Meeting Managed Care's Challenges in Managing
Age-Related Macular Degeneration and Diabetic Retinopathy

RETINAL DISEASES MANAGED CARE TOOLKIT

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PUBLISHER
Jeremy Williams, jwilliams@namcp.org

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4435 Waterfront Drive, Suite 101
Glen Allen, VA 23060
Tel (804) 527-1905
Fax (804) 747-5316

PUBLISHING, EDITORIAL MANAGEMENT AND PRODUCTION SERVICES
Douglas Murphy Communications
Richmond, VA
Tel (804) 387-7580
grant.murphy@douglasmurphy.com

TABLE OF CONTENTS

DISEASE BURDEN OVERVIEW

Age-related Macular Degeneration (AMD)[1-7]

- **AMD** is an **IRREVERSIBLE DESTRUCTION of the MACULA**, which leads to loss of the sharp, fine-detail, central vision required for activities such as reading, driving, recognizing faces, and seeing the world in color.

- **Eighty** to **90 PERCENT** of AMD patients have **non-neovascular or atrophic AMD** ("dry" AMD) and **10** to **20 PERCENT** have **neovascular** or "wet" AMD (nAMD).

- **AMD** is responsible for an estimated **46 PERCENT** of cases of **severe visual loss** (visual acuity 20/200 or worse) in **persons over 40 years of age in the United States (U.S.)**.

- Approximately **19.8 MILLION** individuals are affected with **AMD in the U.S.**

- Approximately **1.75 MILLION** people **AGED 40 YEARS OR OLDER in the U.S.** have **advanced disease** (nAMD or geographic atrophy) in at least one eye, and **7.3 MILLION** have **high-risk features for advanced disease** in one or both eyes.

- **Neovascular age-related macular degeneration** (nAMD) is responsible for nearly **90 PERCENT** of the severe visual acuity loss from AMD.

- **Aging** is the **GREATEST RISK FACTOR**; therefore, the prevalence of AMD **in the U.S.** is **anticipated to increase** as the population continues to age.

- The **RISK** of **having advanced AMD increases** from **2 PERCENT** for those **AGED 50 to 59 YEARS**, to nearly **30 PERCENT** for those **over the age of 75 years**.

- Without treatment, **two-thirds** of those with nAMD **could expect to be legally blind within two years** of developing the disease.

$$$

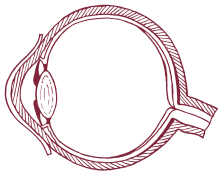
- The **COSTS OF CARE for AMD** are significant with an **AVERAGE ANNUAL ALL-CAUSE COST per patient** of **$24,520**.
- **OUTPATIENT COSTS** account for **63.5 PERCENT** of **total cost** and **JOB LOSS or JOB REDUCTION** accounted for **46 PERCENT** of the cost.
- **SIGNIFICANT DRIVERS of total nAMD-related costs** are **ANTI-VEGF THERAPY** and **ANTI-VEGF INJECTION FREQUENCY**.

QUALITY OF LIFE

- Patients with different degrees of severity of AMD have a **PERCEIVED IMPAIRMENT of their QUALITY OF LIFE (QOL)** that is **96 PERCENT** to **750 PERCENT greater than** the impairment estimated by treating ophthalmologists.
  - ⇨ **Early AMD** causes a **17 PERCENT decrement in QOL** (as that encountered with symptomatic human immunodeficiency virus infection or moderate cardiac angina).
  - ⇨ **Intermediate AMD** produces a **40 PERCENT decrement in QOL** (similar to that associated with permanent renal dialysis or severe cardiac angina).
  - ⇨ **Advanced AMD** causes a **63 PERCENT decrement in QOL** (similar to advanced prostatic cancer with uncontrollable pain or a severe stroke).

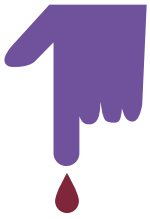
DISEASE BURDEN OVERVIEW

Diabetic Retinopathy (DR) and Diabetic Macular Edema[8-16]



- **DR** is a **LONG-TERM MICROVASCULAR COMPLICATION** of **diabetes mellitus**.
  - In early diabetic retinopathy (non-proliferative), blood vessels weaken, bulge, or leak into the retina.
  - Proliferative DR (PDR), which has new weak blood vessel proliferation, is vision threatening.
  - Diabetic macular edema (DME), which can be present with any level of diabetic retinopathy, is manifested as retinal thickening caused by the accumulation of intraretinal fluid and is vision threatening.

- Over **38 MILLION** adults aged 18 years or older—or **14.7 PERCENT** of all **U.S. ADULTS**—**have DIABETES**.
- An estimated **9.6 MILLION** people **in the U.S.** are **living with DR** and **1.84 MILLION** have **vision-threatening DR** (PDR and DME).



- **Prevalence of DR** is **77.3 PERCENT** in **type 1 diabetes patients** and **25.1 PERCENT** in **type 2 diabetes patients**, out of which approximately **25 PERCENT** to **30 PERCENT** are **expected to develop vision-threatening DME**.
- **DR** is the **MOST COMMON CAUSE OF SEVERE VISION LOSS** in working age adults in the western world.

- The proportion of **people with diabetes developing PDR and severe visual** loss **DECLINED WORLDWIDE between 1980 and 2008** in populations **with improved diabetes control**, but **crude prevalence of visual impairment and blindness caused by DR INCREASED between 1990 and 2015**, mostly **because of increasing cases of Type 2 diabetes**.

- **Early detection and treatment can REDUCE the risk of blindness** from DR by **95 PERCENT**.

- Only about **60 PERCENT** of **people with diabetes have recommended yearly screenings** for DR.

- The American Diabetes Association estimates that diabetic retinopathy **COSTS THE U.S.** at around **$327 BILLION** each year. This includes **$237 BILLION** in direct medical costs, **$90 BILLION** in decreased productivity, and over **$500 MILLION** in blindness-related costs.

