PRIMER

SPOTLIGHT ON RETINAL VEIN OCCLUSION

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

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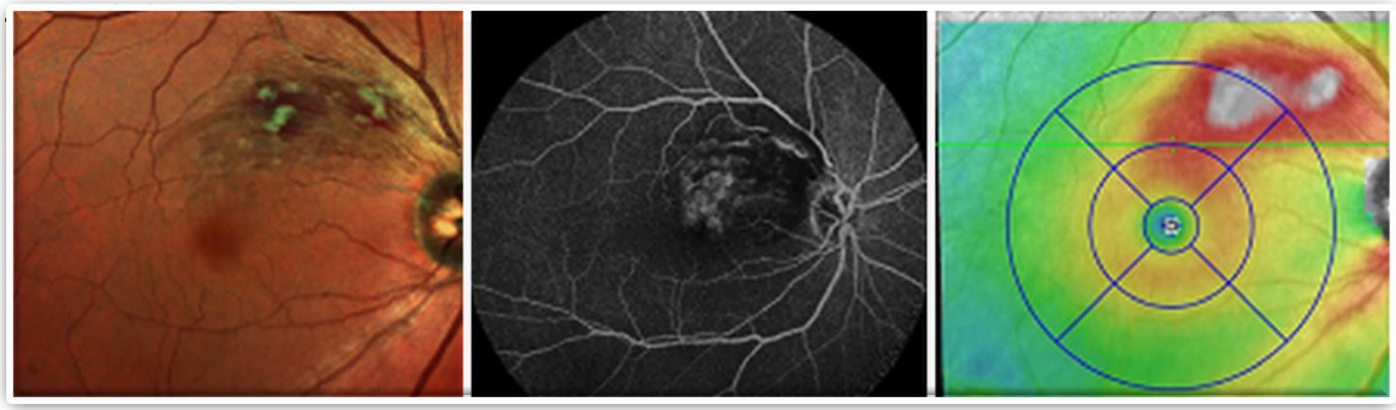
Retinal Vein Occlusion (RVO)

Clinical Primer for Health Care Payers and Purchasers

Disease Overview

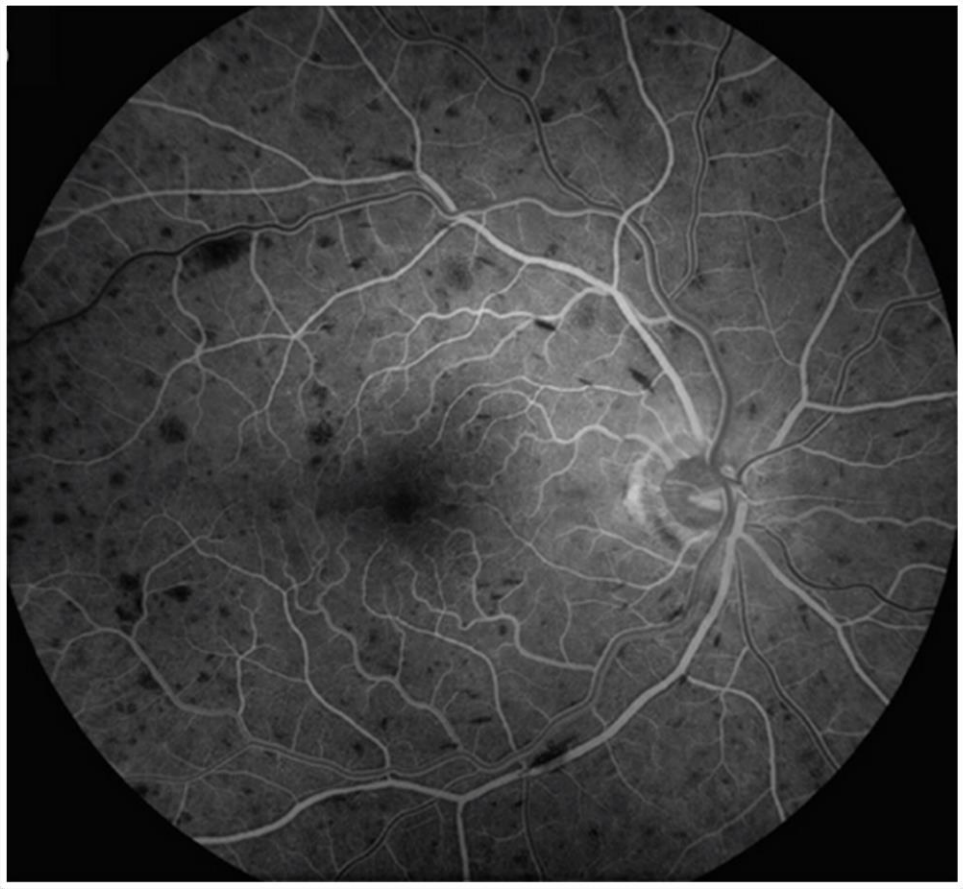
- Retinal vein occlusion (RVO) is the second most common retinal vascular disorder following diabetic retinopathy
  - Incidence of RVO increases with age, with more than half of all cases occurring in patients older than 65 years
  - The Blue Mountain Eye Study showed a 0.7% incidence in patients younger than 60 years, increasing to 4.6% in patients 80 years and older
- RVO is often associated with vision loss and if left untreated can result in permanent vision impairmen



