Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Class Update: Vascular Endothelial Growth Factor (VEGF) Inhibitors

Month/Year of Review: January 2015 **Last Review:** November 2012
PDL Class: Ophthalmic VEGF Inhibitors

Current Status of Preferred Drug List (PDL) Class:
- Preferred Agents: BEVACIZUMAB (AVASTIN ®)
- Non Preferred Agents: AFLIBERCEPT (EYLEA ®), RANIBIZUMAB (LUCENTIS ®), PEGAPTANIB (MACUGEN ®)

Research Questions:
- Is there new comparative effectiveness or safety evidence since the last review of VEGF inhibitors for ocular disorders to warrant a change to the preferred drug list (PDL)?
- Is there evidence that there is a difference in efficacy or safety between any VEGF inhibitors for the treatment of neovascular age-related macular degeneration, diabetic macular edema (DME), or macular edema following retinal vein occlusion (RVO)?

Conclusions:
- There is high quality evidence of no difference between bevacizumab and ranibizumab for the treatment of neovascular age-related macular degeneration (AMD) in gain in visual acuity at one year (RR 0.90; 95% CI 0.73 to 1.11) or loss of visual acuity (RR 1.00; 95% CI 0.98 to 1.02).[1] Two studies have confirmed that there is no difference in efficacy at two years.[2]
- There is moderate quality evidence of no difference serious ocular adverse events between bevacizumab and ranibizumab in the treatment of neovascular AMD. [1]
- For the treatment of neovascular AMD, there was moderate quality evidence of no significant difference in risk of death between bevacizumab and ranibizumab (3.7% vs. 3.4%; RR 1.10; 95% CI 0.78 to 1.57); p=0.59). [3]
- There is moderate to high quality evidence that anti-VEGF therapy improves visual acuity in patients with diabetic macular edema (DME) relative to laser treatment and sham injection, with similar improvements across agents.
- There is conflicting evidence regarding the comparative risk of serious systemic adverse events between bevacizumab and ranibizumab. A recent Cochrane Collaboration systematic review found low quality evidence of no difference in serious systemic adverse events (RR 1.08; 95% CI 0.90 to 1.31; p=0.41); however, when removing unpublished trials there was a significant difference favoring ranibizumab. The current evidence remains imprecise and suggests that if a difference does exist, it is likely to be small. There is evidence of no difference in arterial thrombotic events (RR 1.02; 95% CI 0.65 to 1.60) between ranibizumab and bevacizumab.

- There is insufficient comparative evidence to make conclusions on the relative efficacy and safety of pegaptanib or aflibercept.

Recommendations:

- Overall, there is no difference in efficacy between ranibizumab and bevacizumab with potentially slight differences in systemic adverse events and no differences in mortality. Evaluate comparative costs in executive session to determine appropriate PDL placement. Maintain pegaptanib and aflibercept as non-preferred due to lower strength evidence.

Reason for Review: Routine class update to evaluate new evidence.

Previous P&T Conclusions and Recommendations:

- There is moderate to high quality evidence that VEGF inhibitors improve visual acuity in patients with neovascular AMD and are recommended as first line treatment.
- There is low quality evidence that bevacizumab is equivalent to ranibizumab in improving visual outcomes over two years in neovascular AMD (difference in mean improvement with bevacizumab compared to ranibizumab was -1.4 letters; 95% CI -3.7 to 0.8) and that bevacizumab is associated with a higher rate of serious, nonspecific systemic adverse events over 2 years (31.7% vs. 39.9%; p=0.004, RR 1.30).
- There is insufficient evidence to make comparative conclusions for the use of pegaptanib in AMD.
- There is low quality evidence that aflibercept is equivalent to ranibizumab in maintaining vision at 1 year in the treatment of AMD.
- There is moderate to high quality evidence that anti-VEGF therapy improves visual acuity in patients with diabetic macular edema (DME) relative to laser treatment and sham injection, with similar improvements across agents.
- There is insufficient evidence to determine whether there are clinically meaningful differences in health outcomes between the available agents for the treatment of DME.
- There is insufficient direct comparative evidence comparing intravitreal bevacizumab with ranibizumab in patients with DME.
- There is insufficient evidence to support the use of pegaptanib in the use of DME.
- There is moderate quality evidence that anti-VEGF therapy improves visual acuity compared to sham injections in central retinal vein occlusion (RVO) related macular edema with no direct comparative evidence of any agents.
- Due to a lack of clinical benefit in both AMD and DME over other anti-VEGF agents, make pegaptanib non-preferred.
- There is not strong evidence of superiority of one anti-VEGF agent over another for the treatment of AMD or DME and low quality evidence demonstrating equivalence of bevacizumab to ranibizumab and aflibercept to ranibizumab in AMD. Compare costs of bevacizumab, ranibizumab, and aflibercept.
- Make bevacizumab preferred, with a liberal exception policy for non-preferred agents, and grandfather current patients.