Diagnosis and Coding[6,15,16]

AMD, DR, and DME can be identified on comprehensive eye examinations. This may involve a visual acuity test, visual field testing, pupil dilation to examine the retina, Amsler grid test, fundus photography, and tonometry to measure eye pressure. Testing to confirm a diagnosis may include optical coherence tomography (OCT) which creates cross-sectional images of the retina, OCT angiography, and fluorescein angiography to better examine the blood vessels of the eye, and stereoscopic biomicroscopic examination of the macula. OCT and best corrected visual acuity (BCVA) are used for monitoring the efficacy of therapy.

The American Academy of Ophthalmology (AAO) recommends that people aged 40 to 54 years get a comprehensive eye exam every two to four years to help detect AMD early. People 50 years of age and older should consider getting an eye exam every two years, and people aged 65 years and older should get an eye exam every year.

Those with type 1 diabetes should have annual screenings for DR beginning five years after the onset of their disease, whereas those with type 2 diabetes should have a prompt screening at the time of diagnosis and at least yearly screenings thereafter. If there is no evidence of retinopathy from one or more annual eye exams and glycemic indicators are within the goal range, screening every one to two years may be considered. If any level of diabetic retinopathy is present, subsequent dilated retinal examinations should be repeated at least annually. If retinopathy is progressing or sight-threatening, then examinations will be required more frequently.

Classification of AMD[6]

AMD is categorized into early, intermediate, or advanced stages based on the severity of symptoms, including the number and size of drusen (lipid/protein deposits) accompanied by hyper- or hypo-pigmentary changes and the presence or absence of choroidal neovascularization. The classification of AMD from the Age-Related Eye Disease Study (AREDS) which is used in the AAO practice pattern:

- No AMD (AREDS category 1) – no or few small drusen (less than 63 µm in diameter).
- Early AMD (AREDS category 2) – a combination of multiple small drusen, few intermediate drusen (63 to 124 µm in diameter), or mild retinal pigment epithelium (RPE) abnormalities.
- Intermediate AMD (AREDS category 3) – any of the following features:
    - Numerous intermediate drusen.
    - At least one large drusen (125 µm or more in diameter).
    - Geographic atrophy (a sharply demarcated, usually round, or oval, area of atrophy of the RPE not involving the center of the fovea).
- Advanced AMD (AREDS category 4) - one or more of the following (in the absence of other causes) in one eye:
    - Geographic atrophy of the RPE involving the foveal center.
    - Neovascular maculopathy that includes the following:
- Choroidal neovascularization (CNV) defined as pathologic angiogenesis originating from the choroidal vasculature that extends through a defect in Bruch's membrane.
- Serous and/or hemorrhagic detachment of the neurosensory retina or retinal pigment epithelial.
- Retinal hard exudates (a secondary phenomenon resulting from chronic vascular leakage).
- Subretinal and sub-retinal pigment epithelial fibrovascular proliferation.
- Disciform scar (subretinal fibrosis).

Classification of DR/DME[15,17]

DR is divided into two major forms: non-proliferative (NPDR) and proliferative (PDR), respectively named for the absence or presence of abnormal new blood vessels emanating from the retina. There are different classifications for DR and DME.

Exhibit 1: Diabetic Retinopathy Severity Scale (DRSS)

Disease Severity Level	Findings on Dilated Ophthalmoscopy
No apparent retinopathy	No abnormalities
Mild NPDR	Microaneurysms only
Moderate NPDR	More than just microaneurysms but less than severe NPDR
Severe NPDR	Any of the following (4-2-1 rule) and no signs of proliferative retinopathy: • Severe intraretinal hemorrhages and microaneurysms in each of 4 quadrants • Definite venous beading in 2 or more quadrants • Moderate IRMA in 1 or more quadrants
PDR	One or both of the following: •Neovascularization •Vitreous/preretinal hemorrhage

NPDR = non-proliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; IRMA = intraretinal microvascular abnormalities

Because the risk of visual loss is greatest if macular edema is at the center of the macula, DME is subdivided as either center involved (CI-DME) or non-center involved (NCI-DME). OCT is the best way to detect and quantitate CI-DME.

Early Treatment Diabetic Retinopathy Study (ETDRS) Definition of Clinically Significant Macular Edema (CSME)

- Retinal edema within 500 µm of the center of the fovea.
- Hard exudates within 500 µm of the center of the fovea if associated with adjacent retinal thickening (which may be outside the 500 µm limit).
- Retinal edema one disc area (1500 µm) or larger, any part of which is within one disc diameter of the center of the fovea.

Risk factors for Developing AMD and DR/DME[6,15,17]

Exhibit 2: Risk factors for Developing AMD and DR/DME[6,15,17]

AMD	DR/DME
Non-modifiable: Increasing age Many or large drusen in the eye Northern European ancestry Genetic factors	**Non-modifiable:** Puberty Pregnancy
Modifiable: Smoking	**Modifiable:** Hyperglycemia Hypertension Dyslipidemia Obesity

ICD-10 Diagnostic Codes (most common) for AMD and DR/DME[18]