Mitchell P, et al. *Arch Ophthalmol*. 1996;114(10):1243-1247.
Ehlers JP, et al. *Surv Ophthalmol*. 2011;56(4):281-299.
Cugati S, et al. *Arch Ophthalmol*. 2006;124(5):726-732.
Rogers S, et al. *Ophthalmology*. 2010;117(2):313-319.e1.
Flaxel CJ, et al. *Ophthalmology*. 2020 Feb;127(2):P288-P320.

Clinical Features and Diagnosis

- Acute RVO commonly presents with painless visual disturbances
- Ophthalmoscopic examination findings include varying degrees of dilated and tortuous retinal veins, intraretinal hemorrhages, retinal edema, exudates, and cotton wool spots
- Chronic vein occlusion can be difficult to identify on clinical examination; it is suggested by venous collateral formation and vascular sheathing
- In both acute and chronic RVO, fluorescein angiography (FA) can be used to assess for retinal ischemia, delayed retinal vein filling, and the presence of retinal neovascularization with fluorescein leakage



Flaxel CJ, et al. *Ophthalmology*. 2020 Feb;127(2):P288-P320.

Risk Factors

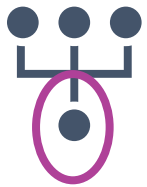
- ✓ Hypertension
- ✓ Hyperlipidemia
  - Diabetes with end organ damage
- ✓ Active smoking
- ✓ Peripheral vascular disease

Of these systemic risk factors, one meta-analysis found that 47.9% of RVO cases were attributed to hypertension, 20.1% to hyperlipidemia, and 4.9% to diabetes mellitus

Flaxel CJ, et al. *Ophthalmology*. 2020 Feb;127(2):P288-P320.
Sperduto RD, et al. *Ophthalmology*. 1998;105(5):765-771.
Bertelsen M, et al. *Ophthalmology*. 2014;121(3):637-642.
O'Mahoney PRA, et al. *Arch Ophthalmol*. 2008;126(5):692-699.

Pathophysiology and Classification

Retinal vein occlusion occurs when there is a partial or complete obstruction of a retinal vein, and it is classified according to extent, anatomic location, and retinal ischemia



An obstruction of the retinal vein at or posterior to the optic nerve head is referred to as a central retinal vein occlusion (CRVO)

A complete or partial obstruction at a branch or tributary of the central retinal vein is referred to as a branch retinal vein occlusion (BRVO)

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Prognosis and Clinical Course

- The prognosis of RVOs varies according to the site of the occlusion and the type of occlusion (ischemic or nonischemic)
  - In general, more-distal RVOs with less occlusion have a better prognosis than more-proximal RVOs with greater ischemia
- CRVOs are associated with glaucoma and have a higher risk of anterior segment neovascularization and neovascular glaucoma
  - BRVOs and hemiretinal vein occlusions have a visible arterial-venous crossing where the occlusion occurs
- Macular edema may complicate both CRVOs and BRVOs

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Best Clinical Practices in RVO Management

1. **First-line treatment for RVO-associated macular edema is anti-vascular endothelial growth factors (anti-VEGFs)**
   a) Intravitreal corticosteroids, with the associated risk of glaucoma and cataract formation, have demonstrated efficacy
   b) Laser photocoagulation surgery in BRVO has a potential role in treatment
2. **Optimizing control of systemic arterial hypertension, diabetes, serum lipid levels, and intraocular pressure (IOP) are all important in the management of systemic risk factors**
   a. The potential for end-organ damage should be communicated to the applicable providers

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RVO Treatment Timing

- Patients with RVO demonstrating poor initial visual acuity showed visual and anatomic benefit with anti-VEGF therapy, most often observed shortly after initiation of treatment

- In CRVO patients, even minor delays between symptom onset and first injection led to less optimistic vision gains and were associated with higher incidence of negative sequelae

Light JG, et al. *Ophthalmol Retina*. 2021;5:888-900.

