PRIMER

SPOTLIGHT ON AGE-RELATED MACULAR DEGENERATION

Facilitating OPTIMAL OUTCOMES for the Management of Retinal Diseases:
Health Plan Best Practice Recommendations

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Age-Related Macular Degeneration (AMD)

Clinical Primer for Health Care Payers and Purchasers

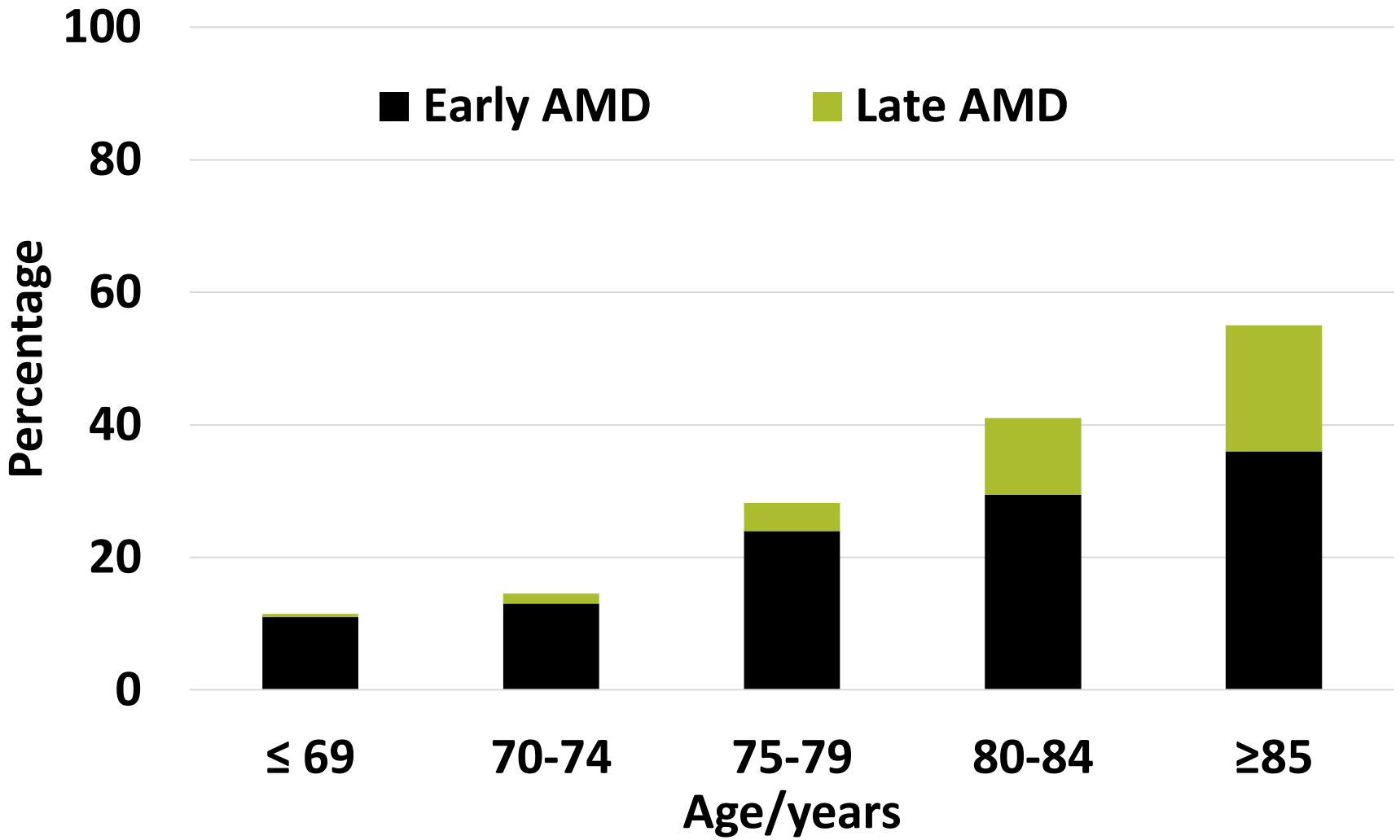
Disease Overview

Age-related macular degeneration (AMD) is characterized by gradual damage or breakdown of the macula over time

Central vision is compromised while side vision is often unaffected

Flaxel CJ, et al. *Ophthalmology*. 2020;127(1):P1-P65.

