliability for follow-up.[14] The 2017 ADA position statement recommends considering early pan-retinal photocoagulation for select patients with T2D who have severe NPDR.[17] Generally, guidelines recommend pan-retinal photocoagulation as first-line for PDR; but if CI-DME is present, intravitreal anti-VEGF agents should be considered.[14,16,17] Of importance, pan-retinal photocoagulation has the potential to exacerbate DME in some patients.[14,16]

Intraocular steroids (eg, fluocinolone acetonide, triamcinolone acetonide) are an additional treatment option for DME refractory to intravitreal anti-VEGF and/or laser treatment.[14,16] The use of intraocular steroids generally as second-line for DME is partially attributed to their effectiveness and side effect profile relative to anti-VEGF agents.[14,17] Evidence has shown that concomitant use of intraocular steroids with anti-VEGF agents for the treatment of DME does not seem to provide additional benefit relative to using anti-VEGF agents alone, and intraocular steroids tend to have a greater risk of causing elevated intraocular pressure (IOP) and cataracts than anti-VEGF intravitreal injections.[14]

Both of the DR guidelines (AOA 2019 and AAO 2022) and the 2017 ADA position statement do not prefer one anti-VEGF agent over another; however, the AOA (2019) and ADA (2017) mention that the most commonly used agents for the treatment of CI-DME at the time of publication were aflibercept, ranibizumab, and bevacizumab (off-label).[16,17] Notably, the 2017 ADA statement predated FDA-approval of the ranibizumab biosimilar for DME/DR (Cimerli), faricimab-svoa, and brolucizumab-dbll.[17] Although brolucizumab-dbll was approved in 2019,[9] recently published guidelines do not mention its use.[14,16] The updated 2022 AAO guideline notes that a 2014 meta-analysis demonstrated that both aflibercept and ranibizumab were superior to conventional laser therapy for improving visual acuity in the treatment of DME,[14] and were non-significantly different from each other.[74] Furthermore, faricimab has demonstrated non-inferiority to aflibercept in 2 randomized controlled trials (RCTs; YOSEMITE, RHINE) for improved visual acuity in the treatment of DME;[14] beyond this detail, faricimab is not mentioned in reviewed guidelines due to the timing of its approval relative to guideline drafting.[14,16] **Table 7** summaries the guideline treatment recommendations for DR and DME.

Table 7. Guideline Recommendations for the Treatment of DME and DR

Diabetic retinopathy preferred practice pattern **(American Academy of Ophthalmology; 2020, updated 2022)**[14] Target age group/population for recommendations: all patients with any type of diabetes mellitus
General recommendations (Strength; LOE, if available)[a]:
• If indicated, aspirin may be used for the management of other medical conditions in patients with DR (**ungraded statement**) • Among patients with diabetes, it is recommended to maintain well-controlled glycemic and blood pressure values to minimize the risk of DR onset or progression (**ungraded statement**) • Intravitreal anti-VEGF agents appear to be safe, with the most serious complication being endophthalmitis. Other complications that rarely occur are cataract formation and elevated IOP, and there is the potential for systemic thromboembolic events to occur after receiving an injection (**Strong recommendation; moderate quality, I+**) • For refractory cases to anti-VEGF or PRP therapy that are indicated for vitrectomy, administering an **anti-VEGF agent** before surgery decreases the surgery duration, the frequency of retinal breaks, and the volume of intra-operative bleeding (**Strong recommendation; moderate quality, I+**)   ○ The use of pre-operative or intra-operative off-label **bevacizumab** may decrease the occurrence of vitreous hemorrhages after surgery (**Strong recommendation; moderate quality, I+**)
Diabetic macular edema (DME) (Strength; LOE, if available)[a]:

• CI-DME with vision loss: preferred initial treatment is intravitreal injections of anti-VEGF agents (**ungraded statement**)
  ○ Both **aflibercept** (dose at 2 mg) and **ranibizumab** were superior to conventional laser therapy for improving visual acuity in the treatment of DME (**Strong recommendation; good quality, I++**)
• Non-CI-DME: the preferred treatment is laser photocoagulation
  ○ Lack of data on the use of intravitreal anti-VEGF agents
• Compared to no intervention, laser photocoagulation decreases visual loss changes and enhances the probability of achieving DME resolution (partial to full) over a span of 1–3 years (**Strong recommendation; moderate quality, I**)
• Compared to monotherapy with an anti-VEGF agent, the combination use of an intravitreal anti-VEGF agent with an intraocular steroid does not provide any additional therapeutic benefit in the treatment of DME (**Strong recommendation; moderate quality, I**)

Diabetic retinopathy (DR) (Strength; LOE, if available)[a]:
• PDR: the preferred treatment is PRP
Eye care of the patient with diabetes mellitus **(American Optometric Association; 2019)**[16] Target age group/population for recommendations: all patients with any type of diabetes mellitus
General recommendations (Strength; LOE, if available)[a]:
• In an effort to minimize the risk of DR onset or progression, patients with diabetes should be educated on the potential long-term benefits of adequately controlling glucose (**Grade A**), lipids (**Grade B**), and blood pressure (**Grade B**). All of the aforementioned risk factors received a **strong recommendation** • Patients with diabetes should be educated on DR signs and symptoms, along with other ocular complications unrelated to the retina that may arise due to diabetes. Moreover, patients should be encouraged to adhere to routine eye examinations and appropriate ocular care (**Consensus statement**) • Vitrectomy should be reserved for patients with macular traction, traction retinal detachment, an epiretinal membrane, or a vitreous hemorrhage (**Recommendation; Grade B**)
Diabetic macular edema (DME) (Strength; LOE, if available)[a]:
• CI-DME: referral to an ophthalmologist is recommended to be treated with deferred or subsequent focal/grid macular laser treatment or intravitreous anti-VEGF agents (**Strong recommendation; Grade A**) • Refractory DME after the use of laser, anti-VEGF agents, or both treatment modalities: referral to an ophthalmologist is recommended to be treated with intraocular steroids (**Strong recommendation; Grade A**)
Diabetic retinopathy (DR) (Strength; LOE, if available)[a]:
• Severe or very severe NPDR, early PDR that is likely to progress, or high-risk PDR: referral to an ophthalmologist is recommended to be treated with either PRP or intravitreal injections of anti-VEGF agents (**Strong recommendation, Grade A**) • PDR, with or without DME: intravitreal injections of anti-VEGF agents are an alternative or adjunctive option to PRP (**Strong recommendation; Grade A**)

[a] *Refer to **Appendix E** for a description of the level of evidence (LOE) and recommendation strength.*

[b] *High-risk characteristics may include optic disc neovascularization sized ≥1 quarter of the disc area, any degree of optic disc neovascularization in the presence of a vitreous hemorrhage, or retinal neovascularization sized ≥ one-half of the disc area in the presence of a vitreous hemorrhage*[17]

Abbreviations: CI-DME: central-involved diabetic macular edema; DME, diabetic macular edema; DR, diabetic retinopathy; IOP, intraocular pressure; LOE, level of evidence; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; PRP, pan-retinal photocoagulation; VEGF, vascular endothelial growth factor

Table 7. Guideline Recommendations for the Treatment of DME and DR

Diabetic retinopathy: a position statement by the American Diabetes Association (American Diabetes Association; 2017)[17] Target age group/population for recommendations: all patients with any type of diabetes mellitus
General recommendations (Strength; LOE, if available)[a]:
• It is recommended to optimize glycemic, serum lipid, and blood pressure control in patients with diabetes to minimize the risk of DR onset or progression (**A**) • Patients with severe NPDR, PDR, or any degree of macular edema should be quickly referred to an ophthalmologist experienced in the management of DR (**A**) • The risk of retinal hemorrhage is not increased in patients who use aspirin, and retinopathy is not a contraindication for use (**A**)
Diabetic macular edema (DME) (Strength; LOE, if available)[a]:
• CI-DME: anti-VEGF agents **(ie, bevacizumab, aflibercept, ranibizumab)**, administered as an intravitreal injection are the preferred first-line treatment for the majority of patients (**A**) ○ For patients with refractory CI-DME to anti-VEGF agents, consider macular laser as adjunctive treatment (**ungraded statement**) ○ For certain cases, intravitreous steroid injections can be used as an alternative option (**ungraded statement**)
Diabetic retinopathy (DR) (Strength; LOE, if available)[a]:
• For patients with high-risk PDR, and in certain cases of severe NPDR, laser photocoagulation decreases the likelihood of vision loss (**A**) ○ Early treatment with PRP can be considered for patients with severe NPDR who have type 2 diabetes mellitus (**ungraded statement**) • PDR: the recommended intraocular treatment is either PRP or anti-VEGF intravitreal injections, particularly if high-risk characteristics[b] are present (**ungraded statement**) ○ Some studies suggest anti-VEGF intravitreal injections can be considered as an alternative option or as adjunct to PRP up to at least 2 years

*[a] Refer to **Appendix E** for a description of the level of evidence (LOE) and recommendation strength.*

[b] High-risk characteristics may include optic disc neovascularization sized ≥1 quarter of the disc area, any degree of optic disc neovascularization in the presence of a vitreous hemorrhage, or retinal neovascularization sized ≥ one-half of the disc area in the presence of a vitreous hemorrhage[17]

Abbreviations: CI-DME: central-involved diabetic macular edema; DME, diabetic macular edema; DR, diabetic retinopathy; IOP, intraocular pressure; LOE, level of evidence; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; PRP, pan-retinal photocoagulation; VEGF, vascular endothelial growth factor

3.3 Macular edema secondary to retinal vein occlusion (ME-RVO)

The partial or entire impairment of venous blood flow within a retinal vein is termed retinal vein occlusion (RVO).[13] RVO can occur at various anatomical locations throughout the retinal venous circulatory system, and is categorized based on the occlusion site[13,75-77]:

- Central retinal vein occlusion (CRVO) occurs in the central vein at or posterior to the optic nerve head, typically near the lamina cribrosa. This type of occlusion is usually caused by thrombosis formation and can be further categorized as non-ischemic or ischemic. Notably, non-ischemic CRVO (a milder form) can progress to ischemic CRVO (a more severe form) if left untreated.
- Branch retinal vein occlusion (BRVO) occurs in a branch or tributary vein from the central vein, usually at a arteriovenous intersection.
- Hemiretinal vein occlusion (HRVO) can occur at a major bifurcation of the central retinal vein leading to blockage of one trunk, called a hemi-CRVO, or more commonly (90% of HRVO cases), occlusion can occur at the optic disc impacting retinal venous drainage of either the inferior or superior hemifield.

Second to DR, RVO is the most common vision-threatening, retinal vascular disorder.[13] Macular edema has the potential to complicate BRVOs and CRVOs, contributing to vision loss and a reduction in vision-related quality of life.[13] Other complications associated with vision loss in the presence of a vein occlusion include retinal/vitreous hemorrhages, macular ischemia, and epiretinal membrane formation.[13] Notably, prognosis is dependent on the location of the occlusion and whether it is non-ischemic or ischemic; in general, prognosis tends to be better when the RVO occurs more distally with less blockage than more proximal RVOs with greater blockage.[13]

Overall, the US prevalence of RVO appears to be around 0.5%.[13,78] RVOs commonly occur in persons aged 60 to 70 years, but onset may occur earlier (persons >40 years of age), and rarely in those younger than 40.[13] Thus, older age is a strong risk factor for CRVO and BRVO.[13] Risk factors for RVO include hyperlipidemia, hypertension, diabetes, arteriosclerosis, smoking, and obesity.[13,75,79] Glaucoma is a specific predisposing risk factor for CRVO.[13,75] It is likely that the presence of hypercoagulable states (eg, factor V Leiden) contribute to the occurrence of RVOs, particularly CRVOs, but a definitive association remains unclear.[13] In general, BRVOs are considerably more prevalent than CRVOs,[13,75] and HRVOs are relatively uncommon.[75]

The symptoms of RVO vary depending on where the occlusion occurs and the presence of macular edema[75]; notably, pain is typically absent unless in very severe cases of CRVO.[75,80]

- Patients with BRVO may exhibit no symptoms,[75] especially if there is no involvement of macular veins or significant temporal branch veins.[13] The occlusion may be detected during routine eye examinations or due to the development of complications (eg, vitreous hemorrhage).[13] Commonly, patients will present with acute symptoms of macular edema (eg, blurred central vision, visual field deficit), or occlusions involving the macula.[13]
- Patients with CRVO often experience blurred vision within the affected eye.[75,80] Patients are rarely asymptomatic[75] but may be if the condition is very mild.[80] There is a potential for patients with CRVO, primarily the more severe ischemic form,[75,77,80] to develop iris neovascularization resulting in

neovascular glaucoma.[13] As a result of the IOP, patients may experience redness and pain,[80] in addition to visual impairments.[75]

- Patients with HRVO typically experience blurred central vision as a result of the occlusion involving the macula.[75]

3.3.1 Guideline treatment recommendations for ME-RVO

Because there are currently no available treatments to re-perfuse occluded retinal veins, treatment modalities for RVO primarily target related sequelae of the occlusion (ie, macular edema, neovascularization).[81] Treatments for RVO include intravitreal anti-VEGF agents, most commonly ranibizumab, aflibercept, and bevacizumab (off-label), intraocular steroids, and laser therapy.[13] Anti-VEGF agents are frequently used to treat macular edema, decrease the severity of anterior segment neovascularization, and diminish the likelihood of ocular angiogenesis.[13] Treatment goals include improving or maintaining visual acuity and vision-related quality of life, diminishing the symptoms of related complications, preventing neovascular glaucoma that may arise in cases of advanced disease, and controlling modifiable predisposing risk factors (eg, hypertension, diabetes).[13,81]

In the presence of macular edema, the 2020 AAO guideline on RVO recommends intravitreal anti-VEGF injections as first-line treatment for BRVO or CRVO, unless there are contraindications.[13] The guideline does not specify a preference for one agent over another. Cited evidence from a meta-analysis revealed no significant differences between bevacizumab, ranibizumab, aflibercept, or triamcinolone with respect to visual improvement when treating macular edema secondary to CRVO. Although intraocular steroids, such as triamcinolone have demonstrated efficacy in the management of RVO, the guideline recommends using them as second-line due to their side effect profile. In addition, laser therapy is an alternative second-line option for patients with BRVO.[13]

For patients with CRVO who develop retinal or iris neovascularization, pan-retinal photocoagulation is recommended as first-line treatment and may potentially mitigate the development of neovascular glaucoma.[13] If angiogenesis is not adequately controlled after pan-retinal photocoagulation, intravitreal anti-VEGF agents may be used adjunctively. Patients with BRVO and neovascular complications may benefit from laser therapy to reduce the risk of vitreous hemorrhage. Notably, intravitreal anti-VEGF therapy may be used initially to supplement laser treatment by providing a transient effect and enhancing the feasibility of performing the laser therapy.[13]

Table 8 summaries the guideline recommendations for the treatment of ME-RVO.

Table 8. Guideline Recommendations for the Treatment of ME-RVO[13]

Retinal vein occlusions preferred practice pattern **(American Academy of Ophthalmology; 2020)[13]** Target age group/population for recommendations: adults aged >40 years
General recommendations (Strength; LOE, if available)[a]:
• Prognosis of RVO is contingent upon the location and nature of the occlusion (ischemic or non-ischemic). Generally, RVOs occurring at more distant sites with relatively minor occlusion exhibit a more favorable prognosis compared to RVOs occurring at proximal sites with greater levels of ischemia (**ungraded statement**) • Both CRVOs and hemi-CRVOs share a similar clinical course by being associated with glaucoma, and an elevated likelihood of developing anterior segment neovascularization and neovascular glaucoma. BRVOs and HRVOs usually occur at arterial venous intersections (**ungraded statement**) • Improving the control of systemic modifiable risk factors involves managing hypertension, hyperlipidemia, diabetes, and IOP for glaucoma. It is equally vital ophthalmologists communicate any indications of end-organ damage to the primary care physician (**ungraded statement**)
Central retinal vein occlusion (CRVO) + neovascularization (Strength; LOE, if available)[a]:
• PRP is advised for patients who develop retinal or iris neovascularization (**ungraded statement**)   ○ If angiogenesis continues despite PRP, intravitreal anti-VEGF injections may be used as adjunct (**ungraded statement**)
Branch retinal vein occlusion (BRVO) + neovascularization (Strength; LOE, if available)[a]:
• Laser treatment can help reduce the occurrence of vitreous hemorrhage (**ungraded statement**)
Branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO) + macular edema (Strength; LOE, if available)[a]:

• Intravitreal anti-VEGF agents (ie, **ranibizumab, aflibercept, bevacizumab**) are first-line treatment for RVO complicated by macular edema (**ungraded statement**)
  ○ Evidence has demonstrated that intravitreal anti-VEGF injections are effective for treating ME-RVO, with minimal adverse effects (**Strong recommendation; good quality, I++**)
  ○ **Bevacizumab, ranibizumab, aflibercept**, and triamcinolone appear to have comparable efficacy for improving visual acuity in the treatment of macular edema secondary to CRVO, but the side effect profile of intraocular steroids (eg, elevated IOP) favor the use of anti-VEGF agents as first-line (**Strong recommendation; good quality, I+**)
• Intraocular steroids are second-line (**ungraded statement**)

Branch retinal vein occlusion (BRVO) + macular edema (Strength; LOE, if available)[a]:
• In addition to intraocular steroids, laser therapy may also be a suitable second-line option (**ungraded statement**)

[a] *Refer to **Appendix E** for a description of the level of evidence (LOE) and recommendation strength.*

Abbreviations: BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; HRVO, hemi-retinal vein occlusion; IOP, intraocular pressure; ME-RVO, macular edema secondary to retinal vein occlusion; PRP, pan-retinal photocoagulation; RVO, retinal vein occlusion; VEGF, vascular endothelial growth factor

3.4 Myopic choroidal neovascularization (mCNV)

Nearsightedness (referred to as myopia), or a specific subset called pathological myopia or degenerative myopia,[20,82] can result in the development of myopic choroidal neovascularization (mCNV).[83] mCNV is a vision-threatening complication causing sudden, progressive decline in central visual acuity due to neovascularization in the subretinal/choroidal space.[84] The pathological cause of mCNV may be partially attributed to physical stress as a result of excessive axial elongation of the eye.[83,85] Although mCNV was historically believed to occur only in eyes affected by pathological myopia, it is accepted that mCNV can manifest in individuals across the entire spectrum of myopia, irrespective of the presence of typical degenerative retinal changes.[83,86] There are three defined stages of mCNV, each with distinctive clinical presentations[††20,83]:

- Active stage: During the active stage, patients usually experience abrupt central visual acuity dysfunction, potentially in conjunction with central scotoma (black, gray, or blind spot in the central part of the visual field) or metamorphopsia (wavy or distorted lines).
- Scar stage: During the scar stage, patients typically undergo a period of stabilization or temporary improvement in visual acuity. The choroidal neovascularization regresses, leading to the formation of a distinctive hyperpigmented region referred to as a Fuchs' spot.
- Atrophic stage: During the atrophic stage, patients tend to experience progressive visual deterioration, and if untreated, may result in legal blindness (20/200 or worse).[87]

In the US, it is estimated that 9.6 million adults have pathological myopia; of these, more than 41,000 have mCNV.[84,87] Within an 8-year timespan, approximately 30% of individuals with mCNV in one eye are expected to develop the condition in their other eye.[87,88] Ocular risk factors for mCNV include the presence of lacquer cracks, patch retinal atrophy, and choroidal thinning.[20] Other predisposing risk factors may include east Asian descent, female sex, older age, and having pathological myopia.[85,87]

3.4.1 Guidance statement recommendations for mCNV

Because no US-based or international guidelines were found for this indication, we included guidance statements based on expert review. Reviewed expert guidance statements recommend intravitreal anti-VEGF injections as a drug class, without preferring one agent over another, as first-line treatment for mCNV, unless contraindicated.[20,21] In these guidance statements, evidence is cited for the use of ranibizumab, bevacizumab, and aflibercept.[20,21] According to the 2018 guidance statement, intravitreal anti-VEGF therapy should be initiated promptly, preferably within a 2-week timeframe following a confirmed diagnosis.[21] Guidance statements recommend administering intravitreal anti-VEGF treatment on an as-needed dosing schedule after receiving 1 to 3 initial monthly injections.[20,21] Patients with recurrent mCNV should be retreated with intravitreal anti-VEGF therapy.[21] Combination treatment with intravitreal triamcinolone acetonide and an anti-VEGF agent can be considered, but evidence within this patient population is lacking.[20] Alternative treatment modalities (eg, verteporfin photodynamic therapy, laser therapy) can be considered in cases where intravitreal anti-VEGF therapy is unsuitable or has failed.[20] **Table 9** provides an overview of the guidance statement recommendations for the treatment of mCNV.