Background:

The major growth factor controlling angiogenesis is vascular endothelial growth factor (VEGF), which plays a key role in neovascularization. Anti-VEGF agents have been developed and studied for the treatment of diabetic macular edema, age-related macular degeneration, and macular edema following retinal vein occlusion (RVO). Bevacizumab, aflibercept, ranibizumab and pegaptanib are currently the only anti-VEGF agents available used intravitreally for eye disorders. Ranibizumab and aflibercept are approved for treatment of neovascular AMD, DME and macular edema following RVO; pegaptanib is only approved for AMD and intravitreal use of bevacizumab is only used off-label for various ocular disorders. Intravenous bevacizumab is approved for several forms of cancer, but has been used off-label intravitreally for vascular diseases of the eye, including AMD and DME.[4] Ranibizumab comes from the same parent molecule as bevacizumab but is a humanized monoclonal antibody fragment that binds active forms of VEGF-A, whereas bevacizumab is a full-length antibody and binds to all types of VEGF. Bevacizumab is significantly less expensive than ranibizumab.[5]

The goal of treatment with VEGF inhibitors is to preserve current visual acuity and reduce the progression to visual loss. Change in visual acuity is one of the common outcomes evaluated in trials of patients with vascular eye diseases. It is commonly measured as the best-corrected visual acuity (BCVA). The Eye Disease Prevalence Research Group (EDPRS) developed a series of charts to standardize evaluation of visual acuity, which are commonly used as a standard outcome measure in randomized controlled trials (RCTs).[6] An improvement of at least 15 letters on the ETDRS eye chart is considered clinically significant and has been shown to correlate with clinically meaningful improvements in patient-perceived visual function. Serious adverse events of interest include endophthalmitis, glaucoma, stroke, myocardial infarction, other cardiovascular events, and death.

Age related macular degeneration is a progressive chronic disease of the central retina and leading cause of vision loss worldwide.[13] Patients are typically over 50 years of age and the goal of treatment is to minimize or reverse loss of vision and to maximize the vision-related quality of life related to AMD. Treatment options for AMD include observation, antioxidant vitamin and mineral supplements, photodynamic therapy (PDT) with verteporfin, intravitreal injection of VEGF inhibitors, and laser photocoagulation surgery.[14] VEGF inhibitors have become the standard of care for neovascular AMD and are recommended first-line. They have demonstrated improved visual outcomes compared with other therapies. 2014 guidelines from The American Academy of Ophthalmology (AAO) recommend VEGF inhibitors as first line treatment for AMD with no specific distinctions between ranibizumab, bevacizumab, or pegaptanib.[15] Two controversies in the treatment of AMD with VEGF inhibitors include the preferred dosing regimen and systemic safety. Trials have evaluated a stricter monthly dosing regimen versus a less frequent, as needed, protocol based on clinical and imaging features. Safety is a concern as the drugs enter the systemic circulation after ocular injection and there is a theoretical higher risk of systemic vascular events. Clinical data on the systemic safety are sparse and available studies are not large enough to address safety concerns.

Retinal vein occlusion is the second most common retinal vascular disease after diabetic retinopathy with main risk factors being age over 50 and hypertension.[17,18] There are two types of RVO: branch retinal vein occlusion (BRVO) occurring 2-3 times more often than central retinal vein occlusion (CRVO).[17,18] Ophthalmological treatments focus on the prevention and management of the main sight-threatening complications – ocular neovascularization and macular edema.[17] In the absence of either of these complications, there is no evidence that treatment improves outcomes, and treatment is associated with some adverse effects. Macular edema is the most common cause of visual loss in patients with RVO. Laser photocoagulation, steroids, and intravitreal injections of anti-VEGF have been evaluated as treatments, with laser photocoagulation and VEGF inhibitors as the primary treatment options.