AMD Prevalence Increases with Age



Jonasson F, et al. *Ophthalmology.* 2011;118(5):825-30.

Risk Factors for Advanced AMD

- ✓ Increasing age
- ✓ Northern European ancestry
- ✓ Genetic factors
- ✓ Cigarette smoking

Smoking cessation is strongly recommended when advising patients who have AMD or are at risk for AMD

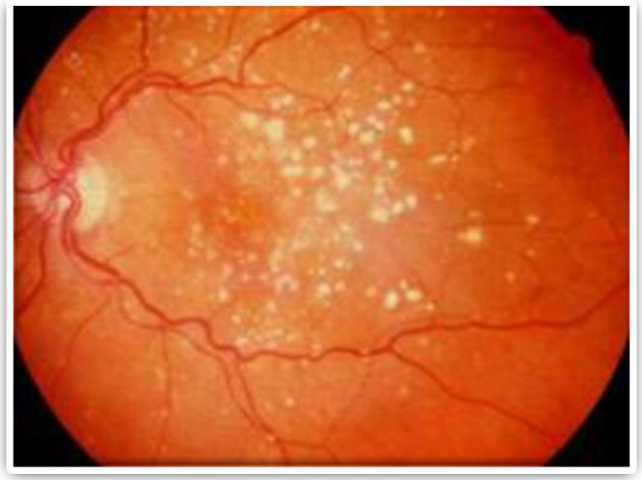
The routine use of genetic testing is not recommended at this time

Flaxel CJ, et al. *Ophthalmology*. 2020;127(1):P1-P65.

Classification of AMD

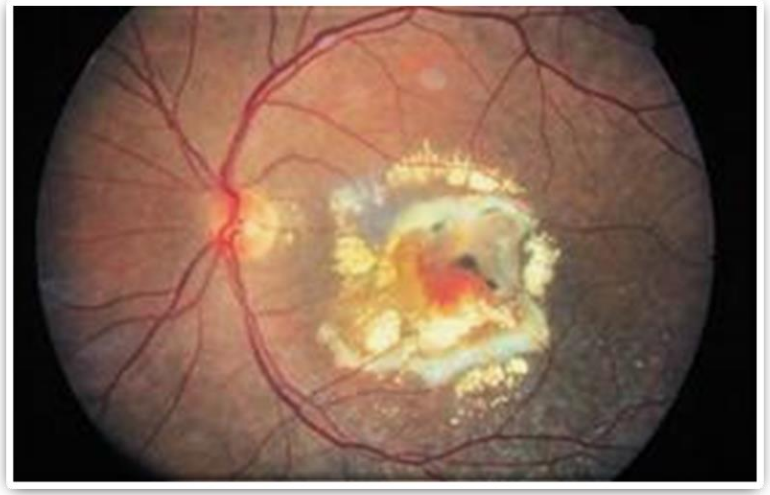
Dry type

- Better visual outcome
- Small deposits called “Drusen” form around the macular area
- No treatment, only regular review



Wet type

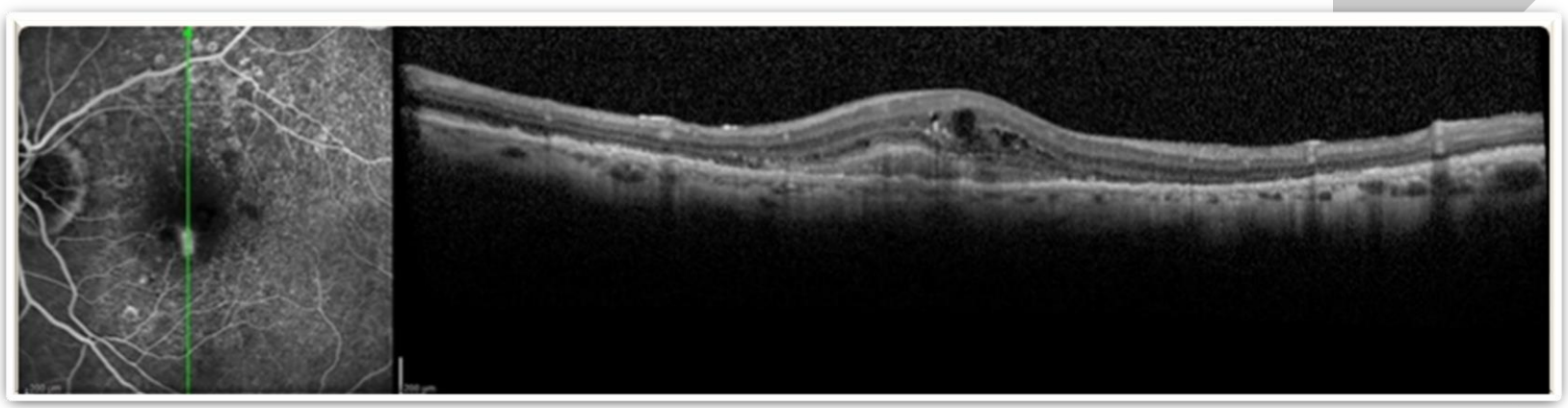
- More severe course/prognosis
- Fluid accumulates underneath retina, causing distortion
- Requires immediate ophthalmological treatment