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†† Note that each stage is associated with differing pathological changes that may aid in the differential diagnosis of mCNV from other retinal diseases (eg, AMD).

Table 9. Guidance Statement Recommendations for the Treatment of mCNV

Diagnosis and treatment guideline for mCNV due to pathologic myopia (Ohno-Matsui et al; 2018)[21] Target age group/population for recommendations: unspecified
Anti-VEGF treatment recommendations (Strength; LOE, if available)[a]:
• Intravitreal anti-VEGF agents should be used as first-line therapy for patients with mCNV (**based on expert opinion**) • Ideally, intravitreal anti-VEGF injections should be administered as needed within 2 weeks of a confirmed diagnosis (**based on expert opinion**) • During the initial 3 months of anti-VEGF therapy, patients should be evaluated monthly by spectral-domain optical coherence tomography, and then every 2–3 months thereafter during the first year. After the first year of anti-VEGF treatment and no signs of recurrent mCNV, patients should be evaluated at periodic intervals (eg, every 6 months) for signs of disease activity; patients should be counseled to seek immediate attention upon experiencing any visual symptoms or changes (**based on expert opinion**) • Patients with recurrent mCNV should be retreated with intravitreal anti-VEGF therapy (**based on expert opinion**)
Myopic choroidal neovascularization: review, guidance, and consensus statement on management (Cheung et al; 2017)[20] Target age group/population for recommendations: unspecified
Anti-VEGF treatment recommendations (Strength; LOE, if available)[a]:
• For patients with mCNV, intravitreal anti-VEGF agents are recommended as first-line therapy (**Class I recommendation; Oxford CEBM level 1**) • The dosing regimen should commence with either 1 or 3 initial monthly injections, with subsequent injections administered as needed (**Class I recommendation; Oxford CEBM level 1**) • It may not be suitable for pregnant patients to use anti-VEGF treatment during the first trimester (**Class IIb recommendation; Oxford CEBM level 4**) • May consider combination therapy of intravitreal triamcinolone acetonide with an anti-VEGF agent (**Class IIb, Oxford CEBM level 4**)
Photodynamic therapy recommendations (Strength; LOE, if available)[a]:
• For cases where anti-VEGF agents are contraindicated (first-line treatment), short-term use of verteporfin photodynamic therapy may be considered for subfoveal/extrafoveal mCNV (**Class IIa recommendation; Oxford CEBM level 1, 4**) • It is not recommended to use verteporfin photodynamic therapy in patients with multiple foci of mCNV (**Class III recommendation; Oxford CEBM level 4**)
Laser therapy recommendations (Strength; LOE, if available)[a]:
• If anti-VEGF agents and verteporfin photodynamic therapy are contraindicated or failed to produce an adequate response, short-term use of laser therapy using thermal laser photocoagulation may be considered for extrafoveal mCNV (**Class IIb recommendation; Oxford CEBM level 4**) • It is not recommended to use thermal laser photocoagulation for juxtafoveal/subfoveal mCNV (**Class III recommendation; Oxford CEBM level 1**)

[a] *Refer to **Appendix E** for a description of the level of evidence (LOE) and recommendation strength.*

Abbreviations: CEBM, Centre for Evidence-Based Medicine; LOE, level of evidence; mCNV, myopic choroidal neovascularization; VEGF, vascular endothelial growth factor

3.5 Retinopathy of prematurity (ROP)

Retinopathy of prematurity (ROP), previously called retrolental fibroplasia,[43] is characterized by incomplete retinal vascular development,[89] potentially culminating in retinal detachment, severe vision impairment, or blindness.[90] ROP primarily occurs in infants who are born prematurely (gestational age <32 weeks) or have a low birth weight (<1,500 grams or approximately 3.3 pounds).[19,89] In rare instances, ROP can develop in full-term infants or infants with a higher birth weight who require oxygen supplementation or have other ROP risk factors (eg, hyperoxemia, prolonged mechanical ventilation [>1 week], blood gas parameter fluctuations, presence of other lung-related comorbidities).[19,89,91]

According to the International Classification of Retinopathy of Prematurity, ROP is classified based on the retinal zone (ie, I, II, posterior zone II, or III) of vascularization/disease, severity (ranging from stage 1, least severe, to stage 5, most severe), extent of ROP, and with or without "plus disease"‡‡.[89,90] Some infants may present with an aggressive form of ROP characterized by sudden emergence of abnormal neovascularization and pronounced "plus disease".[90] Aggressive ROP may not proceed through the typical stages of disease progression.[90] Notably, greater ROP severity typically coincides with lower birth weight and gestational age.[89]

Based on 2019 data, the overall US incidence of ROP among all newborn births was estimated to be 0.76%, up from 0.3% in 2003.[92] The increase in overall incidence may be a result of increased routine ROP screening in at-risk infants and improved survival rates among extremely premature neonates (gestational age <26 weeks).[89] The incidence rate of ROP (any severity) among preterm infants (gestational age <32 weeks) and low-birth-weight infants (<1,500 grams) is estimated to range from 25%−40%, with severe ROP (defined as stage 3 or greater) ranging from 6%−10%.[89]

3.5.1 Guideline treatment recommendations for ROP

Treatment of ROP is determined based on disease classification, including ROP severity. The 2017 Pan American Health Organization (PAHO) guideline and a 2018 statement by the American Academy of Pediatrics (AAP) on the management of ROP use slightly different criteria to determine the need for ROP treatment, as outlined in **Table 10**.[18,19]

‡‡ "Plus disease" is an important indicator of ROP severity, and is distinguished by anomalous dilation and tortuosity of blood vessels within Zone I.[89,90]

Table 10. Recommended Treatment Criteria for Retinopathy of Prematurity[18,19]

Treatment Criteria for Retinopathy of Prematurity[a,b,c]	
American Academy of Pediatrics (2018)[18]	Pan American Health Organization (2017)[19]
• Zone II: stage 3 with plus disease	• Zone III: stage 3 with plus disease
• Zone I: any stage of ROP with plus disease, or stage 3 *without* plus disease • Zone II: stage 2 with plus disease	

[a] *Zones characterize the spatial distribution of ROP on the retina relative to the optic disc, with zone I being the most central posterior region, to Zone III representing the outer most region.*

[b] *Stages characterize disease severity, ranging from stage 1, least severe (visible demarcation line), to stage 5, most severe (total retinal detachment).*

[c] *"Plus disease" is characterized as the anomalous dilation and tortuosity of the retinal blood vessels in at least 2 quadrants of the retina.*

Most cases (85%–90%) of milder ROP spontaneously resolve on their own without treatment or visual impairments.[91] However, even with prompt examination and treatment, few patients may still progress to complete vision loss.[18] Therefore, to prevent serious vision complications, the 2017 PAHO guideline and 2018 AAP statement recommend starting treatment within 72 hours of diagnosis,[18,19] or within 48 hours for those with aggressive posterior ROP.[19]

Importantly, the 2017 PAHO guideline and 2018 AAP statement predate FDA approval of aflibercept (Eylea) for the treatment of ROP, and therefore, recommendations do not specifically address its use.[18,19] Potentially because at the time of publication, the use of any anti-VEGF agent for the treatment of ROP was off-label, the PAHO guideline recommended laser therapy as first-line for infants who require treatment, but treatment with intravitreal anti-VEGF agents could also be considered for certain infants (eg, those who failed laser therapy).[19] The AAP statement specifically recommended considering intravitreal anti-VEGF agents (eg, ranibizumab, bevacizumab) for infants with zone I: stage 3+ ROP.[18] After treatment, neonates should be followed-up within a week to evaluate potential complications or the necessity for retreatment.[18,19] In cases where intravitreal anti-VEGF agents were used, AAP (2018) recommended close monitoring, especially between 45 to 55 weeks' postmenstrual age when the highest risk for ROP reactivation typically occurs, until retinal vascularization is complete, or if not yet complete, until the physician is confident that reactivation of ROP will not occur.[18] Instances of very late proliferative ROP recurrences have been noted with anti-VEGF agents, emphasizing the importance of clinical judgement in deciding when to discontinue surveillance.[18]

Guideline recommendations for the treatment of ROP are provided in **Table 11**.

Table 11. Guideline Recommendations for the Treatment of ROP

Screening examination of premature infants for retinopathy of prematurity — statement[a,b] **(American Academy of Pediatrics; 2018)[18]** Target age group/population for recommendations: infants at risk for ROP (eg, low birth weight, decreased gestational age)
General treatment recommendations[c,d,e]:
• For any of the following scenarios, treatment should be initiated: ○ Zone I: any stage with plus disease, or stage 3 *without* plus disease ○ Zone II: stage 2 with plus disease ○ Zone II: stage 3 with plus disease • Initiating treatment promptly, ideally within 72 hours of diagnosis, is advised to reduce the likelihood of retinal detachment • It is recommended to follow-up within 3 to 7 days after anti-VEGF or laser therapy to assess the necessity for further intervention in regions where the ablative treatment may have been incomplete, or additional anti-VEGF treatment
Anti-VEGF treatment recommendations[c,d]:
• For infants with zone I: stage 3+ ROP, the use of **intravitreal bevacizumab or another anti-VEGF agent** (eg, ranibizumab) may be considered ○ It is imperative to proceed with intravitreal anti-VEGF treatment only after obtaining informed consent, as there are still unresolved inquiries regarding dosage, timing, safety, as well as both visual and systemic outcomes • After receiving an intravitreal anti-VEGF injection, infants should undergo close monitoring until retinal vascularization is complete, or if not yet complete, until the physician is confident that reactivation of ROP will not occur ○ Due to the possibility of late reactivation of proliferative ROP, the physician should not solely depend on the observations of initial ROP regression or reaching 45 weeks' postmenstrual age ○ Infants treated with intravitreal anti-VEGF agents necessitate close monitoring during the period when the risk for disease reactivation is highest, typically occurring between 45 to 55 weeks' postmenstrual age
Clinical practice guidelines for the management of retinopathy of prematurity[a] **(Pan American Health Organization; 2017)[19]** Target age group/population for recommendations: infants at risk for ROP (eg, low birth weight, decreased gestational age)
General treatment recommendations (Strength; LOE, if available)[c,d,e,f]:
• For any of the following scenarios, treatment is recommended (**Strong recommendation for; very low quality**): ○ Zone I: any stage with plus disease, or stage 3 *without* plus disease ○ Zone II: stage 2 with plus disease ○ Zone III: stage 3 with plus disease • For patients with aggressive posterior ROP, it is recommended to commence treatment within the initial 48 hours of diagnosis. In situations not classified as aggressive posterior ROP, treatment initiation is suggested within 72 hours of diagnosis (**Strong recommendation for; very low quality**) • Upon discharge, it is recommended to establish a comprehensive plan for all neonates with ROP, regardless of whether they have received treatment. This plan should encompass regular ophthalmological, neonatal, or pediatric follow-up appointments until the physician deems such appointments are no longer clinically necessary (**Weak recommendation for; very low quality**) • For all treated newborns, it is recommended to conduct a postoperative assessment within the initial week (between 4 to 8 days) to evaluate for potential complications or the necessity for retreatment, with additional follow-up occurring as clinically indicated (**Strong recommendation for; very low quality**)
Laser therapy recommendations (Strength; LOE, if available)[f]:
• Recommended first-line treatment for ROP is transpupillary diode laser (**Strong recommendation for; low quality**)
Anti-VEGF treatment recommendations (Strength; LOE, if available)[f]:
• The use of intravitreal anti-VEGF agents can be considered under the following circumstances when surgical treatment is unavailable (**Weak recommendation for; very low quality**): ○ Failed laser treatment; laser therapy is unfeasible due to the child's condition status, or laser or cryotherapy are unable to be performed due to an inability to visualize the retina; or neonate has aggressive posterior ROP, or "ROP type 1 in zone I"

[a] *Predates FDA approval of aflibercept (Eylea) for the treatment of ROP, the only reviewed intravitreal anti-VEGF agent approved for this indication at the time of writing this report.*

[b] *No recommendations in this policy statement were assigned an evidence rating or recommendation strength; however, cited evidence is provided for each recommendation.*

[c] *Zones characterize the spatial distribution of ROP on the retina relative to the optic disc, with zone I being the most central posterior region, to Zone III representing the outer most region.*

[d] *Stages characterize disease severity, ranging from stage 1, least severe (visible demarcation line), to stage 5, most severe (total retinal detachment).*

[e] *"Plus disease" is characterized as the anomalous dilation and tortuosity of the retinal blood vessels in at least 2 quadrants of the retina.*

[f] *Refer to **Appendix E** for a description of the level of evidence (LOE) and recommendation strength*

Abbreviations: LOE, level of evidence; ROP, retinopathy of prematurity; VEGF, vascular endothelial growth factor

4.0 PHARMACOLOGY

All FDA-approved anti-VEGF agents reviewed in this report directly bind to, or inhibit the interaction of vascular endothelial growth factor-A (VEGF-A), a key signaling glycoprotein,[93] that is believed to contribute to the pathophysiology of several angiogenic ocular diseases, including nAMD, DR, and ROP.[2-9,94] By preventing VEGF-A from binding to VEGF receptors located on the surface of endothelial cells, anti-VEGF agents are able to inhibit endothelial cell proliferation, vascular permeability, and neovascularization.[2-9] In addition to modulating VEGF-A, aflibercept also binds to placental growth factor, an angiogenic VEGF family member that selectively binds to VEGF receptor 1.[5,6,94] Uniquely, faricimab-svoa inhibits angiopoietin-2, in addition to VEGF-A, which is believed to contribute to enhanced vascular stability and reduced blood vessel sensitivity to VEGF-A effects.[2] However, the role of angiopoietin-2 inhibition in the therapeutic effect and clinical response in nAMD and DME remains to be definitively established.[2] The mechanism of action and a brief description for each of these agents is provided in **Table 12**.

Table 12. Mechanism of Action of FDA-approved Anti-VEGF agents for Ocular Use

Generic name (Brand)	Description	Proposed mechanism of action
Ranibizumab (Lucentis)[4] Ranibizumab-eqrn (Cimerli)[7] Ranibizumab-nuna (Byooviz)[8] Ranibizumab ocular implant (Susvimo)[3]	• Humanized recombinant monoclonal antibody fragment (immunoglobulin G1 kappa isotype)	• Prevents VEGF-A, including active forms such as $VEGF_{110}$, from interacting with its receptors (ie, VEGFR-1 and VEGFR-2) by blocking the binding site, thereby decreasing endothelial cell proliferation, vascular permeability, and neovascularization
Aflibercept (Eylea; Eylea HD)[5,6]	• Humanized recombinant fusion protein ○ Extracellular binding domains of VEGFR-1 and VEGFR-2 + Fc region of immunoglobulin G1	• Inhibits the activation of VEGF receptors by binding to VEGF-A and PlGF, thereby disrupting vascular permeability and neovascularization
Faricimab-svoa (Vabysmo)[2]	• Humanized bispecific immunoglobulin G1 antibody	• Dual inhibitor of VEGF-A and angiopoietin-2; decreases endothelial cell proliferation, vascular permeability, and neovascularization, and enhances vascular stability and reduces blood vessel sensitivity to VEGF-A effects
Brolucizumab-dbll (Beovu)[9]	• Humanized recombinant monoclonal antibody fragment (single-chain Fv)	• Prevents VEGF-A from interacting with its receptors (ie, VEGFR-1 and VEGFR-2) by binding to $VEGF_{110}$, $VEGF_{121}$, $VEGF_{165}$, thereby decreasing endothelial cell proliferation, vascular permeability, and neovascularization

Abbreviations: FDA, Food and Drug Administration; PlGF, placental growth factor; VEGF(R), vascular endothelial growth factor (receptor)

According to product labeling (ie, package inserts), no drug interaction studies have been performed for brolucizumab-dbll or ranibizumab and its biosimilars.[4,7-9] Product labeling does not provide information regarding the interaction potential for the remaining intravitreal anti-VEGF agents (ie, aflibercept, ranibizumab ocular implant, faricimab-svoa).[2,3,5,6]

5.0 SPECIAL POPULATIONS

Although the anti-VEGF agents are not contraindicated in **pregnancy**, their mechanism of action and animal studies implicate angiogenesis, VEGF ligands, and VEGF receptor 2 in critical aspects of reproduction, and embryo-fetal and postnatal development.[2-10] Pregnant women should be advised of the potential risk to the fetus, and with their prescriber, should weigh the potential benefit versus risks of therapy. Animal models have demonstrated fetal harm with the reviewed anti-VEGF therapies,[2-10] as further described in **Table 13**. With all FDA-approved intravitreal anti-VEGF agents, embryofetal animal harm was reported at drug exposures higher than the expected human exposure.[2-10] Aflibercept is noted to cause animal embryofetal harm at exposures similar to the expected human exposure too[5,6]; not all agents have information available from animal models at equivalent human exposures.

