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Comparative Clinical and Economic Effectiveness of Anti-vascular Endothelial Growth Factor Agents

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PREFACE

The VA Evidence-based Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of particular importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. QUERI provides funding for four ESP Centers, and each Center has an active University affiliation. Center Directors are recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Centers. The ESP is governed by a Steering Committee comprised of participants from VHA Policy, Program, and Operations Offices, VISN leadership, field-based investigators, and others as designated appropriate by QUERI/HSR&D.

The ESP Centers generate evidence syntheses on important clinical practice topics. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The ESP disseminates these reports throughout VA and in the published literature; some evidence syntheses have informed the clinical guidelines of large professional organizations.

The ESP Coordinating Center (ESP CC), located in Portland, Oregon, was created in 2009 to expand the capacity of QUERI/HSR&D and is charged with oversight of national ESP program operations, program development and evaluation, and dissemination efforts. The ESP CC establishes standard operating procedures for the production of evidence synthesis reports; facilitates a national topic nomination, prioritization, and selection process; manages the research portfolio of each Center; facilitates editorial review processes; ensures methodological consistency and quality of products; produces “rapid response evidence briefs” at the request of VHA senior leadership; collaborates with HSR&D Center for Information Dissemination and Education Resources (CIDER) to develop a national dissemination strategy for all ESP products; and interfaces with stakeholders to effectively engage the program.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP CC Program Manager, at Nicole.Floyd@va.gov.

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EVIDENCE REPORT

INTRODUCTION

Visual impairment among United States (US) Veterans has risen dramatically over recent decades, and worsening visual acuity is responsible for substantial reductions in quality of life and the ability to perform everyday tasks.[1] An estimated 1.5 million Veterans currently have vision-threatening diseases,[2] and as the proportion of elderly Veterans receiving care at the Veterans Health Administration (VHA) continues to grow, vision-related problems will become even more prevalent.

Leading causes of vision loss at the VHA include diseases such as age-related macular degeneration (AMD), diabetic macular edema (DME), and retinal vein occlusion (RVO). AMD is the most common cause of permanent vision loss in elderly populations of developed countries. As the disease progresses to the more severe neovascular ("wet") type of macular degeneration, abnormal growth of blood vessels in the macula can lead to leakage of fluid, bleeding, and scarring of retinal tissue, which can result in severe visual impairment. While AMD primarily affects older adults, diabetic retinopathy is the most common cause of vision loss in working-age adults, usually as a result of leaking retinal blood vessels causing DME. Nearly one million Veterans have DME,[2] and if left untreated, it can cause moderate vision loss (best-corrected visual acuity [BCVA] of 55 to 70 letters or loss of 15 letters on the Early Treatment of Diabetic Retinopathy Study [ETDRS] chart) in an estimated 20% of patients after 3 years.[3] Branch or central retinal vein occlusion (BRVO or CRVO) can also cause macular edema leading to vision loss.

Fortunately, drugs known as anti-vascular endothelial growth factor (anti-VEGF) agents have been developed that target and bind to the factor responsible for this abnormal blood vessel growth and leakage, thus inhibiting its activity. The first such drug designed for ocular administration was ranibizumab (Lucentis® by Genentech), approved by the Food and Drug Administration (FDA) in 2006. Recognizing similarities between this drug and another anti-VEGF agent called bevacizumab (Avastin® by Genentech) initially developed as a cancer treatment, researchers tested its use intravitreally in a large multicenter clinical trial. Results were positive, and since 2005, bevacizumab has been widely used off-label by ophthalmologists to treat patients with AMD, DME, and RVO.[4,5] Because bevacizumab is not FDA-approved for ocular conditions, it either requires aseptic compounding or one-time use of the large vial packaged for use as chemotherapy—the method currently used by the VHA. A third anti-VEGF agent known as aflibercept (Eylea® by Regeneron-Bayer HealthCare; also referred to as VEGF Trap-Eye) was approved for ocular indications in 2011. Aflibercept's unique binding activity is believed to give it a longer duration of action, and thus the drug could require less frequent injections than bevacizumab or ranibizumab.[6] Another agent, pegaptanib (Macugen®), was previously used to treat these conditions, but since other more effective agents became available its use virtually vanished (accounting for 1% of anti-VEGF Medicare claims in 2011).[7]

These anti-VEGF agents have been shown to reduce the burden of AMD, DME, and RVO by slowing or even reversing the vision loss typically associated with these diseases. Several systematic reviews have found evidence of a significant benefit with anti-VEGF agents over sham or other therapies.[8-11] This has led to rapid increases in their use over recent years, with the

number of patients being treated with bevacizumab or ranibizumab at the VHA more than doubling from 2008 to 2011.[7] However, there are substantial cost differences between the drugs, with an estimated cost per dose of $55 for compounded bevacizumab (~$600 for single use of the commercially available vial), $1,170 or $2,023 for ranibizumab (depending on the indication; recommended dose is 0.3 mg for DME and 0.5 mg for AMD and BRVO/CRVO), and $1,850 for aflibercept.[5,12] Since patients need regular intravitreal injections in order to maintain vision, it is no surprise that these treatments represent an enormous cost to US healthcare systems. In fact, Medicare Part B spent nearly $2 billion on bevacizumab and ranibizumab in 2010 alone, accounting for one-sixth of its entire budget.[5] The VHA has a similar patient profile to Medicare, with an aging population and increasing incidence of AMD and diabetes mellitus. However, 2011 data show that the more expensive ranibizumab is used more often within the VHA (52% of patients receiving anti-VEGF drugs compared to 37% of Medicare patients). This is likely due to safety concerns following several VHA patients contracting endophthalmitis in early 2011 and the theoretical risk of increased arterial thrombotic events with bevacizumab treatment, an important concern in the VHA due to the high rate of cardiovascular comorbidities in Veterans.[7] Thus, it is possible that anti-VEGF drugs constitute an even larger proportion of spending within the VHA.

Despite the widespread use of these drugs and the significant resources spent on them, there is uncertainty about their comparative effectiveness and safety. Therefore, the purpose of this systematic review is to compare the effectiveness, harms, and costs of the 3 anti-VEGF drugs currently used for patients with retinal or choroidal neovascularization and/or macular edema due to diseases such as AMD, DME, and RVO.

METHODS

TOPIC DEVELOPMENT

This topic was nominated by Dr. Glenn Cockerham, National Program Director for VHA Ophthalmology Services. The scope and key questions of this report were determined during a topic refinement process that included a preliminary review of published peer-reviewed literature, discussion with internal partners and investigators, and consultation with content experts and key stakeholders. This review follows established systematic review methodology[13] and a protocol describing the review plan was posted to the PROSPERO International Prospective Register of Systematic Reviews website before the review was initiated.[14] The key research questions for this review are as follows:

Key Question 1: What is the comparative clinical effectiveness of anti-VEGF agents for retinal/choroidal neovascularization and/or macular edema in adults?

Key Question 2: What are the comparative harms of anti-VEGF agents for retinal/choroidal neovascularization and/or macular edema in adults?

Key Question 3: What is the comparative cost-effectiveness of anti-VEGF agents for retinal/choroidal neovascularization and/or macular edema in adults?

SEARCH STRATEGY

Search strategies were developed in consultation with a research librarian (**Appendix A**). To identify relevant articles, we searched Ovid MEDLINE from database inception to December 11, 2015 and PubMed, Elsevier EMBASE, and Ovid EMB Reviews (CDSR, DARE, HTA, Cochrane CENTRAL, *etc*) from database inception to February 2, 2016. Grey literature sources included trial registries (ClinicalTrials.gov, International Clinical Trials Registry Platform [WHO ICTRP], and the ISRCTN Registry), regulatory agencies, conference proceedings, and Scientific Information Packet requests for unpublished data from pharmaceutical manufacturers. In addition, the bibliographies of relevant primary studies and recent systematic reviews were reviewed to identify additional eligible studies.

STUDY SELECTION

Titles and abstracts were reviewed for potential relevance to the Key Questions using the online abstract screening software Abstrackr.[15] Potentially relevant articles were reviewed at the full-text level using prespecified inclusion/exclusion criteria (**Table 1).** Two independent reviewers agreed on the final inclusion/exclusion decision for all articles; any disagreements were resolved by consensus or discussion with a third reviewer.

The 3 anti-VEGF agents of interest were: aflibercept (Eylea®), bevacizumab (Avastin®), and ranibizumab (Lucentis®). Studies eligible for inclusion compared at least 2 of these agents in adults with retinal or choroidal neovascularization and/or macular edema and reported at least one outcome of interest (visual acuity, intermediate anatomic outcomes from optical coherence tomography [OCT] or other imaging, functional status, quality of life, harms, or cost). We used a best evidence approach to guide our study design inclusion criteria.[16,17] During an initial scan of

the literature, we identified several large controlled trials examining benefits and harms, and therefore we did not include observational studies for Key Questions 1 or 2. On the other hand, we did include cohort and validated modeling studies in addition to trials for Key Question 3 on costs, although we limited these to studies in the US given the marked variability in drug costs across countries.

Table 1. PICOTS and Key Questions

Key Question (KQ)	**KQ1.** What is the comparative clinical effectiveness of anti-VEGF agents for retinal/choroidal neovascularization and/or macular edema in adults?	**KQ2.** What are the comparative harms of anti-VEGF agents for retinal/choroidal neovascularization and/or macular edema in adults?	**KQ3.** What is the comparative cost-effectiveness of anti-VEGF agents for retinal/choroidal neovascularization and/or macular edema in adults?
Population	Adults treated with anti-VEGF agents due to one of the following conditions: · Diabetic macular edema (DME) · Branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO) with cystoid macular edema · Choroidal neovascularization secondary to age-related macular degeneration (AMD)/neovascular AMD · Vitreous hemorrhage/proliferative diabetic retinopathy/neovascular glaucoma Excluded: Uveitic cystoid macular edema; inflammatory choroidal neovascularization; idiopathic choroidal neovascularization.		
Intervention	Anti-VEGF injection therapy with one of the following agents: · Aflibercept (Eylea; Trap-Eye) · Bevacizumab (Avastin) · Ranibizumab (Lucentis)		
Comparator	One anti-VEGF intervention versus another anti-VEGF intervention (head-to-head)		
Outcomes	· Visual acuity: Mean change in BCVA using the ETDRS chart or other standardized chart; gain or loss of 15 letters/3 lines (or other specified cutoff); percentage of participants reaching pre-specified visual acuity cutoff · Intermediate outcomes: Change in central macular/subfield thickness using OCT; resolution of subretinal/intraretinal fluid; resolution of neovascularization of the iris, disc, or elsewhere; hemorrhage · Functional status/Quality of life (*eg*, NEI VFQ-25) · Other measures of vision (*eg*, reading ability, reading speed, contrast sensitivity)	· Infection/endophthalmitis · Retinal detachment · Glaucoma/elevated intraocular pressure · Ocular arterial occlusion · Retinal atrophy · Injection-related cataract/lens damage · Systemic adverse events · Other reported harms	· Cost · Number of injections needed · Proportion of patients requiring rescue interventions/co-interventions
Timing	Short- and long-term outcomes		
Setting	Outpatient settings		Cost outcomes from outpatient settings in the US.
Study design	Controlled clinical trials (randomized or non-randomized). Excluded: Observational studies, reviews*, opinions, case studies, and case series. *Systematic reviews used to identify eligible trials.		Systematic reviews, meta-analyses, controlled clinical trials (randomized or non-randomized), cohort studies, and validated modeling studies.

Abbreviations: BCVA = best-corrected visual acuity; ETDRS = Early Treatment of Diabetic Retinopathy Study; KQ = Key Question; NEI VFQ-25 = 25-item National Eye Institute Visual Functioning Questionnaire; OCT = optical coherence tomography; US = United States; VEGF = vascular endothelial growth factor.

DATA ABSTRACTION

Data from included studies were abstracted into a customized database by one reviewer and confirmed by a second reviewer. From each study, we abstracted the following information where available: study objective, population characteristics, main participant inclusion and exclusion criteria, number of subjects, duration of follow-up, study interventions and dosing schedules, important co-interventions, visual acuity outcomes, quality of life/functional status, anatomic outcomes, harms, mean number of injections, costs, and funding source.

QUALITY ASSESSMENT

Two reviewers independently assessed the quality of each trial using a tool developed by the Cochrane Collaboration (**Appendix B**),[18] and disagreements were resolved through discussion. Each trial was given an overall summary assessment of low, unclear, or high risk of bias (ROB).

DATA SYNTHESIS

We summarized the primary literature by abstracting relevant data and qualitatively synthesizing the literature for each key question. Our primary outcomes of interest were visual acuity and included the proportion of patients experiencing an improvement in BCVA from baseline (represented by a gain of 15 or more ETDRS letters) and overall mean change in BCVA. Based on discussion with our technical experts, we felt a difference of less than 5 ETDRS letters (one line) between treatment groups in mean change in BCVA was not likely to be clinically meaningful or represent an absolute relative improvement that could be perceived by patients (an ETDRS score change of less than 5 letters is also generally not considered to be reliable[19-21]). We also reported intermediate anatomic outcomes such as macular/subfield thickness and absence of retinal/subretinal fluid using OCT imaging. We prioritized long-term outcomes when these were reported (18 and 24 months), but also reported short-term outcomes if longer-term data were not available (6 and 12 months).

We also considered clinical and methodological diversity as well as statistical heterogeneity to determine the appropriateness of performing meta-analyses to estimate the summary effects. Due to relative homogeneity among studies, we conducted meta-analyses using study-level data for the 2 outcomes that were both the most commonly reported and the most clinically meaningful: mean BCVA change from baseline in ETDRS letters (continuous outcome), and participants gaining 15 or more ETDRS letters (dichotomous outcome). We performed analyses according to clinical populations; however, we also conducted exploratory meta-analyses that combined the different disease populations.

Meta-analyses of mean change in BCVA were performed using the differences between treatments in score change from baseline to follow-up. We used the mean difference between arms reported in the study when it was available (if reported, least squares [LS] mean difference was chosen over raw mean difference); otherwise, we calculated mean differences between treatments based on reported data. If necessary, the correlation between the baseline and follow-up was assumed to be 0.5 to calculate the standard deviation for the change score in each group. Sensitivity analyses using alternative assumptions (0.3 and 0.8) produced similar results. We also performed a sensitivity analysis by calculating treatment difference based on follow-up score and the results were very similar. For the dichotomous outcome of participants gaining 15 or more

ETDRS letters, we used risk ratios to generate a combined estimate. In all meta-analyses, we used the profile-likelihood random-effects model[22] while incorporating variation among studies. We assessed the presence of statistical heterogeneity among the studies using the standard Cochran's chi-square test, and the magnitude of heterogeneity using the I^2 statistic.[23] All analyses were performed using Stata/IC 13.1 (StataCorp, College Station, TX).

RATING THE BODY OF EVIDENCE

We assessed the overall strength of evidence for outcomes using a method developed for the Agency for Healthcare Research and Quality's (AHRQ) Evidence-based Practice Centers.[24] The AHRQ method considers study limitations, directness, consistency, precision, and reporting bias to classify the strength of evidence for individual outcomes independently for randomized controlled trials and observational studies, with supplemental domains of dose-response association, plausible confounding that would decrease the observed effect, and strength of association, as well as separate guidance for applicability.[25] Ratings were based on the following criteria:

- High = Very confident that the estimate of effect lies close to the true effect for the outcome. The body of evidence has few or no deficiencies, the findings are stable, and another study would not change the conclusions.
- Moderate = Moderately confident that the estimate of effect lies close to the true effect for the outcome. The body of evidence has some deficiencies and the findings are likely to be stable, but some doubt remains.
- Low = Limited confidence that the estimate of effect lies close to the true effect for the outcome. The body of evidence has major or numerous deficiencies (or both). Additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
- Insufficient = No evidence, unable to estimate an effect, or no confidence in the estimate of effect for the outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

PEER REVIEW

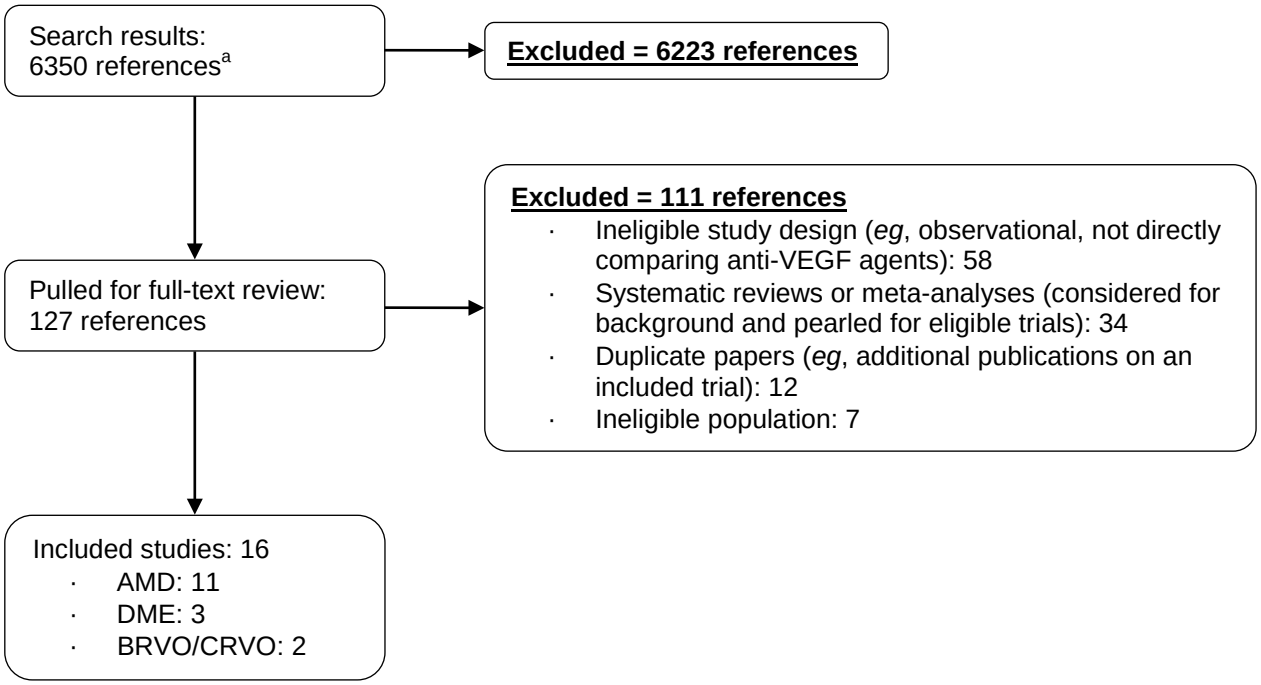
A draft version of this report was reviewed by 6 individuals with technical expertise and clinical leadership. Their comments and our responses are presented in **Appendix C**.

RESULTS

LITERATURE FLOW

Results of the literature search and selection process are summarized in the literature flow diagram (**Figure 1**). The combined literature searches resulted in 6,330 potentially relevant citations and another 20 were identified from the bibliographies of studies and systematic reviews, for a total of 6,350 citations. After reviewing abstracts and titles according to inclusion criteria (**Table 1**), 127 articles were selected for full-text review. After dual review of full-text articles, 16 individual controlled trials reported in 22 publications met inclusion criteria. We received responses to our unpublished data requests from the anti-VEGF drug manufacturers Regeneron and Genentech, but there were no additional comparative trial data that met our inclusion criteria in these materials.

Figure 1. Literature Flow Chart



Abbreviations: AMD = age-related macular degeneration; BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion; DME = diabetic macular edema; VEGF = vascular endothelial growth factor.

[a] 6330 references were identified through database searches (**Appendix A**), and an additional 20 references were identified from the bibliographies of relevant systematic reviews and primary studies

KEY QUESTION 1: What is the comparative clinical effectiveness of anti-VEGF agents for retinal/choroidal neovascularization and/or macular edema in adults?

Overview of Results

We identified 16 trials comparing the clinical effectiveness of anti-VEGF agents (7 with low ROB, 4 with unclear ROB, and 5 with high ROB). The majority (11 trials) examined their effectiveness for choroidal neovascularization secondary to AMD, 3 trials assessed the drugs in patients with DME, and 2 trials included patients with macular edema due to BRVO or CRVO. The majority of studies compared bevacizumab to ranibizumab, but 2 identically-designed trials compared aflibercept to ranibizumab and one study compared all 3 included anti-VEGF drugs. Trials used standard recommended doses of the drugs unless otherwise indicated (aflibercept 2.0 mg; bevacizumab 1.25 mg; ranibizumab 0.5 mg for AMD and BRVO/CRVO, and 0.3 mg for DME).

In patients with AMD, we found consistent, high-strength evidence from 9 randomized controlled trials (RCTs) that bevacizumab and ranibizumab do not differ in mean BCVA improvement at 12 or 24 months. Similarly, no difference was found between drugs in the proportion of patients gaining 15 or more ETDRS letters from baseline, but the estimate at 18 to 24 months was imprecise, leading to a moderate-strength evidence rating. Two trials comparing aflibercept to ranibizumab provide insufficient evidence regarding mean change in BCVA due to conflicting results between the trials, and low-strength evidence of no significant difference between the drugs in the proportion of patients gaining 15 or more letters. No studies compared aflibercept to bevacizumab in AMD patients.

Three trials in patients with DME provide moderate-strength evidence of no difference between bevacizumab and ranibizumab in either mean BCVA change or percentage of patients gaining 15 or more letters at 12 months, and the one trial assessing outcomes at 24 months also found no difference. One large trial provides low-strength evidence of a small benefit with aflibercept over both bevacizumab and ranibizumab in mean BCVA change in patients with DME, particularly in a subgroup of patients with lower baseline BCVA. Significant differences in the proportion of patients gaining 15 or more letters were found between aflibercept and bevacizumab at 12 but not 24 months, and no significant differences were found between aflibercept and ranibizumab for this outcome at either timepoint.

The 2 small trials in patients with BRVO or CRVO found no difference between bevacizumab and ranibizumab in mean BCVA change or proportion of patients gaining 15 or more letters, but the evidence was insufficient to draw firm conclusions due to the small number of patients and a wide confidence interval of the effect estimate.

Trial Characteristics

Treatment arms among the trials ranged in size from 8 patients[26] to 323 patients.[27] The studies were conducted across various countries, including 5 conducted in the US. The majority of trials included patients with a wide range of baseline visual acuity (study means ranging from 34.2 to 68.0 ETDRS letters; mean across studies was 58 letters), from mild vision loss (75 to 90 ETDRS

letters) to severe vision loss (35 to 50 letters).[28] However, the majority of studies included mostly patients with moderate vision loss (55 to 70 letters) at baseline.

Five studies had methodological limitations resulting in high ROB ratings[26,29-32]; ROB was unclear in 4 studies,[33-36] and low in 7 studies[27,37-47] (**Appendix B**). Major limitations included insufficient or unclear methods of randomization or allocation concealment,[26,30-34,36] insufficient blinding,[30,32,36,41,42] and incomplete reporting of outcome data (including unclear loss to follow-up reporting, lack of intention-to-treat [ITT] analyses, and poor reporting of harms).[26,27,30-35,37,38]

Detailed Results

Choroidal Neovascularization Secondary to Age-Related Macular Degeneration (AMD)

Eleven trials comparing anti-VEGF agents for AMD met inclusion criteria, including 6 studies with low ROB, 3 studies with unclear ROB, and 2 studies with high ROB. The trials most commonly compared bevacizumab to ranibizumab, but 2 studies compared ranibizumab to aflibercept. The majority of studies included patients in their late 70s and had mean baseline BCVAs between 55 and 60 ETDRS letters. Treatment schedules varied significantly between studies, although most studies used variations of *pro re nata* (PRN, "as needed") dosing (either from the outset or after 3 monthly loading doses; detailed dosing schedules for each trial are reported in **Appendix D**). Eight of the studies enrolled at least 300 patients, with 3 including over 1000 patients (CATT, N=1208; VIEW 1, N=1217; VIEW 2, N=1240). Study details are found in **Table 2** (additional study information is provided in **Appendix D**).

Aflibercept versus Ranibizumab

Two large collaborative studies (VIEW 1 and VIEW 2)[43] with low ROB compared aflibercept to ranibizumab in patients with AMD. The studies had equivalent designs but VIEW 1 (N=1217) was conducted in the US and Canada, and VIEW 2 (N=1240) was conducted in several European, Middle Eastern, Asian-Pacific, and Latin American countries. While the study compared 3 different dosages of aflibercept (2.0 mg monthly, 0.5 mg monthly, and 2.0 mg every other month after 3 monthly doses) with monthly ranibizumab, we focused on the results using the standard dose of aflibercept (2.0 mg) administered monthly, for comparability to the ranibizumab arm and other studies.

Visual Outcomes. The VIEW 1 trial found a small, statistically significant difference in favor of monthly aflibercept compared to monthly ranibizumab in mean change in BCVA at 12 months (LS mean difference 3.15 letters [95% CI, 0.92 to 5.37], $P = .0054$), while VIEW 2 conversely found a small benefit with monthly ranibizumab, though the difference did not reach statistical significance (LS mean difference -1.95 [95% CI, -4.10 to 0.20], $P = .076$). Interestingly, VIEW 2 also reported that aflibercept administered every other month had a numerically higher mean BCVA change than monthly aflibercept (8.9 vs 7.6 letters, *P*-value not reported), although the reason and significance of this finding is uncertain. Due to inconsistent results between the trials, a meta-analysis combining the 2 studies found considerable statistical heterogeneity ($I^2 = 90.4\%$) despite their equivalent protocols. The studies were conducted in different countries, but the reasons for the conflicting findings are otherwise unclear.

Similar results were found in the percentage of participants gaining 15 or more ETDRS letters from baseline to 12 months, with VIEW 1 showing a slight advantage in favor of aflibercept and

VIEW 2 in favor of ranibizumab, although neither study found a significant difference between the drugs (VIEW 1: *P* = .1042; VIEW 2: *P* = .229). The vast majority of participants in all groups did not lose more than 15 letters (~95% at 12 months and ~92% at 22 months), and approximately 80% of participants either improved or maintained their BCVA (gained 0 or more letters) at 12 months. An analysis combining both studies at 22 months[44] found a slight decline in visual acuity from 12 months, possibly as a result of switching from monthly injections to PRN, but there was no difference between aflibercept and ranibizumab in mean change in BCVA (mean difference 0.20 letters [95% CI, -1.55 to 1.95]) or in percentage of patients gaining 15 or more letters (31.2% for aflibercept monthly vs 31.6% for ranibizumab monthly). VIEW 1 and VIEW 2, as well as the combined 22-month results, found no significant differences in visual acuity between groups receiving bimonthly aflibercept and those receiving monthly ranibizumab.

Quality of Life Outcomes. In terms of vision-related quality of life, both VIEW 1 and VIEW 2 reported improved scores on the 25-item National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25) among all groups. VIEW 2 found a statistically significant advantage for monthly ranibizumab over monthly aflibercept (LS mean difference -2.79 [95% CI, -4.90 to -0.68], *P* = .0097), but VIEW 1 found no significant difference between the drugs (LS mean difference 1.28 in favor of aflibercept [95% CI, -0.73 to 3.28], *P* = .2090).

Anatomic Outcomes. Both studies reported a significant decrease from baseline in central retinal thickness at both 12 and 22 months (> 110 μm for all groups in both studies), although statistical comparisons between groups were not reported.