Clinical Course

An estimated 80% of AMD patients have non-neovascular or atrophic AMD

The neovascular form is responsible for the majority of the severe central visual acuity (VA) loss associated with AMD.

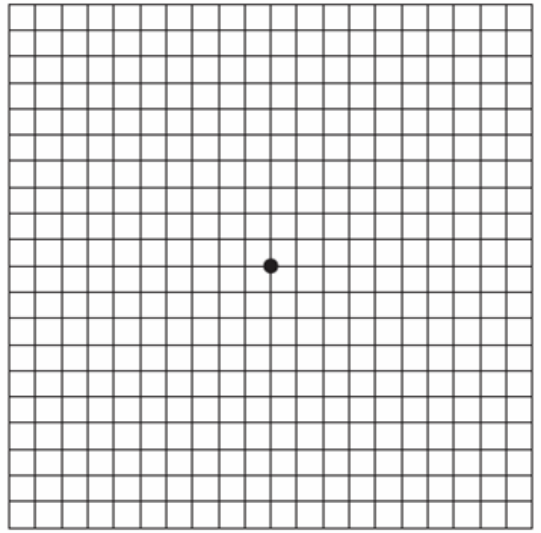


Flaxel CJ, et al. *Ophthalmology*. 2020;127(1):P1-P65.

Diagnosis

Ophthalmoscopy

The Amsler grid can be used at home for self-monitoring



Fluorescein angiography (FA), optical coherence tomography (OCT), and optical coherence tomography angiography (OCTA) are useful diagnostic tests in clinical practice to detect new or recurrent neovascular disease activity and guide therapy

Flaxel CJ, et al. *Ophthalmology*. 2020;127(1):P1-P65.

Best Practices in Clinical Management

In patients with neovascular AMD, early detection and prompt treatment improves the visual outcome

Intravitreal injection therapy using anti-vascular endothelial growth factor (VEGF) agents (eg, aflibercept, bevacizumab, and ranibizumab) is the most effective way to manage neovascular AMD and represents the first line of treatment

Symptoms suggestive of post-injection endophthalmitis or retinal detachment require prompt evaluation

Antioxidant vitamin and mineral supplementation as per the Age-Related Eye Disease Study (AREDS2) should be considered in patients with intermediate or advanced AMD

Flaxel CJ, et al. *Ophthalmology*. 2020;127(1):P1-P65.

“Patient outcome criteria are to reverse or minimize visual loss and improve visual function.”