Table 13. Pregnancy Information, According to Package Inserts

Agent	Animal Harm Observed	Explanation
Ranibizumab	✓	Skeletal abnormalities occurred in monkey fetuses with intravitreal ranibizumab 1 mg/eye every 14 days (yielding an exposure 13-times the predicted human exposure on monthly ranibizumab, or more than 40 times the human exposure with the ranibizumab ocular implant). Yet, no abnormalities were observed at the lower dose of 0.125 mg/eye (yielding similar trough exposures to the human exposure with the ranibizumab ocular implant or conventional monthly injections).[3,4]
Aflibercept	✓ Unknown "no observed adverse effect level" (NOAEL)	Embryo-fetal adverse effects (eg, external, visceral, and skeletal malformations) occurred in rabbits following subcutaneous aflibercept 0.1 mg/kg every 6 days (yielding an exposure about 6 times the predicted human adult exposure after a single 2 mg intravitreal dose, or 0.9 times higher than the human exposure with the 8 mg dose).[5,6]
Faricimab-svoa	✓Unknown "no observed adverse effect level" (NOAEL)	Pregnancy loss in monkeys occurred following weekly faricimab 1 mg/kg intravenous injections (yielding an exposure 158 times the human exposure at the 6 mg monthly dosage).[2]
Brolucizumab-dbll	✓	Fetal loss and a structural abnormality (bilateral absent metatarsal) occurred in monkey fetuses following monthly intravitreal brolucizumab 6 mg/eye (about 10 times the mg/kg-based maximum recommended human dose).[9]
Bevacizumab	✓	Fetal harm (congenital malformations) is reported in the bevacizumab intravenous package insert (Avastin) when used at the clinical dose of 10 mg/kg for certain oncologic disorders.[10]

Product labeling (ie, package inserts) for the reviewed agents, with the exception of the 2 mg dosage form of aflibercept that is approved for ROP,[6] describe that the safety and effectiveness have not been established in the **pediatric population**.[2-5,7-10]

No specific dosage adjustments are recommended for **renal or hepatic impairment** for any of the reviewed intravitreal anti-VEGF agents (ie, any formulation of aflibercept, brolucizumab-dbll, faricimab-svoa, and ranibizumab).[2-9]

6.0 DIRECT COMPARATIVE EVIDENCE

Literature searches for SRs of RCTs with head-to-head (H-H) comparisons between intravitreal anti-VEGF agents, including the off-label use of bevacizumab, identified a total of 295 records, and of those, 67 were selected for full-text screening. Overall, direct comparative evidence was extracted from 10 SRs (see **Table 14**), with comparisons of interest being most frequent for treatment of nAMD and least frequent for treatment of mCNV. No H-H RCTs were found in recent SRs for the treatment of ROP,[22-24] or for Eylea HD (aflibercept 8 mg).

Table 14. Overview of Included Publications with Comparative Results Between Intravitreal Anti-VEGF Agents

Indication	Systematic review (first author, publication year)		Comparisons[a]	
nAMD	• Solomon, 2019[95] • Ye, 2020[31] • Patil, 2022[97]	• Larsen, 2023[96] • Yin, 2022[30] • Chuan, 2022[27]	• BRO vs ALF • FAR vs RAN • RAN vs BEV • RAN vs CIM • RAN (injection) vs RAN (implant)	• RAN vs AFL • FAR vs AFL • BRO vs RAN • RAN vs BYO
DME	• Chen, 2023[33]	• Larsen, 2023[96]	• BRO vs ALF • FAR vs RAN • AFL vs RAN (and BEV)	• FAR vs ALF • BEV vs RAN
ME-RVO	• Cornish, 2023[98]	• Xing, 2023[99]	• AFL vs BEV • RAN vs BEV	• AFL vs RAN
mCNV	• Hu, 2019[100]		• RAN vs BEV	

[a] *Note that some reviewed SRs also explored comparisons between agents using different dosing regimens. For simplicity, specific dosing and regimens are not reported in this table; please refer to the specific comparison section for additional details.*

Abbreviations: ALF, aflibercept; BEV, bevacizumab; BRO, brolucizumab; BYO, Byooviz; CIM, Cimerli; DME, diabetic macular edema; FAR, faricimab; ME-RVO, macular edema secondary to retinal vein occlusion; mCNV, myopic choroidal neovascularization; nAMD, neovascular age-related macular degeneration; RAN, ranibizumab

The following bullet points provide a summary of the direct comparative evidence for each reviewed indication; please refer to the specific section for additional details:

Direct comparative evidence for nAMD:

- Intravitreal **brolucizumab 6 mg** has proven to be non-inferior to intravitreal **aflibercept 2 mg** for improving visual acuity at 48 weeks (primary endpoint) based on 2 phase III RCTs (HAWK and HARRIER); comparable results were also observed after 96 weeks of treatment.[25,26] Two meta-analyses including these trials and a phase II RCT, also showed no difference between brolucizumab and aflibercept with respect to change in best-corrected visual acuity (BCVA) (at 12 weeks and end

of study results).[27,97] However, brolucizumab (3 mg and 6 mg) appears to be more effective than aflibercept in reducing central subfield thickness (CST) by weeks 48 and 96.[25-27]

- While a single-dose RCT (phase I/II) is available for the comparison of **ranibizumab 0.5 mg** versus **brolucizumab 6 mg** for nAMD (showing comparable effects at 1 month for BCVA and CST, after the single dose),[28] longer duration studies are needed to more fully describe how these agents compare to one another as used clinically, over multiple doses.
- Intravitreal **faricimab 6 mg**, administered at 12- or 16-week intervals, appears comparable (after 40-52 weeks of treatment) to monthly intravitreal injections of **ranibizumab 0.5 mg** for visual acuity, anatomical outcomes (CST), and safety based on 1 phase II RCT.[96,101]
- Based on 2 phase III RCTs (TENAYA and LUCERNE), **faricimab 6 mg** (dosing interval tailored to every 8, 12, or 16 weeks based on response), showed no significant differences compared to **aflibercept 2 mg** every 8 weeks regarding visual acuity (non-inferiority demonstrated), anatomical CST outcomes, and adverse effects over 48 weeks.[96,102]
- In the phase III open-label RCT (ARCHWAY), **ranibizumab ocular implant** was non-inferior and equivalent to monthly **ranibizumab 0.5 mg intravitreal injection** for the change in BCVA from baseline averaged over 36−40 weeks.[103] A numerically greater number of ocular AEs of predefined special interest (eg, endophthalmitis, vitreous hemorrhages, rhegmatogenous retinal detachments) were reported in the ranibizumab ocular implant arm compared to the intravitreal ranibizumab arm.[103]
- An RCT (RIVAL) found no significant differences between **ranibizumab 0.5 mg** and **aflibercept 2 mg** (both on a treat-and-extend dosing interval after receiving 3 initial monthly injections) for the mean change in macular atrophy over 24 months (primary outcome) and key secondary outcomes (ie, mean number of injections per year, mean change in BCVA from baseline to month 24).[104] The safety also appeared comparable between treatment groups.[104] Another 2 RCTs (VIEW studies) showed aflibercept 2 mg (dosed monthly or every 2 months) was non-inferior to ranibizumab 0.5 mg monthly for maintaining BCVA at week 52 (primary outcome) and at week 96.[29] However, a significantly higher proportion of participants had no retinal fluid at week 96 with monthly aflibercept 2 mg (54.4%) versus monthly ranibizumab 0.5 mg (45.5%). Additionally, aflibercept treated-participants had significantly fewer mean injections compared to ranibizumab-treated participants during weeks 52 through 96.[§§] The overall incidence of ocular AEs and arterial thromboembolic events from baseline to weeks 52 and 96 appeared similar across treatment groups.[29] Recent systematic review meta-analyses (SRMAs), including the RIVAL and VIEW studies, overall found no significant differences between ranibizumab 0.5 mg and aflibercept (0.5 mg and 2 mg) for various efficacy and/or safety outcomes.[29-32,97,104,105]
- The biosimilars of ranibizumab (**Cimerli and Byooviz**) have each demonstrated equivalency to originator **ranibizumab,** all administered as 0.5 mg intravitreally on a monthly basis (ie, for improvement in BCVA, reduction in CST).[106-108] RCT evidence showed Cimerli and Byooviz have a similar safety profile to originator ranibizumab, including the cumulative incidence of antidrug antibodies.[106-108]

[§§] Participants in all treatment groups were switched to an as-needed (PRN) regimen during weeks 52−96 with a minimum of 12-week dosing intervals

- Based on 7 RCTs,[***] a direct SRMA found a significant difference favoring **ranibizumab** (versus **bevacizumab**) for the change in central macular thickness (CMT) after 12 months, but was no longer significant after 24 months of treatment.[30] Additionally, no significant difference between ranibizumab and bevacizumab was reported for visual acuity (gain of ≥15 letters), risk of death, and arteriothrombotic events after 12 and 24 months.[30] Another SRMA published in 2019 showed consistent results with the previously described SRMA, finding no significant differences between ranibizumab and bevacizumab for improvement or decline in visual acuity after 12 and 24 months.[95] Regarding the reduction in mean central retinal thickness (CRT), results favored ranibizumab over bevacizumab at 12 months, but the difference was not considered clinically meaningful by the authors, and there was no significant difference noted at year 2.[95] Another SRMA found no difference in the incidence of endophthalmitis, retinal vascular occlusion, and generalized intraocular inflammation between ranibizumab 0.5 mg and bevacizumab 1.25 mg.[97] However, Ye et al showed a significant pooled-effect difference in favor of monthly ranibizumab versus bevacizumab PRN for the mean change in BCVA and reduction in CRT from baseline to 12 months.[31,32] In addition, when both ranibizumab and bevacizumab were administered on a fixed monthly regimen, there was a significantly greater reduction in CRT with ranibizumab from baseline to 12 months.[31,32]

Direct comparative evidence for DME:

- A recently published SRMA of 8 trials showed **aflibercept 2 mg** appears comparable to **ranibizumab (0.3 mg and 0.5 mg)** for the change in BCVA and CMT reduction at 6 and 12 months; most included studies used a PRN dosing interval[†††].[33] However, aflibercept-treated participants had a significantly lower mean number of injections compared to ranibizumab-treated participants.[33] An additional short-term RCT (with up to 2 treatment doses per arm over 3 months) favored **aflibercept 2 mg** over **ranibizumab 0.5 mg** for the improvement in CRT at day 90 in a pooled population with phakic and pseudophakic eyes.[34]
- Two-year results from an RCT (Protocol T) comparing **aflibercept 2 mg** to **ranibizumab 0.3 mg** and **bevacizumab 1.25 mg** (all PRN dosing intervals) showed aflibercept was superior to bevacizumab at 2 years for improving visual acuity among the subgroup of participants with worse baseline visual acuity.[35] Aflibercept demonstrated superiority to ranibizumab among participants with worse visual acuity at 1 year,[36] however, no significant difference was observed at year 2.[35] In the overall study population, ranibizumab and aflibercept significantly outperformed bevacizumab for reducing mean CST from baseline to year 2 compared to bevacizumab, and were comparable to each other for this outcome. A higher rate of any vascular events including non-fatal stroke and vascular death occurred with ranibizumab (12%) versus aflibercept (5%) and bevacizumab (8%), according to the Antiplatelet Trialists' Collaboration definition.[35]
- A phase II RCT (BOULEVARD) showed monthly **faricimab 6 mg** was superior to monthly **ranibizumab 0.3 mg** for improving baseline BCVA at week 24 among *treatment-naïve* adults with CI-DME.[37] Furthermore, faricimab 6 mg resulted in a greater reduction in mean CST at week 24 compared to

[***] Most of the included RCTs used ranibizumab 0.5 mg and bevacizumab 1.25 mg, administered on a PRN or monthly regimen after 3 initial monthly injections.
[†††] Some of the included studies by Chen et al (2023) had full-text non-English publications; therefore the dosing and dosing interval was unable to be ascertained for all included studies.

ranibizumab in treatment-naïve and treatment-experienced participants. The overall incidence of ocular AEs appeared comparable between faricimab 6 mg and ranibizumab.[37]

- Two phase III RCTs (KESTREL and KITE) have demonstrated **brolucizumab 6 mg** (every 12 weeks, with the option of every 8 week dosing based on disease activity, following 5 initial loading doses every 6 weeks) was non-inferior to **aflibercept 2 mg** (every 8 weeks, following 5 initial monthly doses) for the mean change in BCVA from baseline to week 52.[38] In KESTREL, there was no significant difference between brolucizumab 6 mg and aflibercept 2 mg for the mean change in CST at week 52 (but the general trend was toward favoring brolucizumab). In the KITE trial, brolucizumab 6 mg was significantly favored over aflibercept 2 mg for the average improvement in CMT from baseline to week 40 through week 52. At week 52, brolucizumab 6 mg was non-inferior to aflibercept 2 mg for improving Diabetic Retinopathy Severity Scale (DRSS) score from baseline. The overall incidence of ocular AEs were similar for brolucizumab 6 mg and aflibercept in both trials.[38]
- According to 2 phase III RCTs (YOSEMITE and RHINE), **faricimab 6 mg**, administered at a maintenance interval of every 8 weeks or personalized, was non-inferior to **aflibercept 2 mg** every 8 weeks for change in visual acuity at 1 year.[109] Notably, a greater reduction in CST was observed with faricimab (at either dosing interval) versus aflibercept at weeks 48, 52, and 56 (primary endpoint visits), and a numerically greater proportion of faricimab-treated participants achieved DME resolution (defined as CST <325 µm) and absence of intraretinal fluid by week 56. The safety profile appears to be comparable across treatment arms and dosing regimens in both trials.[109]
- Three RCTs evaluated intravitreal **bevacizumab (1.25 mg or 1.5 mg)** compared to intravitreal **ranibizumab 0.5 mg**.[39-41] Trial results differed between studies potentially due to the different dosing intervals, thresholds for additional doses, and follow-up timepoints among the studies; but the study results either significantly favored or trended to favor ranibizumab over bevacizumab for improving visual acuity, as measured by the change in BCVA.[39,41]

Direct comparative evidence for ME-RVO:

- **Aflibercept 2 mg** and **ranibizumab 0.5 mg** appear comparable for improving visual acuity and reducing CMT, based on similar results from 5 RCTs.[99] Dosing intervals varied across studies (eg, every 2 months, PRN, or treat-and-extend). Meta-analysis incorporating both RCT and observational data also showed no significant differences in main efficacy endpoints (ie, proportion of patients gaining ≥15 letters, or CMT reduction) over 12 to 24 months, or the occurrence of systemic or ocular AEs.[99]
- Based on 2 RCTs for each comparison, **bevacizumab 1.25 mg** was non-inferior to **aflibercept 2 mg** and **ranibizumab 0.5 mg** for improving visual acuity after 6 months of monthly administration,[110,111] but bevacizumab failed to demonstrate non-inferiority to aflibercept or ranibizumab (at week 100) when using PRN dosing intervals in each treatment arm (following the first 3 monthly injections).[98,112]

Direct comparative evidence for mCNV:

- Three RCTs and an SRMA showed no significant differences in efficacy (eg, improvement in visual acuity and anatomical measures over 6 to 18 months) or major ocular adverse events between **ranibizumab 0.5 mg** and **bevacizumab 1.25 mg**, both administered PRN after the first intravitreal dose.[100,113-115]

6.1 Direct comparative evidence for nAMD

Several H-H SRs/RCTs exist among intravitreal anti-VEGF agents for the treatment of nAMD. Notably, all of the reviewed intravitreal anti-VEGF agents are approved for treating this condition,[2-9] and bevacizumab may be used off-label (rated as *Evidence Favors Efficacy* in Micromedex).[11] Guidelines recommend intravitreal anti-VEGF injections as first-line for nAMD, including the off-label use of bevacizumab.[15] The following H-H comparisons were identified, with additional details discussed below for each comparison pair:

- Intravitreal brolucizumab versus intravitreal aflibercept or intravitreal ranibizumab
- Intravitreal faricimab versus intravitreal ranibizumab or intravitreal aflibercept
- Intravitreal ranibizumab versus intravitreal aflibercept, ranibizumab (ocular implant), ranibizumab biosimilars (Cimerli, Byooviz), or intravitreal bevacizumab

There were no H-H comparison studies identified for other intravitreal anti-VEGF agents for the treatment of nAMD.[30,31,96,97,116-118]

Although not identified from published SRs, we are aware of a H-H phase III trial on the use of an investigational ophthalmic formulation of bevacizumab (ONS-5010/Lytenava) compared to intravitreal ranibizumab for the treatment of nAMD.[119]

6.1.1 Intravitreal brolucizumab versus intravitreal aflibercept

Two phase III, non-inferiority, double-blind RCTs (HAWK[‡‡‡] and HARRIER) have evaluated the efficacy of brolucizumab 6 mg among treatment-naïve patients (aged ≥50 years) with nAMD.[27,97,117] HAWK and HARRIER included an active-control arm consisting of aflibercept 2 mg. In both RCTs, participants randomized to brolucizumab received injections monthly for the initial 3 months, and then every 8 or 12 weeks depending on disease activity; aflibercept-treated participants received injections monthly for the first 3 months, and then at 8-week intervals thereafter.[120] The primary outcome in HAWK and HARRIER was the change in baseline best-corrected visual acuity (BCVA) at week 48[§§§].[120] Secondary outcomes included changes in anatomical measures (eg, retinal thickness, subretinal fluid [SRF]).[120]

Brolucizumab 6 mg demonstrated non-inferiority to aflibercept in the HAWK and HARRIER trials with respect to the change from baseline BVCA at week 48.[25,117,120] In addition, compared to aflibercept, the brolucizumab 6 mg arm had a significant a) reduction in the proportion of treated eyes with disease activity at week 16, b) improvement in CST at weeks 16 and 48, and c) resolution of retinal fluid at 16 and 48 weeks.[25] The most commonly reported ocular adverse effects (AEs) across HAWK and HARRIER and treatment arms were conjunctival hemorrhage and decreased visual acuity.[25,120] Similar to the 48-week results, brolucizumab 6 mg continued to outperform aflibercept for CST reduction at the 96 week follow-up time-point, published separately.[26] **Table 15** provides an overview of select efficacy outcomes from HAWK and HARRIER.