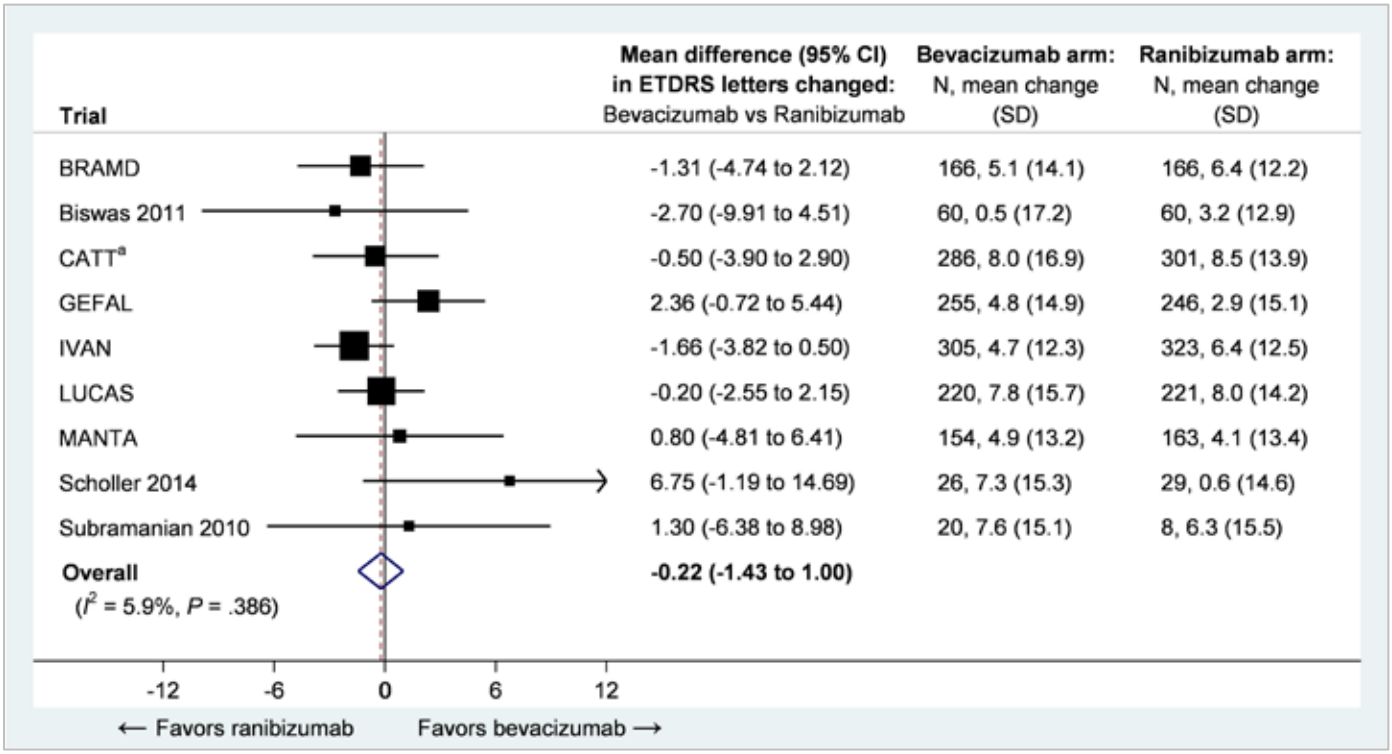
Bevacizumab vs Ranibizumab

Nine trials (combined N=3630) compared bevacizumab to ranibizumab in patients with AMD (4 with low ROB,[27,37-39,41,42,45] 3 with unclear ROB,[33-35]and 2 with high ROB[26,29]). Six of the studies included over 300 participants, and all but one trial[45] used PRN scheduling alone (although specific re-treatment criteria varied) or in addition to groups receiving monthly injections. Most trials followed patients for 12 months, although 3 studies had 24 months of follow-up[37,38,40,42] and one study had 18 months of follow-up.[33] All trials had a mean baseline BCVA between 55 and 62 ETDRS letters with the exception of one very small study (N=28),[26] which included patients with substantially lower baseline visual acuity (mean 34.2 letters).

Visual Outcomes. No individual study comparing bevacizumab with ranibizumab found a significant difference between drugs in mean change in BCVA. Meta-analyses pooling the results of the trials also found no differences between the drugs at 12 months (pooled mean difference -0.218 letters in favor of ranibizumab [95% CI, -1.431 to 0.995], *P* = .725; **Figure 2**), or at 18 to 24 months (-0.126 letters [95% CI, -1.033 to 0.781], *P* = .785; **Figure 3**).

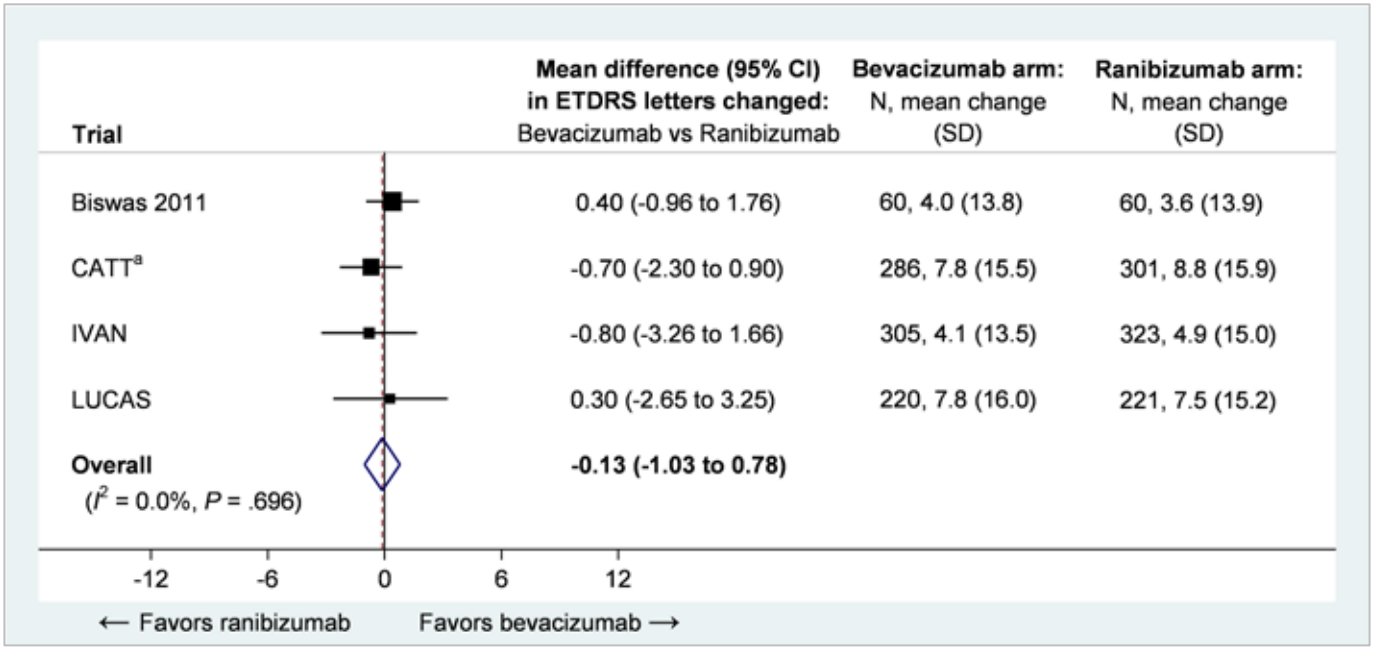
The proportion of patients gaining 15 or more ETDRS letters from baseline varied considerably across the trials, ranging from 12% to 34%. A slightly greater proportion of patients treated with ranibizumab compared to bevacizumab achieved this outcome at 12 months (RR 0.930 [95% CI, 0.804 to 1.075], *P* = .325; **Figure 4**) and at 18 to 24 months (RR 0.835 [95% CI, 0.630 to 1.107], *P* = .210; **Figure 5**), but the differences did not reach statistical significance at either timepoint. The majority of patients in all trials were able to either improve or maintain their vision (within 5 ETDRS letters) throughout the trial (66% to 92%).

Figure 2. Mean change in BCVA at 12 months in AMD patients treated with bevacizumab vs ranibizumab



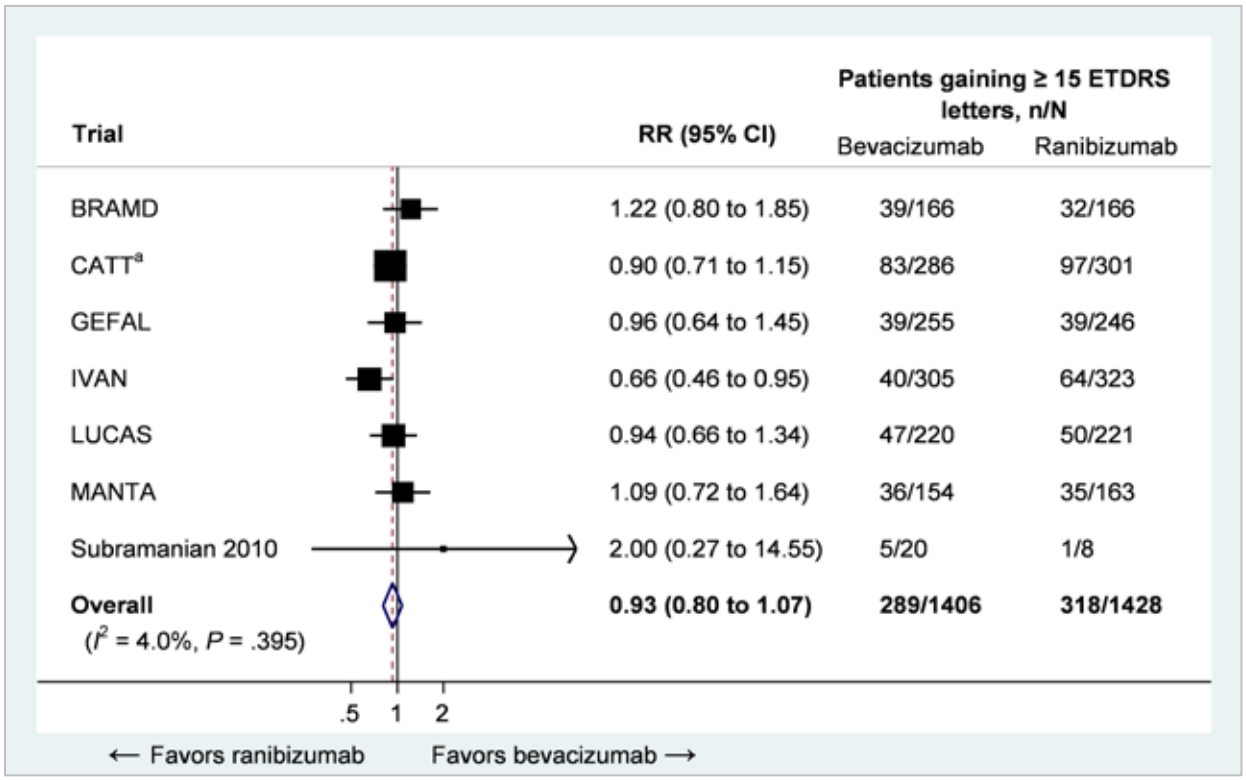
[a] Numbers reported for CATT are from the group randomized to monthly injections only.

Figure 3. Mean change in BCVA at 18-24 months in AMD patients treated with bevacizumab vs ranibizumab



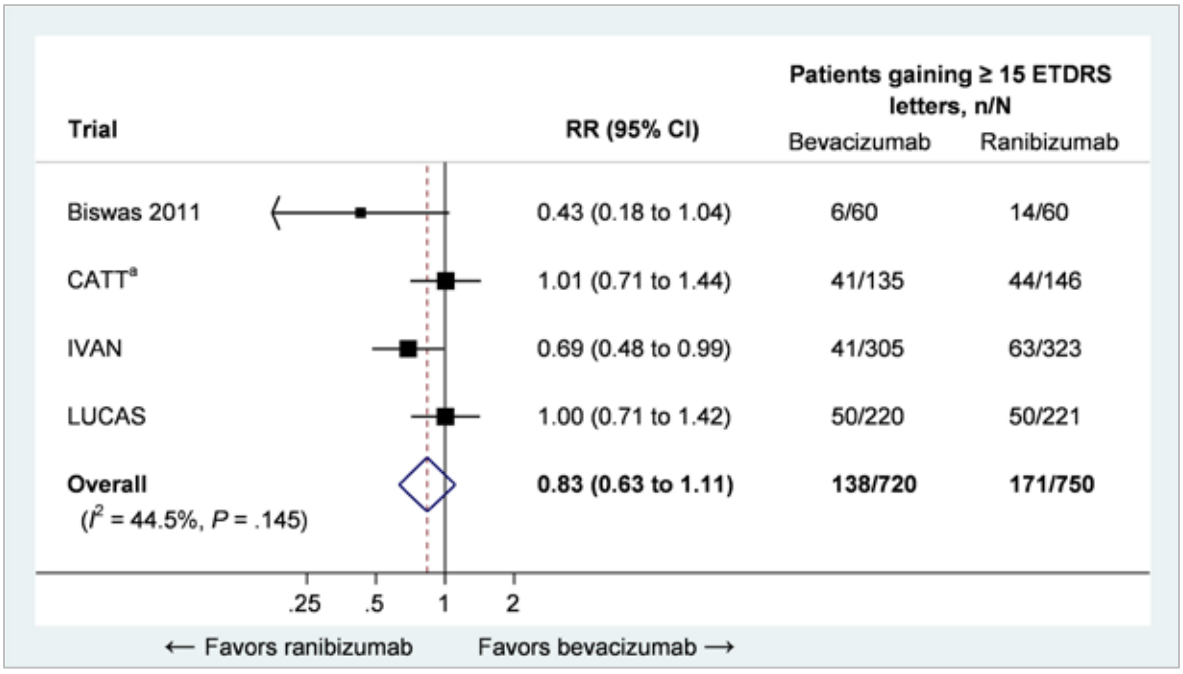
[a] Numbers reported for CATT are from the group randomized to monthly injections only.

Figure 4. Likelihood of gaining 15 or more letters at 12 months in AMD patients treated with bevacizumab vs ranibizumab



[a] Numbers reported are from the group randomized to monthly injections only.

Figure 5. Likelihood of gaining 15 or more letters at 18-24 months in AMD patients treated with bevacizumab vs ranibizumab



[a] Numbers reported are from the group randomized to monthly injections only.

The largest trial (low ROB) was the Comparison of AMD Treatments Trials (CATT),[41,42] which randomized 1208 participants to either bevacizumab or ranibizumab administered either monthly or PRN. Groups remained on the allocated drug for the entire 24-month period, but groups originally randomized to monthly regimens were re-randomized at 12 months to either continue receiving monthly injections or switch to PRN dosing. At 24 months, there was no statistically significant difference in mean change in BCVA between the drugs ($P = .21$; $P = .41$ after adjusting for baseline predictors in the multivariate longitudinal regression model), but the monthly injection regimen was superior to PRN dosing ($P = .046$; $P = .07$ in the multivariate longitudinal regression model). In fact, patients who switched from receiving monthly injections in the first year to receiving injections as needed lost a mean of 2.2 letters in the second year of the trial. All groups achieved a mean BCVA of over 66 ETDRS letters at both 12 and 24 months, and over 60% of all groups achieved a BCVA of 68 or more letters at 24 months.

Four other relatively large studies (IVAN, N=628; LUCAS, N=441; BRAMD, N=327; MANTA, N=321) with low ROB similarly found no significant difference between drugs in mean change in BCVA from baseline.[27,35,37-40,45] The IVAN trial reported that 16% of patients receiving bevacizumab and 24% receiving ranibizumab gained 15 or more ETDRS letters from baseline; however, statistical significance testing was not reported. The other 3 studies reported 21% to 27% of participants gaining 15 or more letters, with no significant differences found between groups. The LUCAS, IVAN, and BRAMD trials reported mean BCVA at 12 months in the range of 65 to 70 ETDRS letters, while MANTA reported a slightly lower achieved mean BCVA (61.4 letters). The 2 trials assessing longer-term outcomes reported a similar achieved BCVA at 24 months (66 to 68 letters).

Quality of Life Outcomes. IVAN was the only trial reporting quality of life outcomes, and it found no difference between groups in general health-related quality of life (European Quality of Life-5 Dimensions [EQ-5D], $P = .51$) or macular degeneration-related quality of life (Macular Disease-dependent Quality of Life [MacDQoL], $P = .74$). Treatment satisfaction was also similar between groups (Macular Disease Treatment Satisfaction Questionnaire [MacTSQ], $P = .23$).

Anatomic Outcomes. Reporting of anatomic outcomes varied significantly, so it is difficult to summarize findings across studies. However, most studies found a significant decrease from baseline in central foveal, retinal, or subfield thickness. No study reported significant differences between drugs.

Differences between drugs were reported in several trials regarding the percentage of patients with no fluid present on OCT imaging. Several studies found ranibizumab statistically superior to bevacizumab for this outcome, including CATT (45.5% vs 30.2% at 24 months, $P = .0003$), LUCAS (55.1% vs 72.1% at 24 months, $P < .001$), and BRAMD (44% vs 59% at 12 months, $P = .020$); the other 2 studies reporting this outcome found no significant differences between the drugs (GEFAL, $P = .14$; IVAN, $P = .065$).

Table 2. Effectiveness of Anti-VEGF Agents for Choroidal Neovascularization Secondary to AMD

Study name; Author year · **Population** · **Number randomized** · **Length of follow-up** · **Population characteristics: mean age, % male, mean baseline BCVA**	**Interventions Groups (number per group)** · **Treatment schedule**	**Main Outcomes:** · **Visual acuity (reported as ETDRS chart letters unless otherwise indicated)** · **Quality of life (QOL) measures** · **Anatomic outcomes (reported in µm unless otherwise indicated)**	**Notes** · **ROB** · **Other notes**
Aflibercept vs Ranibizumab			
VIEW 1 (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD Trial 1); Heier 2012[43] · Active subfoveal CNV lesions or juxtafoveal lesions with leakage affecting the fovea, secondary to AMD. · 1217 (1210 analyzed) · 12 months (22 month results combined with VIEW 2 and reported separately) · 78 years (SD 8.0), 41.2% male, 55.1 letters (SD 13.1)	Group 1: Aflibercept 2.0 mg monthly (n=304) Group 2: Aflibercept 0.5 mg[a] monthly (n=304) Group 3: Aflibercept 2.0 mg every other month (after 3 initial monthly doses; n=303) Group 4: Ranibizumab 0.5 mg monthly (n=306) · Schedule: Patients were seen every 4 weeks and given either active treatment or a sham injection depending on randomization group (*ie*, Group 3 received sham every other visit).	**Aflibercept 2 mg monthly vs Aflibercept 0.5 mg[a] monthly vs Aflibercept 2 mg bimonthly vs Ranibizumab 0.5 mg monthly** *Visual acuity outcomes:* · BCVA, mean change at 12 months: 10.9 (SD 13.8) vs 6.9 (SD 13.4) vs 7.9 (SD 15.0) vs 8.1 (SD 15.3); LS mean difference: § Group 1 vs Group 4: 3.15 (95% CI, 0.92 to 5.37), *P*=.0054 § Group 2 vs Group 4: -0.80 (95% CI, -3.03 to 1.43), *P*=.4793 § Group 3 vs Group 4: 0.26 (95% CI, -1.97 to 2.49), *P*=.8179 · % of participants gaining ≥15 letters at 12 months: 37.5% vs 24.9% vs 30.6% vs 30.9%; LS mean difference: § Group 1 vs Group 4: 6.58 (95% CI, -0.98 to 14.14), *P*=.1042 § Group 2 vs Group 4: -6.00 (95% CI, -13.17 to 1.16), *P*=.1037 § Group 3 vs Group 4: -0.36 (95% CI, -7.74 to 7.03), *P*=.93 · % with BCVA of 20/40 (Snellen chart) or better at 12 months: 45.7% vs 34.9% vs 37.9% vs 34.5%; *P*=NR *QOL outcomes:* · NEI VFQ-25 score, mean change at 12 months: 6.7 (SD 13.5) vs 4.5 (SD 11.9) vs 5.1 (SD 14.7) vs 4.9 (SD 14.0); LS mean difference: § Group 1 vs Group 4: 1.28 (95% CI, -0.73 to 3.28), *P*=.2090 § Group 2 vs Group 4: -0.67 (95% CI, -2.69 to 1.35), *P*=.5128 § Group 3 vs Group 4: -0.60 (95% CI, -2.61 to 1.42), *P*=.5579 *Anatomic outcomes:* · CRT, mean change at 12 months: -116.5 (SD 98.4) vs -115.6 (SD 104.1) vs -128.5 (SD 108.5) vs -116.8 (SD 109.0); *P*=NR · Cystic intraretinal edema and subretinal fluid absent on OCT ("dry retina"):[b] 64.8% vs 56.7% vs 63.4% vs 63.6%; *P*=NR	· Low ROB · Non-inferiority study.

Study name; Author year · **Population** · **Number randomized** · **Length of follow-up** · **Population characteristics: mean age, % male, mean baseline BCVA**	**Interventions Groups (number per group)** · **Treatment schedule**	**Main Outcomes:** · **Visual acuity (reported as ETDRS chart letters unless otherwise indicated)** · **Quality of life (QOL) measures** · **Anatomic outcomes (reported in µm unless otherwise indicated)**	**Notes** · **ROB** · **Other notes**
VIEW 2 (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD Trial 2); Heier 2012[43] · Active subfoveal CNV lesions or juxtafoveal lesions with leakage affecting the fovea, secondary to AMD. · 1240 (1202 analyzed) · 12 months (22 month results combined with VIEW 1 and reported separately) · 73.9 years (SD 8.7), 44.5% male, 52.4 letters (SD 13.9)	Group 1: Aflibercept 2.0 mg monthly (n=313) Group 2: Aflibercept 0.5 mg[a] monthly (n=311) Group 3: Aflibercept 2.0 mg every other month (after 3 initial monthly doses; n=313) Group 4: Ranibizumab 0.5 mg monthly (n=303) · Schedule: Patients were seen every 4 weeks and given either active treatment or a sham injection depending on randomization group (*ie*, Group 3 received sham every other visit).	**Aflibercept 2 mg monthly vs Aflibercept 0.5 mg[a] monthly vs Aflibercept 2 mg bimonthly vs Ranibizumab 0.5 mg monthly** *Visual acuity outcomes:* · BCVA, mean change at 12 months: 7.6 (SD 12.6) vs 9.7 (SD 14.1) vs 8.9 (SD 14.4) vs 9.4 (SD 13.5); LS mean difference: § Group 1 vs Group 4: -1.95 (95% CI, -4.10 to 0.20), *P*=.076 § Group 2 vs Group 4: -0.06 (95% CI, -2.24 to 2.12), *P*=.955 § Group 3 vs Group 4: -0.90 (95% CI, -3.06 to 1.26), *P*=.4131 · % of participants gaining ≥15 letters at 12 months: 29.4% vs 34.8% vs 31.4% vs 34.0%; LS mean difference: § Group 1 vs Group 4: -4.57 (95% CI, -12.02 to 2.88), *P*=.229 § Group 2 vs Group 4: 0.78 (95% CI, -6.91 to 8.46), *P*=.843 § Group 3 vs Group 4: -2.65 (95% CI, -10.18 to 4.88), *P*=.490 · % with BCVA of 20/40 (Snellen chart) or better at 12 months: 32.7% vs 32.4% vs 27.5% vs 35.7%; *P*=NR *QOL outcomes:* · NEI VFQ-25 score, mean change at 12 months: 4.5 (SD 15.0) vs 5.1 (SD 13.7) vs 4.9 (SD 14.7) vs 6.3 (SD 14.8); LS mean difference: § Group 1 vs Group 4: -2.79 (95% CI, -4.90 to -0.68), *P*=.0097 § Group 2 vs Group 4: -0.93 (95% CI, -3.07 to 1.20), *P*=.3917 § Group 3 vs Group 4: -1.95 (95% CI, -4.07 to 0.17), *P*=.0717 *Anatomic outcomes:* · CRT, mean change at 12 months: -156.8 (SD 122.8) vs -129.8 (SD 114.8) vs -149.2 (SD 119.7) vs -138.5 (SD 122.2); *P*=NR · Cystic intraretinal edema and subretinal fluid absent on OCT ("dry retina"):[b] 80.3% vs 63.9% vs 71.9% vs 60.4%; *P*=NR	· Low ROB · Non-inferiority study.
VIEW 1 and VIEW 2 combined 22-month results; Schmidt-Erfurth 2014[44] · Active subfoveal CNV lesions or juxtafoveal lesions with leakage affecting the fovea, secondary to AMD · 2457 (2412 analyzed) · 22 months (96 weeks)	Group 1: Aflibercept 2.0 mg monthly for 12 months, capped PRN months 12-22 (n=617) Group 2: Aflibercept 0.5 mg[a] monthly for 12 months, capped PRN months 12-22 (n=615) Group 3: Aflibercept 2.0 mg every	**Aflibercept 2 mg monthly vs Aflibercept 0.5 mg[a] monthly vs Aflibercept 2 mg bimonthly vs Ranibizumab 0.5 mg monthly** *Visual acuity outcomes:* · BCVA, mean change at 22 months: 7.6 vs 6.6 vs 7.6 vs 7.9; LS mean difference (confidence intervals estimated from a graph): § Group 1 vs Group 4: -0.2 (95% CI, -2.0 to 1.6) § Group 2 vs Group 4: -1.28 (95% CI, -3.0 to 0.4)	· Low ROB for both VIEW 1 and VIEW 2

Study name; Author year · **Population** · **Number randomized** · **Length of follow-up** · **Population characteristics: mean age, % male, mean baseline BCVA**	**Interventions Groups (number per group)** · **Treatment schedule**	**Main Outcomes:** · **Visual acuity (reported as ETDRS chart letters unless otherwise indicated)** · **Quality of life (QOL) measures** · **Anatomic outcomes (reported in µm unless otherwise indicated)**	**Notes** · **ROB** · **Other notes**
· 75.9 years (SD 8.6), 42.8% male, 53.8 letters (SD 13.6)	other month (after 3 initial monthly doses) for 12 months, capped PRN months 12-22 (n=616) Group 4: Ranibizumab 0.5 mg monthly for 12 months, capped PRN months 12-22 (n=609) · Schedule: During follow-up period from 12 to 22 months, patients continued to receive the same dose of study drugs as in the first 12 months, but received injections at least every 12 weeks (capped PRN).	§ Group 3 vs Group 4: -0.25 (95% CI, -2.0 to 1.5) · % of participants gaining ≥15 letters at 22 months: 31.2% vs 28.1% vs 33.4% vs 31.6% · % with BCVA of 20/40 (Snellen chart) or better at 22 months: 34.9% vs 30.7% vs 33.8% vs 34.5%; *P*=NR *Anatomic outcomes:* · CRT, mean change at 22 months: -128 vs -113 vs -133 vs -128; *P*=NR · Retinal fluid absent on OCT at 22 months: 54.4% vs 44.6% vs 50.1% vs 45.5%	
Bevacizumab vs Ranibizumab			
Biswas 2011[33] · Choroidal neovascular membrane secondary to AMD; occult CNV 44% · 120 (104 analyzed) · 18 months · 63.9 years (SD NR), 48% male, 57.5 letters (SD NR)	Group 1: Bevacizumab 1.25 mg (n=60) Group 2: Ranibizumab 0.5 mg (n=60) · Schedule: Both groups injected monthly for 3 months, then PRN.	**Bevacizumab vs Ranibizumab** *Visual acuity outcomes:* · BCVA, mean change: § 12 months: 0.52 vs 3.22; *P*=.463 § 18 months: 3.96 vs 3.56; *P*=.563 · % of participants gaining ≥15 letters at 18 months: 12% vs 26%; *P*=NR *Anatomic outcomes:* · CMT, mean change: § 12 months: -26.44 vs -27.59; *P*=.283 § 18 months: -37.96 vs -44.70; *P*=.281 Subgroup analyses found that mean BCVA change at 18 months was greater in the predominately classic subgroup than the group as a whole (5.4 vs 4.0 bevacizumab group; 5.2 vs 3.6 ranibizumab group).	· Unclear ROB
BRAMD (Bevacizumab to Ranibizumab in Patients with Exudative Age-Related Macular Degeneration); Schauwvlieghe 2016[45] · Primary or recurrent sub- or	Group 1: Bevacizumab 1.25 mg (n=166) Group 2: Ranibizumab 0.5 mg (n=166) · Schedule: Both groups injected	**Bevacizumab vs Ranibizumab** *Visual acuity outcomes:* · BCVA, mean change at 12 months: 5.1 (SD 14.1) vs 6.4 (SD 12.2); *P*=.37 · % of participants gaining ≥15 letters at 12 months: 24% vs 19%	· Low ROB · Non-inferiority study.