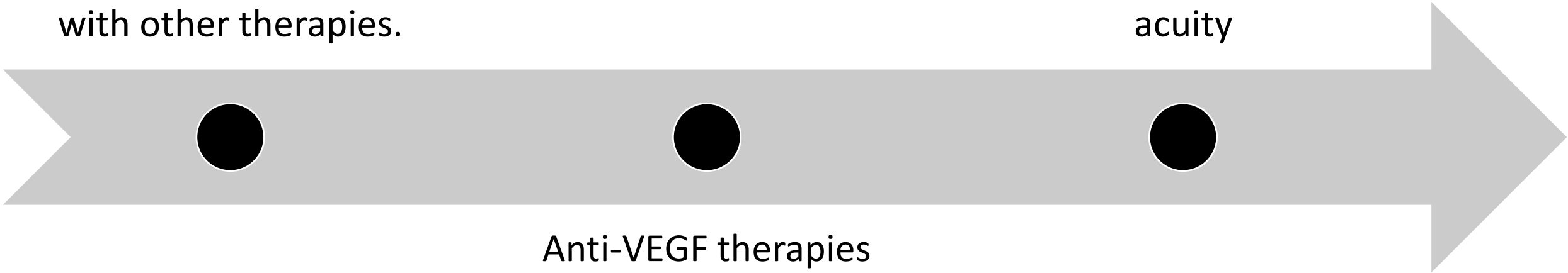
Flaxel CJ, et al. *Ophthalmology*. 2020;127(1):P1-P65.

Rationale for Anti-VEGF Therapy in Neovascular AMD

The VEGF inhibitors have demonstrated improved visual and anatomic outcomes compared with other therapies.

Anti-VEGF therapies have become first-line therapy for treating and stabilizing most cases of neovascular AMD

A Cochrane systematic review demonstrates the effectiveness of these agents to maintain visual acuity



Solomon SD, et al. *Cochrane Database Syst Rev*. 2019;3:CD005139.

Anti-VEGF Therapies

FDA Indicated

- Ranibizumab
- Aflibercept
- Brolucizumab
- Faricimab

Off Label

- Bevacizumab

FDA-Approved Anti-VEGF Dosing Comparison for Neovascular AMD

Anti-VEGF Therapy	Dosage Form	Dosing Schedule
Aflibercept	2 mg/0.05 mL solution 8 mg/0.07 mL solution	• 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months) • 8 mg (0.07 mL) administered by intravitreal injection every 4 weeks (monthly) for the first 3 injections, followed by 8 mg (0.07 mL) every 8 to 16 weeks (2 to 4 months)
Ranibizumab	10 mg/mL solution (0.5 mg)	0.5 mg (0.05 mL) by intravitreal injection once a month (approximately 28 days)
	2 mg (0.02 mL of 100 mg/mL solution)	Implant refilled at least once every 6 months
Brolucizumab	6 mg/0.05 mL solution	6 mg (0.05 mL of 120 mg/mL solution) monthly (approximately every 25-31 days) for the first three doses, followed by one dose of 6 mg (0.05 mL) every 8-12 weeks
Faricimab	120 mg/mL solution	6 mg (0.05 mL of 120 mg/mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 4 doses, followed by a 6 mg dose via intravitreal injection on one of the following three regimens: 1) Weeks 28 and 44; 2) Weeks 24, 36 and 48; or 3) Weeks 20, 28, 36 and 44

EYLEA [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals. Available at: https://www.regeneron.com/downloads/eylea_fpi.pdf. Revised June 2021. Accessed July 2022.
LUCENTIS [package insert]. South San Francisco, CA: Genentech. Available at: https://www.gene.com/download/pdf/lucentis_prescribing.pdf. Revised March 2018. Accessed July 2022
BEOVU [package insert]. East Hanover, NJ: Novartis. Available at: https://www.novartis.us/sites/www.novartis.us/files/beovu.pdf. Revised May 2022. Accessed July 2022
VABYSMO [package insert]. South San Francisco, CA: Genentech. Available at: https://www.gene.com/download/pdf/vabysmo_prescribing.pdf. Revised January 2022. Accessed July 2022