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‡‡‡ HAWK included an additional treatment arm of brolucizumab 3 mg, but results with respect to the FDA-approved dosage of 6 mg is the general focus of this section.
§§§ The predefined non-inferiority margin was established at four letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) letter chart.

Table 15. Select Efficacy Outcomes from HAWK and HARRIER Phase III Trials[25,26]

Efficacy endpoint	HAWK[a]		HARRIER	
	BRO (N=360)	AFL (N=360)	BRO (N=370)	AFL (N=369)
Change from baseline BCVA at week 48 (least squares mean) – *primary endpoint*	+6.6 letters	+6.8 letters	+6.9 letters	+7.6 letters
Difference from AFL (95% CI; p-value)	−0.2 (−2.1 to 1.8; NS) *Non-inferiority demonstrated*		−0.7 (−2.4 to 1.0; NS) *Non-inferiority demonstrated*	
Change from baseline BCVA at week 96 (least squares mean)	+5.9 letters	+5.3 letters	+6.1 letters	+6.6 letters
Proportion with disease activity at week 16	24%	34.5%	22.7%	32.2%
Difference from AFL (95% CI; p-value)	**NR (−17.1% to −3.5%; p=0.001)**		**NR (−15.8% to −3.1%; p=0.002)**	
Reduction in CST from baseline (least squares mean) to:				
Week 16	−161.4 µm	−133.6 µm	−174.4 µm	−134.2 µm
Difference from AFL (95% CI; p-value)	**−45.1 to −10.5; p<0.001**		**−58.9 to −21.6; p<0.001**	
Week 48	−172.8 µm	−143.7 µm	−193.8 µm	−143.9 µm
Difference from AFL (95% CI; p-value)	**−47.6 to −10.4; p=0.001**		**−68.9 to −30.9; p<0.001**	
Week 96	−174.8 µm	−148.7 µm	−197.7 µm	−155.1 µm
Difference from AFL (95% CI; p-value)	**−46.2 to −5.9; p=0.0115**		**−62.0 to −23.3; p<0.0001**	
Proportion with IRF and/or SRF present at:				
Week 16	33.9%	52.2%	29.4%	45.1%
Difference from AFL (95% CI; p-value)	**−25.3% to −10.9%; p<0.001**		**−22.9% to −9.0%; p<0.001**	
Week 48	31.2%	44.6%	25.8%	43.9%
Difference from AFL (95% CI; p-value)	**−20.7% to −6.1%; p<0.001**		**−24.9% to −11.8%; p<0.001**	
Week 96	24.0%	37.0%	24.0%	39.0%
Difference from AFL (95% CI; p-value)	NR; NR		**NR; p<0.0001**	
Proportion with sub-RPE fluid present at:				
Week 16	18.7%	27.3%	16.0%	23.8%
Difference from AFL (95% CI; p-value)	**−14.4% to −2.9; p=0.003**		**−13.0% to −2.7%; p=0.004**	
Week 48	13.5%	21.6%	12.9%	22.0%
Difference from AFL (95% CI; p-value)	**−13.6% to −2.7%; p=0.004**		**−13.8% to −3.9%; p<0.001**	
Week 96	11.0%	15%	17.0%	22.0%
Difference from AFL (95% CI; p-value)	NR; p=0.1213		**NR; p=0.0371**	

Bolded *results are statistically significant*

[a] *Reported results are for brolucizumab 6 mg only; results for brolucizumab 3 mg are not shown because this dosage is not approved by the FDA.*

Abbreviations: AFL, aflibercept; BCVA, best-corrected visual acuity; BRO, brolucizumab; CST, central subfield thickness; FDA, Food and Drug Administration; IRF, intraretinal fluid; NR, not reported; NS, not significant; RPE, retinal pigment epithelium; SRF, subretinal fluid

Recent SRMAs that included the 48-week results from HAWK and HARRIER and a phase II RCT have also shown comparable effects between brolucizumab (3 mg and 6 mg) versus aflibercept for BCVA improvement (at 12 weeks and end of study results).[27,97] One of these SRMAs also showed brolucizumab (3 mg and 6 mg) had significantly greater reductions in CST at month 12 compared to aflibercept.[27] Brolucizumab and aflibercept appear comparable with respect to the incidence of endophthalmitis, retinal vascular occlusion, iritis/iridocyclitis, vitreous haze/floaters, vitritis or "vitreous cells", and generalized intraocular inflammation.[97]

6.1.2 Intravitreal brolucizumab versus intravitreal ranibizumab

In a dosing-finding, 6-month, phase I/II RCT among treatment-naïve participants (≥50 years of age) with nAMD (N=194), participants were randomized to a one-time dose of intravitreal brolucizumab 0.5 mg, 3 mg, 4.5 mg, or 6 mg, or intravitreal ranibizumab 0.5 mg.[28] The primary endpoint was change in CST from baseline to 1 month. The secondary endpoint was the time to receiving post-baseline therapy (PBT; predefined by protocol criteria and determined by investigators' discretion) following the initial injection, which served as a surrogate measurement for effect durability.[28] *Results from this study are reported with respect to brolucizumab 6 mg because that is the FDA-approved dose.*

The single dose of brolucizumab 6 mg was non-inferior to ranibizumab 0.5 mg for the mean change from baseline in CST to 1 month.[28] However, the median duration to receiving PBT was significantly longer with brolucizumab compared to ranibizumab (75 days vs 45 days, respectively).[28]

6.1.3 Intravitreal faricimab versus intravitreal ranibizumab

In a phase II, 52-week RCT (STAIRWAY), treatment-naïve participants with nAMD were randomized to intravitreal faricimab 6 mg every 12 or 16 weeks (after 4 monthly loading doses), or to monthly (every 4 weeks) ranibizumab 0.5 mg.[96,101] Disease activity (using protocol-defined criteria) was evaluated at week 24 in participants receiving the 16 week regimen; if disease activity was detected, participants were switched to the 12 week regimen[****].[96,101] The primary outcome was the mean change in baseline BCVA at week 40.[101]

At week 40, comparable improvements in BCVA were observed between ranibizumab 0.5 mg every 4 weeks (+11.4 letters), and faricimab 6 mg every 12 (+9.3 letters) or 16 weeks (+12.5 letters), with confidence intervals (CI) of each arm overlapping.[101] Participants in the faricimab arm received fewer injections relative to participants in the ranibizumab arm over the 52-week treatment period. Secondary outcomes including anatomic measures (eg, CST) were consistent with the primary outcome findings.[101]

6.1.4 Intravitreal faricimab versus intravitreal aflibercept

Two phase III, double-blind, active-comparator, non-inferiority RCTs (TENAYA [N=671] and LUCERNE [N=658]) evaluated intravitreal faricimab 6 mg to aflibercept 2 mg among treatment-naïve participants ≥50 years of age with nAMD.[96] Both RCTs used identical dosing regimens. Initially, faricimab-treated

[****] No disease activity was detected at week 24 in 61% and 71% of participants treated with faricimab every 16 weeks or every 12 weeks, respectively. No disease activity was detected at week 24 in 94% of ranibizumab participants, dosed at every 4 weeks.

participants received monthly injections up to week 12 (4 injections total), and then were evaluated for disease activity at weeks 20 and 24. Depending on if, or when, disease activity was present, participants' regimen were either every 8, 12, or 16 weeks thereafter. Aflibercept was given monthly for the initial 3 injections, and then at fixed 8-week intervals thereafter.[96] The primary outcome in TENAYA and LUCERNE was the mean change in baseline BCVA (averaged over weeks 40, 44, and 48).[102] Secondary outcomes included anatomical changes (eg, CST).[96,102]

In TENAYA and LUCERNE, faricimab demonstrated non-inferiority to aflibercept with respect to mean adjusted change in baseline BCVA up to week 48.[96,102] Anatomical outcomes (CST at week 48) showed that faricimab, administered up to every 16 weeks was comparable to aflibercept given every 8 weeks.[102] An overview of select efficacy outcomes is provided in **Table 16**.

The safety profile of faricimab 6 mg was comparable to aflibercept 2 mg based on the phase III trials, TENAYA and LUCERNE.[96,102]

Table 16. Select Efficacy Outcomes from TENAYA and LUCERNE Phase III Trials[96,102]

Efficacy endpoint	TENAYA		LUCERNE	
	FAR (N=334)	AFL (N=337)	FAR (N=331)	AFL (N=327)
Adjusted mean change from baseline in BCVA up to week 48 – *primary endpoint*[a]	+5.8 letters	+5.1 letters	+6.6 letters	+6.6 letters
Difference from AFL (95% CI; p-value)	0.7 (−1.1 to 2.5; NS) *Non-inferiority demonstrated*		0.0 (−1.7 to 1.8; NS) *Non-inferiority demonstrated*	
Adjusted mean change from baseline in CST up to week 48[a]	−136.8 µm	−129.4 µm	−137.1 µm	−130.8 µm
Difference from AFL (95% CI; p-value)	−7.4 (−15.7 to 0.8; NS)		−6.4 (−14.8 to 2.1; NS)	

[a] *Averaged over weeks 40, 44, and 48, and measured in the intention-to-treat population.*

Abbreviations: AFL, aflibercept; BCVA, best-corrected visual acuity; CST, central subfield thickness; FAR, faricimab; NS, not significant

6.1.5 Ranibizumab ocular implant versus intravitreal ranibizumab injection

A phase III open-label RCT (ARCHWAY) evaluated the efficacy and safety of ranibizumab ocular implant (n=248) compared to monthly intravitreal injections of ranibizumab 0.5 mg (n=167) for the treatment of nAMD among participants aged 50 years or older.[103] Participants randomized to the ocular implant arm received continuous intravitreal delivery of ranibizumab over the 40-week period, with the refill procedure occurring at week 24 week (6 months). Prior to randomization, participants were required to respond to an intravitreal anti-VEGF agent, and had to have at least 3 previous anti-VEGF injections. If needed, supplemental injections of ranibizumab were offered to participants in the ocular implant arm at the 2 study visits prior to each refill procedure. The primary outcome was the mean change from baseline in BCVA averaged over 36−40 weeks, measured using an ETDRS chart.[103]

Ranibizumab ocular implant was non-inferior (margin of −4.5 ETDRS letters) and equivalent (margin of ±4.5 ETDRS letters) to intravitreal injections of ranibizumab with respect to BCVA change from baseline,

averaged over 36−40 weeks.[103] There was an increase of 0.2 letters in the ocular implant arm, whereas the intravitreal arm had a gain of 0.5 letters, with a treatment difference of −0.3.[3,103,121] The percentage of participants who experienced gains in vision was comparable across treatment groups (57.8% in the ocular implant arm; 58.9% in the intravitreal arm).[121] A numerically greater change in center point thickness was observed in the ocular implant group (+5.4 µm) compared to the intravitreal group (+2.6 µm) at week 36. Compared to the intravitreal arm, the total mean number of injections/procedures, including implantation, refill, and supplemental injections, was less in the ocular implant arm through week 40 (10.7 vs. 2, respectively).[121] Approximately 98% of participants in the ocular implant group did not receive supplemental injections of ranibizumab during the 6 month period prior to the refill procedure.[103,121]

The overall number of participants who experienced at least one ocular AE of predefined special interest was numerically higher in the ranibizumab ocular implant arm compared to the ranibizumab intravitreal injection arm (47 vs 10).[103] Ocular events that occurred more frequently in the ocular implant group included conjunctival bleb or filtering bleb leak (6.5%), cataract (4.4%), endophthalmitis (1.6%), retinal detachments (0.8%), vitreous hemorrhages (5.2%), conjunctival erosions (2.4%), and conjunctival retractions (2.0%). No events of conjunctival bleb or filtering bleb leak, conjunctival erosion or retraction, endophthalmitis, or rhegmatogenous retinal detachment were observed in the intravitreal arm through week 40.[103]

6.1.6 Intravitreal ranibizumab versus intravitreal aflibercept

Three RCTs (RIVAL and VIEW 1 and 2) evaluated ranibizumab to aflibercept among participants with nAMD.[104,105] Participants in RIVAL were randomized to intravitreal ranibizumab 0.5 mg or aflibercept 2 mg on a treat-and-extend dosing protocol after receiving 3 monthly injections[104,105]; whereas in the VIEW studies, participants were randomized to monthly injections of ranibizumab 0.5 mg or aflibercept 0.5 or 2 mg, or bimonthly (every 8 weeks) injections of aflibercept 2 mg, after receiving 3 monthly injections; at week 52, participants in each arm were switched to a PRN regimen through week 96 with a minimum of 12-week dosing intervals.[29]

The RIVAL study found no significant differences between ranibizumab 0.5 mg and aflibercept 2 mg for the mean change in macular atrophy over 24 months (*primary outcome*), and key secondary outcomes (ie, mean number of injections per year, mean change in BCVA from baseline to month 24).[104] Overall, the safety profile appeared comparable between treatment groups.[104] In the VIEW studies, all dosing regimens of aflibercept (0.5 mg monthly, 2 mg monthly, and 2 mg every 2 months) were non-inferior to monthly ranibizumab 0.5 mg for maintaining BCVA (losing <15 letters) at week 52.[29] Similarly, visual acuity gains in BCVA from baseline to week 96 were comparable across treatment groups. However, a significantly higher proportion of participants had no retinal fluid with aflibercept 2 mg (54.4%) versus ranibizumab 0.5 mg (45.5%) at week 96. Additionally, aflibercept-treated participants had significantly fewer number of mean injections compared to ranibizumab-treated participants during weeks 52 through 96. Overall, a greater percentage of participants treated with aflibercept 2 mg received <6 injections versus participants treated with ranibizumab during weeks 52 to 96. The overall incidence of ocular AEs and arterial thromboembolic events from baseline to weeks 52 and 96 appeared similar across treatment groups.[29]

Recent SRMAs overall found no significant differences between ranibizumab 0.5 mg and aflibercept (0.5 mg and 2 mg) based on the aforementioned RCTs.[29-32,97,104,105] The meta-analysis by Yin et al, resulted in no significant differences between ranibizumab and aflibercept regarding changes in BCVA, central macular thickness (CMT), visual acuity (incidence of gain of ≥15 letters), or the risk of death or arteriothrombotic events after 12 months.[30] Furthermore, Patil et al found no significant difference in the incidence of endophthalmitis between treatment with ranibizumab compared to aflibercept.[97] Results from the SRMA by Ye et al (2020) are consistent with Yin et al and Patil et al, showing no significant difference between monthly injections of ranibizumab and monthly or bimonthly injections of aflibercept for visual acuity gains (≥15 letters), arterial thromboembolic events, mean change in BCVA, mean reductions in central retinal thickness (CRT), changes in choroidal neovascularization, and rates of severe ocular AEs from baseline to 12 months.[31,32]

6.1.7 Intravitreal ranibizumab (Lucentis) versus ranibizumab-eqrn (Cimerli)

A 48-week, phase III RCT evaluated the equivalence of intravitreal ranibizumab to the biosimilar Cimerli (ranibizumab-eqrn), also known as FYB201, among treatment-naïve participants (aged ≥50 years) with nAMD.[108] Participants were randomized to the reference agent, ranibizumab (n=239), or FYB201 (n=238), both administered as 0.5 mg intravitreal injections every 4 weeks for 48 weeks. The primary outcome was the change in BCVA from baseline at week 8, prior to the third dose. Secondary endpoints included change in BCVA from baseline at week 48, and anatomical changes in retinal thickness at week 48.[108]

FYB201 (Cimerli) met the primary endpoint demonstrating equivalency to ranibizumab at week 8: ranibizumab had a mean improvement of +5.6 letters, and FYB201 had a mean improvement of +5.1 letters.[108] A sustained improvement in mean change in BCVA from baseline was shown at week 48 in both treatment groups: ranibizumab had +8.0 letters and FYB201 had +7.8 letters. Additionally, FYB201 and ranibizumab showed a comparable sustained reduction in baseline retinal thickness (ie, measured at foveal center point and foveal central subfield) at week 48. Overall, the incidence of systemic and ocular AEs were similar among treatment groups, but in general, a numerically greater number of treatment-related AEs were reported with the reference agent, ranibizumab.[108]

6.1.8 Intravitreal ranibizumab (Lucentis) versus ranibizumab-nuna (Byooviz)

The equivalency of ranibizumab-nuna (Byooviz), also called SB11, to originator ranibizumab was studied in 2 phase III RCTs (N=705) among participants ≥50 years of age with nAMD.[106,107] In both trials, participants were randomized to monthly intravitreal injections of 0.5 mg ranibizumab or SB11.[106,107] In the 52-week, phase III RCT (Bressler et al), the primary outcomes included change in BCVA from baseline, reduction in CST, immunogenicity, and rates of AEs up to 52 weeks.[107] The primary outcomes in the second RCT (Woo et al) was change in baseline BCVA at week 8 and change in CST at week 4.[106]

In the RCT by Bressler et al, visual efficacy outcomes (ie, change in BCVA from baseline, CST reduction) were similar among treatment groups, with an adjusted treatment difference in BCVA of −0.6 letters (90% CI: −2.1 to 0.9) and −14.9 µm (95% CI: −25.3 to −4.5) in CST reduction at week 52.[107] Additionally,

the safety profile was comparable between ranibizumab and SB11. Overall, 32.0% and 29.7% of participants experienced an ocular treatment-emergent AE with SB11 and ranibizumab, respectively. Non-ocular AEs occurred in approximately 55% of SB11-treated participants, and approximately 58% of ranibizumab-treated participants. Likewise, the immunogenicity profiles of SB11 and ranibizumab exhibited similarity, with low cumulative incidence of antidrug antibodies up to week 52 (4.2% for SB11 and 5.5% for ranibizumab).[107]

Results in the shorter RCT by Woo et al also showed no significant differences in BCVA change from baseline at week 8, nor in CST reduction at week 4.[106] The AE profile between treatment groups was comparable, including the rate of serious treatment-emergent AEs. Overall, up to week 24, the cumulative incidence of antidrug antibodies was low across treatment groups (approximately 3% in both groups).[106]