Study name; Author year · **Population** · **Number randomized** · **Length of follow-up** · **Population characteristics: mean age, % male, mean baseline BCVA**	**Interventions Groups (number per group)** · **Treatment schedule**	**Main Outcomes:** · **Visual acuity (reported as ETDRS chart letters unless otherwise indicated)** · **Quality of life (QOL) measures** · **Anatomic outcomes (reported in µm unless otherwise indicated)**	**Notes** · **ROB** · **Other notes**
juxtafoveal CNV secondary to AMD · 332 (327 analyzed) · 12 months · 78 years (SD 7), 44% male, 60 letters (SD 13)	monthly.	*Anatomic outcomes:* · CRT, mean change at 12 months: -131 (SD 129) vs -138 (SD 117); *P*=.31 · Subretinal fluid and intraretinal cysts absent on OCT at 12 months: 44% vs 59%; *P*=.020	
CATT (Comparison of AMD Treatments Trials); Martin 2012[41,42] · Previously untreated active CNV due to AMD · 1208[c] (1105 analyzed at 12 months, 1030 analyzed at 24 months) · 24 months · 79.2 years (SD 7.5), 38.2% male, 60.6 letters (SD 13.5)	Group 1: Bevacizumab 1.25 mg monthly* (n=286) Group 2: Ranibizumab 0.5 mg monthly* (n=301) Group 3: Bevacizumab 1.25 mg PRN (n=300) Group 4: Ranibizumab 0.5 mg PRN (n=298) · Schedule: Monthly regimens were given an injection every 28 days; PRN regimens were given one initial injection and then only when signs of active neovascularization were present. *Patients in the monthly groups were re-randomized at 12 months to either continue with monthly injections or switch to PRN (study drug not changed).	**Bevacizumab monthly vs Ranibizumab monthly vs Bevacizumab PRN vs Ranibizumab PRN** *Visual acuity outcomes:* · BCVA, mean change: § 12 months: 8.0 (SD 15.8) vs 8.5 (SD 14.1) vs 5.9 (SD 15.7) vs 6.8 (SD 13.1); *P*=.16 - Estimated mean change (longitudinal regression model): 7.3 (SE 0.8) vs 7.2 (SE 0.7) vs 6.1 (SE 0.7) vs 6.4 (SE 0.6); *P*=.53 § 24 months:[d] 7.8 (SD 15.5) vs 8.8 (SD 15.9) vs 5.0 (SD 17.9) vs 6.7 (SD 14.6); *P*=.21 between drugs - Estimated mean change (longitudinal regression model): 0.7 letters in favor of ranibizumab (95% CI, -0.9 to 2.3), *P*=.41 · % of participants gaining ≥15 letters: § 12 months: 31.3% vs 34.2% vs 28.0% vs 24.9%; *P*=.09 § 24 months:[d] 31.8% vs 32.8% vs 28.3% vs 30.7%; *P*=NR · % of participants achieving Snellen equivalent of 20/40 or better (ETDRS >68 letters) at 24 months: 60.5% vs 67.9% vs 62.1% vs 63.3% *Anatomic outcomes:* · Total foveal thickness, mean change: § 12 months: -164 (SD 181) vs -196 (SD 176) vs -152 (SD 178) vs -168 (SD 186); *P*=.03 between all groups § 24 months:[d] -180 (SD 196) vs -190 (SD 172) vs -153 (SD 189) vs -166 (SD 190); *P*=.38 between drugs · Fluid absent on OCT: § 12 months: 26.0% vs 43.7% vs 19.2% vs 23.9%; *P*<.001 § 24 months:[d] 30.2% vs 45.5% vs 13.9% vs 22.3%; *P*=.0003 between drugs	· Low ROB · Re-randomization: At 12 months, patients initially assigned to monthly treatment retained their drug assignment but were reassigned randomly to either monthly or PRN (results only recorded here for patients treated with the same dosing regimen for 2 years).

Study name; Author year · **Population** · **Number randomized** · **Length of follow-up** · **Population characteristics: mean age, % male, mean baseline BCVA**	**Interventions Groups (number per group)** · **Treatment schedule**	**Main Outcomes:** · **Visual acuity (reported as ETDRS chart letters unless otherwise indicated)** · **Quality of life (QOL) measures** · **Anatomic outcomes (reported in µm unless otherwise indicated)**	**Notes** · **ROB** · **Other notes**
GEFAL (French Study Group Avastin versus Lucentis for Neovascular AMD trial); Kodjikian 2013[34] · Active subfoveal neovascular AMD · 501 (404 analyzed) · 12 months · 79.2 years (SD 7.1), 33.7% male, 55.2 letters (SD 14.0)	Group 1: Bevacizumab 1.25 mg (n=255) Group 2: Ranibizumab 0.5 mg (n=246) · Schedule: Both groups injected monthly for 3 months, then PRN.	**Bevacizumab vs Ranibizumab** *Visual acuity outcomes:* · BCVA, mean change at 12 months: 4.82 (SD 14.85) vs 2.93 (SD 15.09); mean difference -1.89 letters (95% CI, -1.16 to 4.9) · % of participants gaining ≥15 letters at 12 months: 20.4% vs 21.3%; *P*=.8318 *Anatomic outcomes:* · CST, mean change at 12 months: -94.96 (SD 132.78) vs -107.23 (SD 103.25); *P*=.2725 · Intraretinal and subretinal fluid absent on OCT at 12 months: 50.5% vs 58.2%; *P*=.14	· Unclear ROB · Non-inferiority study.
IVAN (Inhibition of VEGF in Age-related choroidal Neovascularisation trial); Chakravarthy 2013[27,37,38] · Active previously untreated neovascular AMD with neovascular lesion involving the center of the fovea · 628 (610 analyzed) · 24 months · 77.7 years (SD 7.4), 40% male, 61.4 letters (SD 15.3)	Group 1: Bevacizumab 1.25 mg monthly or PRN (n=305)[e] Group 2: Ranibizumab 0.5 mg monthly or PRN (n=323) · Schedule: All groups received injections monthly for 3 months, then received injections according to their allocation group (monthly or PRN).	**Bevacizumab vs Ranibizumab** *Visual acuity outcomes:* · BCVA, mean change: § 12 months: 4.7 (SD 12.5) vs 6.4 (SD 12.8); weighted mean difference -1.66 (95% CI, -3.83 to 0.50) § 24 months: 4.1 (SD 13.5) vs 4.9 (SD 15.0); weighted mean difference -0.80 (95% CI, -3.26 to 1.66) · % of participants gaining ≥15 letters: § 12 months: 16% vs 23%; *P*=NR § 24 months: 16% vs 24%; *P*=NR · Bailey-Love Near Word Visual acuity, mean at 24 months (logMAR): 0.61 vs 0.55; GMR 0.94 (95% CI, 0.85 to 1.04), *P*=.23 · Belfast Reading Speed, median at 24 months: 52.5 vs 50.9; mean difference -1.34 (95% CI, -8.29 to 5.61), *P*=.70 · Pelli-Robson Contrast Sensitivity, mean change at 24 months: 1.7 vs 1.5; mean difference 0.21 (95% CI, -0.62 to 1.04), *P*=.62 *QOL outcomes:* · EQ-5D Utility Index, median change at 24 months: -0.15 (IQR -0.27 to 0.00) vs -0.15 (IQR -0.27 to 0.00); score of 1 (“perfect health”) OR 0.89 (95% CI, 0.64 to 1.25), *P*=.51 · MacDQoL, median at 24 months: -1.39 (IQR -2.73 to -0.41) vs -1.45 (IQR -2.77 to -0.27); GMR 1.05 (95% CI, 0.78 to 1.42), *P*=.74	· Low ROB

Study name; Author year · **Population** · **Number randomized** · **Length of follow-up** · **Population characteristics: mean age, % male, mean baseline BCVA**	**Interventions Groups (number per group)** · **Treatment schedule**	**Main Outcomes:** · **Visual acuity (reported as ETDRS chart letters unless otherwise indicated)** · **Quality of life (QOL) measures** · **Anatomic outcomes (reported in µm unless otherwise indicated)**	**Notes** · **ROB** · **Other notes**
		· MacTSQ treatment satisfaction index, median at 24 months: 65.00 (IQR 60.00 to 69.00) vs 66.00 (IQR 61.50 to 70.00); OR 0.79 (95% CI, 0.54 to 1.16), *P*=.23 *Anatomic outcomes:* · Total foveal thickness, mean change at 24 months: -133.8 (SD 205.0) vs -146.9 (SD 177.4); GMR 0.96 (95% CI, 0.90 to 1.03), *P*=.24 · Fluid absent on OCT at 24 months: 41% vs 50%; OR 0.72 (95% CI, 0.50 to 1.02), *P*=.065 Subgroup analyses[f] found no significant differences for the drug or treatment regimen comparisons (*P*≥.26).	
LUCAS (Lucentis Compared to Avastin Study); Berg 2015[39,40] · Previously untreated active neovascular AMD · 441 (431 analyzed) · 24 months · 78.3 years (SD 7.9), 32.5% male, 61.0 letters (SD 13.5)	Group 1: Bevacizumab 1.25 mg (n=220)[g] Group 2: Ranibizumab 0.5 mg (n=221)[g] · Schedule: "Treat-and-extend" - patients in both groups were injected every 4 weeks until no signs of active AMD were found, at which point the period to the next treatment was extended by 2 weeks at a time, up to a maximum interval of 12 weeks. If examination showed any sign of recurrence, the interval was shortened by 2 weeks at a time, until the disease was considered to be inactive. Interval extension was then restarted, with the maximum final interval being 2 weeks less than the period when the previous recurrence.	**Bevacizumab vs Ranibizumab** *Visual acuity outcomes:* · BCVA, mean change (ITT analysis): § 12 months: 7.8 vs 8.0; mean difference 0.2 (95% CI, -2.2 to 2.5), *P*=.550 § 24 months: 7.8 vs 7.5; mean difference -0.3 (95% CI, -3.2 to 2.7), *P*=.873 · % of participants gaining ≥15 letters: § 12 months: 25.5% vs 26.7%; *P*=NR § 24 months: 29.9% vs 29.1%; *P*=NR *Anatomic outcomes:* · CRT plus subfoveal fluid, mean change (ITT analysis): § 12 months: -108 (SD 102) vs -111 (SD 96); mean difference 3 (95% CI, -16 to 22), *P*=.265 § 24 months: -111 (SD 116) vs -112 (SD 105); mean difference 1 (95% CI , -22 to 20), *P*=.923 · Fluid absent on OCT (intraretinal or subretinal): § 12 months: 47.0% vs 65.2%; *P*<.001 § 24 months: 55.1% vs 72.1%; *P*<.001	· Low ROB · Non-inferiority study.
MANTA (Multicenter Anti-VEFG Trial in Austria); Krebs 2013[35] · Active primary or recurrent subfoveal	Group 1: Bevacizumab 1.25 mg (n=154) Group 2: Ranibizumab 0.5 mg	**Bevacizumab vs Ranibizumab** *Visual acuity outcomes:* · BCVA, mean change at 12 months: 4.9 vs 4.1; *P*=.78	· Unclear ROB · Non-inferiority study.

Study name; Author year · **Population** · **Number randomized** · **Length of follow-up** · **Population characteristics: mean age, % male, mean baseline BCVA**	**Interventions Groups (number per group)** · **Treatment schedule**	**Main Outcomes:** · **Visual acuity (reported as ETDRS chart letters unless otherwise indicated)** · **Quality of life (QOL) measures** · **Anatomic outcomes (reported in µm unless otherwise indicated)**	**Notes** · **ROB** · **Other notes**
lesion with CNV secondary to AMD · 317 (number analyzed unclear) · 12 months · 77.2 years (SD 8.0), 36.3% male, 56.7 letters (SD 13.3)	(n=163) · Schedule: Both groups injected monthly for 3 months, then PRN.	· % of participants gaining ≥15 letters:[h] 23% vs 21%; *P*=.42 *Anatomic outcomes:* · CRT, mean change at 12 months:[i] -86.3 vs -89.9; *P*=.81	
Scholler 2014[29] · Active previously untreated neovascular AMD · 55 (number analyzed unclear) · 12 months · 80.1 years (SD 6.7), 29.1% male, 58.0 letters (SD 11.7)	Group 1: Bevacizumab 1.25 mg (n=29) Group 2: Ranibizumab 0.5 mg (n=26) · Schedule: Both groups injected monthly for 3 months, then PRN.	**Bevacizumab vs Ranibizumab** *Visual acuity outcomes:* · BCVA, mean change[j] at 12 months: 7.3 (SD 15.3) vs 0.6 (SD 14.6); mean difference in BCVA achieved 5.5 letters, *P*=.631 *Anatomic outcomes:* · Mean CRT at 12 months: 350.47 (SD 102.84) vs 315.67 (SD 65.86); *P*=.088	· High ROB
Subramanian 2010[26] · Symptomatic CNV affecting the foveal center; 18% classic or predominantly classic CNV · 28 (22 analyzed) · 12 months · 78.6 years, 95% male, 34.2 letters	Group 1: Bevacizumab (dose NR; n=20) Group 2: Ranibizumab (dose NR; n=8) · Schedule: Both groups injected monthly for 3 months, then PRN	**Bevacizumab vs Ranibizumab** *Visual acuity outcomes:* · BCVA, mean change at 12 months:[k] 7.6 vs 6.3; *P*=.74 · % of participants gaining ≥15 letters: 33% vs 14%; *P*=NR *Anatomic outcomes:* · CMT, mean change at 12 months: -50 vs -91; *P*=.29	· High ROB · VA population

Abbreviations: AMD = age-related macular degeneration; BCVA = best-corrected visual acuity; CI = confidence interval; CNV = choroidal neovascularization; CRT = central retinal thickness; CST = central subfield thickness; DME = diabetic macular edema; EQ-5D = European Quality of Life-5 Dimensions; ETDRS = Early Treatment of Diabetic Retinopathy Study; GMR = geometric mean ratio; IQR = interquartile range; ITT = intention-to-treat; logMAR = Logarithm of the Minimal Angle of Resolution; LS = least squares; MacDQoL = Macular Disease-dependent Quality of Life; MacTSQ = Macular Disease Treatment Satisfaction Questionnaire; NEI VFQ-25 = 25-item National Eye Institute Visual Functioning Questionnaire; NR = not reported; OCT = optical coherence tomography; OR = odds ratio; PRN = *pro re nata* ("as needed"); QOL = quality of life; ROB = risk of bias; SD = standard deviation; VEGF = vascular endothelial growth factor.

[a] Recommended dose is 2.0 mg.
[b] Post hoc analysis.
[c] The trial randomized 1208 patients, but 23 patients at one study center were later excluded because of serious protocol noncompliance.[41]
[d] Participants treated with the same regimen for 2 years (rather than switching from monthly injections to PRN at 12 months).
[e] Results were reported both by drug and treatment schedule; however, as our key questions were not looking at effectiveness according to dosing schedule, only drug comparisons are reported here.

[f] Subgroup analyses were performed for: baseline BCVA in fellow eye, baseline retinal angiomatous proliferation, baseline lesion, baseline choroidal neovascularization size, baseline BCVA, hemorrhage was present at baseline, study eye ≥ 5 letters better than in the fellow eye at baseline.
[g] Patients who developed wet AMD in the non-study eye received the same drug in both eyes; 31 patients in Group 1 and 25 patients in Group 2 were treated in both eyes.
[h] Figures estimated from a graph.
[i] Corrected values, converted to compensate for different OCT machines used.
[j] Calculated based on data reported by the study (baseline and BCVA achieved).
[k] For this study, BCVA was measured using ETDRS at 2 m instead of the recommended 4 m because of examination room size; vision was recorded in the same fashion for all study subjects in both treatment arms.

Diabetic Macular Edema (DME)

We found 3 eligible trials (808 total participants) comparing anti-VEGF agents for DME (one with low ROB, 2 with high ROB). One large trial (DRCR.net Protocol T, N=660) with low ROB compared all 3 anti-VEGF agents over 24 months (patients were also administered focal/grid laser photocoagulation rescue treatment if DME persisted after 6-months of injections),[46,47] and 2 smaller studies with high ROB compared bevacizumab to ranibizumab at 12 months.[30,31] One of these trials used a higher than typical dose of bevacizumab (1.5 mg, rather than the recommended 1.25 mg),[31] and another trial reported using 0.05 mg of ranibizumab (possibly a reporting error).[30] All studies used variations of PRN dosing, although specific criteria for retreatment varied between studies. Participants had a mean age of 60 to 67 years at baseline. None of the trials reported quality of life outcomes; one study calculated some quality of life outcomes based on reported visual acuity and adverse events, rather than using a validated measure of quality of life, and thus this outcome was not abstracted (although the calculated data was used in cost analyses reported in Key Question 3).[48] Study details are found in **Table 3** (additional study information is provided in **Appendix D**).

Aflibercept vs Bevacizumab

Visual Outcomes. DRCR.net Protocol T found that aflibercept was statistically significantly superior to bevacizumab in mean change in BCVA at both 12 months (mean difference 3.5 letters [95% CI, 1.4 to 5.7], $P < .001$) and 24 months (mean difference 2.7 letters [95% CI, 0.3 to 5.2], $P = .02$).[46,47] However, the difference between drugs was small (less than 5 ETDRS letters) at both timepoints and likely not clinically important. The trial reported that both groups achieved a mean BCVA equivalent to 20/32 or better on the Snellen chart at 12 months that continued through 24 months (aflibercept 77.8 vs bevacizumab 74.6 letters, *P*-value not reported). The aflibercept group had a significantly greater proportion of participants gaining 15 or more ETDRS letters compared to bevacizumab at 12 months (42% vs 29%, $P = .028$), but there was no difference between the groups by 24 months (39% vs 35%, $P = .70$).

Subgroup analyses from the DRCR.net Protocol T trial found significant differences in mean BCVA change according to baseline visual acuity. There was a statistically significant and clinically meaningful advantage of aflibercept over bevacizumab in participants with lower baseline visual acuity (BCVA of less than 69 ETDRS letters) at 12 months (mean difference in BCVA change 6.5 letters [95% CI, 2.9 to 10.1], $P < .001$); the difference was significant but smaller by 24 months (4.7 letters [95% CI, 0.5 to 8.8], $P = .02$). Similarly, there was a significantly greater percentage of patients in the aflibercept group gaining 15 or more letters at 12 months (67% vs 41%, $P < .001$), although by 24 months there was no difference between the drugs (58% vs 52%, $P=.74$). In contrast, among patients with higher baseline acuity (69 to 78 ETDRS letters), there was no difference between the drugs at either timepoint with respect to proportion of patients gaining 15 or more letters or mean change in BCVA (mean difference 1.1 letters [95% CI, -1.1 to 3.4]) at 24 months, $P = .51$).[46,47]

Anatomic Outcomes. There was a statistically significant difference favoring aflibercept in mean change in central subfield at both 12 months (169 µm vs 101 µm decrease, $P < .001$) and 24 months (171 µm vs 126 µm decrease, $P < .001$).

Aflibercept vs Ranibizumab

Visual Outcomes. DRCR.net Protocol T reported a statistically significant advantage with aflibercept over ranibizumab in mean change in BCVA at 12 months (mean difference 2.1 letters [95% CI, 0.1 to 4.2], *P* = .034), but not at 24 months (0.7 letters [95% CI, -1.3 to 2.8], *P* = .47); however, the difference was small and likely not clinically meaningful.[46,47] Both groups achieved a mean BCVA of over 77 letters (trial-reported Snellen equivalent 20/32) at 12 and 24 months. There was a marginally significant difference in the proportion of participants gaining 15 or more ETDRS letters in the aflibercept group compared to the ranibizumab group at 12 months (42% vs 32%, *P* = .068), but there was no difference between the drugs at 24 months (39% vs 37%, *P* = .70).

The superiority of aflibercept to ranibizumab was more pronounced in a subgroup of participants with lower baseline BCVA (less than 69 ETDRS letters) at 12 months (mean difference in BCVA change 4.7 letters [95% CI, 1.4 to 8.0], *P* = .003), but not at 24 months (2.3 letters [95% CI, -1.1 to 5.6], *P* = .18). Similar results were found for the percentage of patients gaining 15 or more letters from baseline; significantly more patients in the aflibercept group compared to ranibizumab achieved this outcome at 12 months (*P* = .008), but no difference was found between the groups at 24 months (*P* = .75). There was no difference between the drugs in patients with higher baseline BCVA (69 to 78 ETDRS letters) at either 12 or 24 months (mean difference in BCVA change 0.7 letters [95% CI, -2.9 to 1.5], *P* = .51).

Anatomic Outcomes. We found a small difference in favor of aflibercept with regard to mean change in central subfield difference at 12 months (169 µm vs 147 µm decrease, *P* = .036), and the change in reduction neared significance at 24 months (171 µm vs 149 µm decrease, *P* = .08).

Bevacizumab vs Ranibizumab

Visual Outcomes. The 3 studies comparing bevacizumab to ranibizumab (one trial using a 1.5 mg dose) as well as meta-analyses combining the studies found no significant differences between the drugs at 12 months with regard to mean change in BCVA (pooled mean difference -1.190 [95% CI, -2.889 to 0.509], *P* = .170; **Figure 6**) or in the proportion of participants gaining 15 or more letters from baseline (RR 0.871 [95% CI, 0.670 to 1.133], *P* = .304; **Figure 7**).[30,31,46,47] DRCR.net Protocol T also reported values at 24 months and found no difference between drugs (*P* = .11 for mean change in BCVA, and *P* = .70 for percentage gaining 15 or more letters).[46,47] Subgroup analyses also showed no significant differences between drugs at either 12 months or 24 months among participants with lower baseline visual acuity or with higher baseline visual acuity.

Anatomic Outcomes. The largest trial comparing bevacizumab to ranibizumab found a statistically significant difference in mean decrease in central subfield thickness in favor of ranibizumab at both 12 months (147 µm vs 101 µm; *P* < .001) and 24 months (149 µm vs 126 µm; *P* <.001), however the clinical significance of this difference is unclear.[46,47] The 2 smaller trials did not find a significant difference in mean foveal thickness[30] or mean reduction in central subfield thickness[31] at 12 months.

Figure 6. Mean change in BCVA at 12 months in DME patients treated with bevacizumab vs ranibizumab

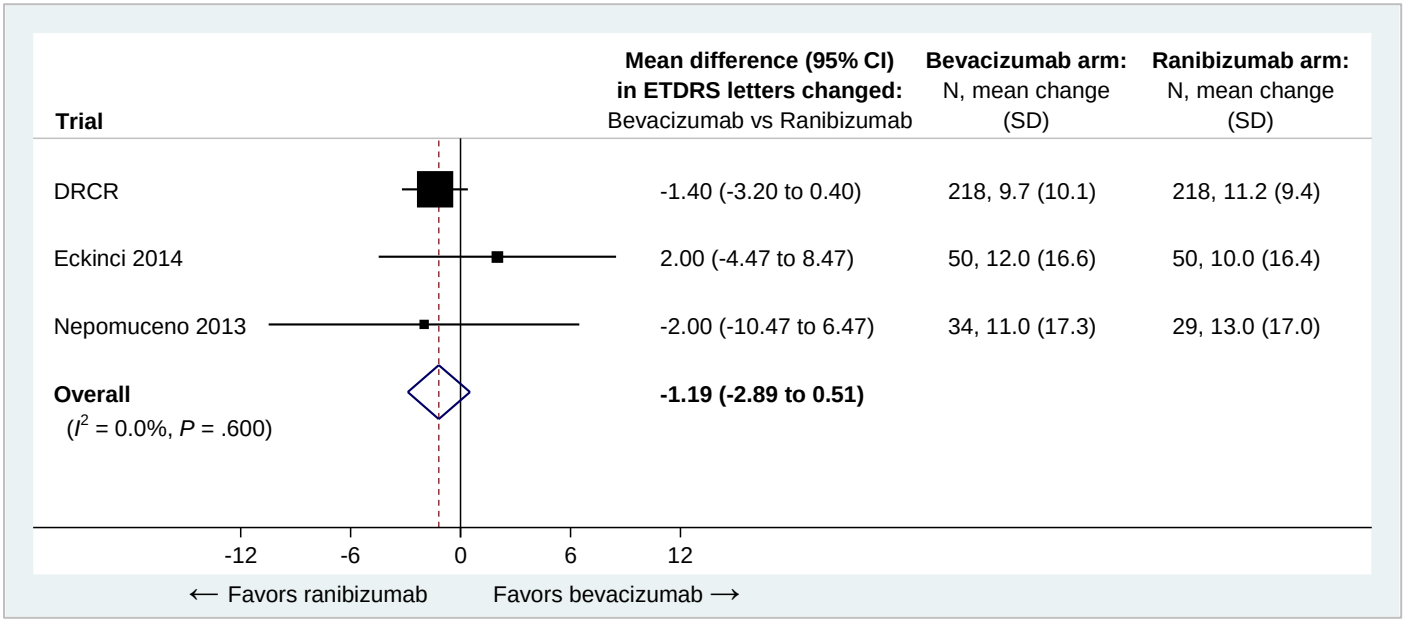
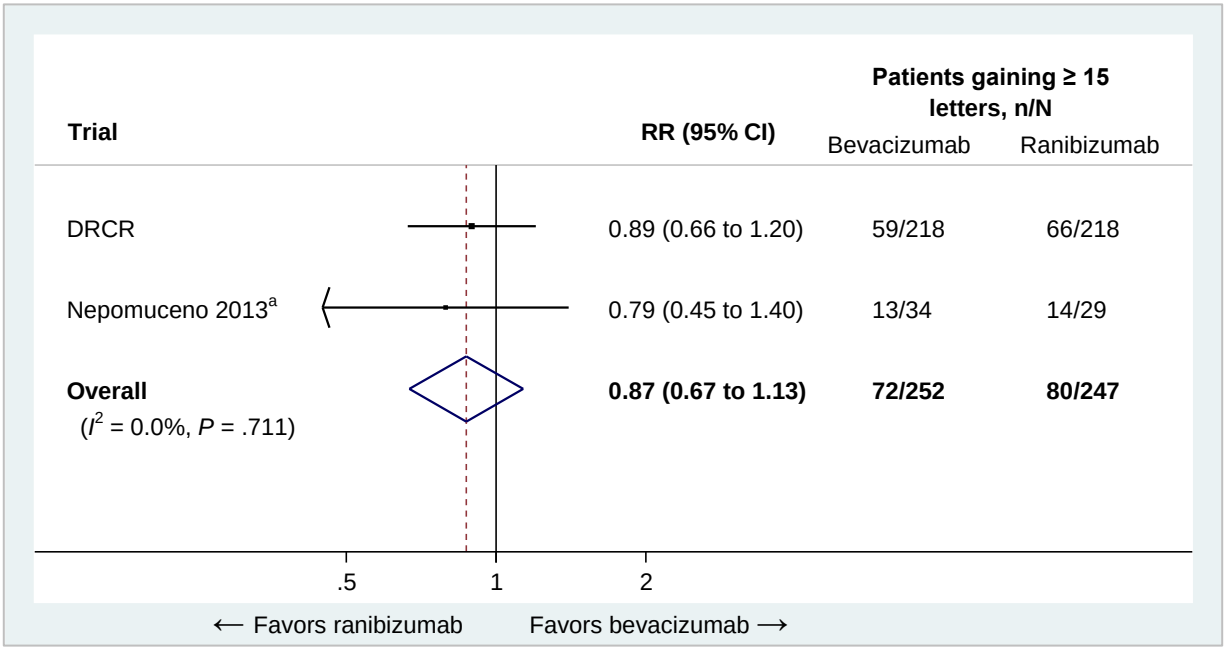


Figure 7. Likelihood of gaining 15 or more letters at 18-24 months in DME patients treated with bevacizumab vs ranibizumab



[a] Data are for number of eyes rather than number of patients, since for this trial patients with both eyes meeting eligibility criteria received different drugs in each eye.