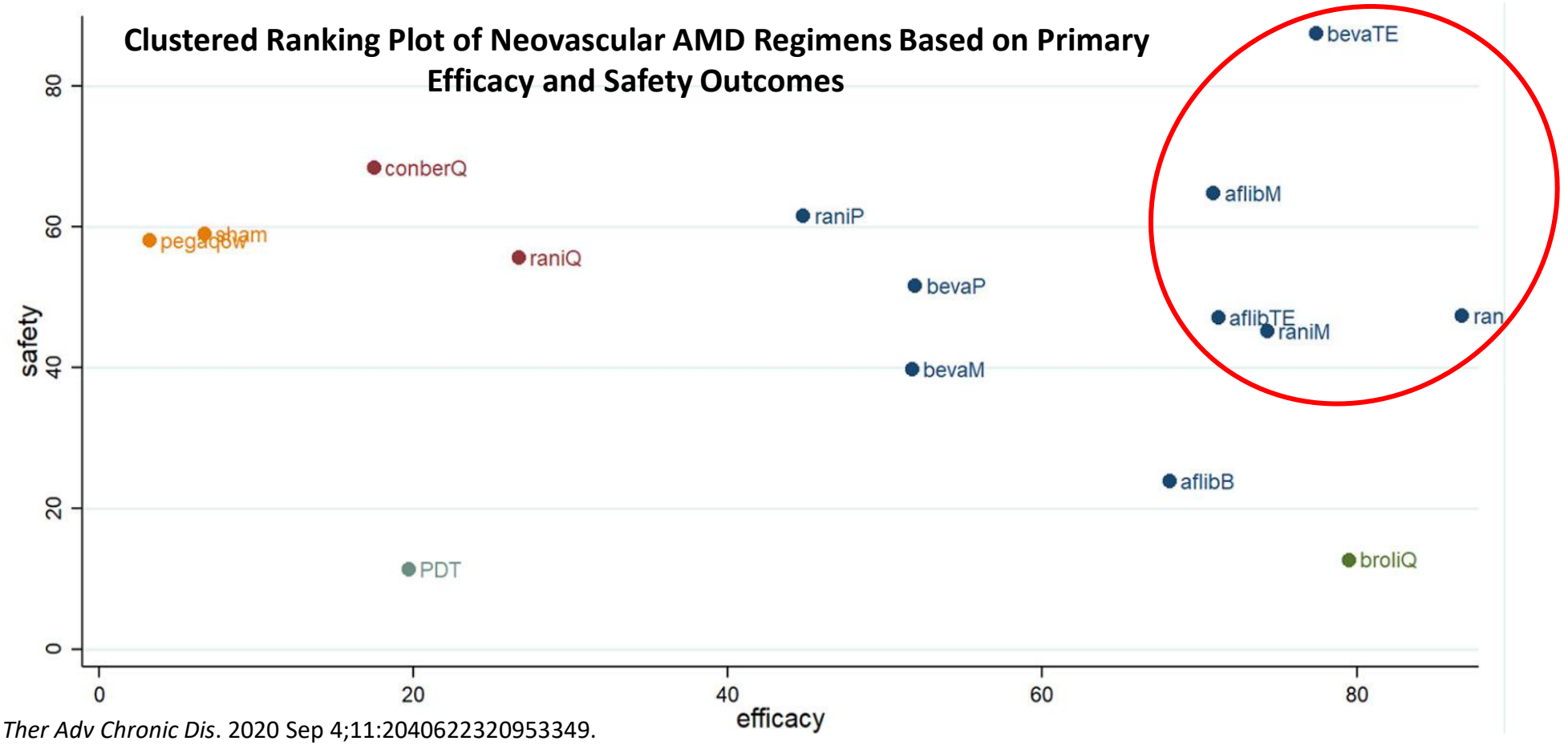
The Role of Anti-VEGF Therapy in Mitigating AMD Disease Burden

- The prevalence of AMD in the United States is anticipated to increase to 22 million by the year 2050 as the population ages
- These predictions are likely to be affected by more effective treatments for the neovascular forms of AMD using anti-vascular endothelial growth factor (VEGF) agents as well as the slowing of the disease progression using antioxidant vitamins with zinc
- The use of anti-VEGF agents will likely reduce the odds of legal blindness from neovascular AMD and could theoretically ***reduce the rate of legal blindness by up to 70% over 2 years***

Bressler NM, et al. *Arch Ophthalmol*. 2011;129(6):709-717.

A Systematic Review and Bayesian Network Meta-analysis Demonstrated a Hierarchy of Preferability Among Anti-VEGF Regimens

"The treat-and-extend regimen of ranibizumab and aflibercept are the preferred anti-VEGF regimens for neovascular AMD. Bevacizumab treat-and-extend regimens need more head-to-head comparisons with other regimens or sham injection for advanced application."