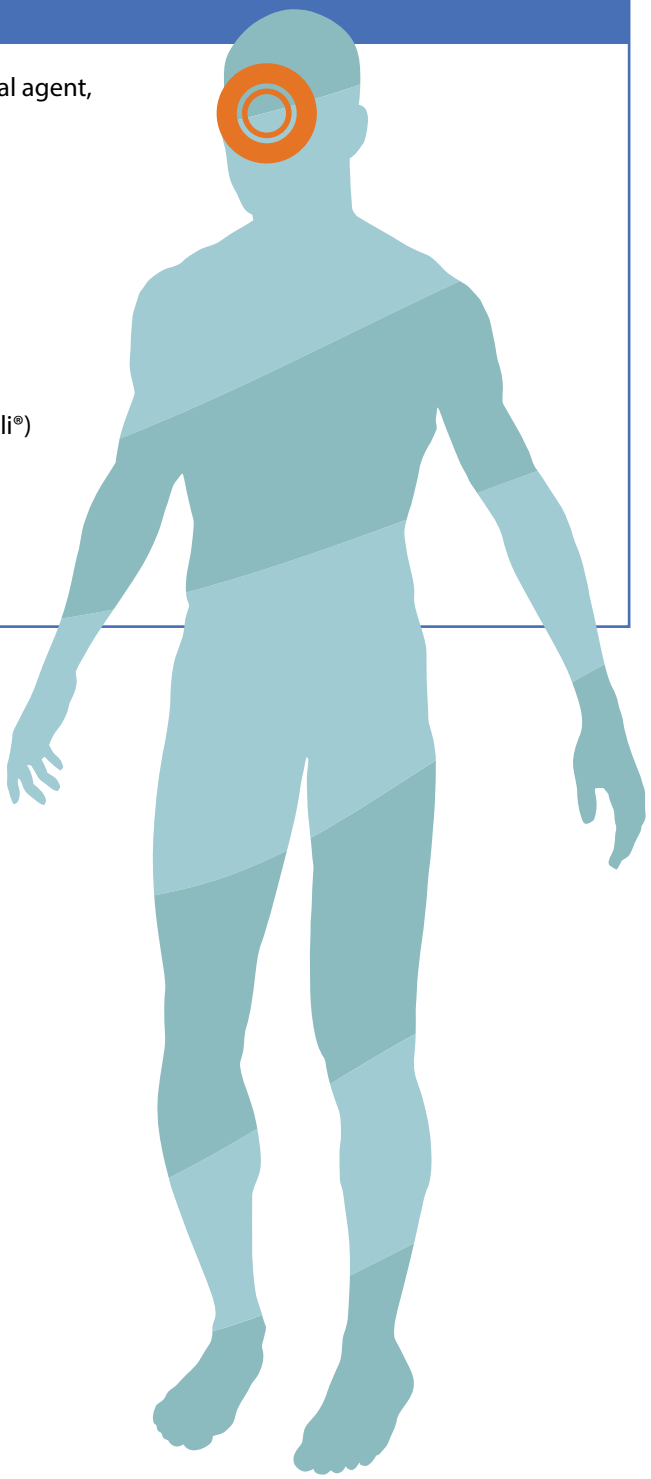
For AMD, only codes for neovascular (exudative) AMD are included.

ICD-10-CM	Description
AMD	
H35.321	Exudative age-related macular degeneration, right eye
H35.3210	Exudative age-related macular degeneration, right eye stage unspecified
H35.3211	Exudative age-related macular degeneration, right eye with active choroidal neovascularization
H35.3212	Exudative age-related macular degeneration, right eye with inactive choroidal neovascularization
H35.3213	Exudative age-related macular degeneration, right eye with inactive scar
H35.322	Exudative age-related macular degeneration, left eye
H35.3220	Exudative age-related macular degeneration, left eye stage unspecified
H35.3221	Exudative age-related macular degeneration, left eye with active choroidal neovascularization
H35.3222	Exudative age-related macular degeneration, left eye with inactive choroidal neovascularization
H35.3223	Exudative age-related macular degeneration, left eye with inactive scar
DR/DME	
E10.32X-34X	Type 1 with mild-to-severe non-proliferative diabetic retinopathy with and without macular edema
E10.351	Type 1 with proliferative diabetic retinopathy with macular edema
E10.359	Type 1 with proliferative diabetic retinopathy without macular edema
E11.320X – 34X	Type 2 with mild-to-severe non-proliferative diabetic retinopathy with and without macular edema
E11.351	Type 2 with proliferative diabetic retinopathy with macular edema
E11.359	Type 2 with proliferative diabetic retinopathy without macular edema

Treatment Codes (most common)

67028	Intravitreal injection of a pharmacological agent, separate procedure
J0177	aflibercept 2 mg (Eylea®)
J0178	aflibercept 8 mg (Eylea HD®)
J3590*	bevacizumab (Avastin®, biosimilars)
J0179	brolucizumab (Beovu®)
J2777	faricimab (Vabysmo®)
J2778	ranibizumab (Lucentis®, Byooviz™ Cimerli®)
J2779	ranibizumab (Susvimo® PDS)
J2781	pegcetacoplan (Syfovre®)
J3490**	avacincaptad pegol (Izervay®)

*Accepted J code may vary by insurer
**unlisted drug (this will change once this agent has an assigned J code)



Treatment

Goals of Therapy

- Identify patients at risk of visual loss related to AMD, DR, and DME
- Educate patients and their families about the disease, risk factors, and preventive measures
- Minimize or reverse visual loss and functional impairment in these patients through appropriate detection, self-assessment, treatment, and follow-up examinations
- Help patients identify expert physicians and resources needed to facilitate improvement or maintenance of vision

AMD Treatment

AMD cannot be cured, but its progression may be slowed or halted with treatment. Treatment is primarily done for nAMD.

AMD Treatment Guidelines[6]

- Treatment with antioxidants and minerals as described in the original AREDS and AREDS2 trials should be considered for patients who have progressed to intermediate or advanced non-neovascular AMD in at least one eye.
- Geographic atrophy (GA) is an advanced form of non-neovascular AMD. Two new treatments have been FDA approved for GA but have not yet been included in the AAO practice pattern.
- Encourage and support those with AMD to quit smoking.
- Intravitreal therapy using anti-vascular endothelial growth factor (VEGF) agents is the most effective way to manage nAMD and is first-line for treating and stabilizing most cases. The use of anti-VEGF agents produces visual acuity gains and may reduce the odds of legal blindness from nAMD.
- The data do not currently support the use of combination therapy with anti-VEGF and intravitreal corticosteroids for nAMD, especially given the long-term adverse effects of glaucoma and cataract that are associated with corticosteroid use.

DR/DME Treatment[19]

There is no cure for DR but treatment works very well to prevent, delay, or reduce vision loss. The sooner it is identified and treated, the more likely that vision will be saved. Treatment options include laser photocoagulation, intravitreal anti-VEGF injections, vitrectomy, and implant or intravitreal corticosteroids. Many people with DR need to be treated more than once as the condition progresses. Exhibit 3 below summarizes the evidence-based benefits of anti-VEGF therapy in DR.