Table 3. Effectiveness of Anti-VEGF Agents for DME

Trial name; Author, year · **Population** · **Number randomized** · **Length of follow-up** · **Population characteristics: mean age, % male, mean baseline BCVA**	**Interventions Groups (number per group)** · **Treatment schedule**	**Main Outcomes:** · **Visual acuity (reported as ETDRS chart letters unless otherwise indicated)** · **Quality of life (QOL) measures** · **Anatomic outcomes (reported in µm unless otherwise indicated)**	**Notes** · **ROB** · **Other notes**
Aflibercept vs Bevacizumab			
DRCR.net (Diabetic Retinopathy Clinical Research Network) Protocol T;[a] Wells 2016[46,47] · DME involving the macular center · 660 (578 analyzed at 24 months) · 24 months · 60.6 years (SD 10), 54% male, 64.8 letters (SD 11.3)	Group 1: Aflibercept 2.0 mg PRN (n=224) Group 2: Bevacizumab 1.25 mg PRN (n=218) · Schedule: Both groups injected every 4 weeks unless visual acuity was 20/20 or better, CST was below the eligibility threshold, and no improvement or worsening observed in response to 2 consecutive injections. · Patients also received focal/grid laser photocoagulation starting at 6-months if DME persisted.	**Aflibercept vs Bevacizumab** *Visual acuity outcomes:* · BCVA, mean change: § 12 months: 13.3 (SD 11.1) vs 9.7 (SD 10.1); mean difference 3.5 (95% CI, 1.4 to 5.7), *P*<.001 § 24 months: 12.8 (SD 12.4) vs 10.0 (SD 11.8); mean difference 2.7 (95% CI, 0.3 to 5.2), *P*=.02 Subgroup analyses found a significant difference in mean change in BCVA between aflibercept and bevacizumab in participants with baseline BCVA < 69 letters at 12 months (mean difference 6.5 letters [95% CI, 2.9 to 10.1] in favor of aflibercept; *P*<001) and 24 months (mean difference 4.7 letters [95% CI, 0.5 to 8.8]; *P*=.02), but found no difference in participants with baseline BCVA 69-78 letters at either timepoint (12 months *P*=.69; 24 months *P*=.51). · % of participants gaining ≥15 letters: § 12 months: 42% vs 29%; *P*=.028 § 24 months: 39% vs 35%; *P*=.70 Subgroup analyses reported a significant difference in percentage of patients gaining ≥15 letters in the group with lower baseline BCVA at 12 months (67% vs 41%, *P*<.001) but not 24 months (58% vs 52%, *P*=.74). No difference was found at either timepoint in the group with higher baseline BCVA (12 months *P*=.73; 24 months *P*=.89). *Anatomic outcomes:* · CST, mean change: § 12 months: -169 (SD 138) vs -101 (SD 121); *P*<.001 § 24 months: -171 (SD 141) vs -126 (SD 143); *P*<.001	· Low ROB

Trial name; Author, year · **Population** · **Number randomized** · **Length of follow-up** · **Population characteristics: mean age, % male, mean baseline BCVA**	**Interventions Groups (number per group)** · **Treatment schedule**	**Main Outcomes:** · **Visual acuity (reported as ETDRS chart letters unless otherwise indicated)** · **Quality of life (QOL) measures** · **Anatomic outcomes (reported in µm unless otherwise indicated)**	**Notes** · **ROB** · **Other notes**
Aflibercept vs Ranibizumab			
DRCR.net (Diabetic Retinopathy Clinical Research Network) Protocol T;[a] Wells 2016[46,47] · DME involving the macular center · 660 (578 analyzed at 24 months) · 24 months · 60.6 years (SD 10), 54% male, 64.8 letters (SD 11.3)	Group 1: Aflibercept 2.0 mg PRN (n=224) Group 3: Ranibizumab 0.3 mg PRN (n=218) · Schedule: Both groups injected every 4 weeks unless visual acuity was 20/20 or better, CST was below the eligibility threshold, and no improvement or worsening observed in response to 2 consecutive injections. · Patients also received focal/grid laser photocoagulation starting at 6-months if DME persisted.	**Aflibercept vs Ranibizumab** *Visual acuity outcomes:* · BCVA, mean change: § 12 months: 13.3 (SD 11.1) vs 11.2 (SD 9.4); mean difference 2.1 (95% CI, 0.1 to 4.2), *P*=.034 § 24 months: 12.8 (SD 12.4) vs 12.3 (SD 10.5); mean difference 0.7 (95% CI, -1.3 to 2.8), *P*=.47 Subgroup analyses found a significant difference in mean change in BCVA between aflibercept and ranibizumab in participants with baseline BCVA <69 letters at 12 months (mean difference 4.7 letters [95% CI, 1.4 to 8.0] in favor of aflibercept, *P*=.003) but not 24 months (*P*=.18). In patients with baseline BCVA 69-78 letters, no significant differences were found at either timepoint (12 months *P*=.69; 24 months *P*=.51). · % of participants gaining ≥15 letters: § 12 months: 42% vs 32%; *P*=.068 § 24 months: 39% vs 37%; *P*=.70 Subgroup analyses reported a significant difference in percentage of patients gaining ≥15 letters in the group with lower baseline BCVA at 12 months (67% vs 50%, *P*=.008) but not 24 months (58% vs 55%, *P*=.75). No difference was found at either timepoint in the group with higher baseline BCVA (12 months *P*=.73; 24 months *P*=.89). *Anatomic outcomes:* · CST, mean change: § 12 months: -169 (SD 138) vs -147 (SD 134); *P*=.036 § 24 months: -171 (SD 141) vs -149 (SD 141); *P*=.08	· Low ROB
Bevacizumab vs Ranibizumab			
DRCR.net (Diabetic Retinopathy Clinical Research Network) Protocol T;[a] Wells 2016[46,47] · DME involving the macular	Group 2: Bevacizumab 1.25 mg PRN (n=218) Group 3: Ranibizumab 0.3 mg PRN (n=218) · Schedule: Both groups	**Bevacizumab vs Ranibizumab** *Visual acuity outcomes:* · BCVA, mean change: § 12 months: 9.7 (SD 10.1) vs 11.2 (SD 9.4); mean difference 1.4 (-0.4 to 3.2), *P*=.12	· Low ROB

Trial name; Author, year · **Population** · **Number randomized** · **Length of follow-up** · **Population characteristics: mean age, % male, mean baseline BCVA**	**Interventions Groups (number per group)** · **Treatment schedule**	**Main Outcomes:** · **Visual acuity (reported as ETDRS chart letters unless otherwise indicated)** · **Quality of life (QOL) measures** · **Anatomic outcomes (reported in µm unless otherwise indicated)**	**Notes** · **ROB** · **Other notes**
center · 660 (578 analyzed at 24 months) · 24 months · 60.6 years (SD 10), 54% male, 64.8 letters (SD 11.3)	injected every 4 weeks unless visual acuity was 20/20 or better, CST was below the eligibility threshold, and no improvement or worsening observed in response to 2 consecutive injections. · Patients also received focal/grid laser photocoagulation starting at 6-months if DME persisted.	§ 24 months: 10.0 (SD 11.8) vs 12.3 (SD 10.5); mean difference 2.0 (95% CI, -0.4 to 4.4), *P*=.11 Subgroup analyses found no significant differences in mean change in BCVA between bevacizumab and ranibizumab in participants with baseline BCVA < 69 (12 months *P*=.21; 24 months *P*=.18) nor in patients with baseline BCVA 69-78 letters (12 months *P*=.69; 24 months *P*=.31). · % of participants gaining ≥15 letters: § 12 months: 29% vs 32%; *P*=.51 § 24 months: 35% vs 37%; *P*=.70 Subgroup analyses found no significant differences in percentage of patients gaining ≥15 letters in the group with lower baseline BCVA or the group with higher baseline BCVA at 12 or 24 months. *Anatomic outcomes:* · CST, mean change: § 12 months: -101 (SD 121) vs -147 (SD 134); *P*<.001 § 24 months: -126 (SD 143) vs -149 (SD 141); *P*<.001	
Ekinci 2014[30] · Clinically significant DME · 100 (85 analyzed) · 12 months · 66.5 years (SD 11.5), 36% male, 0.23 Snellen chart letters (SD 0.12)	Group 1: Bevacizumab 1.25 mg (n=50) Group 2: Ranibizumab 0.05 mg[b] (n=50) · Schedule: Both groups injected monthly for 3 months, then PRN. Additional monthly doses were administered if CMT was >275 µm or if BCVA increased by ≥3 letters compared with baseline.	**Bevacizumab vs Ranibizumab** *Visual acuity outcomes:* · BCVA, mean change at 12 months (converted from the Snellen chart to ETDRS letters)[c]: 12 (SD 16.6) vs 10 (SD 16.4); *P*=NS *Anatomic outcomes:* · Mean foveal thickness at 12 months: 342.3 (SD 121) vs 339.3 (SD 121); *P*=NS	· High ROB · The study excluded patients with certain AEs during follow-up (acute ocular infection, stroke, MI, uncontrolled hypertension, pregnancy, renal failure and cataract formation).

Trial name; Author, year · **Population** · **Number randomized** · **Length of follow-up** · **Population characteristics: mean age, % male, mean baseline BCVA**	**Interventions Groups (number per group)** · **Treatment schedule**	**Main Outcomes:** · **Visual acuity (reported as ETDRS chart letters unless otherwise indicated)** · **Quality of life (QOL) measures** · **Anatomic outcomes (reported in µm unless otherwise indicated)**	**Notes** · **ROB** · **Other notes**
Nepomuceno 2013[31] · DME with central involvement · 63 eyes in 48 patients (60 eyes in 45 patients analyzed)[d] · 11 months (48 weeks) · 63.8 years (SE 8.9), 45% male, 0.62 logMAR (SE 0.06) [approximately equivalent to 68 ETDRS letters][28]	Group 1: Bevacizumab 1.5 mg[e] PRN (n=34 eyes) Group 2: Ranibizumab 0.5 mg[f] PRN (n=29 eyes) · Schedule: Both groups received injection monthly if CST was >275 µm.	**Bevacizumab vs Ranibizumab** *Visual acuity outcomes:* · BCVA, mean change at 11 months (logMAR): -0.23 (SD 0.02) vs -0.29 (SD 0.04) [approximately equivalent to 11 vs 13 ETDRS letters] [28]; *P*=.1886 · % of participants gaining ≥15 letters: 39% vs 48%; *P*=NS *Anatomic outcomes:* · Maximum mean CST reduction: -126 (SE 25) at week 48 vs -136 (SE 23) at week 44; *P*=NS A multivariate analysis comparing BCVA and CST outcomes between the bevacizumab and ranibizumab groups, taking into account number of injections, baseline BCVA, and CST, demonstrated a statistically significant influence of baseline BCVA on follow-up BCVA (*P* < .001).	· High ROB

Abbreviations: BCVA = best-corrected visual acuity; CI = confidence interval; CMT = central macular thickness; CST = central subfield thickness; DME = diabetic macular edema; ETDRS = Early Treatment Diabetic Retinopathy Study; logMAR = Logarithm of the Minimal Angle of Resolution chart; MI = myocardial infarction; NS = not significant; PRN = *pro re nata* ("as needed"); QOL = quality of life; ROB = risk of bias; SD = standard deviation; SE = standard error; VEGF = vascular endothelial growth factor.

[a] This trial involved 3 groups; thus, it is listed under each two-way comparisons.
[b] Ranibizumab 0.05 mg is the dose reported in the published study (potentially an error); the recommended dose is 0.3 mg for patients with DME.
[c] The study did not report mean change, so we calculated it by converting the baseline and achieved BCVA based on the Snellen chart to ETDRS letters.**28.** Colenbrander A, International Council of Ophthalmology. *Visual Standards: Aspects and Ranges of Vision Loss (with Emphasis on Population Surveys)*. 2002; http://www.icoph.org/downloads/visualstandardsreport.pdf. Accessed December 28, 2016.
[d] If both eyes were eligible for treatment and the patient agreed to treat both eyes with anti-VEGF therapy, one eye received the randomized treatment according to a computer-generated sequence and the contralateral eye received the other anti-VEGF agent on the next day.
[e] The standard recommended dose is 1.25 mg.
[f] The recommended dose of ranibizumab for DME is 0.3 mg; however, 0.5 mg is the standard dose for both AMD and BRVO/CRVO.

Macular Edema due to Central Retinal Vein Occlusion (CRVO) or Branch Retinal Vein Occlusion (BRVO)

Two small trials, MARVEL (unclear ROB)[36] and CRAVE (high ROB),[32] examined anti-VEGF agents in 177 total patients with RVO (**Table 4**; additional study information is provided in **Appendix D**). CRAVE included patients with either CRVO or BRVO, and MARVEL included BRVO patients only. Participants in the MARVEL study were significantly younger, with an average age 20 years younger than participants in the CRAVE trial. Both studies compared bevacizumab to ranibizumab at 6 months, but one study used a monthly injection regimen and the other study used PRN dosing. Neither study assessed quality of life outcomes.

Bevacizumab versus Ranibizumab

Visual Outcomes. Although both groups reported large gains in mean BCVA after 6 months of treatment, neither study reported a significant difference between drugs, and a meta-analysis combining the studies also found no difference (pooled mean difference -1.204 letters [95% CI -5.714 to 3.306], *P* = .601; **Figure 8**). Subgroup analyses from one of the trials also found no differences between the drugs in either the BRVO (*P* = .15) or CRVO (*P* = .73) subsets. Similarly, the treatment groups did not differ in proportion of participants gaining 15 or more letters from baseline (RR 0.992 [95% CI, 0.805 to 1.223], *P* = .940; **Figure 9**). The MARVEL study reported that 68.4% in the bevacizumab group and 62.2% of the ranibizumab group achieved a Snellen equivalent of > 20/40 after 6 months of treatment (*P*-value not reported).

Anatomic Outcomes. Both trials reported no significant differences between drugs in mean reduction in central retinal or foveal thickness. CRAVE reported that most participants in both groups had no intraretinal or subretinal fluid present on OCT images (56.3% in the bevacizumab group vs 51.4% in the ranibizumab group; *P* = .81).

Figure 8. Mean change in BCVA at 6 months in BRVO or CRVO patients treated with bevacizumab vs ranibizumab

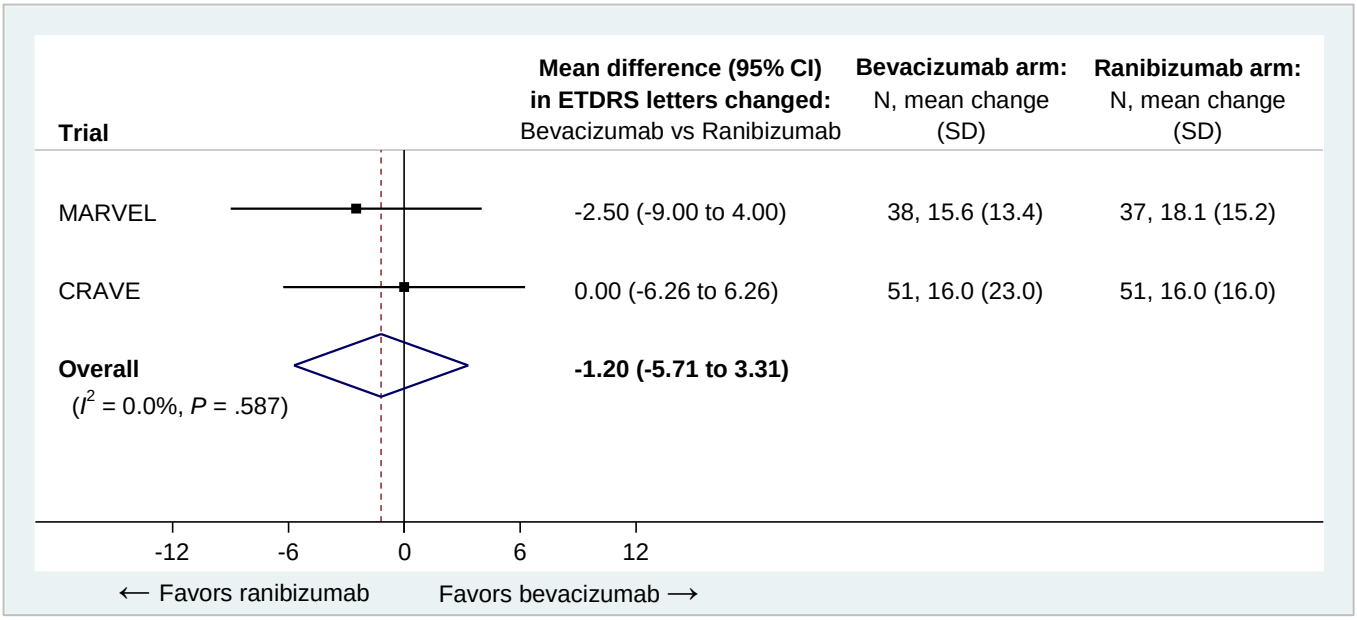


Figure 9. Likelihood of gaining 15 or more letters at 6 months in BRVO or CRVO patients treated with bevacizumab vs ranibizumab

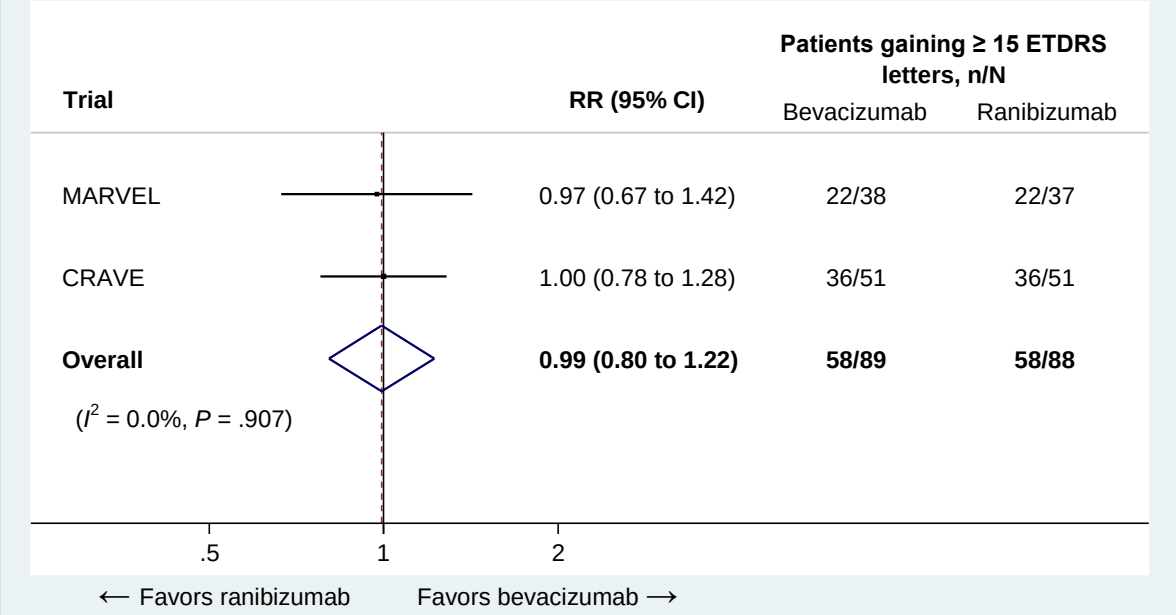


Table 4. Effectiveness of Anti-VEGF Agents for Macular Edema due to CRVO or BRVO

Trial name; Author, year · **Population** · **Number randomized** · **Length of follow-up** · **Population characteristics: mean age, % male, mean baseline BCVA**	**Interventions Groups (number per group)** · **Treatment schedule**	**Main Outcomes:** · **Visual acuity (reported as ETDRS chart letters unless otherwise indicated)** · **Quality of life (QOL) measures** · **Anatomic outcomes (reported in µm unless otherwise indicated)**	**Notes** · **ROB** · **Other notes**
Bevacizumab vs Ranibizumab			
CRAVE (Comparison of Anti-VEGF Agents in the Treatment of Macular Edema from Retinal Vein Occlusion Trial); Rajagopal 2015[32] · Macular edema secondary to RVO (60% of patients with BRVO or hemi-RVO, 40% with central RVO) · 102[a] (98 analyzed) · 6 months · 71.5 years (SD 12), 44.9% female, 0.745 logMAR (SD 0.42)	Group 1: Bevacizumab 1.25 mg monthly (n=51)[a] Group 2: Ranibizumab 0.5 mg monthly (n=51) · Schedule: Both groups received monthly injections for 6 months.	**Bevacizumab vs Ranibizumab** *Visual acuity outcomes:* · BCVA (Snellen chart), mean change at 6 months (logMAR): 0.33 (SD 0.45) vs 0.34 (SD 0.33); *P*=.38 · % of participants gaining ≥0.3 logMAR units at 6 months: 71.4% vs 70.6%; *P*=.94 *Anatomic outcomes:* · Central foveal thickness, mean change at 6 months: : -212.6 (SD 234.8) vs -243.8 (SD 204.2); *P*=.72 · Fluid absent on OCT at 6 months: 56.3% vs 51.4%; *P*=.81 Subgroup analyses observed no differences between drugs among BRVO or CRVO subsets in change in BCVA (BRVO: *P*=.15; CRVO: *P*=.73) or central foveal thickness changes (BRVO: *P*=.37; CRVO: *P*=.92).	· High ROB
MARVEL; Narayanan 2015[36] · Center-involving macular edema due to BRVO · 75 (75 analyzed) · 6 months · 51.7 years (SD 8.6), 54.6% male, 54.4 letters (SD 12.2)	Group 1: Bevacizumab 1.25 mg PRN (n=38) Group 2 Ranibizumab 0.5 mg PRN (n=37) · Schedule: Both groups injected at baseline then PRN.	**Bevacizumab vs Ranibizumab** *Visual acuity outcomes:* · BCVA, mean change at 6 months: 15.6 vs 18.1; mean difference -2.5 letters (95% CI, -8.0 to 5.0), *P*=.74 · % of participants gaining ≥15 letters at 6 months: 57.8% vs 59.4%; *P*=1.0 · % of participants achieving BCVA >20/40 (Snellen equivalent) at 6 months: 68.4% vs 62.2% *Anatomic outcomes:* · CRT, mean change at 6 months: -212.7 (SD 234.8) vs -177.1 (SD 204.2); *P*=.34	· Unclear ROB · Non-inferiority trial

Abbreviations: BCVA = best-corrected visual acuity; BRVO = branch retinal vein occlusion; CI = confidence interval; CRT = central retinal thickness; CRVO = central retinal vein occlusion; ETDRS = Early Treatment Diabetic Retinopathy Study; logMAR = Logarithm of the Minimal Angle of Resolution chart; OCT = optical coherence tomography; QOL = quality of life; PRN = *pro re nata* ("as needed"); ROB = risk of bias; RVO = retinal vein occlusion; SD = standard deviation; VEGF = vascular endothelial growth factor.

[a] Includes 9 patients who were not randomized but rather assigned to bevacizumab for financial reasons.

KEY QUESTION 2: What are the comparative harms of anti-VEGF agents for retinal/choroidal neovascularization and/or macular edema in adults?

Overview of Results

Of the 16 trials comparing anti-VEGF agents in our populations of interest, all but 4 reported detailed information about adverse events (**Table 5**).[26,30,32,33] Most of these studies (9 RCTs) examined adverse events in patients with AMD. Most trials compared bevacizumab to ranibizumab, but the DRCR.net Protocol T trial compared all 3 anti-VEGF agents in patients with DME, and 2 studies (VIEW 1 and VIEW 2) compared aflibercept to ranibizumab for AMD. Adverse events occurring by the longest-term timepoint reported by a study were prioritized over shorter-term timepoints (*eg*, rates of events over the first 12 months of a 24-month trial are generally not discussed). None of the trials were specifically designed to assess harms and thus were not powered to detect differences in adverse events between drugs.

Rates of serious ocular adverse events were very low in all trials, and none of the studies reported a significant difference between drugs in any ocular adverse event. The strength of evidence was low to moderate for trials of AMD and DME patients (depending on the drug comparison; see **Table 6**), and insufficient for RVO trials due to the paucity of studies, small sample sizes, and short duration follow-up. Endophthalmitis occurred in less than 1.5% of all groups in every trial except for 2 small DME studies, which both reported rates of approximately 3% for all patients receiving anti-VEGF injections (one study did not report events by treatment arm, and the other study found endophthalmitis in the ranibizumab arm only but did not report statistical comparisons between arms).[30,31] Rates of other serious ocular adverse events were also low but varied somewhat between trials. The incidence of vitreous hemorrhage was reported in 4 trials and ranged from 0% to 8% of patients (median 0.4%), with the highest rates occurring in the DRCR.net Protocol T trial of DME patients. Retinal detachment occurred in < 1% per group in the 7 studies reporting this outcome, and retinal tear occurred in ≤ 0.5% per group in 5 trials. Treatment-related cataracts occurred in 0% to 1.3% of patients per group in 6 trials (median 0.2%). Elevated intraocular pressure was the most commonly reported ocular adverse event, with a median of 5.9% per group in the 5 trials reporting this outcome, although as high as 17.4% of DME patients in the DRCR.net Protocol T trial experienced increased intraocular pressure during the 24-month trial.

As expected in populations with AMD, DME, and RVO, systemic adverse events were relatively common, although it is unclear how many were caused by intravitreal anti-VEGF treatment. Most trials found no differences between treatment groups, and the strength of evidence was low to moderate for AMD and DME and insufficient for RVO. Rates of patients experiencing at least one serious systemic adverse event ranged from 10% to 40% per treatment group. Rates of arterial thrombotic events as defined by the Anti-Platelet Trialists' Collaboration (vascular death, nonfatal myocardial infarction, or nonfatal stroke) was slightly higher in the DRCR.net trial of DME patients (8.4% total) than in the 7 trials reporting these events in patients with AMD (all groups < 5%). Likewise, hypertension and gastrointestinal disorders were also more common in the DRCR.net trial than in the AMD trials.

Detailed Results

Choroidal Neovascularization Secondary to Age-Related Macular Degeneration (AMD)

Of the 11 trials conducted in patients with AMD, all but 3 (one with unclear ROB[33] and 2 with high ROB[26,29]) reported detailed ocular and systemic adverse events by treatment arm (6 studies with low ROB and 2 studies with unclear ROB). Nine trials compared bevacizumab to ranibizumab and 2 trials compared aflibercept to ranibizumab. Five of these trials reported statistical comparisons between drugs (all bevacizumab versus ranibizumab).[27,34,35,37-39,41,42]

Patients with one or more serious ocular or systemic adverse events varied in the 3 trials reporting this outcome (11% to 21.7% at 12 months; 28% at 24 months in the IVAN trial), but there were no differences between the groups treated with bevacizumab compared to ranibizumab.[27,34,37,38,45] Withdrawals due to adverse events were reported in 5 trials and tended to be low in all groups (<1% to 4.5%; *P*-value between groups not reported in all studies).[27,34,37-39,43,44] The highest rate of withdrawals due to adverse events occurred in the LUCAS trial, with 4.5% in the bevacizumab group and 2.7% in the ranibizumab group (*P*-value between groups not reported).