The Role of Anti-VEGF Therapy in RVO

Intraretinal VEGF mRNA transcription and intraocular VEGF levels are increased in patients with RVO compared with controls

VEGF increases vessel permeability and is an important mediator of the blood-retinal barrier breakdown leading to vascular leakage and macular edema

Therapy that inhibits VEGF is an effective therapeutic modality targeting the underlying pathogenesis of macular edema in RVO

Aiello LP, et al. *N Engl J Med*. 1994;331(22): 1480–7.
Brown DM, et al. *Ophthalmology*. 2010;117:1124-1133 e1121.
Campochiaro PA, et al. *Mol Ther*. 2008;16:791-799.
Noma H, et al. *Am J Ophthalmol*. 2005;140(2): 256–61

Anti-VEGF Therapies

FDA Indicated

Aflibercept

Ranibizumab

Faricimab

Off Label

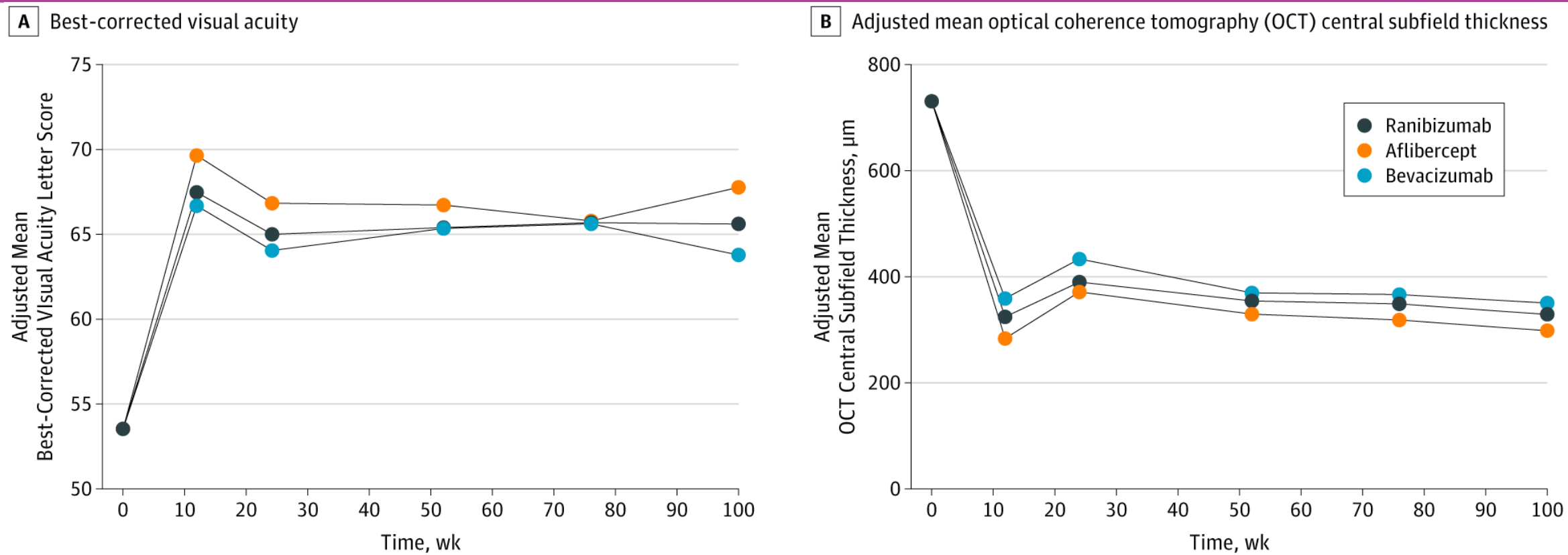
Bevacizumab

FDA-Approved Anti-VEGF Dosing Comparison for Macular Edema Following RVO

Anti-VEGF Therapy	Dosage Form	Dosing Schedule
Aflibercept	2 mg/0.05 mL solution	2 mg (0.05 mL) administered by intravitreal injection once every 4 weeks (approximately every 25 days, monthly)
Ranibizumab	10 mg/mL solution (0.5 mg)	0.5 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days)
Faricimab	120 mg/mL solution	6 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28±7 days, monthly) for 6 months