Exhibit 3: Summary of the Evidence-based Benefits of Anti-VEGF Therapy in DR[19]

Stage of Diabetic Retinopathy (DR)	Application of Anti-VEGF Therapy	Evidence-Based Benefits
Mild non-proliferative DR	None	• N/A
Moderate-to-severe non-proliferative DR	Primary monotherapy	• Prevention of PDR. • Prevention of DME. • Prevention of DRSS worsening.
Proliferative DR	Primary monotherapy	• Prevention of DRSS worsening. • Prevention of DME.
	Alternative to PRP	• Fewer complications. • More ETDRS letters gained. • Reduced risk of future hemorrhage. • Reduced need for future vitrectomy.
	Adjunct to PRP	• Better clinical outcomes compared to PRP alone. • Reduced degree of follow-up burden compared with anti-VEGF therapy alone. • Prevention of the need for additional PRP treatments, reduced adverse ocular events.
	Adjunct to pars plana vitrectomy	• Less intraoperative bleeding and need for endodiathermy. • Reduced rates of iatrogenic retinal breaks. • Reductions in surgical times. • Superior visual acuity up to at least six months. • Shorter time to vitreous clearance. • Lower rates of postoperative hemorrhage. • Decreased likelihood of developing new CI-DME. • Decreased risk of new tractional retinal detachment.

PDR = proliferative diabetic retinopathy; DME = diabetic macular edema; DRSS = diabetic retinopathy severity scale;
ETDRS = Early Treatment Diabetic Retinopathy Study; PRP = panretinal photocoagulation; CI-DME = centrally involved DME.

DR/DME Treatment Guidelines[15,19,20]

The initial management recommendations for DR with or without DME are shown below. Anti-VEGF agents have become first-line therapy for CI-DME over laser photocoagulation. Studies that have demonstrated the benefit of anti-VEGF therapy for CI-DME required visual acuity loss (20/32 or worse). With a monthly or a protocol-driven strategy with anti-VEGF, eyes with vision 20/32 or worse due to CI-DME gained around two lines of vision at two years compared with stabilization of vision with focal laser treatment alone. Intravitreal corticosteroids are second-line for CI-DME if treatment response is unsatisfactory with anti-VEGF. At this time, laser photocoagulation surgery remains the preferred treatment for non-CI-DME.

The AAO guidelines note that a key clinical consideration for determining the use of anti-VEGF versus panretinal photocoagulation (PRP) for severe non-proliferative and proliferative DR is the reliability of patient follow-up. One analysis found that over a four-year period, 22 percent of patients with PDR under treatment with anti-VEGF injections were lost to follow-up. Recent data suggests that in patients with PDR, anti-VEGF is superior to PRP in terms of visual acuity benefit, DME prevention, adverse effect of visual field loss, and the need for future laser treatment.

Additional PRP or anti-VEGF therapy should be considered in situations involving the following:

- failure of the neovascularization to regress
- increasing neovascularization of the retina or iris
- new vitreous hemorrhage
- new areas of neovascularization

Exhibit 4: American Academy of Ophthalmology Initial Management Recommendations for Diabetic Retinopathy with or without Diabetic Macular Edema[15]

Severity of Retinopathy	Presence of Macular Edema	Follow-up (Months)	Panretinal Photocoagulation Laser	Focal and/or Grid Laser*	Intravitreal Anti-VEGF Therapy
Normal or minimal NPDR	No	12	No	No	No
Mild NPDR	No NCI-DME CI-DME**	12 3 – 6 1	No No No	No Sometimes Rarely	No No Usually
Moderate NPDR	No NCI-DME CI-DME**	6 – 12 3 – 6 1	No No No	No Sometimes Rarely	No Rarely Usually
Severe NPDR	No NCI-DME CI-DME**	3 – 4 2 – 4 1	Sometimes Sometimes Sometimes	No Sometimes Rarely	Sometimes Sometimes Usually
Non-high risk PDR	No NCI-DME CI-DME**	3 – 4 2 – 4 1	Sometimes Sometimes Sometimes	No Sometimes Sometimes	Sometimes Sometimes Usually
High risk PDR	No NCI-DME CI-DME**	2 – 4 2 – 4 1	Recommended Recommended Recommended	No Sometimes Sometimes	Sometimes Sometimes Usually

* Adjunctive intravitreal corticosteroids or anti-VEGF agents may be considered. Off-label except for aflibercept and ranibizumab
** Defer treatment until visual acuity worse than 20/25 with some exceptions
NPDR = non-proliferative diabetic retinopathy ; PDR = proliferative diabetic retinopathy ; DME = diabetic macular edema;
NCI = non center involved ; CI = center involved.

Anti-VEGF Therapy

Several anti-VEGF agents are now approved for nAMD and DME. Only ranibizumab and aflibercept (2 mg and 8 mg) are currently approved for DR.

FDA-Approved Indications

The approved indications for each agent are shown in Exhibit 5 below. It is important to note that bevacizumab is used off-label and must be repackaged in syringes or vials by a compounding pharmacy for use in the eye.

Exhibit 5: FDA Approved Indications[21-28]

Agent	Indications
aflibercept 8 mg (Eylea HD®)	• DME, DR, nAMD
aflibercept 2 mg (Eylea®)	• DME, DR, nAMD, Macular Edema Following Retinal Vein Occlusion (RVO), Retinopathy of Prematurity (0.4 mg)
bevacizumab (Avastin®, biosimilars)	• No ophthalmic use currently FDA approved*
brolucizumab (Beovu®)	• DME, nAMD
faricimab (Vabysmo®)	• DME, nAMD, RVO
ranibizumab (Lucentis®, Biosimilars -Byooviz™ and Cimerli®, Susvimo® Implant)	• Lucentis® – DME, DR, nAMD, RVO, Myopic Choroidal Neovascularization (mCNV) • Byooviz™ – nAMD, RVO, mCNV • Cimerli® – DME, DR, nAMD, RVO, mCNV • Susvimo® - nAMD

*Ophthalmic product under investigation

Clinical Efficacy of Intravitreal Anti-VEGF Agents in nAMD, DME, and DR

The FDA-approved agents have all been shown to be effective for the indications for which they are approved. The majority of trials are non-inferiority trials so it is hard to say one agent is better than another. The AAO guidelines for nAMD, DME, and DR do not recommend any specific agent and have not been updated since approval of faricimab and aflibercept 8 mg. Exhibit 6 below highlights comparative data from Cochrane Reviews and meta-analyses; selected individual trials are included.