Methods:
A Medline literature search ending December 2014 for new systematic reviews and RCTs directly comparing VEGF inhibitors for ocular disorders was performed. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources. Placebo controlled trials were excluded from the review and head to head trials included in high quality systematic reviews will not be evaluated separately.

Systematic Reviews:
A recent Cochrane Collaboration systematic review compared the safety of bevacizumab versus ranibizumab for neovascular AMD.[3] Primary outcomes were death and serious adverse events. A literature evaluation through March 2014 identified 9 studies for inclusion (n=3665). Three studies excluded patients at high cardiovascular risk and low precision lowered the strength of the evidence. Overall, there was moderate quality evidence of no significant difference in death between bevacizumab and ranibizumab (RR 1.10; 95% CI 0.78 to 1.57); p=0.59). There was low quality evidence of no difference in serious systemic adverse events (RR 1.08; 95% CI 0.90 to 1.31; p=0.41). The only adverse event that occurred significantly more in the bevacizumab group compared to ranibizumab was a higher risk of gastrointestinal disorders (RR 1.82; 95% CI 1.04 to 3.19). However, removing unpublished studies resulted in a significantly higher rate of serious adverse events with bevacizumab than ranibizumab (RR 1.21; 95% CI 1.06 to 1.37; p=0.04). The authors concluded that the current evidence is imprecise and might vary based on patient risks but suggests that if a difference does exist, it is likely to be small.

Another 2014 Cochrane Collaboration review evaluated the effects of VEGF inhibitors on neovascular AMD.[1] A literature search through March 2014 identified a total of 12 RCTs for inclusion in the review (n=5498). The overall quality of the evidence was very good with most trials having a low risk of bias. The primary outcome was visual acuity, measured by the proportion of patients who gained or lost 15 letters or more of BCVA at one year of follow-up. One trial compared pegaptinib, three trials compared ranibizumab, and two trials compared bevacizumab, to placebo. Six noninferiority trials compared ranibizumab to bevacizumab. Compared to no VEGF inhibitor, any of the three medications demonstrated improved vision, less often lost vision, and were less likely to be legally blind than those without VEGF inhibitors. Compared with control treatments, treatment with ranibizumab or bevacizumab resulted in larger improvements than pegaptanib. No trials compared pegaptanib to another VEGF inhibitor. No significant differences in outcomes were seen between bevacizumab and ranibizumab with the only difference observed being cost. There is high quality evidence of no difference between bevacizumab and ranibizumab for the treatment of neovascular age-related macular degeneration (AMD) in gain in visual acuity (RR 0.90; 95% CI 0.73 to 1.11) and loss of visual acuity (RR 1.00; 95% CI 0.98 to 1.02).[1] Two year data were available from 2 studies and results were consistent with 1 year data, with no difference in the proportion of patients who gained 15 letters or more of visual acuity (RR 0.84; 95% CI 0.63 to 1.11).There is moderate quality evidence of no difference in serious systemic adverse events (RR 1.27; 95% CI 1.06 to 1.52) or serious ocular adverse events. Limited data were available to evaluate quality of life outcomes.

A systematic review and meta-analysis by Wu et al. compared ranibizumab to bevacizumab for ophthalmic diseases related to neovascularization.[19] The primary outcome was change in baseline in the BCVA measured on ETDRS charts after at least 6 months of follow-up. A total of 9 studies were included in the meta-analysis. Five of these included patients with AMD, two on pathologic myopia, and one each on retinal angiomatous proliferation and DME. The overall quality of the studies was good. The weighted mean difference (WMD) in change in visual acuity score from baseline for ranibizumab versus bevacizumab was 0.52

letters (95% CI -0.11 to 1.14; p=0.146) and there was no significant difference in the proportion of patients who gained 15 letters or more (OR 1.10; 95% CI 0.90 to 1.33; p=0.359). Using a fixed-effect model, there was no significant difference in death or death from vascular causes but there was a significantly lower risk of serious systemic adverse events for ranibizumab compared to bevacizumab (RR 0.83; 95% CI 0.73 to 0.94; p=0.0035). However, there was also statistically significant heterogeneity among the studies. There was no difference in ocular serious adverse events. One study compared the two treatments for DME and found no significant difference in the proportion of patients with an increase of 15 or more letters (OR 1.44; 95% CI 0.51 to 4.05).