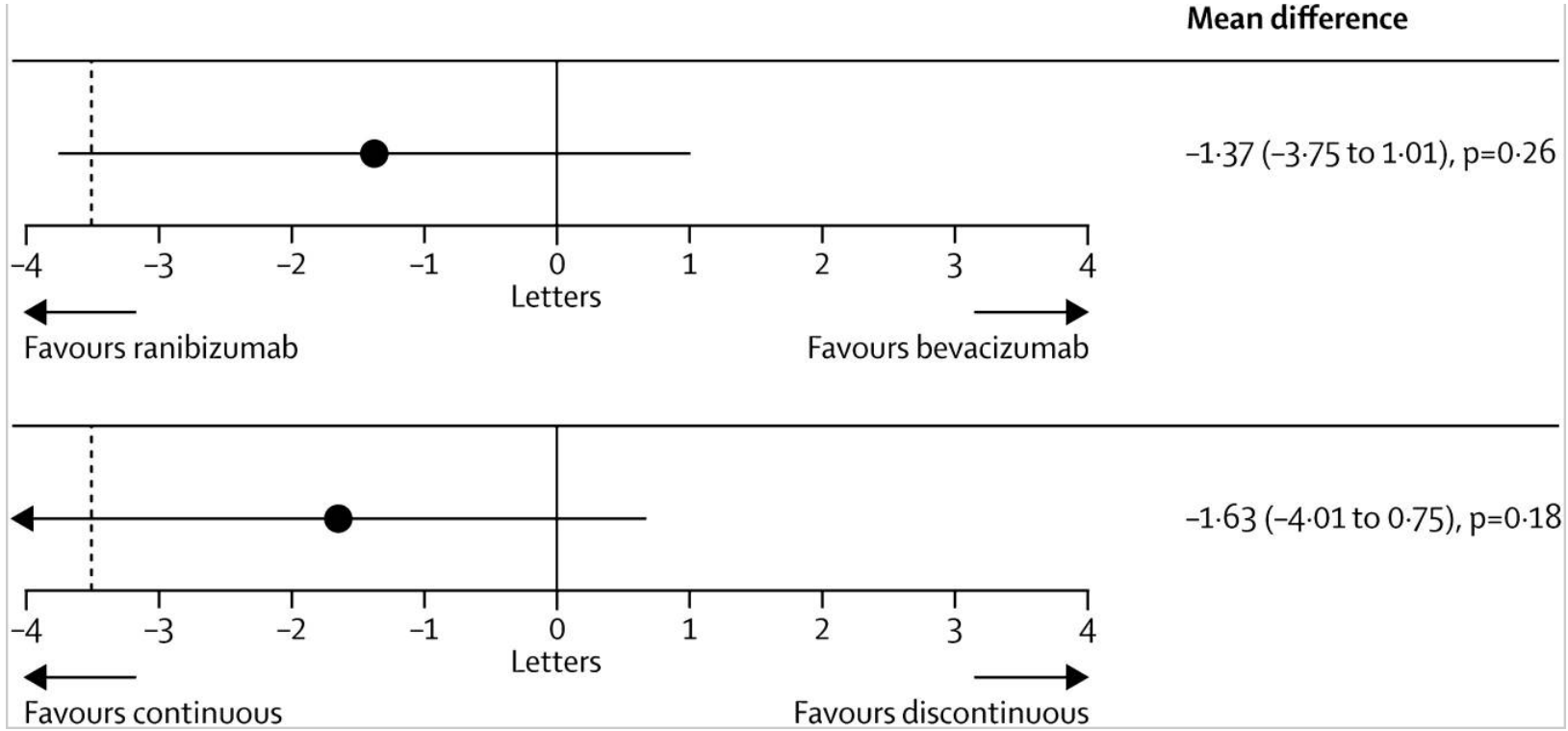


aflibB=aflibercept q2mo;
aflibM=aflibercept q1mo;
aflibTE=aflibercept T&E;
bevaM=bevacizumab q1mo;
bevaP=bevacizumab PRN;
bevaTE=bevacizumab T&E;
broliQ=brolucizumab quarterly;
conberQ=conbercept quarterly;
Pegaq6w=pegaptanib q6w;
raniM=ranibizumab q1mo;
raniP=ranibizumab PRN;
raniQ=ranibizumab quarterly;
raniTE=ranibizumab T&E

Ye L, et al. *Ther Adv Chronic Dis*. 2020 Sep 4;11:2040622320953349.