Exhibit 6: Comparative Data from Cochrane Reviews and Meta-analyses[28-42]

Design	Agents/Dosing	Conclusions/Results
nAMD		
Cochrane Review (2019)	Bevacizumab Ranibizumab	Improved visual acuity with both and equally effective.
Cochrane Review (2016)	Aflibercept 2 mg Ranibizumab	Comparable effectiveness of aflibercept versus ranibizumab for visual acuity and morphological outcomes.
Meta-analysis (2018)	Bevacizumab Ranibizumab Aflibercept 2 mg	Bevacizumab and ranibizumab had equivalent efficacy for BCVA. Ranibizumab had greater reduction in central macular thickness compared to bevacizumab. Aflibercept and ranibizumab had comparable efficacy for BCVA and central macular thickness.
Phase III, randomized, three-group, double-masked, non-inferiority, 96-week trial PULSAR N = 1,011	Aflibercept 8 mg every 12 weeks (8q12) Aflibercept 8 mg every 16 weeks (8q16) Aflibercept 2 mg every 8 weeks (2q8) Three initial monthly doses in all groups. From week 16, dosing intervals for 8 mg groups were shortened if disease activity.	Primary endpoint was change from baseline in BCVA at week 48 Aflibercept 8q12 and 8q16 showed non-inferior BCVA gains versus aflibercept 2q8 (mean BCVA change from baseline +6.7 [SD 12.6] and +6.2 [11.7] versus +7.6 [12.2] letters). Mean BCVA changes were sustained out to week 96 and continued to be non-inferior. Least squares mean differences – aflibercept 8q12 versus 2q8, -0.97 and 8q16 versus 2q8, -1.14 letters (non-inferiority margin at 4 letters) No statistically significant difference in least square mean change in central subfield thickness at 48 and 96 weeks among the 3 groups. Mean number of injections over 96 weeks for 8q12 was 9.7, 8q16 8.2, and 2q8 12.8 87% of 8q12 group and 79% of 8q16 was able to maintain that dosing interval or longer at 96 weeks 31% of the 8q12 and 48% of 8q16 were able to have their dosing intervals extended out to 20 weeks or longer Ocular adverse events - 8q12, 39%; 8q16, 38%; 2q8, 39%

(continued)

Phase II, randomized, single-masked, open-label, 44-week clinical trial conducted in the U.S. CANDELA N = 108	3 monthly doses of aflibercept 8 mg or 2 mg followed by doses at weeks 20 and 32	This trial found trends but not statistical significance in anatomic and visual improvements over 44 weeks with aflibercept 8 mg which suggest additional therapeutic benefit over 2 mg in nAMD. Proportion of eyes without fluid in the central subfield with 8 mg versus 2 mg aflibercept was 50.9% (n = 27) versus 34.0% (p = .08) at week 16 and 39.6% versus 28.3% (p = .22) at week 44. At week 44, mean (SE) change in central retinal thickness was -159.4 (16.4) versus -137.2 (22.8) µm with 8 mg versus 2 mg of aflibercept, respectively (least squares mean difference, -9.5 [95% CI, -51.4 to 32.4]; nominal p = .65). Mean (SE) change in BCVA score was +7.9 (1.5) versus +5.1 (1.5) letters (least squares mean difference, +2.8 [95% CI, -1.4 to +7.0]; nominal p = .20). No differences in safety profiles between the groups were observed.
Two Phase III randomized, double-masked, multicenter, 48 week, non-inferiority trials Treatment-naive patients with nAMD. TENAYA N = 671 LUCERNE N = 658	Faricimab 6 mg up to every 16 weeks. Aflibercept 2 mg every 8 weeks.	BCVA change from baseline was non-inferior. • TENAYA (faricimab adjusted mean change 5.8 letters and aflibercept 5.1 letters; treatment difference 0.7 letters [-1.1 to 2.5]). • LUCERNE (6.6 and 6.6; treatment difference 0.0 [-1.7 to 1.8]). Rates of ocular adverse events were comparable between faricimab and aflibercept (36.3% versus 38.1%, and 40.2% versus 36.2%).
Two Phase III, double-masked, multicenter, non-inferiority, 48-week, randomized trials. Treatment-naive patients with nAMD. HAWK*, HARRIER N = 1,817	Brolucizumab 6 mg every 8 to 12 weeks. Aflibercept 2 mg every 8 weeks	At Week 48, noninferiority in BCVA change from baseline (least squares [LS] mean, +6.6 letters with brolucizumab versus +6.8 letters with aflibercept [HAWK]; +6.9 versus +7.6 aflibercept [HARRIER]; $p < 0.001$ for each comparison). > 50% of brolucizumab 6 mg-treated eyes were maintained on q12w dosing through week 48 (56% and 51%). Better outcomes regarding retinal fluid and retinal thickness with brolucizumab 6.0 mg versus aflibercept at week 16. Rate of serious adverse ocular events – brolucizumab 3.1% and 2.4% versus aflibercept 0.8% and 1.1%.
Multicenter, randomized, double-masked Phase IIIa, 104-week study. Recalcitrant nAMD (persistent residual retinal fluid despite previous frequent anti-VEGF). MERLIN N = 535	Brolucizumab 6 mg every 4 weeks. Aflibercept 2 mg every 4 weeks	Brolucizumab noninferior to aflibercept 2 mg in mean BCVA change from baseline to week 104 (treatment difference 0.4 letters). Proportion of eyes with ≥ 15-letter loss was 6.2% for brolucizumab and 4.7% for aflibercept (p = 0.0014). Greater proportion of eyes were fluid free at week 104 (52.5% brolucizumab versus 28.2% aflibercept; 95% CI, 11.9-37.3; $p < 0.001$) Incidence of intraocular inflammation (including retinal vasculitis and retinal vascular occlusion) was 11.5% (0.8% and 2.2%) for brolucizumab versus 6.1% (0% and 0.6%) for aflibercept, respectively.