Ocular Adverse Events

Reporting and specific rates of ocular adverse events varied between the studies, but were generally low. In the IVAN trial, 2.0% of patients treated with bevacizumab and 2.5% of patients treated with ranibizumab experienced at least one ocular adverse event during the 24-month treatment period (*P*-value between groups not reported). Combined 22-month results of VIEW 1 and VIEW 2 reported a slightly higher incidence of patients with one or more serious ocular adverse events, with 3.6% in the aflibercept arm and 4.4% in the ranibizumab arm (*P*-value between groups not reported).

Endophthalmitis occurred in less than 1% of patients in the 5 trials reporting this outcome.[27,34,37-39,43] The CATT trial reported a slightly higher rate, with 1.2% of the bevacizumab group and 0.7% in the ranibizumab group developing endophthalmitis during the 24-month trial (*P* = .38).[41,42] Of note, in the 12-month results, all incidents of endophthalmitis occurred in the groups receiving monthly injections.[41] Other serious ocular adverse events—such as retinal detachment, retinal or vitreous hemorrhage, retinal tears, and traumatic or treatment-emergent cataracts—were very rare, generally occurring in less than 1% of each group in the 5 large trials reporting these outcomes.[27,34,37-40,43,44]

Systemic Adverse Events

The proportion of patients with one or more serious systemic adverse events varied widely between the trials, ranging from 10% (in GEFAL, which did not enroll patients with uncontrolled hypertension despite medical treatment)[34] to 40%. Of the 6 studies reporting this outcome, the CATT trial reported the highest rates of serious systemic adverse events and was the only trial to find a significant difference between groups. The trial reported 39.9% of patients in the intravitreal bevacizumab arm and 31.7% in the intravitreal ranibizumab arm experienced at least one serious systemic adverse event by the 24-month follow-up visit (*P* = .004), and thus bevacizumab had an adjusted relative risk of 1.30 (95% CI, 1.07 to 1.57; *P* = .009; no difference found between groups receiving monthly compared to PRN injections).[41,42] However, many of

the serious adverse events reported in the group taking intravitreal bevacizumab were not events that have been associated with systemic anti-VEGF treatment in previous (cancer) trials[49] (*ie*, events other than arterial thrombotic events, venous thrombotic events, systemic hemorrhage, hypertension, and vascular death, which are affected by the VEGF pathway), and thus the meaning of this finding is unclear. The other 5 trials reported similar rates between groups.[27,34,37-40,43,44]

Arterial thrombotic events occurred in up to 5% of patients in the trials reporting this outcome, and rates were very similar between treatment arms for most trials. The LUCAS trial reported a higher rate of arterial thrombotic events in the ranibizumab group at 12 months (4.5% vs 1.4% in bevacizumab group, $P = .050$), mostly because of an increased rate of nonfatal myocardial infarction; however, this difference disappeared by 24 months ($P = .289$).[39] No trial reported significant differences between treatment arms in rates of vascular deaths. Interestingly, the combined results of VIEW 1 and VIEW 2 found that the highest rates of arterial thrombotic events occurred in the groups with the lowest anti-VEGF exposure (3.6% at 22 months in the arm receiving 2 mg of aflibercept every 8 weeks, and 3.8% in the arm receiving monthly injections of aflibercept at the lower than typical dose of 0.5 mg), rather than the groups receiving monthly injections at the standard recommended dose (2.4% and 3.2%; *P*-values between groups not reported).[44] None of the trials reported significant differences between groups in rates of stroke or hypertension, and only the LUCAS trial found a difference between drugs in rates of nonfatal myocardial infarction, although the difference did not reach statistical significance (1.4% in the bevacizumab group vs 4.1% in the ranibizumab group, $P = .080$).[39]

No study found a difference between drugs in rates of death (8 RCTs). Two trials reported higher rates of gastrointestinal disorders among patients treated with bevacizumab compared to ranibizumab (IVAN, $P = .06$; and CATT, $P = .005$).[27,37,38,41,42] The 4 other trials reporting this outcome found no difference between the drugs.

Diabetic Macular Edema (DME)

Three RCTs (total N=808) evaluated adverse event outcomes in patients with DME.[30,31,46,47] However, one trial did not report statistical comparisons between groups,[31] and another trial did not report adverse events by treatment arm;[30] both of these studies had serious methodological flaws resulting in high ROB ratings.

Ocular Adverse Events

The largest trial, DRCR.net Protocol T (N=660, low ROB), found no significant differences between drugs in rates of ocular adverse events.[46,47] The most common events reported in the trial were elevated intraocular pressure (occurring in 15.3% of participants, $P = .31$ between groups), and vitreous hemorrhage (6.4% of participants, $P = .37$ between groups). Endophthalmitis only occurred in a single patient during the 24-month trial (0.5% of bevacizumab group; $P = .66$ between groups). Two smaller trials had higher rates of endophthalmitis, with one study reporting 2 patients in the ranibizumab group contracting the infection (7%; *P*-value between groups not reported),[31] and 3 patients overall in the other trial (3%; results not reported by group).[30] Similarly, cataract formation occurred in less than 1% in the DRCR.net trial ($P = .38$ between groups), but was reported in 3% and 4% of the smaller trials (*P*-value between groups not reported).

Systemic Adverse Events

The DRCR.net Protocol T trial reported high rates of serious systemic adverse events (38%; *P* = .90 between groups), although the definition for this outcome was not reported.[46,47] The trial found that the arm treated with intravitreal ranibizumab had significantly higher rates of arterial thrombotic events (5.4% aflibercept vs 7.8% bevacizumab vs 11.9% ranibizumab; aflibercept vs ranibizumab *P* = .047, bevacizumab vs ranibizumab *P* = .20). The group also had slightly higher rates of hypertension (17.4% vs 12.4% vs 20.2%; *P* = .08). As expected in a fairly sick diabetic population (median hemoglobin A1c 7.7 [range 6.8 to 9.2]; mean arterial blood pressure 101 mmHg; median body mass index 32.3 kg/m^2), rates of other systemic adverse events were fairly high, but no differences were reported between groups (death, hospitalization, gastrointestinal disorders, and kidney dysfunction). The 2 smaller trials did not report statistical differences between groups.[30,31]

Macular Edema due to Central Retinal Vein Occlusion (CRVO) or Branch Retinal Vein Occlusion (BRVO)

Two trials (one with unclear ROB[36] and one with high ROB[32]) reported adverse events in patients with BRVO or CRVO (total N=177). However, both studies were relatively small and they did not report statistical comparisons between treatment groups.

Ocular Adverse Events

Neither trial reported any patient with endophthalmitis during the 6-month follow-up period. The MARVEL trial reported that 6.7% of all patients experienced cataract progression (*P*-value between groups not reported), and 7.9% of patients treated with bevacizumab developed an epiretinal membrane (*P*-value not reported). The CRAVE trial reported no instances of serious ocular adverse events.

Systemic Adverse Events

MARVEL reported that 6.7% of patients developed arterial hypertension during the trial (*P*-value between groups not reported); however, the majority of participants (67%) had hypertension at baseline. No other relevant systemic adverse events were reported.

KEY QUESTION 3: What is the comparative cost-effectiveness of anti-VEGF agents for retinal/choroidal neovascularization and/or macular edema in adults?

Overview of Results

Two trials reported comparative costs of anti-VEGF agents in the US: the CATT trial compared ranibizumab and compounded bevacizumab in AMD patients,[41,42] and DRCR.net Protocol T compared all 3 anti-VEGF drugs in patients with DME.[48] No trials evaluated the comparative costs when bevacizumab was not compounded (*ie*, use of the vial for a single patient with the remainder discarded, which is the current method employed by the VHA). However, 13 of the other 16 trials reported the mean or median number of injections per treatment group (including VIEW 1 and VIEW 2, whose results are combined in the 22-month results). Two trials also reported other outcomes that may have cost implications, such as the percentage of patients needing rescue therapy (*eg*, laser photocoagulation).[36,46,47] We found no additional observational or modeling studies assessing comparative costs that met inclusion criteria; however, the DRCR.net Protocol T trial also reported a validated mathematical model to project 10-year cost-effectiveness results.[48] Overall, based on the available data on treatment costs in 2 comparative trials and one long-term cost model, treatment with bevacizumab is associated with considerably lower costs than treatment with the other 2 agents.

Detailed Results

A large study in patients with AMD (CATT trial) reported the average cost of the anti-VEGF drug per patient, based on a per-dose cost of $50 for compounded bevacizumab and $2,000 for ranibizumab. Based on a mean number of injections administered over the 24-month trial period (23.4 for bevacizumab monthly group, 22.4 for ranibizumab monthly, 14.1 for bevacizumab PRN, and 12.6 for ranibizumab PRN; $P = .01$ between PRN groups), the average cost per patient receiving monthly injections was $1,170 for bevacizumab compared to $44,800 for ranibizumab; in the PRN groups, the mean cost was $705 for bevacizumab compared to $25,200 for ranibizumab.[41,42] In other words, ranibizumab treatment was over 35 times more expensive than bevacizumab using PRN dosing and over 38 times more expensive when the drugs were administered monthly. Although the outcome only included the cost of the drug and not other economic considerations such as costs related to clinic visits, rescue treatment, and adverse events, given the dramatic difference in cost between the drugs, it is likely that comparative treatment costs alone give a fair estimate of the total cost differential between the drugs.

In the DRCR.net Protocol T trial of DME patients, total mean costs per participant over one year of treatment—including study eye and non-study eye anti-VEGF injections (based on per-dose wholesale costs of $1,850 for aflibercept, $1,170 for ranibizumab 0.3 mg, and $60 for compounded bevacizumab), laser photocoagulation, and adverse events—were $26,000 (95% CI, $24,400 to 27,700) for aflibercept, $18,600 (95% CI, $17,100 to 20,200) for ranibizumab, and $4,100 (95% CI, $3,000 to 5,200) for bevacizumab (including the cost of drug compounding).[48] The study also calculated quality-adjusted life-years (QALYs) per group based on visual acuity achieved and reported adverse events at monthly intervals and summed over the first year of the trial. Based on the total costs and QALY calculations, the one-year incremental cost-effectiveness ratios (compared to bevacizumab) were $1,110,000 per QALY for aflibercept and $1,730,000 per QALY for ranibizumab ($648,000 per QALY for aflibercept compared to

ranibizumab). A validated model projecting cost-effectiveness compared to bevacizumab over 10 years calculated these ratios to be $349,000 per QALY for aflibercept and $603,000 per QALY for ranibizumab ($203,000 per QALY for aflibercept vs ranibizumab). In the subgroup with lower baseline BCVA (< 69 ETDRS letters), which saw a greater relative advantage with aflibercept treatment in mean change in BCVA, the incremental cost-effectiveness ratio was $287,000 per QALY compared to bevacizumab. All models and sensitivity analyses showed the incremental cost-effectiveness ratios of aflibercept and ranibizumab compared to bevacizumab to be well above the $50,000 to $150,000 per QALY thresholds frequently cited in the cost-effectiveness literature.[48] Thus the study authors concluded that based on the very high costs needed for modest improvements in quality of life, aflibercept and ranibizumab at their current prices are not cost-effective compared to bevacizumab.

In this trial, eyes were treated with focal/grid laser photocoagulation starting at 6 months if DME persisted and was no longer showing improvement. By 24-months follow-up, approximately half of participants required laser photocoagulation at least once and there were significant differences between groups, with the bevacizumab group requiring the most treatment (64% vs 41% in aflibercept arm vs 52% in ranibizumab arm; $P < .05$ for all comparisons). Similarly, the MARVEL trial reported higher rates of rescue macular grid laser photocoagulation among the bevacizumab group (21.0% vs 10.8% for ranibizumab), although the difference was not significant ($P = .34$).

Because treatment schedules and PRN retreatment criteria differed among the studies, there was a wide range in the mean number of injections reported by the studies, ranging from 2.9 to 10.7 injections per 12 months of treatment (median among trials with PRN treatment schedules, calculated as per 12 months: 7.5 for aflibercept, 6.8 for bevacizumab, and 6.4 for ranibizumab). Of the 8 studies reporting statistical significance calculations between bevacizumab and ranibizumab, 4 trials found that significantly more injections were administered in the bevacizumab group,[26,31,39,41,42] while one trial found the opposite;[30] the other 3 trials reported no significant differences between groups.[29,34,35] The VIEW 1 and VIEW 2 combined results reported fewer injections during the "capped PRN" phase (months 12 to 22) in the aflibercept group than in the ranibizumab group (4.7 vs 4.1, $P < .0001$).[44] DRCR.net results comparing all 3 drugs at 24 months also reported fewer aflibercept injections (14.2 vs 15.3 for bevacizumab and 14.8 for ranibizumab), but statistical comparisons between the drugs were not reported.[46-48]

Table 5. Harms and Costs of Anti-VEGF Agents for Retinal/Choroidal Neovascularization and/or Macular Edema

Trial name; Author, year · **Population** · **Number randomized** · **Length of follow-up** · **Population characteristics: mean age, % male, mean baseline BCVA**	**Interventions Groups (number per group)** · **Treatment Schedule**	**Harms Outcomes**[a]	**Cost and Burden Outcomes**	**Notes** · **ROB** · **Other notes**
Choroidal Neovascularization Secondary to Age-Related Macular Degeneration (AMD)				
Biswas 2011[33] · Choroidal neovascular membrane secondary to AMD; occult CNV 44% · 120 (104 analyzed) · 18 months · 63.9 years (SD NR), 48% male, 57.5 letters	Group 1: Bevacizumab 1.25 mg (n=60) Group 2: Ranibizumab 0.50 mg (n=60) · Schedule: Both groups injected monthly for 3 months, then PRN.	**Bevacizumab vs Ranibizumab** · Major complications: 0% vs 0%; *P*=1.0 · Minor complications: 11.1% vs 7.3%; *P*=NR	**Bevacizumab vs Ranibizumab** · Mean number of injections: 4.3 vs 5.6	· Unclear ROB
BRAMD (Bevacizumab to Ranibizumab in Patients with Exudative Age-Related Macular Degeneration); Schauwvlieghe 2016[45] · Primary or recurrent sub- or juxtafoveal CNV secondary to AMD · 332 (327 analyzed) · 12 months · 78 years (SD 7), 44% male, 60 letters (SD 13)	Group 1: Bevacizumab 1.25 mg (n=166) Group 2: Ranibizumab 0.5 mg (n=166) · Schedule: Both groups injected monthly.	**Bevacizumab vs Ranibizumab** · ≥1 serious adverse event: 21.1% vs 22.3%; *P*=.87 · Number of adverse events: 256 vs 299; *P*=.48 · Number of serious adverse events: 34 vs 37; *P*=.87 *Systemic Adverse Events:* · Death due to serious adverse event: 0.6% vs 0.6%; *P*=.6818 · Cardiac disorders: 2.5% vs 3.7% · Gastrointestinal disorders: 1.2% vs 1.2%	NR	· Low ROB · Non-inferiority study.
CATT (Comparison of AMD Treatments Trials); Martin 2012[41,42] · Previously untreated active CNV due to AMD · 1208[b] (1105 analyzed at 12 months, 1030 analyzed	Group 1: Bevacizumab 1.25 mg monthly* (n=286) Group 2: Ranibizumab 0.5 mg monthly* (n=301) Group 3: Bevacizumab 1.25 mg PRN (n=300) Group 4: Ranibizumab 0.5 mg PRN (n=298)	**Bevacizumab vs Ranibizumab**[c] *Ocular Adverse Events:* · Endophthalmitis: 1.2% vs 0.7%; *P*=.38 · Pseudo-endophthalmitis: 0.2% vs 0.2%; *P*=1.0 *Systemic Adverse Events:* · ≥1 serious systemic adverse event: 39.9% vs 31.7%; *P*=.004; adjusted RR 1.30 (95% CI, 1.07 vs 1.57),	**Bevacizumab monthly vs Ranibizumab monthly vs Bevacizumab PRN vs Ranibizumab PRN** · Average cost of drug per patient in US dollars (based on per-dose cost of $50 for compounded bevacizumab	· Low ROB · Re-randomization: At 12 months, patients initially assigned to

Trial name; Author, year · **Population** · **Number randomized** · **Length of follow-up** · **Population characteristics: mean age, % male, mean baseline BCVA**	**Interventions Groups (number per group)** · **Treatment Schedule**	**Harms Outcomes**[a]	**Cost and Burden Outcomes**	**Notes** · **ROB** · **Other notes**
at 24 months) · 24 months · 79.2 years (SD 7.5), 38.2% male, 60.6 letters (SD 13.5)	· Schedule: Monthly regimens were given an injection every 28 days; PRN regimens were given one initial injection and then only when signs of active neovascularization were present. *Patients in the monthly groups were re-randomized at 12 months to either continue monthly injections or switch to PRN dosing (study drug not changed).	*P*=.009[d] · All-cause death: 6.1% vs 5.3%; *P*=.62 · Arterial thrombotic events: 5.0% vs 4.7%: *P*=.89 § Nonfatal stroke: 1.4% vs 1.3%; *P*=1.0 § Nonfatal MI: 1.2% vs 1.5%; *P*=.80 § Vascular death: 2.4% vs 2.0%; *P*=.70 · Venous thrombotic events: 1.7% vs 0.5%; *P*=.054 · HTN: 0.7% vs 0.5%; *P*=.72 · Cardiac disorders: 10.6% vs 7.8%; *P*=.11 · Gastrointestinal disorders: 4.8% vs 1.8%; *P*=.005 · Not previously associated with anti-VEGF treatment (*ie*, events other than arterial thrombotic events, systemic hemorrhage, congestive heart failure, venous thrombotic events, HTN, and vascular death): 34.5% vs 28.4%; *P*=.02	and $2,000 for ranibizumab): § 12 months: 595 vs 23,400 vs 385 vs 13,800 § 24 months: 1,170 vs 44,800 vs 705 vs 25,200 · Mean number of injections : § 12 months (maximum 13): 11.9 (SD 1.2) vs 11.7 (SD 1.5) vs 7.7 (SD 3.5) vs 6.9 (SD 3.0); *P*=.003 between PRN groups § 24 months (maximum 26): 23.4 (SD 2.8) vs 22.4 (SD 3.9) vs 14.1 (SD 7.0) vs 12.6 (SD 6.6); *P*=.01 between PRN groups	monthly treatment retained their drug assignment but were reassigned randomly to either monthly or PRN.
GEFAL (French Study Group Avastin versus Lucentis for Neovascular AMD trial); Kodjikian 2013[34] · Active subfoveal neovascular AMD · 501 (404 analyzed) · 12 months · 79.2 years (SD 7.1), 33.7% male, 55.2 letters (SD 14.0)	Group 1: Bevacizumab 1.25 mg (n=255) Group 2: Ranibizumab 0.5 mg (n=246) · Schedule: Both groups injected monthly for 3 months, then PRN.	**Bevacizumab vs Ranibizumab** · ≥1 serious adverse event: 12.6% vs 12.1%; *P*=.8757 · Withdrawals due to adverse events: 2.8% vs 2.9% *Ocular Adverse Events:* · Eye disorders: 0.8% vs 2.1%; *P*=.2791 · Retinal artery occlusion: 0.4% vs 0% · Subretinal hematoma: 0.4% vs 0.8% · Vitreous hemorrhage: 0% vs 0.4% · Endophthalmitis: 0% vs 0.4% · Retinal detachment: 0% vs 0% · Traumatic cataract: 0% vs 0% *Systemic Adverse Events:* · ≥1 serious systemic adverse event: 12.2% vs 10.0%; *P*=.4510	**Bevacizumab vs Ranibizumab** · Mean number of injections: 6.8 (SD 2.7) vs 6.5 (SD 2.4); *P*=.39 · Patients requiring monthly injections: 4.2% vs 1.6%; *P*=.14	· Unclear ROB · Non-inferiority study.

Trial name; Author, year · **Population** · **Number randomized** · **Length of follow-up** · **Population characteristics: mean age, % male, mean baseline BCVA**	**Interventions Groups (number per group)** · **Treatment Schedule**	**Harms Outcomes**[a]	**Cost and Burden Outcomes**	**Notes** · **ROB** · **Other notes**
		· Death: 0.8% vs 1.3%; *P*=.6818 · Arterial thrombotic events: § MI: 0.4% vs 0.4%; *P*=1.0 § Stroke: 0% vs 0%; *P*=1.0 · Venous thrombotic events: § Pulmonary embolism: 0.4% vs 0%; *P*=1.0 § Phlebitis: 0% vs 0%; *P*=1.0 · TIA: 0% vs 0%; *P*=1.0 · Cardiac disorders: 0.8% vs 2.1%; *P*=.2791 · HTN: 0.4% vs 0.8%; *P*=.6189 · Gastrointestinal disorders: 1.2% vs 2.1%; *P*=.4985		
IVAN (Inhibition of VEGF in Age-related choroidal Neovascularisation trial); Chakravarthy 2013[27,37,38] · Active previously untreated neovascular AMD with neovascular lesion involving the center of the fovea · 628 (610 analyzed) · 24 months · 77.7 years (SD 7.4), 40% male, 61.4 letters (SD 15.3)	Group 1: Bevacizumab 1.25 mg monthly or PRN (n=305)[e] Group 2: Ranibizumab 0.5 mg monthly or PRN (n=323)[e] · Schedule: All groups received injections monthly for 3 months, then received injections according to their allocation group (monthly or PRN).	**Bevacizumab vs Ranibizumab** · ≥1 serious adverse event: 28.3% vs 27.7% · Withdrawals due to serious adverse events: 1.3% vs 1.9% *Ocular Adverse Events:* · ≥1 ocular adverse event: 2.0% vs 2.5% · Endophthalmitis: 0% vs 0% · Retinal detachment: 0% vs 0.3% · Retinal hemorrhage: 0% vs 0.3% · Retinal pigment epithelial tear: 0.3% vs 1.0% · Traumatic cataract: 0.3% vs 0.3% · Vitreous hemorrhage: 0.3% vs 0% · RVO: 0% vs 0.3% · Uveitis: 0.3% vs 0% · Infection: 0.3% vs 0.0% *Systemic Adverse Events:* · ≥1 serious systemic adverse event: 27.0% vs 25.8%; OR 0.96 (95% CI, 0.66 to 1.39), *P*=.82 · All-cause death: 5.1% vs 4.8%; OR 0.96 (95% CI, 0.46 to 2.02), *P*=.91	**Ranibizumab vs Bevacizumab** · Median number of injections: 18 (IQR 11 to 23) vs 19 (IQR 12 to 23)	· Low ROB

Trial name; Author, year · **Population** · **Number randomized** · **Length of follow-up** · **Population characteristics: mean age, % male, mean baseline BCVA**	**Interventions Groups (number per group)** · **Treatment Schedule**	**Harms Outcomes**[a]	**Cost and Burden Outcomes**	**Notes** · **ROB** · **Other notes**
		· Any vascular event, heart failure, or all-cause death: 9.5% vs 12.1%; OR 1.36 (95% CI, 0.80 to 2.29), *P*=.25 · Arterial thrombotic event: 3.4% vs 4.1%; OR 1.24 (95% CI, 0.53 to 2.86) § Nonfatal MI: 1.4% vs 1.3% § Nonfatal stroke: 1.0% vs 1.9% § Vascular death: 1.4% vs 1.0% · Heart failure: 0.7% vs 2.2% · Arterial thrombotic events or heart failure: 4.1% vs 6.4%; OR 1.69 (95% CI, 0.80 to 3.57), *P*=.16 · Venous thrombotic events: 1.4% vs 1.0% · TIA: 0.3% vs 0.3% · Hospitalized for angina: 1.0% vs 2.2% · Cardiac disorders: 6.4% vs 6.4% · Gastrointestinal disorders: 3.0% vs 1.0%; OR 0.31 (95% CI 0.08 to 1.16), *P*=.06		
LUCAS (Lucentis Compared to Avastin Study); Berg 2015[39,40] · Previously untreated active neovascular AMD · 441 (431 analyzed) · 24 months · 78.3 years (SD 7.9), 32.5% male, 61.0 letters (SD 13.5)	Group 1: Bevacizumab 1.25 mg (n=220)[f] Group 2: Ranibizumab 0.5 mg (n=221)[f] · Schedule: "Treat-and-extend" - patients in both groups were injected every 4 weeks until no signs of active AMD were found, at which point the period to the next treatment was extended by 2 weeks at a time, up to a maximum interval of 12 weeks. If	**Bevacizumab vs Ranibizumab** · Withdrawals due to adverse events: 7.3% vs 4.1% *Ocular Adverse Events:* · Endophthalmitis: 0.5% vs 0%; *P*=.499 · Pseudo-endophthalmitis: 1.4% vs 0%; *P*=.123 · Macular hemorrhage: 1.4% vs 0%; *P*=.123 · Retinal tear: 0.5% vs 0%; *P*=.499 · Pigment epithelial rupture: 0.5% vs 0%; *P*=.499 · Acute glaucoma: 0.5% vs 0%; *P*=.499 *Systemic Adverse Events:* · ≥1 serious systemic adverse event: 29.1% vs 30.3%; *P*=.778 · All-cause death: 6.8% vs 5.9%; *P*=.687 · Arterial thrombotic events: 4.1% vs 6.3%; *P*=.289	**Bevacizumab vs Ranibizumab** · Mean number of injections: 18.2 vs 16.0; mean difference 1.2 (95% CI, -3.4 to -1.0), *P*≤.001 · Average treatment interval in weeks: 6.5 vs 7.6 · % patients receiving injections at treatment interval: § 4 weeks: 27% vs 20%; *P*=.002 § 12 weeks: 10% vs 17%; *P*=.002	· Low ROB · Non-inferiority study.

Trial name; Author, year · **Population** · **Number randomized** · **Length of follow-up** · **Population characteristics: mean age, % male, mean baseline BCVA**	**Interventions Groups (number per group)** · **Treatment Schedule**	**Harms Outcomes**[a]	**Cost and Burden Outcomes**	**Notes** · **ROB** · **Other notes**
	examination showed any sign of recurrence, the interval was shortened by 2 weeks at a time, until the disease was considered to be inactive. Interval extension was then restarted, with the maximum final interval being 2 weeks less than the period when the previous recurrence.	§ Nonfatal MI: 1.4% vs 4.1%; *P*=.080 § Nonfatal stroke: 1.4% vs 1.8%; *P*=1.0 § Vascular death: 1.4% vs 0.9%; *P*=.685 · Venous or other thrombotic event: 0% vs 1.4%; *P*=.248 · TIA: 1.4% vs 0%; *P*=.123 · HTN: 0.9% vs 0.9%; *P*=1.0 · Cardiac disorder: 5.5% vs 8.6%; *P*=.197 · Gastrointestinal disorder: 3.2% vs 5.0%; *P*=.341		
MANTA (Multicenter Anti-VEFG Trial in Austria); Krebs 2013[35] · Active primary or recurrent subfoveal lesion with CNV secondary to AMD · 317 (number analyzed unclear) · 12 months · 77.2 years (SD 8.0), 36.3% male, 56.7 letters (SD 13.3)	Group 1: Bevacizumab 1.25 mg (n=154) Group 2: Ranibizumab 0.5 mg (n=163) · Schedule: Both groups injected monthly for 3 months, then PRN.	**Bevacizumab vs Ranibizumab** *Ocular Adverse Events:* 0% vs 0%; *P*=1.0 *Systemic Adverse Events:* · Death: 1.9% vs 1.2%; *P*=.61 · Vascular disorders: § Heart attack: 1.9% vs 1.2%; *P*=.61 § Stroke: 0.6% vs 0.6%; *P*=.94 § Mesenteric artery occlusion: 0.6% vs 0%; *P*=.30 · Arrhythmia: 0.6% vs 0.6%; *P*=.94 · Nervous system disorder: 1.3% vs 0.6%; *P*=.53 · Infection: 1.9% vs 1.8%; *P*=.94 · Injury or procedural complication: 1.3% vs 1.8%; *P*=.70 · Gastrointestinal disorder: 0% vs 0%; *P*=1.0	**Bevacizumab vs Ranibizumab** · Mean number of re-treatments: 6.1 (SD 2.8) vs 5.8 (SD 2.7); *P*=.26	· Unclear ROB · Non-inferiority study.