New Guidelines:
The American Academy of Ophthalmology developed preferred practice guidelines for the treatment of age-related macular degeneration based on evidence methods from the Scottish Intercollegiate Guideline Network (SIGN) and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) groups.[15] Based on good evidence, a strong recommendation endorses therapy with VEGF inhibitors is the most effective way to manage neovasulcar AMD and it represents the first line of treatment. No preference is given between aflibercept, bevacizumab, or ranibizumab.

Guidance from the National Institute of Clinical Excellence evaluated the use of ranibizumab for treatment DME in 2013.[20] The guidance was based on a submission from the manufacturer which did not contain a comparison of ranibizumab with bevacizumab. The evidence review group questioned the manufacturer's argument that there is a lack of robust evidence on clinical effectiveness or safety of bevacizumab in the treatment of DME and felt that there is sufficient evidence to provide an indirect comparison. The following guidance was provided:

- Ranibizumab is recommended as an option for treating visual impairment due to DME only if:
    - The eye has a central retinal thickness of 400 micrometers or more at the start of treatment AND
    - The manufacturer provides ranibizumab with the agreed upon discount in the patient access scheme
- Treatment should be given monthly and continued until maximum visual acuity is reached (stable for 3 consecutive months). The interval between doses should not be shorter than 1 month.

The American Optometric Association (AOA) released 2014 guidelines on the eye care of the patient with Diabetes Mellitus.[21] The following recommendations are provided:

- Once clinically significant macular edema develops, treatment with focal laser photocoagulation or intravitreal anti-VEGF injection is indicated (Evidence Strength A, Recommendation A).
- The current standard of care for treatment of center-involved DME in persons with BCVA of 20/32 or worse is VEGF inhibitors (Evidence Strength: A, Recommendation: A).

No preference is given to one VEGF inhibitor over another.

New Safety Alerts:
None identified.

New Formulations or Indications:
Aflibercept received FDA approval for DME in July 2014 and for macular edema following RVO in October 2014.[22]

Approval for macular edema following RVO comes from 2 clinical studies (COPERNICUS AND GALILEO) in patients with central retinal vein occlusion (CRVO) and in one study (VIBRANT) with branch retinal vein occlusion (BRVO). [22] All three studies compared aflibercept injections to sham injections.[23–25] The primary outcome was the proportion of patients who gained at least 15 letters in BCVA compared to baseline and at week 24, aflibercept was superior to the control group (56% vs. 12% in COPERNICUS and 60% vs. 22% in GALILEO). In the VIBRANT study, patients were randomized to aflibercept every 4 weeks or laser photocoagulation and significantly more patients gained at least 15 letters in BCVA from baseline in the aflibercept group (52.7% vs. 26.7%).

For the treatment of DME, aflibercept was assessed in 2 RCT's (VIVID and VISTA).[26] In both studies, patients were randomized to aflibercept 2 mg every 8 weeks following 5 initial monthly injections, aflibercept every 4 weeks, or laser photocoagulation. Efficacy of aflibercept, as defined by mean change from baseline in BCVA at week 52, was statistically superior to the control group.