(continued)

DME		
Phase II/III, randomized, double-masked, non-inferiority at 138 hospitals and specialty retina clinics in seven countries PHOTON N = 658	Aflibercept 8 mg every 12 weeks (8q12) Aflibercept 8 mg every 16 weeks (8q16) Aflibercept 2 mg every 8 weeks (2q8) Following initial monthly dosing From week 16, dosing intervals for 8 mg groups were shortened if disease activity	Primary endpoint was change from baseline in BCVA at week 48 (non-inferiority margin of 4 letters). Aflibercept 8q12 and 8q16 were non-inferior to aflibercept 2q8 for BCVA gains (BCVA mean change from baseline 8.8 letters [SD 9.0] in the 8q12 group, 7.9 letters [8.4] in the 8q16 group, and 9.2 letters [9.0] in the 2q8 group). Difference in least squares means was -0.57 letters between 8q12 and 2q8 and -1.44 letters between aflibercept 8q16 and 2q8. Ocular adverse events were similar across groups (8q12, 32%; 8q16, 29%; 2q8, 28%). In extension of this trial, 88% of aflibercept 8 mg patients had a last assigned dosing interval of ≥ 12 weeks at week 156, while sustaining visual and anatomic improvements achieved in the first 96 weeks. In extension of this trial, patients switched from 2 mg to 8 mg experienced substantially slower fluid reaccumulation.
Randomized, multicenter, 52 weeks CI-DME DRCR Protocol T N = 660	Aflibercept 2 mg Bevacizumab 1.25 mg Ranibizumab 0.3 mg Every 4 weeks	Baseline to 1 year, mean visual-acuity letter score (range, 0 to 100, with higher scores indicating better visual acuity; a score of 85 is approximately 20/20) improved by 13.3 with aflibercept, 9.7 with bevacizumab, and 11.2 with ranibizumab ($p < 0.001$ for aflibercept versus bevacizumab and $p = 0.03$ for aflibercept versus ranibizumab), the difference was driven by the eyes with worse visual acuity at baseline ($p < 0.001$ for interaction). With baseline visual-acuity letter score of 78 to 69 (= 20/32 to 20/40), the mean improvement was 8.0 with aflibercept, 7.5 with bevacizumab, and 8.3 with ranibizumab ($p > 0.50$ for each pairwise comparison). When baseline letter score was less than 69 (20/50 or worse), mean improvement was 18.9 with aflibercept, 11.8 with bevacizumab, and 14.2 with ranibizumab ($p < 0.001$ for aflibercept versus bevacizumab, $p = 0.003$ for aflibercept versus ranibizumab, and $p = 0.21$ for ranibizumab versus bevacizumab). Authors concluded that at worse levels of initial visual acuity, aflibercept was more effective at improving vision. No significant differences in serious adverse events, hospitalization, death, or major cardiovascular events.
Two randomized, double-masked, noninferiority, 2-year, Phase III trials, CI-DME with BCVA 25 to 73 letters YOSEMITE and RHINE N = 940 and 951	Faricimab 6 mg every 8 weeks, Faricimab 6 mg treat and extend (T and E) Aflibercept 2 mg every 8 weeks.	Noninferior year 1 visual acuity gains were maintained through year 2 Mean BCVA change from baseline at 2 years with faricimab every 8 weeks (+10.7/+10.9 letters) or T and E (+10.7/+10.1 letters) were comparable with aflibercept every 8 weeks (+11.4/+9.4 letters). Median number of study drug injections was lower with faricimab T and E (10/11 injections) versus faricimab every 8 weeks (15 injections) and aflibercept every 8 weeks (14 injections). In the faricimab T and E arms, > 60% of patients were every 16-week dosing and 80% were every 12-week or longer dosing at week 96. Mean CST reductions were greater with faricimab (faricimab every 8 weeks -216.0/

(continued)

		-202.6 µm, faricimab T and E -204.5/-197.1 µm, aflibercept every 8 weeks -196.3/-185.6 µm; nominal $p < 0.0001$ and $p = 0.0150$). Percentage of patients with absence of DME (CST < 325 µm; faricimab every 8 weeks 87%-92%/88%-93%, faricimab T and E 78%-86%/85%-88%, aflibercept every 8 weeks 77%-81%/80%-84%, $p < 0.05$ for faricimab 8 weeks versus aflibercept). Percentage of patients with absence of intraretinal fluid (faricimab every 8 weeks 59%-63%/56%-62%, faricimab T and E 43%-48%/45%-52%, aflibercept every 8 weeks 33%-38%/39%-45%; $p < 0.05$ for faricimab 8 weeks versus aflibercept). Serious ocular adverse effects were comparable - faricimab q8w 4%, 4%, faricimab T and E 4%, 6%, and aflibercept q8w 2%, 4% patients.
Phase III, Double-masked, 100-week, multicenter, randomized trial. CI-DME with BCVA score 23 to 78 letters KITE (KESTRAL study in same report but used brolucizumab 3.0 and 6.0 mg dose with similar results) N = 360	Brolucizumab 6 mg Aflibercept 2 mg	At Week 52, brolucizumab was noninferior to aflibercept in mean change in BCVA from baseline (+10.6 letters versus +9.4 letters; $p < .001$), more subjects achieved central subfield thickness (CSFT) < 280 µm (54% versus 40.1%, no p given), and fewer had persisting subretinal and/or intraretinal fluid versus aflibercept (54.2% versus 72.9%, no p given). More than half of brolucizumab 6 mg subjects maintained on q12w dosing. The incidence of ocular serious adverse events was 2.2% (brolucizumab) and 1.7% (aflibercept).
DR		
Cochrane Review (2023) **PDR**	Bevacizumab Ranibizumab Aflibercept 2 mg	Twelve studies included people with PDR, and 11 studies included those with high-risk PDR. Anti-VEGFs ± PRP compared with PRP alone probably increase visual acuity, but the degree of improvement is not clinically meaningful. For secondary outcomes, anti-VEGFs ± PRP produce a regression of new vessels, reduce vitreous hemorrhage, and may reduce the need for vitrectomy compared with eyes that received PRP alone. Did not find differences in visual acuity in subgroup analyses comparing the type of anti-VEGFs, the severity of the disease, time to follow-up (< 12 months versus 12 or more months), and treatment with anti-VEGFs + PRP versus anti-VEGFs alone.
Double-masked, 100-week randomized, multi-center trial **Severe NPDR** N = 402	Aflibercept 2 mg every 16 weeks Aflibercept 2 mg every 8 weeks, PRN dosing beginning at week 56. Sham injection control group.	At 24 weeks, aflibercept resulted in a 2-step or greater improvement in DRSS level in 58.4% versus 6.0% in the control group. At 52 weeks, 65.2% in the aflibercept 2q16 group (adjusted difference, 50.1%; 95% CI, 40.1% to 60.1%) and 79.9% in the aflibercept 2q8/PRN group (adjusted difference, 64.8%; 95% CI, 55.8% to 73.9%) compared with 15.0% in the control group ($p < .001$ for both comparisons) showed a 2-step or greater improvement in DRSS level. Fewer eyes treated with aflibercept versus sham injections developed vision-threatening complications and/or CI-DME through week 100 (16.3% 2q16 group, 18.7% 2q8/PRN group, 50.4% control group; $p < .001$ for both comparisons)