Trial name; Author, year · **Population** · **Number randomized** · **Length of follow-up** · **Population characteristics: mean age, % male, mean baseline BCVA**	**Interventions Groups (number per group)** · **Treatment Schedule**	**Harms Outcomes**[a]	**Cost and Burden Outcomes**	**Notes** · **ROB** · **Other notes**
Scholler 2014[29] · Active previously untreated neovascular AMD · 55 (number analyzed unclear) · 12 months · 80.1 years (SD 6.7), 29.1% male, 58.0 letters (SD 11.7)	Group 1: Bevacizumab 1.25 mg (n=29) Group 2: Ranibizumab 0.5 mg (n=26) · Schedule: Both groups injected monthly for 3 months, then PRN.	**Bevacizumab vs Ranibizumab** *Ocular Adverse Events:* · Subretinal bleeding: 0% vs 7.7% *Systemic Adverse Events:* · TIA: 0% vs 3.8%	**Bevacizumab vs Ranibizumab** · Mean number of injections: 5.80 (SD 2.28) vs 5.00 (SD 1.67); *P*=.084	· High ROB
Subramanian 2010[26] · Symptomatic CNV affecting the foveal center; 18% classic or predominantly classic CNV · 28 (22 analyzed) · 12 months · 78.6 years, 95% male, 34.2 letters	Group 1: Bevacizumab (dose NR; n=20) Group 2: Ranibizumab (dose NR; n=8) · Schedule: Both groups injected monthly for 3 months, then PRN.	· No major ocular or systemic adverse events reported in any subjects who completed the 1-year follow-up visit (no data for patients not completing 1-year visit). · Minor adverse events (*eg*, subconjunctival hemorrhage, transient post-injection pain, and elevated IOP) occurred but data was not reported. · No reports of anterior chamber inflammation, vitreous hemorrhage, retinal detachment, endophthalmitis, or systemic adverse events in patients completing 1-year follow-up.	**Bevacizumab vs Ranibizumab** · Mean number of injections: 8 (range 3-8) vs 4 (range 3-6); *P*=.001	· High ROB · VA population
VIEW 1 (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD Trial 1); Heier 2012[43] · Active subfoveal CNV lesions or juxtafoveal lesions with leakage affecting the fovea, secondary to AMD. · 1217 (1210 analyzed) · 12 months (22 month	Group 1: Aflibercept 2.0 mg monthly (n=304) Group 2: Aflibercept 0.5 mg[g] monthly (n=304) Group 3: Aflibercept 2.0 mg every other month (after 3 initial monthly doses; n=303) Group 4: Ranibizumab 0.5 mg monthly (n=306) · Schedule: Patients were	**Aflibercept (all groups)**[h] **vs Ranibizumab** · Withdrawals due to adverse events: 1.3% vs 1.3% *Ocular Adverse Events:* · ≥1 serious ocular adverse event: 1.8% vs 3.3% · Endophthalmitis: 0.3% vs 1.0% · Retinal hemorrhage: 0.2% vs 0.7% · Posterior capsule opacification: 0% vs 0% · Increased IOP: 4.5% vs 7.2% · Treatment-emergent serious retinal detachment: 0.1% vs 0%	NR for 12 months (when monthly or bimonthly dosing schedules was used); 22-month results combined with VIEW 2	· Low ROB · Non-inferiority study.

Trial name; Author, year · **Population** · **Number randomized** · **Length of follow-up** · **Population characteristics: mean age, % male, mean baseline BCVA**	**Interventions Groups (number per group)** · **Treatment Schedule**	**Harms Outcomes**[a]	**Cost and Burden Outcomes**	**Notes** · **ROB** · **Other notes**
results combined with VIEW 2 and reported separately) · 78 years (SD 8.0), 41.2% male, 55.1 letters (SD 13.1)	seen every 4 weeks and given either active treatment or a sham injection depending on randomization group (*ie*, Group 3 received sham every other visit).	· Treatment-emergent serious cataract: 0.1% vs 0% *Systemic Adverse Events:* · ≥1 serious systemic adverse events: 15.5% vs 18.8% · Arterial thrombotic event: 1.6% vs 1.6% § Vascular death: 0.5% vs 0.3% § Nonfatal MI: 0.7% vs 1.3% § Nonfatal stroke: 0.4% vs 0% · HTN: 9.0% vs 9.5% · Venous thrombotic events: 0.1% vs 0.3% · Congestive heart failure: 0.4% vs 0.7% · Gastrointestinal perforation or fistula: 0% vs 0% · Non-ocular hemorrhagic event: 0.7% vs 0.3%		
VIEW 2 (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD Trial 2); Heier 2012[43] · Active subfoveal CNV lesions or juxtafoveal lesions with leakage affecting the fovea, secondary to AMD. · 1240 (1202 analyzed) · 12 months (22 month results combined with VIEW 1 and reported separately) · 73.9 years (SD 8.7), 44.5% male, 52.4 letters (SD 13.9)	Group 1: Aflibercept 2.0 mg monthly (n=313) Group 2: Aflibercept 0.5 mg[g] monthly (n=311) Group 3: Aflibercept 2.0 mg every other month (after 3 initial monthly doses; n=313) Group 4: Ranibizumab 0.5 mg monthly (n=303) · Schedule: Patients were seen every 4 weeks and given either active treatment or a sham injection depending on randomization group (*ie*, Group 3 received sham every other visit).	**Aflibercept (all groups)**[h] **vs Ranibizumab** · Withdrawals due to adverse events: 2.5% vs 0.7% *Ocular Adverse Events:* · ≥1 serious ocular adverse event: 2.2% vs 3.1% · Endophthalmitis: 0% vs 0% · Retinal hemorrhage: 0.4% vs 0.3% · Posterior capsule opacification: 0% vs 0.7% · Increased IOP: 5.9% vs 6.5% · Treatment-emergent serious retinal detachment: 0.2% vs 0.3% · Treatment-emergent serious cataract: 0.2% vs 0.3% *Systemic Adverse Events:* · ≥1 serious systemic adverse events: 12.2% vs 8.9% · Arterial thrombotic event: 1.9% vs 1.7% § Vascular death: 0.4% vs 0.3% § Nonfatal MI: 1.0% vs 0.7% § Nonfatal stroke: 0.4% vs 0.7% · HTN: 8.8% vs 10.0%	NR for 12 months (when monthly or bimonthly dosing schedules was used); 22-month results combined with VIEW 1	· Low ROB · Non-inferiority study.

Trial name; Author, year · **Population** · **Number randomized** · **Length of follow-up** · **Population characteristics: mean age, % male, mean baseline BCVA**	**Interventions Groups (number per group)** · **Treatment Schedule**	**Harms Outcomes**[a]	**Cost and Burden Outcomes**	**Notes** · **ROB** · **Other notes**
		· Venous thrombotic events: 0% vs 0% · Congestive heart failure: 0.1% vs 0.3% · Gastrointestinal perforation or fistula: 0.2% vs 0% · Non-ocular hemorrhagic event: 0.3% vs 0%		
VIEW 1 and VIEW 2 combined 22-month results; Schmidt-Erfurth 2014[44] · Active subfoveal CNV lesions or juxtafoveal lesions with leakage affecting the fovea, secondary to AMD · 2457 (2412 analyzed) · 22 months (96 weeks) · 75.9 years (SD 8.6), 42.8% male, 53.8 letters (SD 13.6)	Group 1: Aflibercept 2.0 mg monthly for 12 months, capped PRN months 12-22 (n=617) Group 2: Aflibercept 0.5 mg[g] monthly for 12 months, capped PRN months 12-22 (n=615) Group 3: Aflibercept 2.0 mg every other month (after 3 initial monthly doses) for 12 months, capped PRN months 12-22 (n=616) Group 4: Ranibizumab 0.5 mg monthly for 12 months, capped PRN months 12-22 (n=609) · Schedule: During follow-up period from 12 to 22 weeks, patients continued to receive the same dose of study drugs as in the first 12 months, but received injections at least every 12 weeks (capped PRN).	**Aflibercept (all groups)[h] vs Ranibizumab** · Withdrawals due to adverse events: 4.1% vs 2.6% *Ocular Adverse Events:* · ≥1 serious ocular adverse event: 3.6% vs 4.4% · Serious ocular injection-related adverse event rate (per 1000 injections) at 12 months: 0.3 vs 0.8 · Endophthalmitis: 0.3% vs 0.8% · Retinal detachment: 0.2% vs 0.5% · Retinal hemorrhage: 0.7% vs 0.7% · Retinal pigment epithelial tear: 0.2% vs 0.2% · Cataract: 0.6% vs 0.2% · Increased IOP: 1.6% vs 0.2% · Any intraocular inflammatory response: 0.8% vs 1.5% · Posterior capsule opacification: 0% vs 0.3% *Systemic Adverse Events:* · ≥1 serious systemic adverse event: 24.0% vs 24.5% · Arterial thrombotic events: 3.3% vs 3.2% § Nonfatal MI: 1.4% vs 2.0% § Nonfatal stroke: 0.7% vs 0.8% § Vascular death: 1.3% vs 0.5% · Congestive cardiac failure: 0.9% vs 0.8% · Coronary artery disease: 0.4% vs 0.8% · Atrial fibrillation: 1.3% vs 0.8% · TIA: 0.9% vs 0.2% · Cerebrovascular accident: 0.8% vs 0.7% · Death: 2.8% vs 2.7%	**Aflibercept 2 mg monthly vs Aflibercept 0.5 mg monthly vs Aflibercept 2 mg bimonthly vs Ranibizumab 0.5 mg monthly** · Mean number of injections at week 96: 16.0 (SD 3.2) vs 16.2 (SD 4.0) vs 11.2 (SD 2.9) vs 16.5 (SD 2.7) · Mean number of injections from months 12-22 (PRN schedule): 4.1 (SD 1.8) vs 4.6 (SD 2.2) vs 4.2 (SD 1.7) vs 4.7 (SD 2.2); *P*<.0001 aflibercept 2.0mg monthly then PRN vs ranibizumab monthly then PRN; *P*<.0001 for aflibercept 2.0mg every other month then PRN vs ranibizumab monthly then PRN	· Low ROB for both VIEW 1 and VIEW 2

Trial name; Author, year · **Population** · **Number randomized** · **Length of follow-up** · **Population characteristics: mean age, % male, mean baseline BCVA**	**Interventions Groups (number per group)** · **Treatment Schedule**	**Harms Outcomes**[a]	**Cost and Burden Outcomes**	**Notes** · **ROB** · **Other notes**
Diabetic Macular Edema (DME)				
DRCR.net (Diabetic Retinopathy Clinical Research Network) Protocol T; Wells 2016[46-48] · DME involving the macular center · 660 (578 analyzed at 24 months) · 24 months · 60.6 years (SD 10), 54% male, 64.8 letters (SD 11.3)	Group 1: Aflibercept 2.0 mg PRN (n=224) Group 2: Bevacizumab 1.25 mg PRN (n=218) Group 3: Ranibizumab 0.3 mg PRN (n=218) · Schedule: All groups injected every 4 weeks unless visual acuity was 20/20 or better, CST was below the eligibility threshold, and no improvement or worsening observed in response to 2 consecutive injections. · Patients also received focal/grid laser photocoagulation starting at 6-months if DME persisted.	**Aflibercept vs Bevacizumab vs Ranibizumab** *Ocular Adverse Events:* · Endophthalmitis: 0% vs 0.5% vs 0%; *P*=.66 · Inflammation: 2.7% vs 1.4% vs 1.8%; *P*=.69 · Retinal detachment (traction, rhegmatogenous, or unspecified): 0.9% vs 0.9% vs 0.9%; *P*=1.0 · Retinal tear: 0.4% vs 0.5% vs 0.5%; *P*=1.0 · Vitreous hemorrhage: 6.7% vs 7.8% vs 4.6%; *P*=.37 · Injection-related cataract: 1.3% vs 0.9% vs 0%; *P*=.38 · Increased IOP: 17.4% vs 12.4% vs 16.5%; *P*=.31 *Systemic Adverse Events:* · ≥1 serious systemic adverse event: 39.3% vs 37.2% vs 37.6%; *P*=.90 · Arterial thrombotic events: 5.4% vs 7.8% vs 11.9%; global *P*=.09 (aflibercept vs ranibizumab *P*=.047) § Nonfatal MI: 3.1% vs 1.4% vs 2.8% § Nonfatal stroke: 0.9% vs 2.8% vs 5.0% § Vascular death (from any potential vascular or unknown cause): 1.3% vs 3.7% vs 4.1% · Death: 2.2% vs 6.0% vs 5.0%; *P*=.12 · Hospitalization: 34.4% vs 32.6% vs 33.5%; *P*=.93 · Gastrointestinal disorders: 29.9% vs 29.4% vs 27.5%; *P*=.85 · Renal and urinary disorder events: 22.3% vs 21.1% vs 16.1%; *P*=.22 · HTN: 17.4% vs 12.4% vs 20.2%; *P*=.08	**Aflibercept vs Bevacizumab vs Ranibizumab** · Total mean costs during one year:[i] $26,100 vs $4,100 vs $18,600 · Incremental cost-effectiveness ratio over 10 years (model): $349,000 vs reference vs $603,000 per QALY § Subgroup with lower baseline BCVA (<69 ETDRS letters): $287,000 vs reference vs $817,000 per QALY[j] · Mean number of injections: § 12 months: 9.2 (SD 2.0) vs 9.7 (SD 2.3) vs 9.4 (SD 2.1); *P*-value not reported for mean, but for median number of injections *P*=.045 for aflibercept vs bevacizumab (*P*=NS for other comparisons) § 24 months (*completers only*): 14.2 (SD 4.6) vs 15.3 (SD 5.3) vs 14.8 (SD 5.0); *P*-value not reported for mean, but for median number of injections *P*=.08 for overall comparison	· Low ROB

Trial name; Author, year · **Population** · **Number randomized** · **Length of follow-up** · **Population characteristics: mean age, % male, mean baseline BCVA**	**Interventions Groups (number per group)** · **Treatment Schedule**	**Harms Outcomes**[a]	**Cost and Burden Outcomes**	**Notes** · **ROB** · **Other notes**
			· Laser photocoagulation performed at least once: § 12 months: 37% vs 56% vs 46%; *P*<.001 § 24 months: 41% vs 64% vs 52%; *P*<.001 aflibercept vs bevacizumab, *P*=.04 aflibercept vs ranibizumab, and *P*=.01 ranibizumab vs bevacizumab	
Ekinci 2014[30] · Clinically significant DME · 100 (85 analyzed) · 12 months · 66.5 years (SD 11.5), 36% male, 0.23 Snellen chart letters (SD 0.12)	Group 1: Bevacizumab 1.25 mg (n=50) Group 2: Ranibizumab 0.05 mg[j] (n=50) · Schedule: Both groups injected monthly for 3 months, then PRN. Additional monthly doses were administered if CMT was >275 µm or if BCVA increased by ≥3 letters compared with baseline.	· Patients with acute ocular infection (endophthalmitis after intravitreal injection, n=3), stroke, MI (n=2), uncontrolled HTN (n=4), renal failure (n=1) and cataract formation during follow-up period (n=4) were excluded from the study. These events were not reported by group.	**Bevacizumab vs Ranibizumab** · Mean number of injections: 5.1 (SD 0.74) vs 6.5 (SD 0.85); *P*<.05	· High ROB · The study excluded patients with certain adverse events during follow-up (acute ocular infection, stroke, MI, uncontrolled HTN, pregnancy, renal failure, and cataract formation).
Nepomuceno 2013[31] · DME with central involvement · 63 eyes in 48 patients (60	Group 1: Bevacizumab 1.5 mg[l] PRN (n=32 eyes) Group 2: Ranibizumab 0.5 mg PRN (n=28 eyes)	**Bevacizumab vs Ranibizumab** (percentages based on number of eyes) *Ocular Adverse Events:* · Clinically significant cataract progression: 3% vs 0%	**Bevacizumab vs Ranibizumab** · Mean number of injections: 9.84 (SEM 0.55) vs 7.67 (SEM 0.60); *P*=.005	· High ROB

Trial name; Author, year · **Population** · **Number randomized** · **Length of follow-up** · **Population characteristics: mean age, % male, mean baseline BCVA**	**Interventions Groups (number per group)** · **Treatment Schedule**	**Harms Outcomes**[a]	**Cost and Burden Outcomes**	**Notes** · **ROB** · **Other notes**
eyes in 45 patients analyzed)[k] · 11 months (48 weeks) · 63.8 years (SE 8.9), 45% male, 0.62 logMAR (SE 0.06)	· Schedule: Both groups received injection monthly if CST was >275 μm.	· Transient vitreous hemorrhage after acute posterior vitreous detachment: 3% vs 0% · Endophthalmitis: 0% vs 7% *Systemic Adverse Events:* · Increased blood pressure: 0% vs 4% · Transient worsening of renal function: 1 patient receiving both treatments · No patient experienced MI, stroke, or gastrointestinal bleeding throughout the study period.	· Eyes meeting rescue therapy criteria (85% received additional anti-VEGF injections, and 15% received rescue laser therapy): 28% vs 14%; *P*=.042	
Macular Edema due to Central Retinal Vein Occlusion (CRVO) or Branch Retinal Vein Occlusion (BRVO)				
CRAVE (Comparison of Anti-VEGF Agents in the Treatment of Macular Edema from Retinal Vein Occlusion Trial); Rajagopal 2015[32] · Macular edema secondary to RVO (60% of patients with BRVO or hemi-RVO, 40% with CRVO) · 102[m] (98 analyzed) · 6 months · 71.5 years (SD 12), 44.9% female, 0.745 logMAR (SD 0.42)	Group 1: Bevacizumab 1.25 mg monthly (n=51)[n] Group 2: Ranibizumab 0.5 mg monthly (n=51) · Schedule: Both groups received monthly injections for 6 months.	*Ocular Adverse Events:* "No instances of ophthalmic serious adverse events including endophthalmitis, noninfectious uveitis, retinal detachment, retinal tear, or traumatic cataract were encountered. Injection site pain and irritation were the most adverse events." *Systemic Adverse Events:* "One patient died from complications of pneumonia. No patients suffered MI or cerebrovascular accident during the study."	NR	· High ROB
MARVEL; Narayanan 2015[36] · Center-involving macular edema due to BRVO · 75 (75 analyzed)	Group 1: Bevacizumab 1.25 mg PRN (n=38) Group 2 Ranibizumab 0.5 mg PRN (n=37) · Schedule: Both groups	**Bevacizumab vs Ranibizumab** *Ocular Adverse Events:* · Endophthalmitis: 0% vs 0% · Progression of cataract: 7.9% vs 5.4% · Increased IOP: 2.6% vs 0%	**Bevacizumab vs Ranibizumab** · Mean number of injections: 3.0 (SD 1.4) vs 3.2 (SD 1.5) · Received rescue grid laser photocoagulation: 21.0% vs	· Unclear ROB · Non-inferiority trial

Trial name; Author, year · **Population** · **Number randomized** · **Length of follow-up** · **Population characteristics: mean age, % male, mean baseline BCVA**	**Interventions Groups (number per group)** · **Treatment Schedule**	**Harms Outcomes**[a]	**Cost and Burden Outcomes**	**Notes** · **ROB** · **Other notes**
· 6 months · 51.7 years (SD 8.6), 54.6% male, 54.4 letters (SD 12.2)	injected at baseline then PRN.	· Developed a BRVO in the fellow eye: 0% vs 2.7% · Epiretinal membrane: 7.9% vs 0% *Systemic Adverse Events:* · Systemic arterial HTN: 5.3% vs 8.1% · Hospitalization (for fractured foot and fever): 0% vs 5.4%	10.8%; *P*=.34 · Received sector laser photocoagulation due to the development of neovascularization in the retina: 2.6% vs 5.4%	

Abbreviations: AMD = age-related macular degeneration; BCVA = best-corrected visual acuity; BRVO = branch retinal vein occlusion; CI = confidence interval; CMT = central macular thickness; CNV = choroidal neovascularization; CRVO = central retinal vein occlusion; CST = central subfield thickness; DME = diabetic macular edema; ETDRS = Early Treatment Diabetic Retinopathy Study; IQR = interquartile range; logMAR = Logarithm of the Minimal Angle of Resolution chart; MI = myocardial infarction; NR = not reported; OR = odds ratio; PRN = *pro re nata* ("as needed"); QALY = quality-adjusted life-year; ROB = risk of bias; RR = relative risk; RVO = retinal vein occlusion; SD = standard deviation; SE = standard error; TIA = transient ischemic attack; VEGF = vascular endothelial growth factor.

[a] Ocular adverse events are reported for the study eyes only.

[b] The trial randomized 1208 patients, but 23 patients at one study center were later excluded because of serious protocol noncompliance.[41-42]

[c] Monthly and PRN groups for each drug were combined. Adverse events within the first 12 months were reported by drug as well as by treatment schedule (monthly or PRN) in the 12-month publication.[41]

[d] RR for patients treated PRN compared to monthly: 1.20 (95% CI, 0.98 to 1.47), *P*=.08.

[e] Results were reported both by drug and treatment schedule; however, as our key questions were not looking at effectiveness according to dosing schedule, only drug comparisons are reported here.

[f] Patients who developed neovascular AMD in the non-study eye received the same drug in both eyes; 31 patients in the bevacizumab group and 25 patients in the ranibizumab group were treated in both eyes.

[g] The recommended dose is 2.0 mg.

[h] Adverse events by individual treatment group are reported in the main publication.[43]

[i] Included study eye and non-study eye anti-VEGF injections (per-dose cost $1,850 for aflibercept, $1,170 for ranibizumab, and $60 for compounded bevacizumab), laser photocoagulation, and adverse events.

[j] Ranibizumab 0.05 mg is the dose reported in the published study (potentially an error); the recommended dose is 0.3 mg for patients with DME.
[k] If both eyes were eligible for treatment and the patient agreed to treat both eyes with anti-VEGF therapy, 1 eye received the randomized treatment according to a computer-generated sequence and the contralateral eye received the other anti-VEGF agent on the next day.
[l] The recommended dose is 1.25 mg.
[m] Includes 9 patients who were not randomized but were assigned to bevacizumab for financial reasons.

SUMMARY AND DISCUSSION

SUMMARY OF THE EVIDENCE

In this systematic review, we examined the effectiveness, harms, and costs of intravitreal anti-VEGF treatment for retinal or choroidal neovascularization and/or macular edema. Key results are summarized in **Table 6**. Overall, we found no evidence of a clinically meaningful difference in visual acuity gains between the drugs for the treatment of AMD, DME, or BRVO/CRVO, although one DME trial suggests that there may be an advantage associated with aflibercept in patients with lower baseline BCVA. Most trials found no differences between drugs in rates of ocular or systemic adverse events. Because of the comparative effectiveness and harms but marked differences in price between the drugs, compounded bevacizumab was found to be the most cost-effective agent.

In patients with AMD and DME, we found moderate- to high-strength evidence that there was no difference in clinically important visual outcomes between bevacizumab and ranibizumab. We found insufficient to low-strength evidence of either no difference or a small visual acuity benefit for aflibercept over both bevacizumab and ranibizumab, particularly in patients with poorer visual acuity at baseline. The very limited evidence found for BRVO and CRVO populations is insufficient from which to draw conclusions about the comparative effectiveness of bevacizumab and ranibizumab (no evidence for the other drug comparisons).

Ocular adverse events generally occurred very rarely in the included trials and we found low- to moderate-strength evidence of no difference between the anti-VEGF agents. Rates of systemic adverse events were also similar between drugs in most trials (low- to moderate-strength evidence), although one trial reported higher rates of arterial thrombotic events with intravitreal ranibizumab compared to intravitreal aflibercept in patients with DME (low-strength evidence). There was insufficient evidence about adverse events for BRVO/CRVO patients; however, because most of the adverse events associated with these treatments are usually related to the intraocular injection rather than the clinical condition, it is likely that the comparative rates of adverse events in patients with RVO are similar to those found in the other populations.

Regarding comparative costs, one DME trial and one AMD trial provided moderate-strength evidence that treatment with both ranibizumab and aflibercept is considerably more expensive than compounded bevacizumab and provide no incremental cost-effectiveness benefits. Ten-year modeling, sensitivity analyses, and subgroup analyses of patients with lower baseline BCVA confirm the substantial cost-effectiveness of compounded bevacizumab compared to the other agents. In patients with DME, ranibizumab was more cost-effective than the more expensive aflibercept (moderate-strength evidence). No studies assessed the costs of bevacizumab when it was not compounded (the current method employed by the VHA).