6.1.9 Intravitreal ranibizumab versus intravitreal bevacizumab (off-label)

Based on 7 RCTs, a direct SRMA by Yin et al (2022) reported a significant difference favoring ranibizumab (versus bevacizumab) for the change in CMT after 12 months (weighted mean difference for bevacizumab versus ranibizumab, 10.69; 95% CI, 1.38 to 20.00; p-value = 0.024); however, no significant difference was found after 24 months.[30] Additionally, no significant difference between ranibizumab and bevacizumab was reported for visual acuity (gain of ≥15 letters), risk of death, and arteriothrombotic events after 12 and 24 months.[30] Another SRMA published in 2019 (Solomon et al), which included an additional RCT (SAVE-AMD)[122] not included by Yin et al, showed consistent results with Yin et al, finding no significant differences between ranibizumab and bevacizumab for improvement or decline in visual acuity after 12 months and 24 months.[95] Regarding the reduction in mean CRT, results favored ranibizumab over bevacizumab at 12 months, but the difference was not considered clinically meaningful by the authors, and there was no significant difference noted at year 2.[95] Most of the RCTs included by Yin et al and Solomon et al used ranibizumab 0.5 mg and bevacizumab 1.25 mg, administered on a PRN or monthly interval after 3 initial monthly injections.[123-128]

Meta-analyses by Patil et al (2022) and Ye et al (2020) incorporated the same studies included by Yin et al (2022),[30] but each SR included one additional RCT.[31,97,129,130] Patil et al found no difference in the incidence of endophthalmitis, retinal vascular occlusion, and generalized intraocular inflammation between intravitreal ranibizumab 0.5 mg and intravitreal bevacizumab 1.25 mg.[97] Unlike previously mentioned SRMAs that pooled data from various dosing intervals altogether per agent, Ye et al, evaluated differences among various agents and unique dosing intervals.[31,32] No significant differences were found between the following dosing regimens regarding the proportion of patients achieving a gain in visual acuity (≥15 letters) and the occurrence of arterial thromboembolic events[31,32]:

- Monthly injections of ranibizumab compared to monthly or PRN dosing regimens of bevacizumab
- Ranibizumab PRN compared to monthly or PRN regimens of bevacizumab
- Treat-and-extend regimens of ranibizumab and bevacizumab compared to each other

However, Ye et al found a significant pooled-effect difference in favor of monthly ranibizumab versus bevacizumab PRN for the mean change in BCVA (standardized mean difference [SMD], 0.17; p-value = 0.04) and reduction in CRT (SMD, −0.25; p-value = 0.00) from baseline to 12 months.[31,32] In addition,

when both ranibizumab and bevacizumab were administered on a fixed monthly interval, there was a significantly greater reduction in CRT with ranibizumab from baseline to 12 months.[31,32]

6.1.10 Intravitreal ranibizumab versus ONS-5010 (investigational ophthalmic formulation of bevacizumab)

Topline results (not yet published in a peer reviewed journal) for the primary endpoint from the pivotal phase III trial (NORSE TWO; N=228) showed that a significantly greater proportion of participants who received monthly intravitreal bevacizumab-vikg (ONS-5010) compared to those who received intravitreal ranibizumab (Lucentis), administered monthly for the first 3 months and then every 12 weeks,[51,52] improved BCVA by ≥15 letters from baseline at month 11.[51] Additionally, the key secondary endpoint of the mean change in BCVA from baseline to month 11 was significantly greater for ONS-5010 (achieved 11.2 letters) compared to ranibizumab (achieved 5.8 letters). Regarding safety, the most common AE (≥5%) in the ONS-5010 arm was conjunctival hemorrhage as a result of the injection procedure, and one event of ocular inflammation occurred during the trial, which resolved without sequelae. Across all three completed NORSE trials, ONS-5010 seems to display a favorable and consistent safety profile.[51]

The drug sponsor is in close collaboration with the FDA while applying for review and approval.[131] In the future, the drug sponsor plans to conduct additional clinical trials to evaluate the effectiveness of ONS-5010 for treating DME and branch RVO.[51,131]

6.2 Direct comparative evidence for DME

Except for the ranibizumab ocular implant and Byooviz (ranibizumab biosimilar),[3,8] all of the reviewed anti-VEGF agents are approved for the treatment of DME.[2,4-7,9] Bevacizumab also has a recognized off-label use for DME per Micromedex (rated as *Evidence Favors Efficacy*).[11] Notably, the approved dosage of ranibizumab for DME is 0.3 mg rather than 0.5 mg, which is used for its other indications.[4] Reviewed guidelines tend to recommend intravitreous anti-VEGF agents as first-line treatment for CI-DME,[14,17] especially in patients with reduced visual acuity (20/30 or worse).[14]

Of the reviewed intravitreal agents, ranibizumab, including its biosimilar Cimerli, and aflibercept are indicated for the treatment of DR,[2-9] and bevacizumab may be used off-label to treat DR per Micromedex (rated as *Evidence Favors Efficacy*).[11] Generally, guidelines recommend anti-VEGF therapy as a treatment option for DR, but it depends on disease severity.[14,16,17] No H-H studies evaluating an anti-VEGF agent to another were identified for the treatment of proliferative diabetic retinopathy (PDR) through June 2022 by a Cochrane SR.[132]

The following H-H comparisons were identified in the setting of DME, with additional details discussed below for each comparison pair:

- Intravitreal aflibercept versus intravitreal ranibizumab or intravitreal bevacizumab
- Intravitreal brolucizumab versus intravitreal aflibercept
- Intravitreal faricimab versus intravitreal aflibercept or intravitreal ranibizumab
- Intravitreal bevacizumab versus intravitreal ranibizumab

6.2.1 Intravitreal aflibercept versus intravitreal ranibizumab

In a recently published SR (Chen et al, 2023), aflibercept 2 mg was compared to ranibizumab (0.3 mg and 0.5 mg) for the treatment of DME.[33] Across all included studies, there were approximately 530 eyes per treatment group. Most included studies used a PRN dosing interval.[††††] Based on individual RCTs, and the meta-analyses of 8 trials, aflibercept appears comparable to ranibizumab with respect to changes in BCVA and CMT reduction at 6 and 12 months. Aflibercept-treated participants received a significantly lower mean number of injections compared to ranibizumab-treated participants (weighted mean difference, −0.47; p-value = 0.03). Although a numerically lower number of AEs were reported with aflibercept than ranibizumab, there was no significant difference between treatment groups.[33]

An additional RCT (Morioka et al, 2018), not included by Chen et al, compared aflibercept 2 mg to ranibizumab 0.5 mg (up to 2 doses per arm) for changes in CRT and anterior flare intensity (AFI) among participants with DME and phakia (n=40) or pseudophakia (n=60).[34] The second dose of aflibercept or ranibizumab was permitted during the 3 months following the initial injection for participants who had a CRT >350 µm[‡‡‡‡].[34]

Among phakic and pseudophakia participants, no significant differences in AFI were observed between aflibercept and ranibizumab at day 7, 30, or 90.[34] Compared to aflibercept, ranibizumab had a significantly higher CRT at 90 days among pooled phakic and pseudophakic participants; however, no difference was observed among individual patient populations (phakic or pseudophakic) at 90 days or any other timepoint. The change in BCVA at 90 days was comparable across phakic and pseudophakic participant groups, and did not significantly differ between aflibercept- and ranibizumab-treated groups.[34]

6.2.2 Intravitreal aflibercept versus intravitreal ranibizumab versus intravitreal bevacizumab (off-label)

Protocol T, a 3-arm active comparator RCT, evaluated the effectiveness of aflibercept 2 mg (n=224) versus ranibizumab 0.3 mg (n=218) and bevacizumab 1.25 mg (n=218) for CI-DME, using a PRN regimen (based on visual acuity and anatomical response) across all treatment groups following initial monthly injections.[35,133,134] The study had a follow-up duration of 2 years.[35] Starting at month 6, focal/grid laser therapy was used in cases of persistent DME without signs of improvement.[35]

Similar improvement in visual acuity was observed across all treatment groups, but some significant differences were observed in the strata of participants with worse baseline visual acuity. Among participants with worse baseline visual acuity (20/50 to 20/320), aflibercept was superior to bevacizumab but not to ranibizumab for mean improvement in BCVA at year 2.[35] While aflibercept demonstrated superiority to ranibizumab among participants with worse visual acuity at 1 year,[36] no significant difference was observed at 2 years.[35] In the overall study population, ranibizumab and

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†††† Some of the included studies by Chen et al (2023) had full-text non-English publications; therefore the dosing and dosing interval was unable to be ascertained for all included studies.

‡‡‡‡ Among phakic and pseudophakic participants, none underwent retreatment at day 30, and very few participants in the ranibizumab arm (n=2, phakic; n=1, pseudophakic) and aflibercept arm (n=1, phakic; n=1, pseudophakic) received an additional injection at 90 days.

aflibercept had significantly greater reductions in mean CST from baseline to year 2 compared to bevacizumab, and were comparable to each other for this outcome. The median number of injections and incidence of ocular and systemic AEs were similar across treatment groups. However, a higher rate of any vascular events including non-fatal stroke and vascular death occurred with ranibizumab (12%) versus aflibercept (5%) and bevacizumab (8%), according to the Antiplatelet Trialists' Collaboration definition.[35] **Table 17** provides an overview of select efficacy outcomes from Protocol T, based on the 2-year follow-up results.

Table 17. Select Efficacy Outcomes from the 2-year Results of Protocol T[35]

Efficacy endpoint	Treatment groups		
	AFL (N=224)	BEV (N=218)	RAN (N=218)
Change in visual acuity (VA)	+12.8 letters	+10.0 letters	+12.3 letters
Subgroup analyses:			
Baseline VA 20/50 or worse (letter score <69; SD)	+18.1 ± 13.8 (n=98)	13.3 ± 13.4 (n=92)	16.1 ± 12.1 (n=94)
Difference from AFL (95% CI; p-value)	**4.7 (0.5 to 8.8; p=0.02)**		2.3 (−1.1 to 5.6; p=0.18)
Difference from RAN (95% CI; p-value)	2.4 (−1.0 to 5.8; p=0.18)		
Baseline VA 20/32 or 20/40 (letter score 69 to 78; SD)	+7.8 ± 8.4 (n=103)	+6.8 ± 8.8 (n=93)	+8.6 ± 7.0 (n=97)
Difference from AFL (95% CI; p-value)	1.1 (−1.1 to 3.4; p=0.51)		−0.7 (−2.9 to 1.5; p=0.51)
Difference from RAN (95% CI; p-value)	1.9 (−0.9 to 4.7; p=0.31)		
Reduction in mean CST (SD) from baseline	171 ± 141 µm	126 ± 143 µm	149 ± 141 µm
Difference from AFL (95% CI; p-value)	**−48.5 (−70.0 to −27.0; p<0.001)**		−15.5 (−33.0 to 2.0; p=0.08)
Difference from AFL (95% CI; p-value)	**−33.0 (−53.4 to −12.6; p<0.001)**		

Bolded *results are statistically significant.*

Abbreviations: AFL, aflibercept; BEV, bevacizumab; CST, central subfield thickness; RAN, ranibizumab; SD, standard deviation; VA, visual acuity

6.2.3 Intravitreal brolucizumab versus intravitreal aflibercept

Two phase III RCTs (KESTREL and KITE) compared brolucizumab (3 mg and/or 6 mg) to aflibercept 2 mg for the treatment of DME, both with a 100-week follow up.[38] KITE (N=360) and KESTREL (N=566) included two treatment arms: brolucizumab 6 mg and aflibercept 2 mg; KESTREL also included a lower dosage arm of brolucizumab (3 mg). Both trials administered brolucizumab every 12 weeks (with the option of every 8 week dosing based on disease activity), following 5 initial loading doses every 6 weeks; aflibercept was given at fixed bimonthly (every 8 weeks) intervals after 5 initial monthly doses. The primary outcome of both trials was the change in BCVA from baseline at week 52. Select secondary outcomes included change in Diabetic Retinopathy Severity Scale (DRSS) score and anatomical changes.[38]

In KESTREL and KITE, brolucizumab 6 mg was non-inferior (margin of 4 letters) to aflibercept 2 mg for mean change in BCVA from baseline to week 52.[38] For the mean change in CST from baseline at week 52,

brolucizumab 6 mg did not result in a significant difference from aflibercept 2 mg in KESTREL (yet it trended toward favoring brolucizumab); whereas, brolucizumab 6 mg was significantly favored over aflibercept 2 mg for the average change from baseline to week 40 through week 52 (p-value = 0.001) in the KITE trial. Brolucizumab 6 mg was non-inferior to aflibercept 2 mg for improving DRSS score (≥2 step) from baseline to week 52, with each treatment group providing a clinically meaningful difference from baseline. The overall incidence of ocular AEs were similar for brolucizumab 6 mg and aflibercept in both KESTREL and KITE.[38]

An overview of select efficacy outcomes from KESTREL and KITE are provided in **Table 18**.

Table 18. Select Efficacy Outcomes from KESTREL and KITE Phase III Trials[38]

Efficacy endpoint	KESTREL[a]		KITE	
	BRO (N=189)	AFL (N=187)	BRO (N=179)	AFL (N=181)
Mean change in baseline BCVA at week 52 – *primary endpoint*	+9.2 letters	+10.5 letters	+10.6 letters	+9.4 letters
Difference from AFL (95% CI; p-value)	−1.3 (−2.9 to 0.3; NS) *Non-inferiority demonstrated*		1.2 (−0.6 to 3.1; NS) *Non-inferiority demonstrated*	
Mean change in baseline CST at week 52	−166 µm	−160 µm	−197.0 µm	−164.0 µm
Difference from AFL (95% CI; p-value)	−5.0 (−22.0 to 12.0; NS)		**−33.0 (−53.0 to −13.0; NR)[b]**	

***Bolded** results are significantly significant.*

[a] Reported results are for brolucizumab 6 mg only; results for brolucizumab 3 mg are not shown because this dosage is not approved by the FDA.

[b] Specifically starting at week 40 and continuing through week 52, brolucizumab 6 mg was superior to aflibercept 2 mg for mean change in baseline CST (p-value = 0.001)

Abbreviations: AFL, aflibercept; BRO, brolucizumab; BCVA, best-corrected visual acuity; CST, central subfield thickness; FDA, Food and Drug Administration; NR, not reported; NS, not significant;

6.2.4 Intravitreal faricimab versus intravitreal aflibercept

Two phase III RCTs (YOSEMITE [N=940] and RHINE [N=951]) have evaluated faricimab 6 mg versus aflibercept 2 mg for the treatment of CI-DME in adults (≥18 years of age).[96,109] Both trials used identical regimens of faricimab and aflibercept, but the maintenance dosing intervals varied for faricimab-treated participants: participants were randomized to either every 8 weeks or a personalized treatment interval (every 4 weeks up to every 16 weeks depending on disease activity). Participants randomized to faricimab every 8 weeks received 6 initial monthly loading doses. Those randomized to the personalized treatment interval received monthly injections until achieving a CST <325, at which point the interval was extended to every 8 weeks and personalized thereafter by maintaining, or reducing, or extending, by at least 4-week increments. Aflibercept was administered at fixed 8-week intervals after 5 initial monthly injections. The primary endpoint in both trials was mean change in BCVA from baseline at 1 year, averaged over the primary endpoint visits (weeks 48, 52 and 56). Select secondary endpoints were anatomical changes (eg, CST), and absence of DME (defined as CST <325 µm) and intraretinal fluid up to week 56.[109]

Both YOSEMITE and RHINE showed faricimab, given on a fixed 8-week interval or personalized treatment interval, was non-inferior (margin of 4 letters) to aflibercept (fixed 8-week interval) with respect to visual acuity gains at 1 year among the intention-to-treat population (ITT).[109] Both regimens of faricimab were favored over aflibercept for CST reductions measured at primary endpoint visits in both trials (significance not reported). Additionally, a numerically greater proportion of participants achieved DME resolution with faricimab (77% to 90% depending on trial and dosing interval) than aflibercept (64% to 77% depending on trial) by week 56. Similar findings favoring faricimab over aflibercept were also observed for the absence of intraretinal fluid in both trials. The incidence of ocular AEs, including those classified as serious, and non-ocular AEs were generally comparable across treatment arms and dosing regimens in both trials.[109] **Table 19** summarizes select efficacy outcomes from YOSEMITE and RHINE.