* HAWK included a 3.0 mg brolucizumab group but this dose is not FDA approved so data not included.
DRCR = Diabetic Retinopathy Clinical Research; NPDR = non-proliferative diabetic retinopathy;
CI-DME = central involved-diabetic macular edema; DRSS = diabetic retinopathy severity scale; BCVA, best corrected visual acuity

Pharmacy Coverage and Benefit Design

Available Anti-VEGF Agents

Exhibit 7: Available Anti-VEGF Agents[21-27,43]

Drug	Available Dose and Dosing Schedule	Relative Cost for Single Dose*	Comments
Aflibercept	8 mg (Eylea HD®) every 4 weeks for 3 months then once every 8 or 16 weeks 2 mg (Eylea®) every 4 weeks for 3 months then once every 8 weeks	8 mg $2,625 2 mg $1,850	8 mg – Single dose vial 2 mg – Single dose prefilled syringe and vial
Bevacizumab	1.25 mg (Avastin®) every 4 weeks, extended intervals may be possible.	$67.86 (Medicare 2022 reimbursement)	Repacked from high dose vial into single dose prefilled syringe or vial Has been used since 2005
Brolucizumab	6 mg (Beovu®) monthly for the first 3 doses, then every 8 or 12 weeks (nAMD) 6 mg every six weeks for the first 5 doses, then every 8 or 12 weeks (DME)	$2,118	Single dose prefilled syringe and vial.
Faricimab	6 mg (Vabysmo®) monthly for 4 doses, then extended to 8 or 12 weeks	$2,190	Single dose prefilled syringe and vial.
Ranibizumab	0.3 mg monthly (DME/DR) 0.5 mg monthly (nAMD) 2 mg via implant every 24 weeks (nAMD)	$1,170 to $1,950 (Lucentis®) $1,130 (Byooviz™) $816 to $1,360 (Cimerli®) $8,950 (Susvimo® Implant)	With the ocular implant, supplemental treatment with 0.5 mg intravitreal ranibizumab injection may be administered in the affected eye if clinically necessary. Initial implantation, refill-exchange, and implant removal (if necessary) procedures must be done under strict aseptic conditions.

*WAC August 2023 cost unless otherwise specified.
Costs are only for the medication or implant (not refill of implant).
Does not include injection cost. Medicare reimbursement for injection is $115.28 (average across U.S. for 2024).

Potential Issues with Bevacizumab Off-Label[44-48]

Bevacizumab has been used off-label for almost 20 years to treat nAMD and other eye diseases but this use has not been without controversy. There have been reports of sub-visible particles being found in repacked bevacizumab and patients have had silicone oil droplets found in the eye. The silicone droplets appear to come from the use of insulin syringes with silicone lubricated needles. If bevacizumab is used, silicone free needles are necessary. It is important the clinicians using off-label bevacizumab also ensure that the supplier uses appropriate aseptic technique when preparing doses. Additionally, in recent years there have been serious supply chain issues with bevacizumab availability.

FDA-approved products come either in sterile prefilled syringes or single-dose vials. Some single-dose vials are packaged with filter needles and some have syringes and filter needles for administration. No matter what product is used, aseptic technique must be used by the clinicians preparing the dose and doing the injection.

The American Society of Retina Specialists and American Academy of Ophthalmology oppose step therapy which requires bevacizumab first before other agents because it increases the treatment burden on patients and creates significant administrative hurdles for retina specialists especially when the vulnerable supply chain for the repackaged drug is disrupted. These two groups have been working with Medicare to remove step therapy from Medicare Advantage plans. Ophthalmologists and managed care plans must carefully consider the implications of using an off-label repacked injection which is being introduced into the eye. As noted previously, a bevacizumab intravitreal product is close to being submitted to the FDA for approval.

Adverse Events[6,15,24,49]

- Intravitreal anti-VEGF therapy is well tolerated with mostly minor adverse events.
- Rare serious adverse events include endophthalmitis, noninfectious inflammation, retinal tear, or retinal detachment.
- The most serious complication of anti-VEGF injections is infectious endophthalmitis with rates between 0.019 percent and 0.09 percent in clinical trial settings.
- The ranibizumab implant has a black box warning related to a three-fold higher rate of endophthalmitis compared to monthly intravitreal injections of ranibizumab and was subject to a voluntary recall due to a part of the implant dislodging. It was redesigned and reintroduced to the U.S. market in 2024.
- Guidelines recommend topical povidone iodine application before intravitreal injections to reduce risk of endophthalmitis.
- Routine antibiotic eye drops are not recommended before or following intravitreal injection procedures, because they do not decrease the risk of endophthalmitis.
- Other complications, such as cataract formation and sustained elevated intraocular pressure are also rare.

Overall, the risks of anti-VEGF therapy originate more from the injection itself rather than the agent used. There are robust clinical data suggesting that intravitreal anti-VEGF agents are safe and effective, and there are no data to suggest an increase in mortality or adverse systemic events, or risk of retinal detachment, compared with sham injection.