Table 6. Summary of the Evidence on Anti-VEGF Agents for the Treatment of Retinal/Choroidal Neovascularization and/or Macular Edema

Outcome	N studies (N=total patients randomized)	Summary of findings[a]	Combined summary estimate	Strength of Evidence[b]	Comments
Choroidal Neovascularization Secondary to Age-Related Macular Degeneration (AMD)					
Aflibercept vs Bevacizumab					
	None	---	---	No evidence	
Aflibercept vs Ranibizumab					
Mean change in BCVA	2 RCTs (N=2457)[c]	Mixed findings. Neither study reported a clinically meaningful difference between drugs, and pooled results show no statistically significant difference between drugs; however, despite identical designs, the 2 trials had conflicting results (one showing benefit in favor of aflibercept and the other in favor of ranibizumab), resulting in very high statistical heterogeneity.[d]		Insufficient	Conflicting results from 2 large trials.
% patients gaining ≥15 letters	2 RCTs (N=2457)[c]	No difference. Neither study reported a statistically significant difference between drugs, but one of the trials trended toward significance in favor of aflibercept and the other in favor of ranibizumab, resulting in high statistical heterogeneity.[e]	*12 months:* no difference	Low	
Ocular adverse events	2 RCTs (N=2457)[c]	Low rates of serious ocular adverse events (2.3% at 12 months, 3.8% at 22 months) and likely no difference between drugs. By 22 months, endophthalmitis occurred in 0.8% of monthly ranibizumab groups and 0.7% of monthly aflibercept 2.0 mg groups. Intraocular pressure elevation was the most common event, reported in up to 7.2% of participants.	---	Moderate	Statistical comparison between drugs NR.
Systemic adverse events	2 RCTs (N=2457)[c]	Arterial thrombotic events[f] potentially related to intravitreal anti-VEGF agents were reported in both groups: 3.2% of monthly ranibizumab groups and 2.4% of monthly aflibercept 2.0 mg groups by 22 months. There was no evidence of a dose-response relationship for aflibercept (highest rate of exposure generally had lowest rate of events).	---	Low	Statistical comparison between drugs NR.
Costs	2 RCTs (N=2457)[c]	No direct cost data was reported. Combined results from 2 trials show slightly less frequent dosing required for aflibercept compared to ranibizumab (4.1 vs 4.7 injections during the 10-month PRN portion of trial; $P<.001$). Based on current drug prices, this likely represents a small benefit for aflibercept during the PRN phase of the trial (~$7600 vs $9500).	---	Low	

Outcome	N studies (N=total patients randomized)	Summary of findings[a]	Combined summary estimate	Strength of Evidence[b]	Comments
Bevacizumab vs Ranibizumab					
Mean change in BCVA	9 RCTs (N=3630)	No short-term or long-term significant difference between drugs.	*12 months* (7 trials): Pooled ES -0.218 (-1.431 to 0.995); I^2=5.9% *18-24 months* (3 trials): Pooled ES -0.126 (-1.033 to 0.781); I^2=0%	High	Large number of trials with fairly consistent results and precise estimate.
% patients gaining ≥15 letters	7 RCTs (N=3455)	No short-term or long-term significant difference between drugs.	*12 months:* RR 0.930 (0.804 to 1.075); I^2=4.0% *18-24 months* (4 trials): RR 0.835 (0.630 to 1.107); I^2=44.5%	Moderate	Large number of trials but the long-term estimate is imprecise and encompasses both no difference and a substantial benefit in favor of ranibizumab.
Ocular adverse events	6 RCTs (N=3427)	Low rates of serious ocular adverse events and there were no significant differences reported between drugs. Endophthalmitis typically occurred in <1% of patients in each treatment group (except in the CATT trial which reported 1.4% in one treatment arm at 12 months). Other specific serious ocular adverse events were also very rare (typically <1% of patients per arm).	---	Moderate	Reporting of ocular adverse events varied between trials, and very few reported statistical differences between groups.
Systemic adverse events	6 RCTs (N=3427)	Similar rates of serious systemic adverse events between drugs were reported in 5 of the 6 trials. Arterial thrombotic events[f] occurred in up to 5% of each arm, and no significant differences were found between drugs in 4 of 5 trials at 12 months; the one trial finding a difference between drugs at 12 months found no difference by 24 months. No differences were found between drugs in rates of death. Bevacizumab was associated with higher rates of gastrointestinal events in 2 of 6 trials.	---	Moderate	
Cost	1 RCT (N=1208)	Per-dose and two-year injection costs of compounded bevacizumab[g] were substantially lower than ranibizumab in one trial (PRN groups $705 vs $25,200 per patient; monthly groups $1,170 vs $44,800 per patient). Based on injection frequencies reported in other trials, differential costs were likely similar. No evidence of incremental cost-effectiveness benefit for the more expensive ranibizumab.	---	Moderate	

Outcome	N studies (N=total patients randomized)	Summary of findings[a]	Combined summary estimate	Strength of Evidence[b]	Comments
		Diabetic Macular Edema (DME)			
Aflibercept vs Bevacizumab					
Mean change in BCVA	1 RCT (N=442)	Some benefit in favor of aflibercept. Results of one trial showed a benefit for aflibercept over bevacizumab at 12 and 24 months, but the difference was likely not clinically meaningful[a] (12-month mean difference 3.5 letters [95% CI, 1.4 to 5.7], *P*<.001; 24-month mean difference 2.7 letters [95% CI, 0.3 to 4.2], *P*=.02). However, the benefit of aflibercept over bevacizumab was clinically meaningful at 12 months in a subgroup analysis of patients with lower baseline BCVA (mean difference 6.5 letters [95% CI, 2.9 to 10.1]; *P*<001). The difference was significant but smaller in this subgroup by 24 months (mean difference 4.7 letters [95% CI, 0.5 to 8.8]; *P*=.02).	---	Low	One trial showed a small difference between drugs that was likely not clinically meaningful; however, the difference was clinically meaningful in a subgroup of patients with lower baseline BCVA.
% patients gaining ≥15 letters	1 RCT (N=442)	Small benefit for aflibercept in the short-term but not long-term. Results of one trial showed a benefit with aflibercept over bevacizumab at 12 months (*P*=.028), but no difference was found by 24 months (*P*=.70). Similar results were found in a subgroup analysis of patients with lower baseline BCVA (*P*<.001 at 12 months; *P*=.74 at 24 months).	---	Low	One trial showed a difference between drugs at 12 months that was not present by 24 months.
Ocular adverse events	1 RCT (N=442)	No difference. Rates of most ocular adverse events within 24 months were very low (including endophthalmitis, <0.5% of both arms), with the exception of vitreous hemorrhage (7% of patients) and elevated intraocular pressure (15% of patients), but no differences were found between groups.	---	Low	
Systemic adverse events	1 RCT (N=442)	No difference. Rates of arterial thrombotic events[f] were similar between groups at 24 months (5.4% vs 7.8%, *P*=.34). Rates of other events were high, likely due to poor health at baseline, but no differences were found between groups.	---	Low	
Cost	1 RCT (N=442)	Total one-year treatment costs (including injections, rescue laser photocoagulation, and adverse events) were substantially lower for compounded bevacizumab[g] than for aflibercept ($4,100 vs $26,100 per patient). Validated 10-year modeling projections found no incremental cost-effectiveness benefit for the more expensive aflibercept (very high cost for modest quality of life gains), including for the subgroup with lower baseline BCVA.	---	Moderate	

Outcome	N studies (N=total patients randomized)	Summary of findings[a]	Combined summary estimate	Strength of Evidence[b]	Comments
Aflibercept vs Ranibizumab					
Mean change in BCVA	1 RCT (N=442)	Small benefit with aflibercept in the short-term but not long-term. Results of one trial showed a benefit for aflibercept over ranibizumab at 12 months, but the difference was likely not clinically meaningful (mean difference 2.1 letters [95% CI, 0.1 to 4.2], *P*=.034). This benefit was more pronounced in a subgroup of patients with lower baseline BCVA (mean difference 4.7 letters [95% CI, 1.4 to 8.0], *P*=.003). No significant differences were found between the drugs at 24 months in either the full analysis or subgroup analyses by baseline BCVA.	---	Low	One trial showed a small difference between the drugs at 12 months that was likely not clinically meaningful; the benefit was more significant in a subgroup with lower baseline BCVA, but no differences were found in either group by 24 months.
% patients gaining ≥15 letters	1 RCT (N=442)	No significant difference was found between drugs at 12 (*P*=.068) or 24 months (*P*=.70). However, subgroup analyses of patients with lower baseline BCVA showed a greater relative benefit with aflibercept at 12 months (*P*=.008), but not by 24 months (*P*=.75).	---	Low	
Ocular adverse events	1 RCT (N=442)	No difference. Rates of most ocular adverse events within 24 months were very low (no occurrences of endophthalmitis), with the exception of vitreous hemorrhage (6% of patients) and elevated intraocular pressure (17% of patients), but no differences were found between groups.	---	Low	
Systemic adverse events	1 RCT (N=442)	Higher rates of arterial thrombotic events[f] were reported in the intravitreal ranibizumab arm (5.4% vs 11.9% at 24 months, *P*=.047). Rates of other events were high, likely due to poor health at baseline, but no differences were found between groups.	---	Low	
Cost	1 RCT (N=442)	Total one-year treatment costs (including injections, rescue laser photocoagulation, and adverse events) were lower for ranibizumab than aflibercept ($18,600 vs $26,100 per patient). Validated 10-year modeling projections found no incremental cost-effectiveness benefit for the more expensive aflibercept,[h] including for the subgroup with lower baseline BCVA.	---	Moderate	
Bevacizumab vs Ranibizumab					
Mean change in BCVA	3 RCTs (N=584)	No difference. Pooled results of 3 trials showed no difference between drugs at 12 months, and 24-month results of one trial also found no difference (mean difference 2.0 letters [95% CI, -0.4 to 4.4]).	*12 months:* Pooled ES -1.190 (-2.889 to 0.509);	Moderate	Fairly wide confidence interval in pooled results of 3 trials.

Outcome	N studies (N=total patients randomized)	Summary of findings[a]	Combined summary estimate	Strength of Evidence[b]	Comments
			I^2=0%		
% patients gaining ≥15 letters	2 RCTs (N=484)	No difference. Pooled results of 2 trials showed no difference between drugs at 12 months, and 24-month results of one trial also found no difference (*P*=.70).	*12 months:* RR 0.871 (0.670 to 1.133); I^2=0%	Moderate	
Ocular adverse events	3 RCTs (N=584)	Mixed findings. One large trial reported very low rates of endophthalmitis (<0.5% in both arms), while a smaller trial reported 7% affected in one treatment group (statistical difference between drugs NR). Another study reported an overall rate of 3% but results were not reported by group. No differences reported between groups for other ocular adverse events and rates were generally low, except for vitreous hemorrhage (6% of patients) and elevated intraocular pressure (14% of patients) in one large trial.	---	Moderate	
Systemic adverse events	3 RCTs (N=584)	No difference. Rates of arterial thrombotic events[f] were similar between groups at 24 months (7.8% vs 11.9%, *P*=.20) in one large trial. Rates of other events were high, likely due to poor health at baseline, but no differences were found between groups.	---	Low	Data primarily from 1 large trial; 2 smaller trials had no events or insufficient reporting of events by group.
Cost	1 RCT (N=336)	Total one-year treatment costs (including injections, rescue laser photocoagulation, and adverse events) were substantially lower for compounded bevacizumab[g] than for ranibizumab ($4,100 vs $26,100 per patient). Validated 10-year modeling projections found no incremental cost-effectiveness benefit for the more expensive ranibizumab.	---	Moderate	
		Macular Edema due to Central Retinal Vein Occlusion (CRVO) or Branch Retinal Vein Occlusion (BRVO)			
Aflibercept vs Bevacizumab					
	None	---	---	No evidence	
Aflibercept vs Ranibizumab					
	None	---	---	No evidence	
Bevacizumab vs Ranibizumab					
Mean change in BCVA	2 RCTs (N=177)	No difference. Pooled results of 2 relatively small trials found no difference between drugs at 6 months.	*6 months:* Pooled ES -1.204 (-5.714 to 3.306); I^2=0%	Insufficient	Two small short-term trials provide an imprecise estimate.
% patients gaining ≥15 letters	2 RCTs (N=177)	No difference. Pooled results of 2 relatively small trials found no difference between drugs at 6 months.	*12 months:* RR 0.992 (0.805 to 1.223); I^2=0%	Insufficient	Two small short-term trials.

Outcome	N studies (N=total patients randomized)	Summary of findings[a]	Combined summary estimate	Strength of Evidence[b]	Comments
Ocular adverse events	2 RCTs (N=177)	Two small trials provide insufficient data. Serious ocular adverse events were relatively rare in 2 small trials, and there were no instances of endophthalmitis.	---	Insufficient	Two small short-term trials with low event rates.
Systemic adverse events	2 RCTs (N=177)	Two small trials provide insufficient data.	---	Insufficient	Two small short-term trials with low event rates.
Cost	None	---	---	No evidence	

Abbreviations: AMD = age-related macular degeneration; BCVA = best-corrected visual acuity; BRVO = branch retinal vein occlusion; CATT = Comparison of AMD Treatments Trials; CI = confidence interval; CRVO = central retinal vein occlusion; DME = diabetic macular edema; ES = effect size; N = number; NR = not reported; PRN = *pro re nata* ("as needed"); RCT = randomized controlled trial; RR = relative risk; VEGF = vascular endothelial growth factor

[a] A clinically meaningful difference in mean change in BCVA was defined as a difference of ≥ 5 ETDRS letters between drugs.

[b] The overall quality of evidence for each outcome is based on the consistency, coherence, and applicability of the body of evidence, as well as the internal validity of individual studies. The strength of evidence is classified as follows:

- High = Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Insufficient = Any estimate of effect is very uncertain.

[c] N=1226 for the 2 main groups of interest, the recommended dose of each drug administered monthly (2.0 mg aflibercept monthly vs 0.5 mg ranibizumab monthly).

[d] Pooled results showed a nonsignificant difference in mean BCVA change of 0.592 letters (95% CI, -4.406 to 5.590; *P*=.817), but should be interpreted with caution due to significant statistical heterogeneity (I^2=90.4%).

[e] Pooled results showed a nonsignificant RR of 1.045 (95% CI, 0.767 to 1.425; *P*=.780), but should be interpreted with caution due to significant statistical heterogeneity (I^2=72.6%).

[f] Defined by the Anti-Platelet Trialists' Collaboration as vascular death, nonfatal myocardial infarction, or nonfatal stroke.

[g] Compounded bevacizumab is not currently available within the VHA.

[h] Cost-effectiveness calculations for this study were based on the ranibizumab dose recommended for DME patients (0.3 mg); the cost of ranibizumab at the dose recommended for AMD and BRVO/CRVO (0.5 mg) is more expensive than aflibercept.

Our findings on the comparative effectiveness of anti-VEGF agents are consistent with other recent population-specific systematic reviews which found no significant differences between drugs. Two recent comparative effectiveness reviews of AMD trials found no differences in visual acuity improvements between aflibercept and ranibizumab,[6] or between bevacizumab and ranibizumab (mean difference in BCVA change -1.15 letters [95% CI, -2.82 to 0.51] at 2 years; likelihood of gaining 15 or more letters RR 0.90 [95% CI, 0.73 to 1.11] at one year).[9] The most recent systematic review of DME trials was published before results were available for DRCR.net Protocol T, by far the largest trial completed in this population; however, the review and a network meta-analysis using indirect data from 5 trials also found no differences in visual acuity between bevacizumab and ranibizumab.[8,50] No comparative systematic reviews were found for RVO, but a network meta-analysis found no differences between aflibercept, bevacizumab, and ranibizumab.[51]

In the individual trials included in our systematic review, relatively large standard deviations in mean change in BCVA (≥ 10 ETDRS letters/2 lines in all studies reporting this outcome) indicate that there was substantial variability in patients' responses to the anti-VEGF agents, with some gaining significantly more letters than others. Several studies have examined the reason for this variation and have found several factors that predict response to anti-VEGF treatment, such as younger age, prompt treatment initiation, and smaller area of neovascularization.[52,53] Genetic factors also appear to moderate response to anti-VEGF treatment, as studies have found several single nucleotide polymorphisms associated with change in visual acuity.[52,54-58] A combination of these and other factors likely explain why some patients respond very positively to anti-VEGF treatment, while others continue to lose visual acuity despite frequent injections.[57] While individual patients may respond differently to each anti-VEGF agent, it is unclear whether there are specific subgroups of patients who can be proactively identified as more favorably responding to one anti-VEGF agent versus another.

Another important factor involved in treatment response is visual acuity at baseline; studies have shown that higher baseline BCVA is associated with smaller BCVA gains during treatment,[52,53,59,60] including subgroup analyses of the DRCR.net Protocol T trial included in our review.[46,47] This phenomenon suggests that there may be a ceiling effect of anti-VEGF treatment, wherein visual acuity improvement plateaus after a ceiling BCVA is achieved (such as ≥ 70 ETDRS letters, as proposed by Sivaprasad 2014).[59] Thus, even though patients with good baseline BCVA are more likely to report good BCVA at follow-up, these patients will be less likely to show substantial improvement during the trial period—the primary outcome in most studies. The majority of the trials discussed in this review had inclusion criteria that allowed the enrollment of patients with baseline BCVA well above this threshold, which may help explain some of the variance in treatment response.

It is important to note that due to the rare nature of most serious systemic adverse events, the majority of studies included in this review were not powered to detect differences between groups for harms. However, our findings are consistent with a recent systematic review of 9 published and unpublished AMD trials which found that intravitreal bevacizumab and ranibizumab had similar rates of serious systemic adverse events (24% bevacizumab vs 22.2% ranibizumab; RR 1.08 [95% CI, 0.90 to 1.31]).[61] A sensitivity analysis excluding unpublished studies increased this relative risk to 1.21 (95% CI, 1.06 to 1.37), indicating possible publication bias that favors studies showing a difference between the drugs; in fact, this is very similar to the risk reported by another recent systematic review that did not include several recent studies (RR

1.27 [95% CI, 1.06 to 1.52]).[9] The review also found no differences in rates of death (3.7% bevacizumab vs 3.4% ranibizumab; RR 1.10 [95% CI, 0.78 to 1.57]) or arterial thrombotic events (3.2% bevacizumab vs 3.5% ranibizumab; RR 0.92 [95% CI, 0.62 to 1.37]).[61] However, gastrointestinal disorders were more common in the intravitreal bevacizumab groups (2.9% bevacizumab vs 1.6% ranibizumab; RR 1.82 [95% CI, 1.04 to 3.19]), and they tended to have more systemic infections (5% bevacizumab vs 3.7% ranibizumab; RR 1.34 [95%, 0.97 to 1.86]), although the difference did not reach statistical significance. Another systematic review found no difference between bevacizumab and ranibizumab in rates of major cardiovascular events (odds ratio [OR] 0.94 [95% CI, 0.59 to 1.52]) or non-ocular hemorrhage (OR 2.56 [95% CI, 0.78 to 8.38]), but bevacizumab was associated with higher rates of venous thromboembolic events (OR 3.45 [95% CI, 1.25 to 9.54]).[62]

Since bevacizumab is often compounded (where the contents of the sterile vial in which the drug comes packaged are separated into smaller doses for use in intravitreal injections), there is the potential to introduce contaminants that can cause infections like endophthalmitis.[63] However, the trials included in this review found no significant differences in the incidence of endophthalmitis between drugs, suggesting that proper aseptic compounding techniques can make bevacizumab as safe as the drugs packaged specifically for intravitreal injection. On the other hand, it is possible that these strictly controlled trials with very specific protocols regarding drug handling had lower incidences of endophthalmitis than is found with normal clinical practice. Furthermore, some studies also used antibacterial measures (such as topical antibiotics for several days after the injection) that may not be commonplace in routine practice. However, meta-analyses that included both clinical trials and observational studies also reported a very low incidence of endophthalmitis after anti-VEGF injection (ranging from 0.038% to 0.065%),[64] and 3 fairly recent large retrospective studies found either no difference between drugs,[65] or slightly lower rates after injection with bevacizumab (0.012%-0.017% vs 0.018-0.025% after ranibizumab injection and 0.031% after aflibercept).[66,67]

While very few differences were found between intravitreal anti-VEGF agents in rates of systemic adverse events in both our review and previous reviews, it is important to note that intravitreal anti-VEGF agents have been shown to pose an increased risk for some systemic harms when compared with sham injections or other treatments. This increased risk is presumably because a portion of the anti-VEGF agents injected into the eye reach the body's bloodstream and reduce systemic VEGF levels; there have also been reports that plasma anti-VEGF levels may be higher after intravitreal bevacizumab injections than the other 2 anti-VEGF drugs (likely due to its longer half-life),[68,69] but the clinical significance of this finding is unclear given the scarcity of empiric data showing higher rates of adverse events with intravitreal bevacizumab compared to the other anti-VEGF agents. A systematic review comparing intravitreal aflibercept or ranibizumab to sham and laser treatments in patients with DME found that the intravitreal anti-VEGF agents were associated with significantly increased rates of death (OR 2.98 [95% CI, 1.44 to 6.14]), cerebrovascular accidents (OR 2.33 [95% CI, 1.04 to 5.22]), and vascular death (OR 2.51 [95% CI, 1.08 to 5.82).[70] Another systematic review including various clinical populations found no increased risk of mortality or major cardiovascular (arterial thrombotic) events with anti-VEGF treatment, but patients treated with intravitreal ranibizumab had a slightly greater risk of non-ocular hemorrhage compared to sham/control groups (OR 1.57 [95% CI, 1.01 to 2.44]).[62] Patients with the conditions included in this review often have an increased risk of cardiovascular events, and thus clinicians and patients at high risk need to

weigh the additional risk of systemic adverse events with the improved visual acuity offered by intravitreal anti-VEGF injections.

LIMITATIONS

There are several limitations in the body of evidence included in this review. While many of the included trials had low ROB, a number of studies had methodological limitations that should be considered, such as lack of ITT analysis, poor reporting on adverse events, and unclear or insufficient methods of randomization, allocation concealment, and blinding. In addition, the paucity of trials enrolling patients with BRVO and CRVO limited the conclusions we could make about anti-VEGF agents in these populations. Aflibercept was also studied less often than the other agents, likely due to its relatively recent FDA approval. Several trials excluded patients with cardiovascular risk factors, limiting their applicability to many patients receiving anti-VEGF treatment.

Both trials that contributed evidence on costs used compounded bevacizumab; thus, we have limited evidence about comparative costs when the commercially available bevacizumab vial is used for only one injection (approximately 10 times the cost of compounded bevacizumab). This may be even more relevant in the future, as the FDA published a draft guidance document in February 2015 stating that repackaged biologic products must be used or discarded within 4 hours; if approved, this will effectively preclude the use of compounded bevacizumab.[71,72] Nevertheless, because the cost of the bevacizumab vial is less than per-dose costs of the other drugs and given their comparative effectiveness and harms, non-compounded bevacizumab is likely still more cost-effective than the other agents. However, in choosing amongst these drugs, clinicians may also need to consider factors such as patient preference, convenience, and distance to facility. Unlike most patients in the general population, many VHA patients must travel hundreds of miles to receive anti-VEGF injections, and thus the less frequent dosing possible with aflibercept could translate to reduced burden to the physician and patient as well as lower transportation expenses, although the cost implications of this were not specifically addressed in the studies. A large ongoing trial (estimated N=706) comparing ranibizumab PRN to bimonthly aflibercept in patients with AMD should help clarify the possible differences in dosing frequency between these drugs (NCT01958918 at ClinicalTrials.gov).

Another limitation of this systematic review was our decision to include only controlled trials for effectiveness and harms data. This may have omitted important data from observational studies, such as information about longer-term effects and rare harms. However, randomized controlled trials are considered the “gold standard” for determining the effectiveness of interventions and therefore provided the best evidence for answering these key questions. The large size and detailed adverse event reporting of many of the included trials provided strong evidence about potential harms, although it should be noted that they were not powered to detect differences between drugs in rates of these relatively rare adverse events. In addition, a recently published review by the Canadian Agency for Drugs and Technologies in Health assessed the data on the bevacizumab’s safety from any study design and came to the same conclusion as our review, finding that both the body of evidence as a whole as well as the most credible evidence indicate that bevacizumab is not associated with an increased risk of either cardiovascular and ophthalmic adverse events compared to ranibizumab.[73]

Another potential limitation of our review was our decision to examine the evidence according to clinical condition, which may have limited our power to detect differences between drugs. However, while the disease entities may share certain similarities, such as VEGF as a driving force, we felt that the distinct pathophysiology for each disease precluded the appropriateness of combining the conditions. Furthermore, exploratory meta-analyses pooling data from all disease groups (AMD, DME, and BRVO/CRVO) resulted in similar findings to the disease-specific summary estimates, with no significant differences found between drugs.

RESEARCH GAPS/FUTURE RESEARCH

While we identified several large RCTs with low ROB in patients with AMD, and one large low-ROB trial in patients with DME, there were no large, high-quality trials in patients with RVO. Fortunately, there are a few ongoing trials expected to be completed in the coming years that should help to ameliorate this evidence gap. An RCT currently being completed at the University of Amsterdam is comparing bevacizumab to ranibizumab treatment over 6 months in 296 BRVO patients (NCT01635803). Another large RCT (expected N=362), expected to be completed in March 2019, is comparing 6 months of treatment with aflibercept to bevacizumab in patients with CRVO (SCORE 2, NCT01969708). The third study included a fewer number of patients with CRVO (N=40), but will compare aflibercept and ranibizumab over 18 months (NCT02274259); results will likely be published shortly.

We also found very few studies reporting data on functional status and quality of life. While visual acuity outcomes are arguably the most important outcome when comparting intravitreal anti-VEGF agents, how the drugs affect patients' functioning and well-being is an important clinical consideration and one for which there is very little evidence. Also, as mentioned previously, our current evidence on cost outcomes are mostly limited to the cost of the drugs themselves, and thus future research should consider other costs associated with anti-VEGF treatment (*eg*, office visits, OCT imaging, and adverse events).

Only a few of the included studies evaluated the anti-VEGF agents for follow-up periods longer than one year, and the longest follow-up occurred after 2 years of treatment. Several retrospective studies or open-label extensions of trials have reported outcomes for up to 5 years of treatment, but they did not compare anti-VEGF agents.[74-76] We therefore have insufficient data regarding whether there are differences in effectiveness or harms between the drugs after longer periods of use. Since repeated injections are needed to avoid deteriorating visual acuity, future RCTs or large, methodologically rigorous observational studies should compare outcomes after the long-term use of these agents.

Finally, more trials are needed to determine the effectiveness of aflibercept compared to both bevacizumab and ranibizumab. Because the DRCR.net Protocol T trial in patients with DME found important differences in effectiveness between patients with lower compared to higher baseline visual acuity, future studies should also consider stratifying change in visual acuity by baseline BCVA in order to determine whether this is finding is reproduced in other disease populations as well.

CONCLUSIONS

This systematic review found intravitreal aflibercept, bevacizumab, and ranibizumab to have comparable effects on visual acuity and similar rates of ocular and systemic harms. Although no drug had a clear, consistent, clinically meaningful advantage over another agent, one trial of DME patients reported a small benefit for aflibercept over both bevacizumab and ranibizumab that was diminished or no longer significant after 24 months of treatment; however, the benefit of aflibercept was clinically meaningful at 12 months in a subgroup of patients with lower baseline visual acuity. Thus, more research is needed to characterize the potential benefits of aflibercept over the other agents. On the other hand, costs of treatment with compounded bevacizumab were shown to be substantially and consistently lower and thus the drug had a cost-effectiveness advantage over the other 2 agents. Potential tradeoffs for bevacizumab's cost-effectiveness include the inconvenience of slightly more frequent dosing and theoretical safety concerns related to compounding and higher blood plasma levels of the drug, although we found limited empirical data of any difference in harms between bevacizumab and the other anti-VEGF agents. Clinicians should also consider factors such as patient preference, individual treatment response, convenience, and distance to treatment facility when choosing amongst these 3 anti-VEGF agents.

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APPENDIX A. SEARCH STRATEGIES

SEARCH STRATEGY OVERVIEW

Databases Searched:

- Ovid Medline
- PubMed
- Elsevier Embase (http://Embase.com)
- Ovid EBM Reviews (Cochrane Central Register of Controlled Trials; Cochrane Database of Systematic Reviews; Health Technology Assessment; NHS Economic Evaluation Database)

Clinical Trial Registries:

- ClinicalTrials.gov (https://clinicaltrials.gov/ct2/search/advanced)
- WHO ICTRP (http://apps.who.int/trialsearch/)
- ISRCTN Registry (http://www.isrctn.com/)

Regulatory Agencies:

- FDA
- EMA

Conference Proceedings:

- Association for Research in Vision and Ophthalmology
- American Academy of Ophthalmology
- American Society of Retina Specialists
- COS Conference Papers Index

Scientific Information Packet Requests:

- LUCENTIS ® (ranibizumab); Genentech (Novartis)
- AVASTIN ® (bevacizumab); Genentech (Roche)
- EYLEA® (aflibercept); Regeneron Pharmaceuticals, Inc.