Randomized Controlled Trials:

Two-year findings of the IVAN trial were published in 2013. At the time of the last P&T review, this trial was ongoing and interim 1-year results were reported. The IVAN trial was conducted to compare the efficacy and safety of ranibizumab and bevacizumab in AMD in a noninferiority trial. A total of 610 patients were randomized to 4 groups: ranibizumab or bevacizumab, given either every month or as-needed.[27] Both groups received 3 months of treatment and then were allocated to continuous or as needed treatment. Patients and clinicians were blinded to drug allocation but not to treatment regimen allocation. The primary outcome was best-corrected distance visual acuity measured as ETDRS letters, with a noninferiority limit of 3.5 letters. The difference between drugs (bevacizumab minus ranibizumab) at one year was -1.99 letters (95% CI -4.04 to 0.06) and between treatment regimens was -0.35 letters (95% CI -2.40 to 1.70), favoring continuous therapy. [27] Overall, the comparison between study drugs was inconclusive using the 3.5 letter limit and as-needed treatment was equivalent to monthly treatment. There were no significant differences between drugs or regimens for quality of life. There were no differences at year 1 between drugs or treatment regimens in terms of mortality serious adverse events. Arteriothrombotic events occurred infrequently, but more often with ranibizumab than bevacizumab. [27]

At 2 years, there was no difference between the drugs for any of the primary or secondary efficacy outcomes.[2] BCVA was similar between both groups as well as between continuous and discontinuous treatment groups. Continuous administration was superior for secondary outcomes of near visual acuity, contrast sensitivity, and total lesion thickness at fovea. For safety outcomes at 2 years, the rate of arterial thrombotic events or heart failure hospitalization was not significantly different between ranibizumab and bevacizumab or between continuous and as-needed administration. In addition, systemic serious adverse events and mortality was also similar between the two drugs.

The authors also pooled the results of the CATT and IVAN trials. They found bevacizumab to be noninferior to ranibizumab in BCVA and as-needed treatment inferior to continuous monthly treatment. The two trials used different as-needed regimens. Ranibizumab was also associated with a lower risk of serious systemic adverse events compared to bevacizumab (OR 0.76; 95% CI 0.63 to 0.93) and there no difference in death (RR 0.89; 95% CI 0.59-1.33) or arterial thrombotic events (RR 1.02; 95% CI 0.65 to 1.60).

References:

1. Solomon SD, Lindsley K, Vedula SS, Krzystolik MG, Hawkins BS. Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. *Cochrane Database Syst Rev*. 2014;8:CD005139. doi:10.1002/14651858.CD005139.pub3.

2. Chakravarthy U, Harding SP, Rogers CA, et al. Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. *The Lancet*. 2013;382(9900):1258-1267. doi:10.1016/S0140-6736(13)61501-9.

3. Moja L, Lucenteforte E, Kwag KH, et al. Systemic safety of bevacizumab versus ranibizumab for neovascular age-related macular degeneration. *Cochrane Database Syst Rev*. 2014;9:CD011230. doi:10.1002/14651858.CD011230.pub2.

4. Goyal S, Lavalley M, Subramanian ML. Meta-analysis and review on the effect of bevacizumab in diabetic macular edema. *Graefes Arch Clin Exp Ophthalmol*. 2011;249(1):15-27. doi:10.1007/s00417-010-1452-4.

5. Hutton D, Newman-Casey PA, Tavag M, Zacks D, Stein J. Switching to less expensive blindness drug could save medicare part B $18 billion over a ten-year period. *Health Aff (Millwood)*. 2014;33(6):931-939. doi:10.1377/hlthaff.2013.0832.

6. Ollendorf D, Migliaccio-Walle K, Colby J, Person S. Anti-vascular endothelial growth factor treatment for diabetic macular edema [Internet]. Boston (MA): Institute for Clinical and Economic Review (ICER); 2012. http://www.icer-review.org/index.php/Completed-Appraisals/dme.html.

7. Zechmeister-Koss I, Huic M. Vascular endothelial growth factor inhibitors (anti-VEGF) in the management of diabetic macular oedema: a systematic review. *Br J Ophthalmol*. 2012;96(2):167-178. doi:10.1136/bjophthalmol-2011-300674.

8. Grover D, Li TJ, Chong CCW. Intravitreal steroids for macular edema in diabetes. *Cochrane Database Syst Rev*. 2008;(1):CD005656. doi:10.1002/14651858.CD005656.pub2.

9. Fortin P, Mintzes B, Innes M. A Systematic Review of Intravitreal Bevacizumab for the Treatment of Diabetic Macular Edema [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2012 (Rapid Response Report: Peer-Reviewed Summary with Critical Appraisal). http://www.cadth.ca/media/pdf/RD0028_avastin_L3_e.pdf.