Adherence[50-58]

- A primary challenge of VEGF inhibitor therapy is the need for repeated intravitreal injections which contributes to nonadherence, undertreatment, and high discontinuation rates (25 to 38.8% over 1 to 6 years).
- Many patients have to travel long distances to retina specialists and may require caregiver assistance to get to these visits.
- Long-term follow-up studies have shown that visual acuity gains achieved in the first year of therapy are lost over time. Much of this loss is accounted for by the number of injections falling off over time and discontinuation rates.
- Real-world studies have shown that the number of annual injections (12 for monthly, 6.9 to 7.5 for q8w and PRN versus 4.3 to 7.3) and visual acuity gains (5.9 to 11.3 versus -0.7 to 3 BCVA letters) are lower compared to those in clinical trials.
- An analysis of six years of data from the Intelligent Research in Sight (IRIS) Registry found that every additional injection resulted in a 0.68 letter improvement from baseline to year one.
- Treat and extend (T and E) regimens can be used to improve adherence. Initially the patient is treated monthly until disease activity stabilization and then the treatment interval is gradually extended in increments of two to four weeks, up to a maximum interval of 12 to 16 weeks based on response. Treatment intervals are shortened when disease activity recurs.
- Efforts to improve adherence and persistence with injections or implant refills and longer acting agents/extended dosing intervals may mitigate visual acuity loss over time.

Value/Cost Effectiveness/Cost Utility[59-64]

Anti-VEGF therapies are expensive with retail costs of $1,000 to $2,500 per injection; annual traditional Medicare costs for anti-VEGF therapy for ocular indications was $4.02 billion in 2019. These therapies have several benefits, including patient visual and quality of life benefit, societal value, and cost effectiveness. Although far from exhaustive, an overview of some of these benefits are reviewed here.

Improved vision from anti-VEGF therapies (current treatment scenario of fewer injections) used for nAMD in the 65 years of age and older population generated significant patient benefit ($1.1 billion in year 1 and $5.1 billion in year 3), whereas more frequent injections generated $1.6 billion (year 1) and $8.2 billion (year 3). Improved adherence and lower discontinuation rates raised patient benefit significantly over these time periods ($7.3/$11.4 billion with improved adherence and $9.7/$15.0 billion with best-case scenario). Societal value (patient benefits net of treatment cost) ranged from $0.9 billion to $4.3 billion across three years. Three cost benefit analyses have found significant return on investment to society in treating nAMD with anti-VEGF therapy. For example, this treatment produced a net return of $28.5 billion to society (patients and insurers) over 11 years and contributed $12.2 billion to the Gross Domestic Product over those years.

In terms of cost effectiveness, an analysis based on published clinical trial data for aflibercept 2 mg preventing progressive DR (PDR or CI-DME) found the cost required to prevent one case of PDR was $80,000

in a hospital-based facility and $72,400 in a non-hospital setting (Medicare costs). To prevent one case of CI-DME with vision loss, the cost was $154,000 and $133,000, respectively. For all CI-DME, with and without vision loss, the costs to prevent a case were $70,900 and $59,500 for aflibercept 2 mg every 16 weeks and $90,000 and $88,800 for aflibercept 2 mg every eight weeks PRN. The cost per unit change in DRSS was $2,700 and $2400/DRSS over two years.

A cost-risk tradeoff analysis from policymakers' perspective of two years of anti-VEGF therapy for nAMD found that bevacizumab (as current off-label use) is the preferred first-line therapy. Using published prices and fees and an injection protocol that follows published clinical studies, results showed that the mean cost per patient were $16,859, $32,949, $39,831, and $53,056 for bevacizumab, brolucizumab, aflibercept 2 mg, and ranibizumab, respectively. Recommendation for second-line therapy depends on the extent of the policymaker's risk aversion because of the trade-off between cost and risk of blindness because of treatment.

Future[65,66]

More therapies for nAMD, DR, and DME are under investigation. Oral fenretinide, a synthetic derivative of all-trans-retinoic acid, is being developed to slow the progression of geographic atrophy. Sozinibercept in combination with standard-of-care anti-VEGF therapies is being studied in nAMD and DME. Gene therapy, as a surgical procedure and intravitreal injection, is also under investigation. Another concept under investigation is that transplanted stem cells may be able to replace the retinal cells that die off in advanced non-neovascular AMD.

Overall Comments[67]

- The use of anti-VEGF agents improves visual acuity in nAMD, DME, and DR and will likely reduce the odds of legal blindness from these diseases.
- To get the maximum benefit over time, patients need to be adherent and persistent with injections or implant refills.
- Extended treatment intervals may help improve adherence while preserving vision benefits and may be cost effective compared to monthly injections.
- Primary cost management strategies currently are step therapy requiring bevacizumab first and prior authorization for any product other than bevacizumab.
- FDA approval of an ocular bevacizumab product may have a major impact on the overall market and costs depending on the cost of this product. According to a 2023 market analysis, aflibercept 2 mg held a 43.4 percent market share, bevacizumab 34 percent, ranibizumab 9.4 percent and faricimab 7.6 percent. Biosimilar ranibizumab products have not yet had significant uptake despite lower prices. An FDA-approved product will be more expensive than off-label bevacizumab but retina specialists have long-term experience with it and may shift their current use of other anti-VEGF agents.

SAMPLE MONOGRAPH TEMPLATE for P&T REVIEW and BENEFIT DESIGN CONSIDERATION[64]

Retinal Diseases Formulary Monograph Template

INDIVIDUAL DRUG REVIEW

Generic Name:	[Name]
Brand Name:	[Name]
Manufacturer:	[Text]
Date of Review:	[Month/Year]
Reason for Review:	[Text]

TABLE OF CONTENTS:

Additional information on the content of each section and a template in Word document format are available at the AMCP website.

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COVER INSET PHOTOS:

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→ Eye closeup (Photo by v2osk on Unsplash)
→ Blood glucose test (Photo by Artem Podrez on Pexels)

PAGE 5: Ophthalmologist/ophthalmoscope image (Photo by CDC on Unsplash)

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