The Literature Demonstrates Differences in Outcomes Among Available Anti-VEGF Therapies and Dosing Strategies

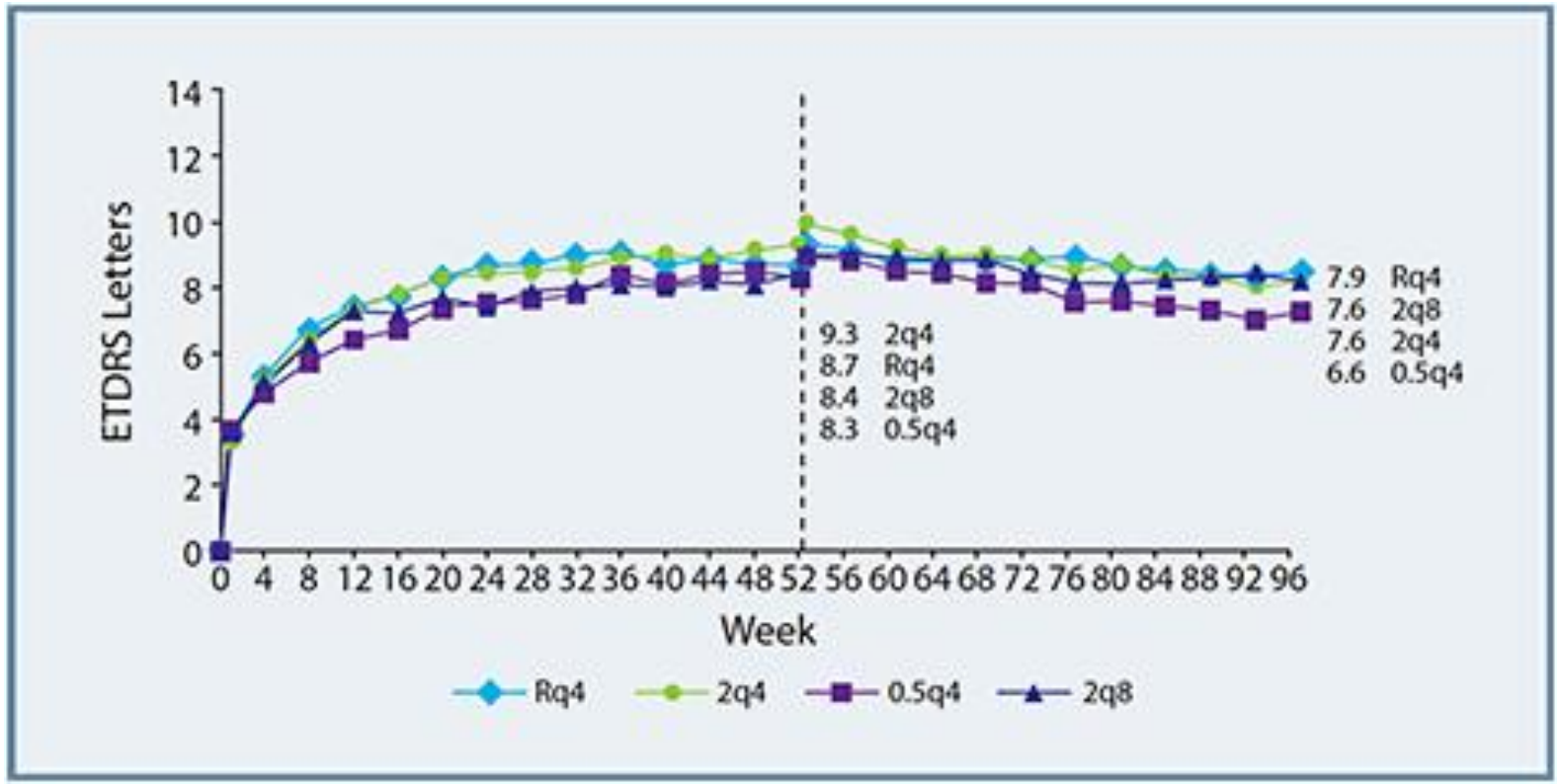
- N=610 adults aged ≥50 years with active, previously untreated nAMD randomized to either bevacizumab or ranibizumab in either continuous or discontinuous dosing regimens
- Primary outcome: best corrected distance visual acuity (BCVA)
- Bevacizumab was neither inferior nor non-inferior to ranibizumab
- Discontinuous treatment was neither inferior or non-inferior to continuous treatment