10. American Diabetes Association. Standards of medical care in diabetes--2012. *Diabetes Care*. 2012;35 Suppl 1:S11-S63. doi:10.2337/dc12-s011.

11. American Academy of Ophthalmology. /Vitreous Panel, Preferred Practice Patterns Committee. Diabetic retinopathy. San Francisco (CA): American Academy of Ophthalmology (AAO); 2008. 39 p.

12. American Optometric Association. Optometric Clinical Practice Guideline. Care of the Patient with Diabetes Mellitus. 2009. http://www.aoa.org/documents/CPG-3.pdf.

13. Lim LS, Mitchell P, Seddon JM, Holz FG, Wong TY. Age-related macular degeneration. *Lancet*. 2012;379(9827):1728-1738. doi:10.1016/S0140-6736(12)60282-7.

14. American Academy of Ophthalmology. Age-related macular degeneration. San Francisco (CA): American Academy of Ophthalmology (AAO); 2008.37p. [152 references].

15. American Academy of Opthalmology (AAO). Preferred Practice Pattern® (PPP) Committee. Preferred Practice Pattern® guidelines. Diabetic Retinopathy. San Francisco, CA: American Academy of Ophthalmology. 2014. http://www.aao.org/ppp. Accessed December 28, 2014.

16. National Institute for Health and Clinical Excellence. Ranibizumab and pegaptanib for the treatment of age-related macular degeneration. NICE technology appraisal guidance 155. 2008. http://www.nice.org.uk/nicemedia/live/12057/41719/41719.pdf.

17. Kiire CA, Chong NV. Managing retinal vein occlusion. *BMJ*. 2012;344:e499.

18. Coscas G, Loewenstein A, Augustin A, et al. Management of retinal vein occlusion--consensus document. *Ophthalmologica*. 2011;226(1):4-28. doi:10.1159/000327391.

19. Wu B, Wu H, Liu X, Lin H, Li J. Ranibizumab versus bevacizumab for ophthalmic diseases related to neovascularisation: a meta-analysis of randomised controlled trials. *PLoS ONE*. 2014;9(7):e101253. doi:10.1371/journal.pone.0101253.

20. American Diabetes Association. Standards of medical care in diabetes – 2014. Diabetes Care. 2014;37 Suppl 1:S14–S80.

21. American Optometric Association (AOA). Evidence-based clinical practice guideline: eye care of the patient with diabetes mellitus. St. Louis (MO): American Optometric Association; 2014. 83 p.

22. Eylea (aflibercept) injection. Prescribing Information. 10/2014. Regeneron Pharmaceuticals, Inc.

23. Campochiaro PA, Clark WL, Boyer DS, et al. Intravitreal Aflibercept for Macular Edema Following Branch Retinal Vein Occlusion: The 24-Week Results of the VIBRANT Study. *Ophthalmology*. 2014. doi:10.1016/j.ophtha.2014.08.031.

24. Heier JS, Clark WL, Boyer DS, et al. Intravitreal aflibercept injection for macular edema due to central retinal vein occlusion: two-year results from the COPERNICUS study. *Ophthalmology*. 2014;121(7):1414-1420.e1. doi:10.1016/j.ophtha.2014.01.027.

25. Korobelnik J-F, Holz FG, Roider J, et al. Intravitreal Aflibercept Injection for Macular Edema Resulting from Central Retinal Vein Occlusion: One-Year Results of the Phase 3 GALILEO Study. *Ophthalmology*. 2014;121(1):202-208. doi:10.1016/j.ophtha.2013.08.012.

26. Korobelnik J-F, Do DV, Schmidt-Erfurth U, et al. Intravitreal aflibercept for diabetic macular edema. *Ophthalmology*. 2014;121(11):2247-2254. doi:10.1016/j.ophtha.2014.05.006.

27. Chakravarthy U, Harding SP, Rogers CA, et al. Ranibizumab versus Bevacizumab to Treat Neovascular Age-related Macular Degeneration: One-Year Findings from the IVAN Randomized Trial. *Ophthalmology*. 2012. doi:10.1016/j.ophtha.2012.04.015.