EYLEA [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals. Revised June 2021. Accessed July 2022. https://www.regeneron.com/downloads/eylea_fpi.pdf. LUCENTIS [package insert]. South San Francisco, CA: Genentech. Revised March 2018. Accessed July 2022. https://www.gene.com/download/pdf/lucentis_prescribing.pdf. VABYSMO [package insert]. South San Francisco, CA: Genentech. Revised October 2023. Accessed December 2023. https://www.gene.com/download/pdf/vabysmo_prescribing.pdf.

Comparative Efficacy of Anti-VEGF Treatment Options in RVO: Visual and OCT Outcomes



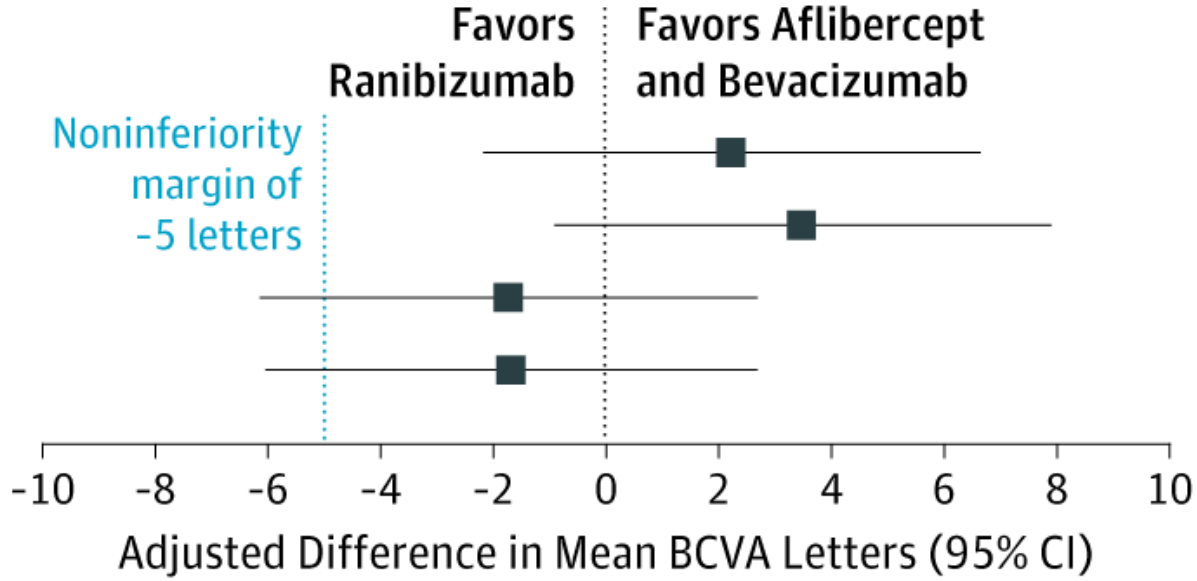
A. Adjusted mean difference between groups at 100 weeks: aflibercept vs ranibizumab, –29.3 (95% CI, –60.9 to 2.3); bevacizumab vs ranibizumab, –21.9 (95% CI, –9.7 to 53.4).

B. Adjusted mean difference between groups at 100 weeks: aflibercept vs ranibizumab, –29.3 (95% CI, –60.9 to 2.3); bevacizumab vs ranibizumab, 21.9 (95% CI, –9.7 to 53.4).

Hykin P, et al. *JAMA Ophthalmol*. 2019;137(11):1256-1264.