Table 19. Select Efficacy Outcomes from YOSEMITE and RHINE Phase III Trials[109]

Efficacy endpoints[a]	YOSEMITE			RHINE		
	FAR Q8W (N=315)	FAR PTI (N=313)	AFL Q8W(N=312)	FAR Q8W (N=317)	FAR PTI (N=319	AFL Q8W (N=315)
Adjusted mean change in BCVA from baseline at 1 year[b] – *primary endpoint*	+10.7 letters	+11.6 letters	+10.9 letters	+11.8 letters	+10.8 letters	+10.3 letters
Difference from AFL using Q8W(97.52% CI)	−0.2 (−2.0 to 1.6) *Non-inferiority demonstrated*			1.5 (−0.1 to 3.2) *Non-inferiority demonstrated*		
Difference from AFL using PTI (97.52% CI)	0.7 (−1.1 to 2.5) *Non-inferiority demonstrated*			0.5 (−1.1 to 2.1) *Non-inferiority demonstrated*		
Adjusted mean change in CST from baseline at the primary endpoint visits (µm)	−206.6	−196.5	−170.3	−195.8	−187.6	−170.1

[a] *Measured in the intention-to-treat (ITT) population.*

[b] *Averaged over the primary endpoint visits at weeks 48, 52, and 56.*

Abbreviations: AFL, aflibercept; BCVA, best-corrected visual acuity; CST, central subfield thickness; FAR, faricimab; PTI, personalized treatment interval; Q, every; VEGF, vascular endothelial growth factor; W, weeks

6.2.5 Intravitreal faricimab versus intravitreal ranibizumab

A phase II RCT (BOULEVARD)[37] compared faricimab to aflibercept for the treatment of CI-DME in adults (≥18 years of age).[96] A total of 229 participants were enrolled in BOULEVARD; of these, 168 were treatment-naïve, and 61 had previous treatment with anti-VEGF therapy.[37] Participants were randomized based on prior treatment status: treatment-naïve participants received either faricimab 1.5 mg or 6 mg, or ranibizumab 0.3 mg; whereas, those previously treated with anti-VEGF therapy were randomized to faricimab 6 mg or ranibizumab 0.3 mg. Regardless of treatment allocation, participants received injections on a monthly basis for 20 weeks, with a follow-up period to week 36. The primary outcome was a comparison between faricimab and ranibizumab for mean change in baseline BCVA at week 24 among *treatment-naïve participants*. A key secondary endpoint was mean change in baseline CST at week 24.[37]

Among treatment-naïve participants, faricimab 6 mg demonstrated superiority over ranibizumab 0.3 mg for improvement in BCVA from baseline at week 24 (+13.9 letters vs +10.3 letters; p-value = 0.03).[37] Participants previously treated with anti-VEGF therapy had a gain of 8.3 letters and 9.6 letters in the ranibizumab and faricimab groups, respectively. Compared to ranibizumab 0.3 mg, faricimab 6 mg resulted in a greater reduction in mean baseline CST at week 24 in both participant groups (treatment-naïve and treatment-experienced). The overall incidence of ocular AEs appeared comparable between faricimab 6 mg and ranibizumab.[37]

6.2.6 Intravitreal bevacizumab (off-label) versus intravitreal ranibizumab

Three RCTs evaluated intravitreal bevacizumab (1.25 mg or 1.5 mg) versus intravitreal ranibizumab 0.5 mg (a dosage exceeding the approved 0.3 mg).[39-41] Each trial found differing results (described further below), potentially due to the different dosing intervals and assessment timepoints. Nonetheless, the study results either significantly favored or trended to favor ranibizumab over bevacizumab for improving visual acuity, as measured by the change in BCVA; the longest follow-up of these studies ranged from 24 to 40 weeks.[39,41] Inconsistent results were found for the mean number of injections between treatment groups, which may be influenced by dosing interval variations and different thresholds for PRN injections between studies: one RCT reported that bevacizumab had a significantly higher number of mean injections than ranibizumab, both administered on a monthly PRN basis, based on CST response, after the first injection[39]; another RCT found bevacizumab had a significantly lower number of mean injections than ranibizumab, both administered PRN, based on CMT or BCVA response, following 3 initial monthly injections.[40]

The first RCT (Nepomuceno et al, 2013) assessed the visual acuity efficacy of intravitreal bevacizumab 1.5 mg versus intravitreal ranibizumab 0.5 mg among participants with CI-DME (defined as CST >300 µm).[39] A total of 45 participants (60 treated eyes) were included. Participants were randomized to ranibizumab or bevacizumab, with monthly PRN injections if CST >275 µm. Optional rescue therapy with focal/grid laser photocoagulation or the originally assigned anti-VEGF agent was permitted for 3 consecutive visits if CST did not reduce by ≥10% or BCVA did not increase by ≥5 letters from baseline.[39]

Ranibizumab produced a significantly greater improvement in mean BCVA change from baseline to weeks 8 and 32 compared to bevacizumab, with the difference at weeks 28, 36, and 40 trending towards favoring ranibizumab.[39] However, no significant difference was observed between ranibizumab and bevacizumab for a gain of ≥15 letters or for mean CST reduction at week 48. Notably, a significantly higher proportion of eyes treated with ranibizumab achieved a CST ≤275 µm at weeks 4, 28, 36, and 44 compared to bevacizumab. Overall, the mean number of injections was significantly higher with bevacizumab versus ranibizumab (9.84 vs 7.67, respectively).[39]

The second RCT (Ekinci et al, 2014) evaluated intravitreal injections of bevacizumab 1.25 mg (n=50) versus ranibizumab 0.5 mg (n=50) among participants with DME.[40] Both treatment groups received monthly injections for the initial 3 doses, and then switched to a PRN regimen with subsequent injections given based on disease activity (ie, CMT or BCVA response).[40] The measurements at month 12 for key outcomes including CMT and BCVA were not significantly different between treatment groups.[40] However, participants treated with bevacizumab had a significantly lower number of mean injections at

the end of the 12-month period compared to participants treated with ranibizumab (5.1 vs 6.5, respectively).[40]

The third RCT (Vader et al, 2020) randomized adult participants with DME to intravitreal monthly injections of bevacizumab 1.25 mg (n=86) or ranibizumab 0.5 mg (n=84) for 6 months.[41] Ranibizumab significantly outperformed (and demonstrated non-inferiority to) bevacizumab for improving BCVA from baseline to 6 months (primary outcome; +6.7 letters vs +4.9 letters, respectively; treatment difference of 1.8 letters). Additionally, ranibizumab resulted in a significant decrease in central area thickness compared to bevacizumab (138.2 µm vs 64.2 µm, respectively; p<0.001) at 6 months. In a post hoc subgroup analysis of participants with a baseline BCVA score of 69 letters or lower, ranibizumab significantly improved BCVA and central area thickness from baseline to 6 months; however, no significant differences were observed among participants with a baseline BCVA score of 70 letters or higher. Overall, rates of AEs and serious AEs were comparable between treatment groups.[41]

6.3 Direct comparative evidence for ME-RVO

Of the reviewed anti-VEGF agents, aflibercept (dosed at 2 mg) and ranibizumab, including its biosimilars are approved for the treatment of ME-RVO,[4,6-8] and intravitreal bevacizumab may be used off-label per Micromedex (rated as *Evidence Favors Efficacy*).[11] Bevacizumab is among guideline-recommended first-line treatment options along with the approved anti-VEGF agents for ME-RVO.[13] According to prescribing information, the recommended dosing interval for intravitreal aflibercept 2 mg and ranibizumab 0.5 mg is once a month[4,6-8]; however, more recently these agents have been studied in other dosing regimens using a PRN or extended interval approach based on disease activity.

Two recent SRs included H-H RCT information regarding anti-VEGF therapies for ME-RVO.[98,99] The following comparisons were identified, with additional details discussed below for each comparison pair:

- Intravitreal aflibercept versus intravitreal ranibizumab or intravitreal bevacizumab
- Intravitreal ranibizumab versus intravitreal bevacizumab

6.3.1 Intravitreal aflibercept versus intravitreal ranibizumab

Among recently published SRs (2023), there are 5 RCTs of aflibercept 2 mg versus ranibizumab 0.5 mg for the treatment of ME-RVO.[98,99] Four of the 5 studies included fewer than 40 eyes per treatment arm, and 1 study included approximately 150 eyes per treatment arm.[99] The dosing interval varied across studies (eg, every 2 months, PRN, or treat-and-extend). The largest RCT used a PRN interval and had follow-up out to 100 weeks; whereas the other 4 RCTs had follow-up between 3 to 12 months.[99,112]

Based on individual RCT results at their final follow-up time point, there were no significant differences between aflibercept 2 mg and ranibizumab 0.5 mg for mean CMT reduction or mean BCVA improvement from baseline.[112,135-138] Additionally, there were no significant differences in the proportion of patients gaining ≥15 letters after 12 to 24 months.[99] A meta-analysis, which included direct comparative data from these RCTs and additional observational studies also showed no significant differences in visual acuity improvement or mean CMT reduction over 12 to 24 months, in addition to the occurrence of systemic or ocular AEs.[99] SR authors concluded that aflibercept was at least equally as effective as (or non-inferior to)[98] ranibizumab for improving vision and reducing CMT, without significant AE

differences.[99] An advantage of aflibercept is that it appears to require a lower mean number of injections (when using a PRN interval) compared to ranibizumab.[99] Cornish et al (2023) elaborated that "The choice of VEGF inhibitor does not appear to be important with similar visual and anatomic outcomes, as long as it is given as often as required, and patients [are] kept under close observation when treatment is given PRN"[98] (page 334).

6.3.2 Intravitreal aflibercept versus intravitreal bevacizumab (off-label)

Based on a 2023 SR, 2 RCTs have compared aflibercept 2 mg to bevacizumab 1.25 mg (SCORE 2 and LEAVO) for the treatment of macular edema due to central retinal vein occlusion (CRVO).[98] SCORE 2, with 362 treated patients, found bevacizumab to be non-inferior to aflibercept for improving visual acuity at month 6 (with both agents given on a scheduled monthly basis).[110] The secondary outcome of central retinal vein thickness measurement was also similar between groups; however, upon post hoc analysis, the odds of complete resolution of macular edema by month 6 was significantly higher with aflibercept (54% with resolution) versus bevacizumab (29% with resolution).[110]

In the LEAVO RCT, bevacizumab 1.25 mg and aflibercept 2 mg (about 150 patients per arm) were given PRN, after the first 3 monthly injections, out to week-100.[98,112] The comparison of bevacizumab to aflibercept was a post-hoc assessment; bevacizumab did not meet non-inferiority at week-100, with respect to mean change in visual acuity.[112] SR authors concluded that bevacizumab was non-inferior to aflibercept if each are administered on an ongoing monthly basis, but bevacizumab does not appear non-inferior if each are given on a PRN basis.[98]

6.3.3 Intravitreal ranibizumab versus intravitreal bevacizumab (off-label)

Although a 6 month RCT, with 463 treated eyes, showed monthly bevacizumab 1.25 mg was non-inferior to monthly ranibizumab 0.5 mg for improving visual acuity,[111] a longer duration RCT with 150 patients per arm and a PRN dosing regimen, found that bevacizumab 1.25 mg did not perform non-inferior to ranibizumab 0.5 mg at week 100.[112] Changes in central area thickness (secondary outcome) were comparable between ranibizumab and bevacizumab in each study.[111,112] Severe AEs (7.1% with bevacizumab vs. 9.2% with ranibizumab) were similar between treatments in the 6 month study, and the frequency of ocular AEs were also similar between treatments in the longer study.[111,112]

6.4 Direct comparative evidence for mCNV

Of the reviewed intravitreal anti-VEGF therapies, ranibizumab and its biosimilars (Cimerli and Byooviz) are the only agents approved for mCNV.[2-9] Off-label use of bevacizumab for this disease is recognized in Micromedex (rated as *Evidence Favors Efficacy*), and other sources also cite evidence for use of aflibercept.[20,21]

Among the SR evidence identified, 3 H-H RCTs were reported for ranibizumab versus bevacizumab, with no other comparison pairs identified for this indication.[100,139]

6.4.1 *Intravitreal ranibizumab versus intravitreal bevacizumab (off-label)*

SRs identified 3 RCTs for ranibizumab 0.5 mg versus bevacizumab 1.25 mg for the treatment of mCNV.[100,139] RCTs included between 32 and 78 total eyes treated, with a final follow-up duration ranging from 6 to 9 months.[113-115] In each RCT, anti-VEGF therapy was administered PRN after the first intravitreal dose (based on response at monthly follow-up examinations). Individual RCTs along with an SRMA found no significant differences between agents for key efficacy outcomes between 6 to 18 months (eg, improvement of BCVA,[100,113-115] foveal center thickness reduction,[115] reduction in CMT,[113,114] choroidal neovascularization area).[114] One RCT highlighted that the ranibizumab arm required significantly fewer injections (mean of 2.5 vs 4.7; p-value <0.001) over the 18-week study duration[114]; however, the other 2 RCTs showed a similar number of injections between treatment groups over the first year of treatment (mean of 2.3 with ranibizumab and 2.7 with bevacizumab; p-value=0.09)[113] or over 6 months.[115] There were no significant differences in major ocular or systemic AEs between treatment arms in each study.[100,113-115]

6.5 Direct comparative evidence for ROP

Of the reviewed intravitreal anti-VEGF therapies, aflibercept (Eylea) is the only one approved for ROP.[2-9] Nonetheless, off-label use of bevacizumab for ROP is recognized by Micromedex (rated as *Evidence Favors Efficacy*).[11]

Recent SRs regarding comparative RCTs for the treatment of ROP are absent of H-H studies between intravitreal anti-VEGF therapies.[22-24] The most recent SR (Chang et al [2022]) searched for RCTs regarding treatment with bevacizumab, ranibizumab, or aflibercept; however, it did not find any comparative H-H RCTs.[22] The 3 aforementioned anti-VEGF agents have thus far been compared to laser therapy in RCTs.[22]

7.0 SAFETY

The following subsections provide a summary of common adverse events (AEs), contraindications, and warnings and precautions as reported in the prescribing information (ie, product labeling) for the reviewed FDA-approved anti-VEGF agents. Notably, as biosimilar products, both ranibizumab-eqrn (Cimerli) and ranibizumab-nuna (Byooviz) have demonstrated a comparable safety profile to the reference agent, ranibizumab, in patients with nAMD[106-108]; approval of other respective indications was based on extrapolation of clinical data.[140,141]

Immunogenicity: Similar to other therapeutic proteins, it is possible for treated patients to develop antibodies to intravitreal anti-VEGF agents,[2,4-9] including the ocular implant, Susvimo.[3] For most intravitreal anti-VEGF agents, including the ranibizumab implant, the presence of positive antibodies did not meaningfully affect clinical efficacy or safety,[3,6,9] but the significance remains to be determined for ranibizumab and its biosimilars.[4,7,8] The following bullets list the incidence of immunoreactivity for each agent pre- and post-treatment, according to prescribing information:

- Ranibizumab (Lucentis), including ranibizumab-eqrn (Cimerli) and ranibizumab-nuna (Byooviz) (across treatment groups)[4,7,8]:
    - Pre-treatment: 0% to 5% of patients
    - Post-treatment (dosed monthly for 6−24 months): 1% to 9% of patients
        - Among those with the greatest immune response, iritis or vitritis was observed in some patients with nAMD
- Aflibercept (Eylea)[6]:
    - Pre-treatment (AMD, DME, and RVO clinical trials, across treatment groups): 1% to 3% of patients
    - Post-treatment (ROP clinical trials): <1% of patients
    - Post-treatment (dosed for 24−100 weeks): actual incidence is not reported in the prescribing information for other indications, but it is noted that the percentage range of patients with immunoreactivity was similar to pre-treatment
- Aflibercept (Eylea HD)[5]:
    - Pre-treatment: not reported in the prescribing information
    - Post-treatment (after 48 weeks): 2.7% of patients (nAMD or DME)
- Faricimab-svoa (Vabysmo)[2]:
    - Pre-treatment (nAMD and DME clinical trials, across treatment groups): 0.8% (DME) and 1.8% (nAMD) of patients
    - Post-treatment: 8.4% (DME) and 10.4% (nAMD) of patients
- Brolucizumab-dbll (Beovu)[9]:
    - Pre-treatment: 36% to 64% of patients
    - Post-treatment: (≥1 serum sample): 53% to 76% of patients
        - Immune-mediated AEs: intraocular inflammation (6% of patients with positive antibodies); usually retinal vascular occlusion and/or retinal vasculitis occurred in conjunction with intraocular inflammation
- Ranibizumab ocular implant (Susvimo)[3]:
    - Pre-insertion: 2.1% of treatment-experienced patients
    - Post-insertion: 12% of treatment-experienced patients

7.1 Common adverse events (AEs)

Based on prescribing information (ie, package inserts), the following bullets list the most common AEs reported in clinical studies:

- Ranibizumab (Lucentis),[4] ranibizumab-eqrn (Cimerli),[7] and ranibizumab-nuna (Byooviz)[8]:
    - Most common AEs (≥5% difference from control): conjunctival hemorrhage, vitreous floaters, eye pain, and increased intraocular pressure (IOP)
- Ranibizumab ocular implant (Susvimo)[3]:
    - Most common AEs (≥10% in patients receiving Susvimo): conjunctival hemorrhage, conjunctival hyperemia, iritis, and eye pain

- Aflibercept (Eylea)[6]:
    - Most common AEs (≥5% in aflibercept-treated patients): conjunctival hemorrhage, vitreous floaters, eye pain, cataract, vitreous detachment, and increased IOP
- Aflibercept (Eylea HD)[5]:
    - Most common AEs (≥3% in aflibercept-treated patients): conjunctival hemorrhage, vitreous floaters, eye discomfort/pain/irritation, cataract, vitreous detachment, increased IOP, blurred vision, retinal hemorrhage, and corneal epithelium defect
- Faricimab-svoa (Vabysmo)[2]:
    - Most common AEs (≥5% in patients receiving faricimab-svoa): conjunctival hemorrhage and cataract
- Brolucizumab-dbll (Beovu)[9]:
    - Most common AEs (≥5% in patients receiving brolucizumab-dbll): blurred vision, conjunctival hemorrhage, cataract, eye pain, and vitreous floaters

7.2 Contraindications

All of the reviewed FDA-approved intravitreal anti-VEGF agents are contraindicated in patients who experienced a hypersensitivity reaction (eg, intraocular inflammation, rash, urticaria, pruritus) to the active ingredient or any excipient(s), and those with an active periocular or ocular infection.[2-9] Except for ranibizumab and its two biosimilars, the remaining products are also contraindicated in patients with active intraocular inflammation.[2,3,5,6,9]

7.3 Warnings and precautions

All of the reviewed FDA-approved intravitreal anti-VEGF injectable agents carry warnings for the potential of endophthalmitis, retinal detachment(s), elevated IOP, and arterial thromboembolic events (ATEs).[2,4-9] Susvimo also carries a risk of endophthalmitis and retinal detachment (other unique warnings and precautions of this product are discussed in **Section 7.3.1.4**).[3] **Table 20** provides an overview of the labeled warnings/precautions for the reviewed intravitreal anti-VEGF agents, with additional details for each of these warnings/precautions provided after the table.

Table 20. Labeled Warnings and Precautions for FDA-approved Intravitreal Anti-VEGF Agents

	Ranibizumab[4] (Lucentis)	**Ranibizumab-eqrn**[7] (Cimerli)	**Ranibizumab-nuna**[8] (Byooviz)	**Aflibercept**[5,6] (Eylea; Eylea HD)	**Faricimab-svoa**[2] (Vabysmo)	**Brolucizumab-dbll**[9] (Beovu)	**Ranibizumab ocular implant**[3] (Susvimo)
Endophthalmitis	✓	✓	✓	✓	✓	✓	✓
Retinal detachment[a]	✓	✓	✓	✓	✓	✓	✓
Increased intraocular pressure	✓	✓	✓	✓	✓	✓	
Arterial thromboembolic events[b]	✓	✓	✓	✓	✓	✓	
Fatalities in patients with DME and DR at baseline	✓	✓					
Ongoing ROP monitoring				**✓ (Eylea only)**			
Retinal vascular occlusion and/or retinal vasculitis						✓	
Implant- and/or procedural-related reactions (eg, implant dislocation, septum dislodgment, conjunctival reactions)							✓
Vitreous hemorrhage							✓
Temporary postoperative reduction in visual acuity							✓

[a] Ranibizumab ocular implant (Susvimo) is associated with the occurrence of a particular type of retinal detachment, rhegmatogenous retinal detachment.

[b] Events classified as arterial thromboembolic events were nonfatal stroke, nonfatal myocardial infarction, or vascular death (including those of undetermined cause).