Chakravarthy U, et al. *Lancet.* 2013;382:1258–67

Ranibizumab and Aflibercept Demonstrate Similar Efficacy in nAMD Across Different Dosing Schedules

- N=2,457 patients with nAMD
- Baseline to week 52: randomized to 0.5 mg intravitreal ranibizumab every 4 weeks (Rq4), 2 mg aflibercept every 4 weeks (2q4), 0.5 mg aflibercept every 4 weeks (0.5q4), or 2 mg aflibercept every 8 weeks (2q8) after 3 monthly injections
- Weeks 52 through 96: original dosing assignment using an as-needed regimen
- All aflibercept and ranibizumab groups were equally effective in improving BCVA and preventing BCVA loss at 96 weeks
- The 2q8 aflibercept group was similar to ranibizumab in visual acuity outcomes over 96 weeks, but with an average of 5 fewer injections



Heier JS, et al. *Ophthalmology*. 2012;119:2537-48.
Schmidt-Erfurth U, et al. *Ophthalmology*. 2014;121:193-201.

Potential Concerns with Compounded Bevacizumab

Bevacizumab is used off-label and currently it must be repackaged in much smaller aliquots containing a small fraction of the dose used in cancer therapy

Ophthalmologists look to compounding pharmacies to create single-use vials of the appropriate dose

The process requires aseptic technique and compliance with USP General Chapter 797

The **repackaging of bevacizumab** has given rise to concerns about impurities that could be introduced during the process, sterility, and dosage consistency

CATT Research Group, Martin DF, Maguire MG et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med 2011; 364:1897-1908.

Considerations on Use of Biosimilars in Ophthalmic Practice

"The successful and cost effective off-label use of bevacizumab for eye disease for over 15 years represents a unique history of a well-studied biologic agent injected into the eye, which has yet to be duplicated for bevacizumab biosimilars."

"Before a biosimilar is required to be used for treatment or included in a step therapy regimen, it should be FDA-approved for the ophthalmic indication."

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"CMS has learned that some MA plans are using biosimilars to Avastin (i.e., Zirabev and Mvasi) as substitutes for Avastin to treat eye issues…"

"Unlike Avastin, the off-label use of these biosimilars in MA step therapy programs is not supported by widely used treatment guidelines or clinical literature. CMS remains concerned that off-label use of drugs without support from clinical research is potentially dangerous to MA enrollees and is prohibited by regulation."

CMS

American Academy of Ophthalmology. Available at: https://www.aao.org/clinical-statement/use-of-biosimilars-in-ophthalmic-practice.
Centers for Medicare and Medicaid Services. Available at: https://www.asrs.org/content/documents/hpms-step-therapy-memo.pdf.

Coding Considerations

ICD-9 CM	ICD-10 CM
Macular degeneration, dry – 362.51	Nonexudative AMD – H35.31
Macular degeneration, wet – 362.52	Exudative AMD – H35.32
Macular drusen – 362.57	Drusen (degenerative) of macula – H35.36-

ICD = International Classification of Diseases; CM = Clinical Modification used in the United States

- AMD = age-related macular degeneration; does not require laterality indicators
- Macular drusen; (–) = 1, right eye; 2, left eye; 3, bilateral

Additional information for ICD-10 codes:

- Certain ICD-10 CM categories have applicable 7th characters. The applicable 7th character is required for all codes within the category, or as the notes in the Tabular List instruct. The 7th character must always be the 7th character in the data field. If a code that requires a 7th character is not 6 characters, a placeholder X must be used to fill in the empty characters.
- For bilateral sites, the final character of the codes in the ICD-10 CM indicates laterality. If no bilateral code is provided and the condition is bilateral, separate codes for both the left and right side should be assigned. Unspecified codes should only be used when there is no other code option available.
- When the diagnosis code specifies laterality, regardless of which digit it is found in (i.e., 4th digit, 5th digit, or 6th digit):
  - Right is always 1
  - Left is always 2
  - Bilateral is always 3

Flaxel CJ, et al. *Ophthalmology*. 2020;127(1):P1-P65.