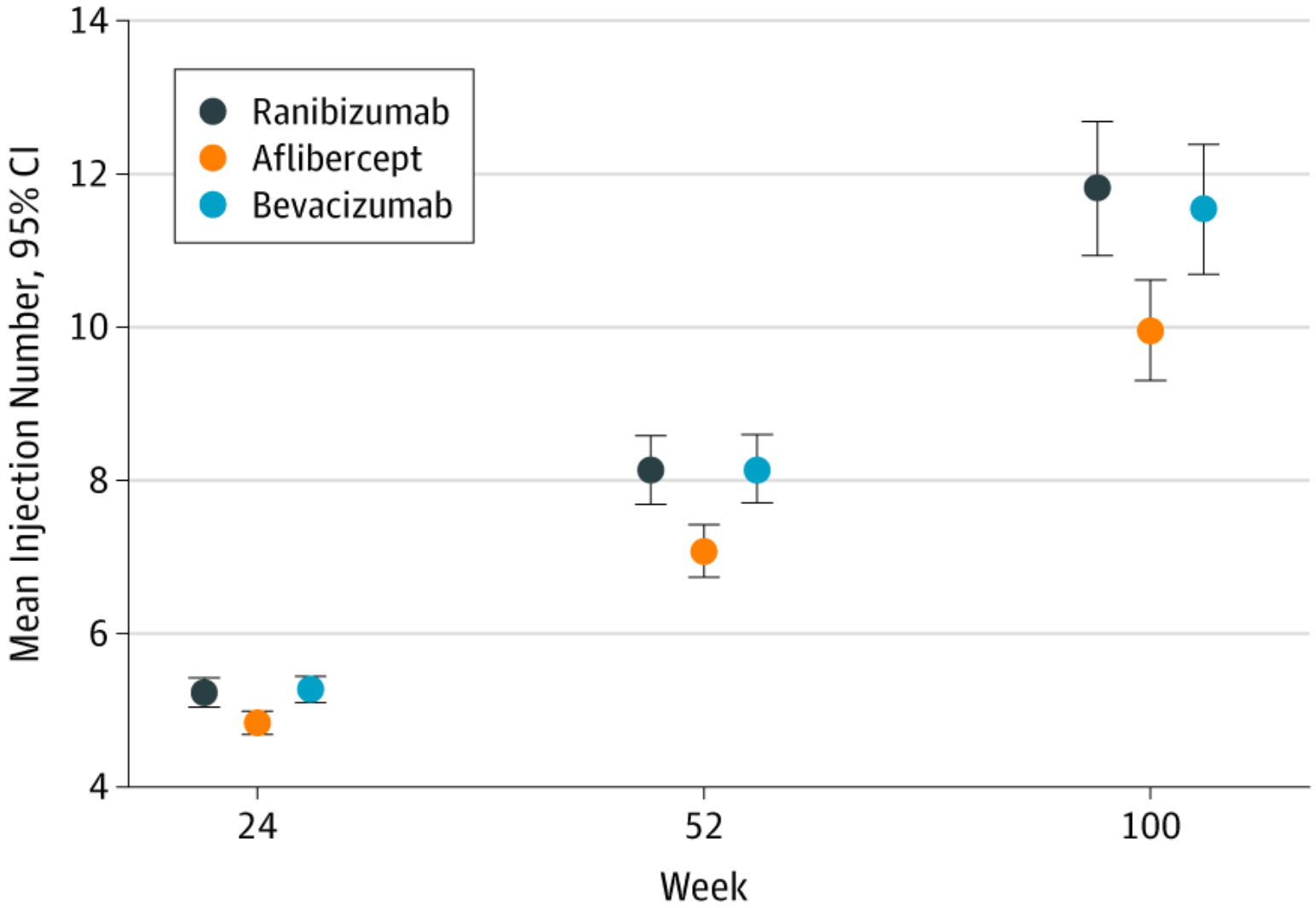
Although Outcomes are Similar Among Anti-VEGF Agents for RVO, Results Favor FDA-Approved Agents

Investigational Agent and Comparator	Difference in Means (95% CIs)
Aflibercept vs ranibizumab: ITT	2.23 (-2.17 to 6.63)
Aflibercept vs ranibizumab: PP	3.49 (-0.91 to 7.88)
Bevacizumab vs ranibizumab: ITT	-1.73 (-6.12 to 2.67)
Bevacizumab vs ranibizumab: PP	-1.67 (-6.02 to 2.68)



Hykin P, et al. *JAMA Ophthalmol*. 2019;137(11):1256-1264.

Anti-VEGF Agents Also Differ with Respect to Dosing/Number of Injections



Hykin P, et al. *JAMA Ophthalmol*. 2019;137(11):1256-1264.

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
Central retinal vein occlusion	362.35	H34.811 H34.812 H34.813
Venous tributary (branch) occlusion	362.36	H34.831 H34.832 H34.833
Venous engorgement	362.37	H34.821 H34.822 H34.823

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

Additional information for ICD-10 codes:

- 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 be used only 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

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