Abbreviations: DME, diabetic macular edema; DR, diabetic retinopathy; FDA, Food and Drug Administration; ROP, retinopathy of prematurity; VEGF, vascular endothelial growth factor

Endophthalmitis and retinal detachment(s): Intravitreal anti-VEGF injections, and the ranibizumab implant,[3] can cause exogenous endophthalmitis,[2,4-9] an infection of the intraocular space resulting in inflammation, and if untreated, can cause permanent vision loss.[3,142] Notably, the incidence rate of endophthalmitis varies depending on the route of ranibizumab administration; the rate is increased by 3-fold for the implant (Susvimo) compared to the intravitreal monthly injection (1.7% vs. 0.5%, respectively).[3] Furthermore, all of these products contain a warning for the potential risk for retinal detachment(s)[2,4-9]; the ranibizumab implant has been associated with rhegmatogenous retinal detachments.[3]

Appropriate aseptic technique and/or special handling precautions for the ocular implant should be used by the managing ophthalmologist to minimize the risk of endophthalmitis.[2-9] After receiving the injection, patients should be monitored and advised to immediately report any symptoms and/or signs of endophthalmitis or retinal detachment (eg, light sensitivity, redness, pain, vision changes) to allow for prompt medical treatment, if necessary.[2,4-9] The refill-exchange procedure for the ranibizumab implant should be postponed until resolution of endophthalmitis or retinal detachment or break.[3] Before inserting the ocular implant, treating any areas with retinal breaks or irregular vitro-retinal adhesion should first be carried out.[3]

Elevated intraocular pressure (IOP): All of the reviewed FDA-approved injectable intravitreal anti-VEGF products carry a warning for the potential risk of increased IOP, which has been observed both before and after injection.[2,4-9] With the exception of brolucizumab-dbll,[9] all the other agents have been found to cause an acute rise in IOP within 60 minutes of the injection[2,4-8]; however, in the case of brolucizumab-dbll, this increase has been observed within 30 minutes of the injection.[9] Repeated intravitreal administration of anti-VEGF inhibitors has also been associated with prolonged elevation in IOP.[5,6,9] Thus, it is important to monitor IOP and optic nerve head perfusion after administering the injection, taking appropriate measures as needed.[2,4-9] Moreover, for ranibizumab and its biosimilars, it is advised to also monitor IOP before administering the injection.[4,7,8]

Arterial thromboembolic events (ATEs): Intravitreal injectable anti-VEGF products carry a potential risk of ATEs, even though clinical trials showed a low occurrence.[2,4-8] Summarized below are the incidence rates of ATEs observed in clinical trials, based on labeled indication.

- Ranibizumab (Lucentis; also applies to ranibizumab-eqrn [Cimerli] **and** ranibizumab-nuna [Byooviz])[4,7,8]:
    - nAMD: During the first year of 3 controlled trials, the ATE rate was 1.9% in the ranibizumab-treated group compared to 1.1% in the control group. During the second year of the AMD-1 and AMD-2 trials, the incidence rate increased to 2.6% in the ranibizumab group compared to 2.9% in the control group. A pooled analysis of these 2-year controlled studies and a third ranibizumab study (used as adjunct to verteporfin photodynamic therapy), showed that the stroke rate, which included ischemic and hemorrhagic origins, was 2.7% in patients receiving ranibizumab 0.5 mg compared to 1.1% in the control group.
    - ME-RVO: During the first 6 months of 2 RVO trials, the ATE rate was 0.8% in both the ranibizumab arm (a combined group of patients treated with either 0.3 mg or 0.5 mg) and control arm; the stroke rate was 0.2% vs. 0.4%, respectively.

- Ranibizumab (Lucentis; also applies to ranibizumab-eqrn [Cimerli], **not** ranibizumab-nuna [Byooviz])[4,7]:
    - DME and DR: A pooled analysis of 2 DME and DR trials showed an ATE incidence rate at year 2 among ranibizumab-treated patients was 7.2% in the 0.5 mg group and 5.6% in the 0.3 mg group, compared to the control group rate of 5.2%; the stroke rate was 3.2%, 1.2%, and 1.6%, respectively. At 3 years, the ATE incidence rate increased among ranibizumab-treated patients to 10.4% with the 0.5 mg dose and 10.8% with the 0.3 mg dose; the stroke rate was 4.8% and 2.0%, respectively (the ATE and stroke rate of the control group at 3 years was not reported).
- Aflibercept (Eylea)[6]:
    - nAMD: During the first year, the incidence of reported ATEs was numerically higher in the aflibercept arm (1.8%) compared to those treated with ranibizumab (1.5%). However, by 96 weeks, the incidence was similar among both groups (3.3% in the aflibercept group and 3.2% in the ranibizumab group).
    - DME: The incidence of ATEs was numerically higher in patients treated with aflibercept (3.3%) compared to the control group (2.8%) at week 52; this trend continued throughout week 100, with the incidence increasing to 6.4% in the aflibercept-treated group compared to 4.2% in the control group.
    - ME-RVO: No ATEs were reported among aflibercept-treated patients after 6 months of treatment.
- Aflibercept (Eylea HD)[5]:
    - nAMD: From baseline through week 48, the incidence of reported ATEs was 0.4% among patients who received aflibercept 8 mg (Eylea HD) and 1.5% among patients who received aflibercept 2 mg (Eylea).
    - DME: From baseline to week 48, the incidence of reported ATEs was 3.1% among patients treated with aflibercept 8 mg (Eylea HD) and 3.6% among patients treated with aflibercept 2 mg (Eylea).
- Faricimab-svoa (Vabysmo)[2]:
    - nAMD: During the first year of clinical trials, the frequency of reported ATEs was 1% among patients who received faricimab-svoa, which was comparable to the ATE incidence among patients treated with aflibercept (1%).
    - DME: From baseline to week 100, the occurrence of reported ATEs was similar in patients who received faricimab-svoa (5%) and those who received aflibercept (5%).[2]
- Brolucizumab-dbll (Beovu)[9]:
    - nAMD: The incidence of ATEs during two 96-week trials was similar in the pooled brolucizumab arms (4.5%) and the pooled aflibercept arms (4.7%).

7.3.1 Unique warnings and precautions

Certain agents within the intravitreal anti-VEGF class have specific and distinct warnings. The following subsections provide a summary of the unique warnings and precautions carried by the reviewed FDA-approved intravitreal anti-VEGF agents.

7.3.1.1 Ranibizumab (Lucentis) and ranibizumab-eqrn (Cimerli)

Fatalities in patients with DME and DR at baseline: According to a pooled analysis of two trials that enrolled participants with DME and DR at baseline, the rate of fatalities in the first 2 years was numerically higher for those who received monthly injections of ranibizumab (4.4% for those treated with the 0.5 mg dose; 2.8% for those treated with the 0.3 mg dose) compared to controls (1.2%).[4,7] Over a span of 3 years, fatalities occurred in 6.4% and 4.4% of ranibizumab-treated patients who received 0.5 mg and 0.3 mg, respectively. Notably, the incidence of fatal events was low and included mortality events which are consistent with those commonly found in patients with advanced diabetic complications. Nevertheless, a possible connection between these events and the use of intravitreal ranibizumab (and by extension Cimerli) cannot be ruled out.[4,7] Because ranibizumab-nuna (Byooviz) is not indicated for the treatment of DME or DR, it does not carry this warning.[8]

7.3.1.2 Aflibercept (Eylea)

ROP monitoring, including for prolonged periods, and the need for additional treatment: Infants treated with aflibercept (Eylea) for ROP should be closely monitored after receiving the injection for abnormal angiogenesis and tortuosity until the physician is confident that ROP reactivation is unlikely to occur, or it is ensured that retinal vascularization has completed.[6] Infants who undergo treatment with aflibercept (Eylea) for ROP will likely require prolonged periods of monitoring, and subsequent injections and/or laser therapy in cases of ROP reactivation may be required.[6] Elyea HD (8 mg product of aflibercept) does not contain this warning because it is not approved for the treatment of ROP.[5]

7.3.1.3 Brolucizumab-dbll (Beovu)

Retinal vascular occlusion and/or retinal vasculitis: The use of brolucizumab-dbll has been associated with cases of retinal vascular occlusion, retinal vasculitis, or both, usually in conjunction with intraocular inflammation.[9] These immune-mediated AEs can occur after receiving a single injection. If a patient experiences retinal vascular occlusion and/or retinal vasculitis, treatment with brolucizumab-dbll should be discontinued. Patients who receive brolucizumab-dbll and develop intraocular inflammation should be carefully monitored, as they may be at risk of developing retinal vascular occlusion and/or retinal vasculitis. Patients should be advised to promptly report any visional changes during treatment.[9]

7.3.1.4 Ocular implant of ranibizumab (Susvimo)

Implant-related events: The ranibizumab implant carries risks of implant-related events such as dislocation of the implant, implant damage (via implant septum dislodgement), improper filling of the implant reservoir due to air bubbles, implant deflection, and conjunctival reactions (ie, retraction, erosion, bleb)[3]; preventing these events relies heavily on proper device handling/implant procedures. Patients must be advised to immediately report any suggestive signs or symptoms, but there may be instances where these occurrences do not manifest any related symptoms.[3]

- *Dislocation of the implant:* Cases of implant displacement into the vitreous cavity, or into outside regions (eg, subconjunctival space) have occurred.[3] Should the device dislocate, prompt surgical intervention is required.[3]
- *Implant damage:* Implant damage, as a result of the implant septum (which is the self-sealing component for filling the implant) dislodging into the body of the implant, has been reported in

clinical trials; this can hinder the ability to continue treatment through refills.[3] Examinations to evaluate whether septum dislodgement has occurred should be conducted before and after the refill-exchange procedure. If septum dislodgement is confirmed, treatment should be stopped, and removal of the implant should be considered, if the benefits outweigh the risks.[3]

- *Improper filling of the implant reservoir due to air bubbles:* To avoid slower drug release, it is important to minimize the presence of air in the implant reservoir.[3] The implant should not be used if an excessive amount of air is observed after filling the implant. In the event that excess air bubbles are noticed after the refill-exchange procedure, it may be necessary to repeat the procedure.[3]
- *Implant deflection:* Caution should be exercised while performing ophthalmic procedures (eg, scleral depression, gonioscopy, B-scan ophthalmic ultrasound) that may result in implant deflection and consequent harm.[3]
- *Conjunctival reactions:* Conjunctival erosions (1.6% of patients), retractions (3.6% of patients), and bleb (5.9% of patients), with some cases requiring surgical management, have been reported in clinical trials among patients with the ranibizumab implant.[3] An increased risk of endophthalmitis has been linked to conjunctival erosions or retractions, particularly if the implant becomes exposed. Regular monitoring of both the implant and the surrounding tissue is essential after insertion and refill-exchange procedures to enable timely surgical management, if needed. Careful surgical techniques (eg, suture placement), and proper intraoperative handling to maintain tissue integrity may lower the occurrence of conjunctival reactions.[3]

Vitreous Hemorrhage: Among clinical trials, vitreous hemorrhages were observed in 5.2% of patients treated with ranibizumab ocular implant.[3] Most hemorrhages were reported within the first month after the surgical implantation, and majority of cases spontaneously resolved. Patients taking antithrombotic agents, such as oral anticoagulants, nonsteroidal anti-inflammatory drugs, or aspirin, may be predisposed to vitreous hemorrhages. Prescribing information advises temporarily discontinuing antithrombotic agents before the implant insertion procedure to decrease this risk. The refill-exchange procedure should be postponed if a vitreous hemorrhage poses a risk to the patient's vision. In cases of persistent vitreous hemorrhage (non-clearing), vitrectomy may be required.[3]

Postoperative reduction in visual acuity: Visual acuity tends to temporarily decrease after initial implantation of the device; on average, during the first postoperative month, visual acuity reduced by 4 letters, and by 2 letters during the second postoperative month.[3]

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APPENDIX A: PREPARATION, ADMINISTRATION, AND STORAGE INFORMATION

Product labeling (ie, package inserts) recommended storing intravitreal anti-VEGF products in the refrigerator (between 36°F to 46°F) in the original packaging until ready to be used.[2,4-9] Faricimab-svoa and brolucizumab-dbll can be kept at room temperature for up to 24 hours in the unopened packaging,[2,9] and it is recommended that faricimab-svoa reach room temperature before administration.[2] Intravitreal anti-VEGF agents are required to be administered by a qualified practitioner[2,5,6,9] such as an ophthalmologist or retina specialist.[44] Because these agents are injected into the eye, aseptic techniques should be used when preparing (eg, using a sterile filter needle with glass vials) and administering (eg, using sterile gloves, hand disinfection, sterile eyelid speculum, sterile drape) these agents.[2,4-9] Product labeling for faricimab-svoa and brolucizumab-dbll recommend that these agents be administered immediately after preparing the dose for injection.[2,9] Before injecting the product, it should be visually examined for cloudiness, discoloration, or particulates; if the solution contains any of these abnormalities, or if the packaging is damaged or the product is expired, it should not be used.[2,6,9] Notably, with aflibercept (Eylea), some residual volume may be present in the pre-filled syringe after injecting the product[6]; it is not recommended to administer any residual solution after injecting the recommended volume,[6] and any unused volume should be discarded.[2,5,6]

Similarly, implant-related procedures for Susvimo should be conducted under aseptic conditions.[3] Susvimo should be stored in the refrigerator (between 36°F to 46°F) in the original packaging; unopened vials that are protected from light may be kept at room temperature for up to 24 hours. If a scheduled refill-exchange procedure is missed, it should be conducted as soon as possible, with consecutive refill-exchange procedures occurring as recommended (ie, every 24 weeks).[3] However, certain conditions (eg, endophthalmitis, implant damage, sight threatening events) would require a refill-exchange procedure to be withheld.[3]

APPENDIX B: LITERATURE SEARCH STRATEGIES

Ovid-Medline Systematic Reviews Search, Conducted August 30, 2023

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to August 28, 2023

#	Searches	Results
1	(ranibizumab or Lucentis or Cimerli or Byooviz or Susvimo or aflibercept or Eylea or faricimab or Vabysmo or brolucizumab or Beovu).ti,ab,kw,kf.	7,096
2	ranibizumab/ or aflibercept/ or faricimab/ or brolucizumab/	4,765
3	1 or 2	8,303
4	meta-analysis/ or (metaanaly$ or meta-analy$).ti,ab,kw,kf. or "Systematic Review"/ or ((systematic* adj3 review*) or (systematic* adj2 search*) or cochrane$ or (overview adj4 review)).ti,ab,kw,kf. or (cochrane$ or systematic review?).jw.	535,240
5	(MEDLINE or Embase or PubMed or systematic review).tw. or meta analysis.pt.	501,724
6	4 or 5	621,956
7	3 and 6	451
8	limit 7 to yr="2020 -Current"	**172**

Focused Ovid-Medline Systematic Reviews Search for myopic choroidal neovascularization (mCNV), Conducted September 25, 2023

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to September 22, 2023

#	Searches	Results
1	(ranibizumab or Lucentis or Cimerli or Byooviz).ti,ab,kw,kf.	5,154
2	ranibizumab/	4,769
3	1 or 2	6,457
4	(myopi* adj3 (choroid* or neovascular* or degener* or maculopathy or retinopathy or pathologic*)).ti,ab.	2,209
5	exp Neovascularization, Pathologic/ or exp Choroidal Neovascularization/	58,177
6	4 or 5	59,741
7	meta-analysis/ or (metaanaly$ or meta-analy$).ti,ab,kw,kf. or "Systematic Review"/ or ((systematic* adj3 review*) or (systematic* adj2 search*) or cochrane$ or (overview adj4 review)).ti,ab,kw,kf. or (cochrane$ or systematic review?).jw.	539,758
8	(MEDLINE or Embase or PubMed or systematic review).tw. or meta analysis.pt.	505,928
9	7 or 8	627,040
10	3 and 6 and 9	58
11	limit 10 to yr="2019"	**4**

Epistemonikos Systematic Reviews Search, Conducted August 30, 2023

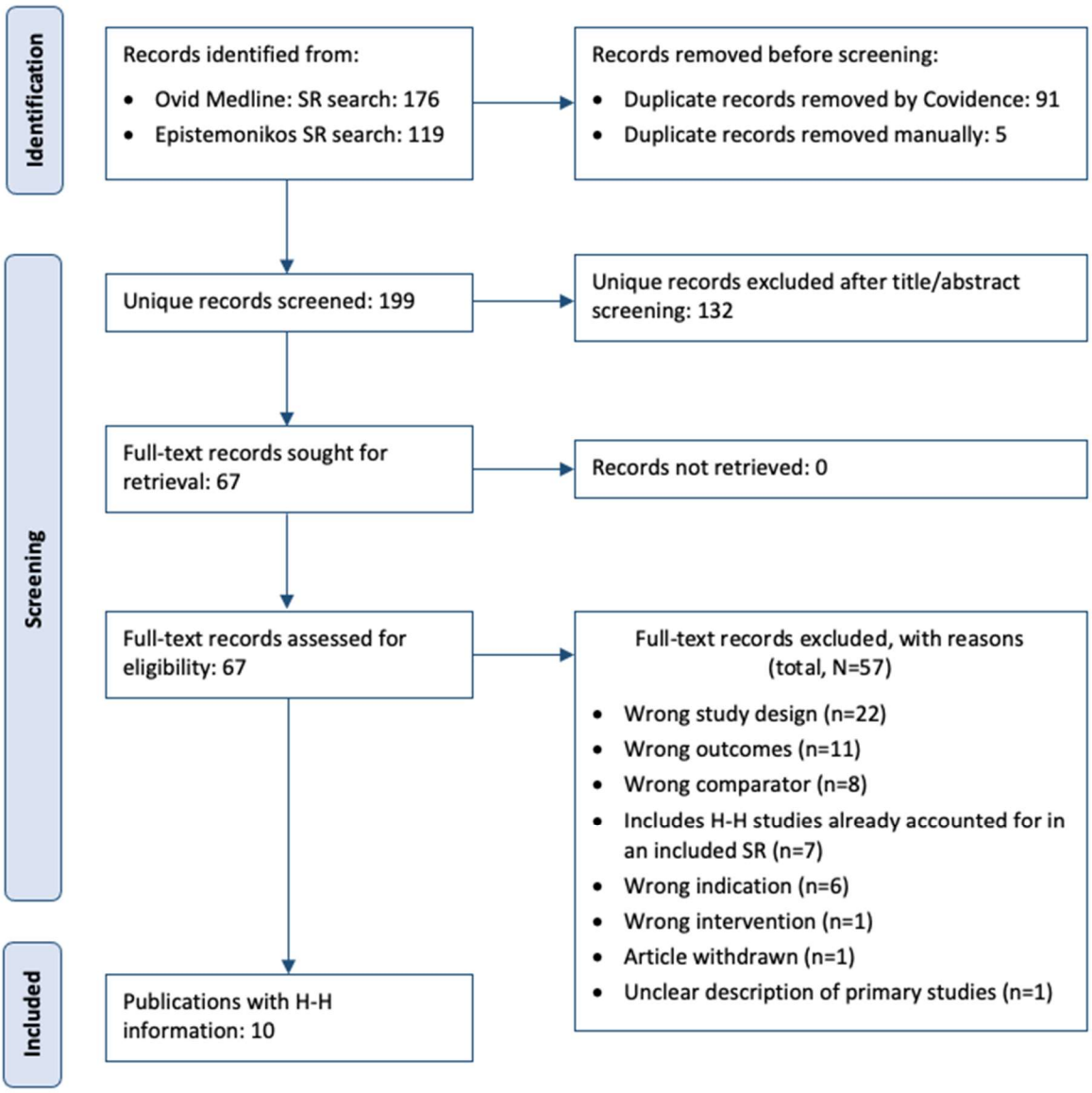
Restricted years: 2020–2023

(title:((ranibizumab OR Lucentis OR Cimerli OR Byooviz OR Susvimo OR aflibercept OR Eylea OR faricimab OR Vabysmo OR brolucizumab OR Beovu)) OR abstract:(ranibizumab OR Lucentis OR Cimerli OR Byooviz OR Susvimo OR aflibercept OR Eylea OR faricimab OR Vabysmo OR brolucizumab OR Beovu))

APPENDIX C: LITERATURE SCREENING PROCESS

Our literature screening process is outlined in the diagram below. This flow chart shows the unique number of records excluded at the identification and screening phases, and ultimately highlights the number of systematic reviews (SRs) included in this report.

Figure C1. PRISMA Flow Chart[a] for Literature Screening



[a] *Modified from Page et al 2021*[143]

Abbreviations: H-H, head-to-head; SR, systematic review

APPENDIX D: INCLUDED AND EXCLUDED REFERENCES AT FULL-TEXT SCREENING

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List of excluded references, by criterion

Wrong study design:

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Wrong outcomes:

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4. Lim SY, Wong WM, Seah I, et al. Treat and extend regimen for diabetic macular oedema-a systematic review and meta-analysis. *Graefes Arch Clin Exp Ophthalmol*. 2023;261(2):303-315. doi:10.1007/s00417-022-05770-y
5. Matonti F, Korobelnik JF, Dot C, et al. Comparative Effectiveness of Intravitreal Anti-Vascular Endothelial Growth Factor Therapies for Managing Neovascular Age-Related Macular Degeneration: A Meta-Analysis. *J Clin Med*. 2022;11(7)doi:10.3390/jcm11071834

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10. Xie X, Lian C, Zhang Z, et al. Aflibercept for long-term treatment of diabetic macular edema and proliferative diabetic retinopathy: a meta-analysis. *Front Endocrinol (Lausanne)*. 2023;14:1144422. doi:10.3389/fendo.2023.1144422
11. Zhang B, Zhou Z, Zhang B, Wang D. Efficacy and Safety of Various Treatments for Proliferative Diabetic Retinopathy: A Systematic Review and Network Meta-Analysis. *Front Pharmacol*. 2021;12:709501. doi:10.3389/fphar.2021.709501

Wrong comparator:

1. Chaudhary V, Sarohia GS, Phillips MR, et al. Role of anti-vascular endothelial growth factor in the management of non-proliferative diabetic retinopathy without centre-involving diabetic macular oedema: a meta-analysis of trials. *Eye (Lond)*. 2023;37(10):1966-1974. doi:10.1038/s41433-022-02269-y
2. Dong L, Li G, Song Z, Cheng X, Bai J, Zhang C. Comparison of antivascular endothelial growth factor treatment for myopia choroidal neovascularisation: a systematic review and meta-analysis of randomised controlled trials. *BMJ Open*. 2023;13(7):e067921. doi:10.1136/bmjopen-2022-067921
3. Falcão M. Impact of Intravitreal Ranibizumab Therapy on Vision Outcomes in Diabetic Macular Edema Patients: A Meta-Analysis. *Ophthalmologica*. 2020;243(4):243-254. doi:10.1159/000505070
4. Lees JS, Dobbin SJH, Elyan BMP, et al. A systematic review and meta-analysis of the effect of intravitreal VEGF inhibitors on cardiorenal outcomes. *Nephrol Dial Transplant*. 2023;38(7):1666-1681. doi:10.1093/ndt/gfac305
5. Martinez-Zapata MJ, Salvador I, Martí-Carvajal AJ, et al. Anti-vascular endothelial growth factor for proliferative diabetic retinopathy. *Cochrane Database Syst Rev*. 2023;3(3):Cd008721. doi:10.1002/14651858.CD008721.pub3
6. Rosenberg D, Deonarain DM, Gould J, et al. Efficacy, safety, and treatment burden of treat-and-extend versus alternative anti-VEGF regimens for nAMD: a systematic review and meta-analysis. *Eye (Lond)*. 2023;37(1):6-16. doi:10.1038/s41433-022-02020-7
7. Shalchi Z, Mahroo O, Bunce C, Mitry D. Anti-vascular endothelial growth factor for macular oedema secondary to branch retinal vein occlusion. *Cochrane Database Syst Rev*. 2020;7(7):Cd009510. doi:10.1002/14651858.CD009510.pub3

8. Wu XR, Liang FM, Song S. Meta-analysis of long-term efficacy of combined regimen in treatment of macular edema secondary to branch retinal vein occlusion. *International Eye Science*. 2021;21(1):92-98. doi:10.3980/j.issn.1672-5123.2021.1.19

Includes head-to-head studies already accounted for in an included systematic review:

1. Dascalu AM, Rizzo M, Rizvi AA, et al. Safety and Outcomes of Intravitreal Aflibercept in Diabetic Macular Edema - A Systematic Review. *Curr Pharm Des*. 2022;28(21):1758-1768. doi:10.2174/1381612828666220425101030
2. Ehlers JP, Yeh S, Maguire MG, et al. Intravitreal Pharmacotherapies for Diabetic Macular Edema: A Report by the American Academy of Ophthalmology. *Ophthalmology*. 2022;129(1):88-99. doi:10.1016/j.ophtha.2021.07.009
3. Nanji K, Khan M, Khalid MF, et al. Treat-and-extend regimens of anti-vascular endothelial growth factor therapy for retinal vein occlusions: a systematic review and meta-analysis. *Acta Ophthalmol*. 2022;100(6):e1199-e1208. doi:10.1111/aos.15068
4. Nanji K, Sarohia GS, Kennedy K, et al. The 12- and 24-Month Effects of Intravitreal Ranibizumab, Aflibercept, and Bevacizumab on Intraocular Pressure: A Network Meta-Analysis. *Ophthalmology*. 2022;129(5):498-508. doi:10.1016/j.ophtha.2021.11.024
5. Plyukhova AA, Budzinskaya MV, Starostin KM, et al. Comparative Safety of Bevacizumab, Ranibizumab, and Aflibercept for Treatment of Neovascular Age-Related Macular Degeneration (AMD): A Systematic Review and Network Meta-Analysis of Direct Comparative Studies. *J Clin Med*. 2020;9(5)doi:10.3390/jcm9051522
6. Radke NV, Mohamed S, Brown RB, et al. Review on the Safety and Efficacy of Brolucizumab for Neovascular Age-Related Macular Degeneration From Major Studies and Real-World Data. *Asia Pac J Ophthalmol (Phila)*. 2023;12(2):168-183. doi:10.1097/apo.0000000000000602
7. Pham B, Thomas SM, Lillie E, et al. Anti-vascular endothelial growth factor treatment for retinal conditions: a systematic review and meta-analysis. *BMJ Open*. 2019;9(5):e022031. doi:10.1136/bmjopen-2018-022031

Wrong indication:

1. Giannaccare G, Pellegrini M, Bovone C, et al. Anti-VEGF Treatment in Corneal Diseases. *Curr Drug Targets*. 2020;21(12):1159-1180. doi:10.2174/1389450121666200319111710
2. Hatamnejad A, Patil NS, Mihalache A, et al. Efficacy and safety of anti-vascular endothelial growth agents for the treatment of polypoidal choroidal vasculopathy: A systematic review and meta-analysis. *Surv Ophthalmol*. 2023;68(5):920-928. doi:10.1016/j.survophthal.2023.04.002
3. Mihalache A, Hatamnejad A, Patil NS, et al. Anti-vascular endothelial growth factor therapy regimens for polypoidal choroidal vasculopathy: a systematic review. *Ophthalmologica*. 2023, 10.1159/000533529doi:10.1159/000533529
4. Ramji S, Nagi G, Ansari AS, Kailani O. A systematic review and meta-analysis of randomised controlled trials in the management of neovascular glaucoma: absence of consensus and variability in practice. *Graefes Arch Clin Exp Ophthalmol*. 2023;261(2):477-501. doi:10.1007/s00417-022-05785-5

5. Rittiphairoj T, Roberti G, Michelessi M. Anti-vascular endothelial growth factor for neovascular glaucoma. *Cochrane Database Syst Rev*. 2023;4(4):Cd007920. doi:10.1002/14651858.CD007920.pub4
6. Simha A, Aziz K, Braganza A, Abraham L, Samuel P, Lindsley KB. Anti-vascular endothelial growth factor for neovascular glaucoma. *Cochrane Database Syst Rev*. 2020;2(2):Cd007920. doi:10.1002/14651858.CD007920.pub3

Unclear description of primary studies:

1. Huang C, Yi GG, Fu M. Efficacy of intravitreal injection of Aflibercept vs Ranibizumab in the treatment of diabetic retinopathy. *International Eye Science*. 2021;21(5):757-763. doi:10.3980/j.issn.1672-5123.2021.5.03

Wrong intervention:

1. Patil NS, Dhoot AS, Nichani PAH, Popovic MM, Muni RH, Kertes PJ. Safety and Efficacy of a Treat-and-Extend Regimen of Anti-Vascular Endothelial Growth Factor Agents for Diabetic Macular Edema or Macular Edema Secondary to Retinal Vein Occlusion: A Systematic Review and Meta-Analysis. *Ophthalmic Surg Lasers Imaging Retina*. 2023;54(3):131-138. doi:10.3928/23258160-20230221-04

Article withdrawn:

1. Zhinan Liu, Jun Zhang, Yufei Xu, Fan Xu, Guohua Deng, Zhou D. Efficacy of Four Anti-Vascular Endothelial Growth Factor Agents and Laser Treatment for Retinopathy of Prematurity: A Network Meta-Analysis. 2023, 10.2139/ssrn.4441369doi:10.2139/ssrn.4441369

APPENDIX E: DEFINITIONS OF GUIDELINE, EXPERT GUIDANCE, OR STATEMENT LEVEL OF EVIDENCE AND RECOMMENDATION STRENGTH

Table E1. Definitions of Guideline/ Expert Guidance/ Statement Level of Evidence and Strength of Recommendation

American Academy of Ophthalmology guidelines (2020)[13-15]

To assign an evidence rating to each individual study, the following scale developed by SIGN was used:

- I++: high-quality experimental studies (ie, SRs of RCTs, meta-analyses, or RCTs) that have a very low RoB
- I+: well-designed experimental studies (ie, SRs of RCTs, meta-analyses, or RCTs) that have a low RoB
- I-: experimental studies (ie, SRs of RCTs, meta-analyses, RCTs) that have a high RoB
- II++: high-quality SRs of cohort or case-control studies or individual observational studies (ie, case-control, cohort) that have a very low RoB or confounding, and a high degree of certainty that a causal relationship exists
- II+: well-designed observational studies (ie, cohort, case-control) that have a low RoB or confounding, and a moderate degree of certainty that a causal relationship exists
- II-: observational studies (ie, cohort, case-control) that have a high RoB or confounding, and a high degree of certainty that a causal relationship does not exist
- III: nonanalytic studies (eg, case series, case reports)

The following definitions by GRADE were used to determine the evidence quality and the strength of recommendations:

- Evidence quality:
  - Good: "Further research is very unlikely to change our confidence in the estimate of effect"[14] (Page P73)
  - Moderate: "Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate"[14] (Page P73)
  - Insufficient: "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"[14] (Page P73)
- Recommendation strength:
  - Strong recommendation: the benefits distinctly outweigh the risks or vice versa
  - Discretionary recommendation: the risk-benefits of the intervention are more uncertain due to an equipoise between the risks and benefits or low evidence quality

Cheung et al expert guidance statement (2017)[20]

- Recommendation class:
  - Class I: consensus and/or evidence support the beneficial, practical, or efficacious nature of a specific intervention; statements of this class are recommended
  - Class II: divergent viewpoints or conflicting evidence exist about the utility or effectiveness of a particular intervention
    - Class IIa: the preponderance of evidence and/or expert consensus support the utility and/or efficacy of the intervention; statements of this class should be considered
    - Class IIb: based on available evidence and/or expert opinion, the degree of support in favor of the utility and/or efficacy of the intervention is less firmly established; statements of this class may be considered
  - Class III: consensus and/or evidence suggest that a specific intervention lacks utility or effectiveness, and in certain cases, may carry potential harm; statements of this class are *not* recommended
- Oxford Centre for Evidence-based Medicine (CEBM) level of evidence:
  - Level 1: SRs of RCTs or "*n-of-1* trials"
  - Level 2: "Randomized trial or observational study with dramatic effect"[20] (page 1693)
  - Level 3: "Nonrandomized controlled cohort/follow-up study"[20] (page 1693)
  - Level 4: "Case series, case-control, or historically controlled study"[20] (page 1693)
  - Level 5: "Mechanism-based reasoning"[20] (page 1693)

American Optometric Association guideline (2019)[16]

Quality of evidence was rated according to the following:

- Grade A: meta-analyses, SRs, well-designed RCTs, diagnostic studies
  - Diagnostic studies were graded A if they had all of the following conditions: broad population, used a validated reference standard, and did not contain disease/condition case-control studies
- Grade B: weaker designed RCTs, prospective or retrospective cohort studies, diagnostic studies
  - Diagnostic studies were graded B if they had one of the following conditions: a narrow population, the study population was not generalizable to the population that would be suitable for the test, did not use a validated reference standard, used an unblinded comparison, or contained disease/condition case-control studies
- Grade C: case-control studies, non-randomized trials, well-designed studies with uncertain conclusions regarding generalizations, research design, bias, sample size, and diagnostic studies
  - Diagnostic studies were graded C if they had ≥2 of the following conditions: a narrow population, the study population was not generalizable to the population that would be suitable for the test, did not use a validated reference standard, or used an unblinded comparison

Abbreviations: CEBM, Centre for Evidence-Based Medicine; GRADE, Grading of Recommendations Assessment, Development and Evaluation; RCTs, randomized controlled trials; RoB, risk-of-bias; SIGN, Scottish Intercollegiate Guideline Network; SRs, systematic reviews

Table E1. Definitions of Guideline/ Expert Guidance/ Statement Level of Evidence and Strength of Recommendation

- Grade D: cross-sectional studies, case series or reports, expert opinion including reviews, position papers, and reasoning from principle

Recommendation strength:

- Strong recommendation: the benefits distinctly outweigh the risks or vice versa, and the evidence quality is high (Grade A or B). In some instances, a strong recommendation can be made based on lower quality evidence; this occurs when higher quality evidence is unavailable and the benefits decisively outweigh the risks. Recommendations assigned this strength should be adhered to unless a robust rationale exists to use an alternative method.
- Recommendation: the benefits outweigh the risks or vice versa, but the quality of evidence is lower (Grade B or C). In some instances, a recommendation can be made based on lower quality evidence; this occurs when higher quality evidence is unavailable and the benefits decisively outweigh the risks. In general, recommendations assigned this strength should be adhered to, but it is recommended to be mindful of current information.
- Discretional: unable to ascertain the relationship between risks and benefits of the recommendation. This may be due to insufficient evidence, the evidence quality is poor, or results are conflicting. Recommendations assigned this strength are important to be aware of, but individualized clinical decision-making may play a role, including being mindful of current information.

American Diabetes Association position statement (2017)[17]

Recommendations were given an evidence rating according to the quality of evidence[144]:

- A: based on well-designed, adequately powered generalizable RCTs; well-conducted meta-analyses; convincing nonexperimental evidence
- B: based on well-designed cohort or case-control studies
- C: based on poorly controlled or uncontrolled studies, including experimental or observational studies with methodological weaknesses, or case reports or case series, or conflicting evidence exists but the majority of the evidence favors the recommendation
- E: expert opinion or consensus, or clinical experience

Pan American Health Organization guideline (2017)[19]

The following definitions by GRADE were used to determine the evidence quality and the strength of recommendations:

- Evidence quality:
  - Grade A: it is highly improbable that new studies will significantly alter the level of confidence in the estimated effect; high certainty (judgment)
  - Grade B: it is probable that new studies will exert a substantial influence on the level of confidence in the estimated effect, and could potentially cause the estimated effect to change; moderate certainty (judgment)
  - Grade C: it is highly probable that new studies will significantly alter the level of confidence in the estimated effect, and the estimated effect is likely to change; low certainty (judgment)
  - Grade D: any estimated effect is very uncertain; very low certainty (judgment)
- Recommendation strength; strong recommendations are “recommended”, whereas weak recommendations are “suggested”:
  - Strong for: the benefits clearly outweigh the risks
  - Weak for: the benefits probably outweigh the risks
  - Weak against: the risks probably outweigh the benefits
  - Strong against: the risks clearly outweigh the benefits
  - Good practice point: based on clinical experience

American Academy of Pediatrics policy statement (2018)[18]

An evidence rating nor a recommendation strength was assigned to recommendations, which are primarily targeted to screening practices for ROP. However, cited evidence for their recommendations are provided.

Ohno-Matsui et al expert guidance statement (2018)[21]

All treatment recommendations were based on expert opinion of the authors.

Abbreviations: CEBM, Centre for Evidence-Based Medicine; GRADE, Grading of Recommendations Assessment, Development and Evaluation; RCTs, randomized controlled trials; RoB, risk-of-bias; SIGN, Scottish Intercollegiate Guideline Network; SRs, systematic reviews