Future Research:

- NIH Reporter (https://projectreporter.nih.gov/reporter.cfm)
- AHRQ Gold (http://gold.ahrq.gov/projectsearch/)

ELECTRONIC SEARCH STRATEGIES

Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1946 to November Week 3 2015,
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 11, 2015
Date Searched: December 11, 2015

1	exp Angiogenesis Inhibitors/	38860
2	Antibodies, Monoclonal, Humanized/	30005
3	Endothelial Growth Factors/	8163
4	exp Vascular Endothelial Growth Factors/	42393
5	((endothelial adj2 growth adj2 factor*) or VEGF or VEGF-A or ((anti* or inhibit*) adj2 VEGF*) or antiVEGF* or anti-VEGF* or VEGF TRAP* or ((anti* or inhibit*) adj2 angiogen*)).tw.	72844
6	(aflibercept* or EYLEA* or bevacizumab* or Avastin* or ranibizumab* or Lucentis*).tw.	12368
7	or/1-6	129921
8	Visual acuity/	62548
9	(visual* or vision or ETDRS or BCVA).tw.	511121
10	or/8-9	530892
11	Diabetic Retinopathy/	20770
12	Glaucoma, Neovascular/	710
13	Macular Degeneration/	12937
14	Macular Edema/	5087
15	Wet Macular Degeneration/	956
16	Choroidal Neovascularization/	4602
17	Vitreous Hemorrhage/	1734
18	Retinal Vein Occlusion/	3355
19	((macula* adj3 (edema* or oedema* or degenerat*)) or (retin* adj3 (angiogenesis* or vein* or occlu* or obstruct* or clos* or stricture* or steno* or block* or embolism*)) or (proliferat* adj3 retinopath*) or (glaucoma* adj4 (neovascular* or haemorrhag* or hemorrhag* or thrombo* or congestive or rubeot*)) or (neovascular* adj2 (retinopath* or retinal* or intraocular* or intravitreal* or glaucoma* or choroidal)) or (vitreous adj2 (haemorrhag* or hemorrhag*)) or new blood vessel* or retinopath* or maculopath* or CME or CSME or CMO or CSMO or DMO or DME or NVG or NVI or BRVO or RVO or AMD or WAMD or CNV).tw.	83310
20	or/11-19	93025
21	and/7,10,20	4393
22	remove duplicates from 21	4166
23	limit 22 to (case reports or comment or editorial or letter or news)	689
24	**22 not 23 (GENERAL SEARCH RESULTS)**	**3477**
25	7 and 20	10749
26	(ae or co or de).fs.	5215408
27	(harm or harms or harmful or safe or safety or side effect* or undesirable effect* or treatment emergent or tolerability or toxic* or adrs or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes))).tw.	1331876
28	or/26-27	5972462
29	25 and 28	5489
30	limit 29 to (meta analysis or systematic reviews)	183
31	**30 not 24 (ADVERSE EVENTS/HARMS SEARCH RESULTS)**	**65**

Note: Bevacizumab/ and Ranibizumab/ are new MeSH Terms as of 2016, but currently do not have any results linked to the subject terms, and therefore these were not used in the search. Future search strategies however should include these MeSH terms.

PubMed

Date Searched: February 4, 2016

#14	**Search (#13 OR #7) (ALL SEARCH RESULTS)**	**450**
#13	**Search (#12 NOT #7) (ADVERSE EVENTS/HARMS SEARCH RESULTS)**	**34**
#12	Search (#11 AND english [language])	148
#11	Search (#10 AND #5)	154
#10	Search (#9 AND #8)	795
#9	Search (harm[Title/Abstract] OR harms[Title/Abstract] OR harmful[Title/Abstract] OR safe[Title/Abstract] OR safety[Title/Abstract] OR side effects[Title/Abstract] OR undesirable effect*[Title/Abstract] OR treatment emergent[Title/Abstract] OR tolerability[Title/Abstract] OR toxic*[Title/Abstract] OR adrs[Title/Abstract] OR adverse effect[Title/Abstract] OR adverse effects[Title/Abstract] OR adverse reaction[Title/Abstract] OR adverse reactions[Title/Abstract] OR adverse event[Title/Abstract] OR adverse events[Title/Abstract] OR adverse outcome[Title/Abstract] OR adverse outcomes[Title/Abstract])	1350876
#8	Search (#1 AND #3)	2656
#7	**Search (#6 AND english [language]) (GENERAL SEARCH RESULTS)**	**416**
#6	Search (#4 AND #5)	429
#5	Search ((publisher [sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR inprocess [sb] OR pubmednotmedline [sb] OR pmcbook OR (publisher [sb] AND (pubstatusnihms OR pubstatuspmcsd)))	2783356
#4	Search (#1 AND #2 AND #3)	1826
#3	Search (((macula*[Title/Abstract] AND (edema*[Title/Abstract] OR oedema*[Title/Abstract] OR degenerat*))[Title/Abstract] OR (retin*[Title/Abstract] AND (angiogenesis*[Title/Abstract] OR vein*[Title/Abstract] OR occlu*[Title/Abstract] OR obstruct*[Title/Abstract] OR clos*[Title/Abstract] OR stricture*[Title/Abstract] OR steno*[Title/Abstract] OR block*[Title/Abstract] OR embolism*))[Title/Abstract] OR (proliferat*[Title/Abstract] AND retinopath*)[Title/Abstract] OR (glaucoma*[Title/Abstract] AND (neovascular*[Title/Abstract] OR haemorrhag*[Title/Abstract] OR hemorrhag*[Title/Abstract] OR thrombo*[Title/Abstract] OR congestive[Title/Abstract] OR rubeot*))[Title/Abstract] OR (neovascular*[Title/Abstract] AND (retinopath*[Title/Abstract] OR retinal*[Title/Abstract] OR intraocular*[Title/Abstract] OR intravitreal*[Title/Abstract] OR glaucoma*[Title/Abstract] OR choroidal))[Title/Abstract] OR (vitreous[Title/Abstract] AND (haemorrhag*[Title/Abstract] OR hemorrhag*))[Title/Abstract] OR new blood vessel*[Title/Abstract] OR retinopath*[Title/Abstract] OR maculopath*[Title/Abstract] OR CME[Title/Abstract] OR CSME[Title/Abstract] OR CMO[Title/Abstract] OR CSMO[Title/Abstract] OR DMO[Title/Abstract] OR DME[Title/Abstract] OR NVG[Title/Abstract] OR NVI[Title/Abstract] OR BRVO[Title/Abstract] OR RVO[Title/Abstract] OR AMD[Title/Abstract] OR WAMD[Title/Abstract] OR CNV[Title/Abstract]))	59871
#2	Search ((visual*[Title/Abstract] or vision[Title/Abstract] or ETDRS[Title/Abstract] or BCVA[Title/Abstract]))	515210
#1	Search ((aflibercept*[Title/Abstract] OR EYLEA*[Title/Abstract] OR bevacizumab*[Title/Abstract] OR Avastin*[Title/Abstract] OR ranibizumab*[Title/Abstract] OR	12614

	Lucentis*[Title/Abstract]))	

Elsevier EMBASE.COM

Date Searched: February 3, 2016

#34	**#33 NOT #28 (ADVERSE EVENTS/HARMS SEARCH RESULTS)**	**99**
#33	#30 OR #31 AND ([systematic review]/lim OR [meta analysis]/lim)	202
#32	#30 OR #31	6,445
#31	#29 AND (harm:ab,ti OR harms:ab,ti OR harmful:ab,ti OR safe:ab,ti OR safety:ab,ti OR side:ab,ti AND effect*:ab,ti OR undesirable:ab,ti AND effect*:ab,ti OR treatment:ab,ti AND emergent:ab,ti OR tolerability:ab,ti OR toxic*:ab,ti OR adrs:ab,ti OR (adverse NEAR/2 (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes)):ab,ti)	1,636
#30	#29 AND ('adverse drug reaction'/lnk OR 'complication'/lnk OR 'side effect'/lnk)	5,716
#29	#10 AND #23	18,185
#28	**#25 NOT (#26 OR #27) (GENERAL SEARCH RESULTS)**	**5,131**
#27	#25 AND ([editorial]/lim OR [letter]/lim) 420	420
#26	#25 AND 'case report'/de 910	910
#25	#10 AND #13 AND #23 AND [embase]/lim 6,298	6,298
#24	#10 AND #13 AND #23 6,815	6,815
#23	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 127,711	127,711
#22	(macula* NEAR/3 (edema* OR oedema* OR degenerat*)):ab,ti OR (retin* NEAR/3 (angiogenesis* OR vein* OR occlu* OR obstruct* OR clos* OR stricture* OR steno* OR block* OR embolism*)):ab,ti OR (proliferat* NEAR/3 retinopath*):ab,ti OR (glaucoma* NEAR/4 (neovascular* OR haemorrhag* OR hemorrhag* OR thrombo* OR congestive OR rubeot*)):ab,ti OR (neovascular* NEAR/2 (retinopath* OR retinal* OR intraocular* OR intravitreal* OR glaucoma* OR choroidal)):ab,ti OR (vitreous NEAR/2 (haemorrhag* OR hemorrhag*)):ab,ti OR new:ab,ti AND blood:ab,ti AND vessel*:ab,ti OR retinopath*:ab,ti OR maculopath*:ab,ti OR cme:ab,ti OR csme:ab,ti OR cmo:ab,ti OR csmo:ab,ti OR dmo:ab,ti OR dme:ab,ti OR nvg:ab,ti OR nvi:ab,ti OR brvo:ab,ti OR rvo:ab,ti OR amd:ab,ti OR wamd:ab,ti OR cnv:ab,ti 91,083	91,083
#21	'retina vein occlusion'/exp 6,089	6,089
#20	'vitreous hemorrhage'/de 4,949	4,949
#19	'subretinal neovascularization'/de 7,248	7,248
#18	'wet macular degeneration'/de	520
#17	'macular edema'/exp	12,382
#16	'macular degeneration'/exp	22,598
#15	'neovascular glaucoma'/de	1,724
#14	'diabetic retinopathy'/exp	30,963
#13	#11 OR #12	657,503
#12	visual*:ab,ti OR vision:ab,ti OR etdrs:ab,ti OR bcva:ab,ti	631,128
#11	'visual acuity'/de	85,654
#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	528,436
#9	aflibercept*:ab,ti OR eylea*:ab,ti OR 'trap eye':ab,ti OR bevacizumab*:ab,ti OR avastin*:ab,ti OR ranibizumab*:ab,ti OR lucentis*:ab,ti	20,686
#8	'ranibizumab'/de	5,100
#7	'bevacizumab'/de	38,277
#6	'aflibercept'/de	2,484

#5	(endothelial NEAR/2 growth NEAR/2 factor*):ab,ti OR ((anti* OR inhibit*) NEAR/2 vegf*):ab,ti OR antivegf*:ab,ti OR 'anti vegf*':ab,ti OR (vegf NEAR/2 trap*):ab,ti OR ((anti* OR inhibit*) NEAR/2 angiogen*):ab,ti	79,695
#4	'vasculotropin'/de	77,826
#3	'endothelial cell growth factor'/de	2,066
#2	'monoclonal antibody'/exp	391,126
#1	'angiogenesis inhibitor'/exp	102,979

Ovid EBM Reviews

Cochrane Central Register of Controlled Trials December 2015
Cochrane Database of Systematic Reviews 2005 to January 29, 2016
D**atabase of Abstracts of Reviews of Effects** 2nd Quarter 2015
Health Technology Assessment 1st Quarter 2016
NHS Economic Evaluation Database 1st Quarter 2016

Date Searched: February 4, 2016

1	(aflibercept* or EYLEA* or bevacizumab* or Avastin* or ranibizumab* or Lucentis*).tw.	2147
2	(visual* or vision or ETDRS or BCVA).tw.	46966
3	((macula* adj3 (edema* or oedema* or degenerat*)) or (retin* adj3 (angiogenesis* or vein* or occlu* or obstruct* or clos* or stricture* or steno* or block* or embolism*)) or (proliferat* adj3 retinopath*) or (glaucoma* adj4 (neovascular* or haemorrhag* or hemorrhag* or thrombo* or congestive or rubeot*)) or (neovascular* adj2 (retinopath* or retinal* or intraocular* or intravitreal* or glaucoma* or choroidal)) or (vitreous adj2 (haemorrhag* or hemorrhag*)) or new blood vessel* or retinopath* or maculopath* or CME or CSME or CMO or CSMO or DMO or DME or NVG or NVI or BRVO or RVO or AMD or WAMD or CNV).tw.	6283
4	and/1-3	570
5	limit 4 to english language [Limit not valid in CDSR,DARE; records were retained]	434
6	and/1,3	749
7	(harm or harms or harmful or safe or safety or side effect* or undesirable effect* or treatment emergent or tolerability or toxic* or adrs or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes))).tw.	194241
8	and/6-7	311
9	limit 8 to english language [Limit not valid in CDSR,DARE; records were retained]	238
10	limit 9 to full systematic reviews [Limit not valid in CCTR,DARE,CLHTA,CLEED; records were retained]	226
11	limit 10 to new reviews [Limit not valid in CCTR; records were retained]	193
12	limit 11 to recently updated reviews [Limit not valid in CCTR,DARE,CLHTA,CLEED; records were retained]	174
13	12 not 5	21
14	13 or 5	455

ClinicalTrials.gov

Date Searched: February 7, 2016

11 studies found for: Interventional Studies | (aflibercept OR EYLEA OR trap-eye) and (bevacizumab OR Avastin) | Adult, Senior | Phase 3, 4
18 studies found for: Interventional Studies | (aflibercept OR EYLEA OR trap-eye) and (ranibizumab OR Lucentis) | Adult, Senior | Phase 3, 4

27 studies found for: Interventional Studies | (bevacizumab OR Avastin) and (ranibizumab OR Lucentis) | Adult, Senior | Phase 3, 4

WHO ICTRP

Date Searched: February 2, 2016

1	diabetic retinopath* OR neovascular* glaucoma OR AMD OR macular degeneration OR macular edema* OR macular oedema* OR vitreous hemorrhag* OR vitreous haemorrhag* OR choroidal neovascularization* OR choroidal neovascularisation* OR retinal vein occlusion*
2	aflibercept OR EYLEA OR trap-eye OR bevacizumab OR Avastin OR ranibizumab OR Lucentis
3	1 AND 2 = 1084 records for 739 trials*
*Of 1084 records, 797 were ClinicalTrials.gov records which were removed from the total number of results, and 287 records were downloaded	

ISRCTN Registry

Date Searched: February 2, 2016

Text Search	aflibercept OR EYLEA OR trap-eye OR bevacizumab OR Avastin OR ranibizumab OR Lucentis	61 results
Limit	Eye Diseases	22 results*
*Of 22 result records, 19 were on specified conditions and downloaded		

Association for Research in Vision and Ophthalmology (-2009 captured in COS Conference Papers Index)

Date Searched: February 8, 2016

2009-present conference content unavailable on Association website.

American Academy of Ophthalmology (-2007 captured in COS Conference Papers Index)

Date Searched: February 8, 2016

aflibercept* OR EYLEA* OR bevacizumab* OR Avastin* OR ranibizumab* OR Lucentis* = 0 results*

*Website conference database was not working correctly on search day, unable to view specific conference programs.

American Society of Retina Specialists

Date Searched: February 2, 2016

Past conference content unavailable on Society website and conference paper indices.

COS Conference Papers Index

Date Searched: February 8, 2016

(all(aflibercept*) OR all(EYLEA*) OR all(bevacizumab*) OR all(Avastin*) OR all(ranibizumab*) OR all(Lucentis*)) AND (all(Diabetic Retinopath*) or all(neovascular glaucoma) or all(macular degeneration) or all(macular edema) or all(choroidal neovasculari?ation) or all(vitreous haemorrhag*) or all(vitreous hemorrhage*) or all(retinal vein occlusion)) = 426 results

NIH Reporter

Date Searched: February 3, 2016

(aflibercept or EYLEA or bevacizumab or Avastin or ranibizumab or Lucentis) AND ;Search in: Projects AdminIC: All; Fiscal Year: Active Projects = 2 results

AHRQ Gold

Date Searched: February 3, 2016

aflibercept or EYLEA or bevacizumab or Avastin or ranibizumab or Lucentis = 0 results

APPENDIX B. QUALITY ASSESSMENT

CRITERIA USED IN QUALITY ASSESSMENT

Risk of Bias Assessment for Randomized Controlled Trials (RCTs): The Cochrane Collaboration Risk of Bias tool[18]

Overview

Domain	Description	Review authors' judgment
Sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Was the allocation sequence adequately generated?
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of or during enrollment.	Was allocation adequately concealed?
Blinding of participants, personnel and outcome assessors *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Was knowledge of the allocated intervention adequately prevented during the study?
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes).*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Were incomplete outcome data adequately addressed?
Selective outcome reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Are reports of the study free of suggestion of selective outcome reporting?
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Was the study apparently free of other problems that could put it at a high risk of bias?

Specific Criteria Details for Judging Risk of Bias by Domain

SEQUENCE GENERATION **Was the allocation sequence adequately generated? [Short form: *Adequate sequence generation*?]**	
Criteria for a judgment of 'YES' (*ie*, low risk of bias)	The investigators describe a random component in the sequence generation process such as: § Referring to a random number table; using a computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization.* *Minimization may be implemented without a random element, and this is considered

	to be equivalent to being random.
Criteria for the judgment of 'NO' (*ie*, high risk of bias)	The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: § Sequence generated by odd or even date of birth; § Sequence generated by some rule based on date (or day) of admission; § Sequence generated by some rule based on hospital or clinic record number. Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgment or some method of non-random categorization of participants, for example: § Allocation by judgment of the clinician; § Allocation by preference of the participant; § Allocation based on the results of a laboratory test or a series of tests; § Allocation by availability of the intervention.
Criteria for the judgment of 'UNCLEAR' (*ie*, uncertain risk of bias)	Insufficient information about the sequence generation process to permit judgment of 'Yes' or 'No'.
ALLOCATION CONCEALMENT **Was allocation adequately concealed? [Short form: *Allocation concealment*?]**	
Criteria for a judgment of 'YES' (*ie*, low risk of bias)	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: § Central allocation (including telephone, web-based, and pharmacy-controlled randomization); § Sequentially numbered drug containers of identical appearance; § Sequentially numbered, opaque, sealed envelopes.
Criteria for the judgment of 'NO' (*ie*, high risk of bias)	Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: § Using an open random allocation schedule (*eg*, a list of random numbers); § Assignment envelopes were used without appropriate safeguards (*eg*, if envelopes were unsealed or non-opaque or not sequentially numbered); § Alternation or rotation; § Date of birth; § Case record number; § Any other explicitly unconcealed procedure.
Criteria for the judgment of 'UNCLEAR' (*ie*, uncertain risk of bias)	Insufficient information to permit judgment of 'Yes' or 'No'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgment; for example, if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.
BLINDING OF PARTICIPANTS, PERSONNEL AND OUTCOME ASSESSORS **Was knowledge of the allocated interventions adequately prevented during the study? [Short form: *Blinding*?]**	
Criteria for a judgment of 'YES' (*ie*, low risk of bias)	Any one of the following: § No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding; § Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken; § Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.

Criteria for the judgment of 'NO' (*ie*, high risk of bias)	Any one of the following: § No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding; § Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken; § Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.
Criteria for the judgment of 'UNCLEAR' (*ie*, uncertain risk of bias)	Any one of the following: § Insufficient information to permit judgment of 'Yes' or 'No'; § The study did not address this outcome.
INCOMPLETE OUTCOME DATA **Were incomplete outcome data adequately addressed? [Short form: *Incomplete outcome data addressed*?]**	
Criteria for a judgment of 'YES' (*ie*, low risk of bias)	Any one of the following: § No missing outcome data; § Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); § Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; § For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; § For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; § Missing data have been imputed using appropriate methods.
Criteria for the judgment of 'NO' (*ie*, high risk of bias)	Any one of the following: § Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; § For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; § For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; § 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; § Potentially inappropriate application of simple imputation.
Criteria for the judgment of 'UNCLEAR' (*ie*, uncertain risk of bias)	Any one of the following: § Insufficient reporting of attrition/exclusions to permit judgment of 'Yes' or 'No' (*eg*, number randomized not stated, no reasons for missing data provided); § The study did not address this outcome.
SELECTIVE OUTCOME REPORTING **Are reports of the study free of suggestion of selective outcome reporting? [Short form: *Free of selective reporting*?]**	
Criteria for a judgment of 'YES' (*ie*, low risk of bias)	Any of the following: § The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; § The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

Criteria for the judgment of 'NO' (*ie*, high risk of bias)	Any one of the following: § Not all of the study's pre-specified primary outcomes have been reported; § One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (*eg*, subscales) that were not pre-specified; § One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); § One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; § The study report fails to include results for a key outcome that would be expected to have been reported for such a study.
Criteria for the judgment of 'UNCLEAR' (*ie*, uncertain risk of bias)	Insufficient information to permit judgment of 'Yes' or 'No'. It is likely that the majority of studies will fall into this category.
OTHER POTENTIAL THREATS TO VALIDITY **Was the study apparently free of other problems that could put it at a risk of bias? [Short form: *Free of other bias*?]**	
Criteria for a judgment of 'YES' (*ie*, low risk of bias)	The study appears to be free of other sources of bias.
Criteria for the judgment of 'NO' (*ie*, high risk of bias)	There is at least one important risk of bias. For example, the study: § Had a potential source of bias related to the specific study design used; or § Stopped early due to some data-dependent process (including a formal-stopping rule); or § Had extreme baseline imbalance; or § Has been claimed to have been fraudulent; or § Had some other problem.
Criteria for the judgment of 'UNCLEAR' (*ie*, uncertain risk of bias)	There may be a risk of bias, but there is either: § Insufficient information to assess whether an important risk of bias exists; or § Insufficient rationale or evidence that an identified problem will introduce bias.

QUALITY ASSESSMENT OF INCLUDED STUDIES

Author, Year; Trial name	**Sequence generation:** Was the allocation sequence adequately generated?	**Allocation concealment:** Was allocation adequately concealed?	**Blinding:** Was knowledge of the allocated intervention adequately prevented during the study?	**Incomplete outcome data:** Were incomplete outcome data adequately addressed?	**Selective outcome reporting:** Are reports of the study free of suggestion of selective outcome reporting?	**Other sources of bias:** Was the study apparently free of other problems that could put it at a high risk of bias?	**Overall assessment of potential for bias:** Low/Unclear/High
Choroidal Neovascularization Secondary to Age-Related Macular Degeneration (AMD)Trials							
Biswas 2011[33]	Yes: random number tables.	Unclear: blinding of random number table allocation not reported.	Assessors: Yes. Participants: Unclear. Providers: Yes.	Unclear: loss to follow-up acceptable (16.6% and 10%), but reasons were not reported. Analyses were not ITT.	No: protocol or registration number not provided. Definitions of "minor complications" not reported.	Unclear: effectiveness of randomization is unclear as more men were randomized to bevacizumab (56%) than to ranibizumab (41%).	Unclear
BRAMD; Schauwvlieghe 2016[45]	Yes: computer-generated using TENALEA Clinical Trial Data Management System and stratified by center, BCVA in study eye and fellow eye.	Yes: upon randomization an automatized email notification containing the allocation result was sent to the site's pharmacy.	Assessors: Yes. Participants and providers: Yes.	Yes: ITT analyses reported; acceptable and equal loss to follow-up (19.0%). Missing values imputed using last observation carried forward (LOCF) approach. BCVA at the moment of switch was used for patients who were switched to the other treatment due to non-response.	Unclear: all outcomes pre-specified in the protocol are reported. However, reporting of adverse events was not entirely clear (not separated by ocular vs systemic, just reports "occurrence of serious adverse events") and not all *P*-values reported.	Yes	Low

Author, Year; Trial name	**Sequence generation:** Was the allocation sequence adequately generated?	**Allocation concealment:** Was allocation adequately concealed?	**Blinding:** Was knowledge of the allocated intervention adequately prevented during the study?	**Incomplete outcome data:** Were incomplete outcome data adequately addressed?	**Selective outcome reporting:** Are reports of the study free of suggestion of selective outcome reporting?	**Other sources of bias:** Was the study apparently free of other problems that could put it at a high risk of bias?	**Overall assessment of potential for bias:** Low/Unclear/High
CATT; Martin 2012[41,42]	Yes: computer-generated randomization schedules using a web-based data management system, stratified according to clinical center with the use of a permuted-block method with a randomly chosen block size.	Yes: allocated using a web-based data management system.	Assessors: Yes Participants: No ("Patients were not informed of their drug assignment; however, insurance and billing documents specified ranibizumab but not study-supplied bevacizumab. Therefore, patients may have learned or deduced their assigned drug from these financial documents.") Providers: Yes (although not masked to dosing schedule, monthly or PRN).	Unclear: methods reported using ITT analyses but 1-year outcomes did not include 103 patients (8.6%) lost to follow-up (due to missing data). Three alternative approaches for handling missing data from the 52-week examination were performed as sensitivity analyses.	Yes: all outcomes pre-specified in the protocol are reported.	Yes	Low
GEFAL; Kodjikian 2013[34]	Unclear: randomized using "pre-established lists."	Yes: allocation completed by local hospital pharmacies.	Assessors: Yes. Participants and providers: Yes.	Unclear: 25% lost to follow-up and reasons were reported. Primary analysis was per protocol but ITT analysis also reported, although 97 (19.3%) patients were not included.	Unclear: specific secondary outcomes reported in publication were not reported in ClinicalTrials.gov protocol, and "time before re-injection" from the protocol was not reported in publication.	Unclear: some baseline differences in medical history and total choroidal neovascularization area; however, unlikely to have affected outcomes of interest.	Unclear

Author, Year; Trial name	**Sequence generation:** Was the allocation sequence adequately generated?	**Allocation concealment:** Was allocation adequately concealed?	**Blinding:** Was knowledge of the allocated intervention adequately prevented during the study?	**Incomplete outcome data:** Were incomplete outcome data adequately addressed?	**Selective outcome reporting:** Are reports of the study free of suggestion of selective outcome reporting?	**Other sources of bias:** Was the study apparently free of other problems that could put it at a high risk of bias?	**Overall assessment of potential for bias:** Low/Unclear/High
IVAN; Chakravarthy 2013[27,37,38]	Yes: computer-generated by a third party in blocks and stratified by center.	Yes: concealed using an internet-based system provided by Sealed Envelope Ltd.	Assessors: Yes. Participants and providers: Yes.	Unclear: 18 patients (9 in each group) were excluded from the analyses because they were randomized in error or were not treated, leaving 610 patients who received ≥1 injection. One-year results not reported for 49 (8%) participants and 2-year results not reported for 85 (13.9%). Reasons for withdrawals and missing data thoroughly reported. Multiple imputation using a series of chained regression equations was used to impute missing data.	Yes: all outcomes pre-specified in the protocol are reported.	Yes	Low
LUCAS; Berg 2015[39,40]	Yes: computer-generated with the use of the block method and stratified by center.	Yes: randomization completed by a third party.	Assessors: Yes Participants and providers: Yes	Yes: ITT and per-protocol analyses reported. Attrition was acceptable and even (15%).	Yes: protocol published on ClinicalTrials.gov, all outcomes pre-specified are reported.	Unclear: the patients in the ranibizumab group more often had a history of myocardial infarctions than the patients in the bevacizumab group; increased cardiac events in ranibizumab occurred during trial.	Low
MANTA; Krebs 2013[35]	Unclear: "Randomisation was stratified according to the	Yes: central allocation by members of the	Assessors: Yes. Participants and providers: Yes (injecting physician	Unclear: Efficacy analysis was ITT; last observation carried forward method used to handle missing	Unclear: Data for some measures had to be estimated from graphs.	Yes	Unclear

Author, Year; Trial name	**Sequence generation:** Was the allocation sequence adequately generated?	**Allocation concealment:** Was allocation adequately concealed?	**Blinding:** Was knowledge of the allocated intervention adequately prevented during the study?	**Incomplete outcome data:** Were incomplete outcome data adequately addressed?	**Selective outcome reporting:** Are reports of the study free of suggestion of selective outcome reporting?	**Other sources of bias:** Was the study apparently free of other problems that could put it at a high risk of bias?	**Overall assessment of potential for bias:** Low/Unclear/High
	clinical centre using a permuted block method with a fixed block size of 20," but process of selecting the blocks was not specified.	Department of Clinical Pharmacology at Medical University of Vienna, which was otherwise not involved in the study.	not blinded, but was not involved in the collection of data).	data for 69 (21.4%) patients. Loss to follow-up information not reported.			
Scholler 2014[29]	Yes: computer-generated list of random numbers.	Unclear: not reported.	Assessors: Unclear (not reported). Participants and providers: Unclear (not reported).	No: method of handling incomplete data not reported, unclear whether ITT analysis conducted (reports exclusion of 9 patients, but not whether they were included in analyses), uneven number of exclusions between groups.	No: registration numbers provided appear to be for a different trial. Did not provide mean change calculations for BCVA or anatomic outcomes.	No: Small study and power calculation not reported. Funding source not reported.	High
Subramanian 2010[26]	Unclear: "all subjects were assigned a study number."	Yes: central allocation by research pharmacist.	Assessors: Yes. Participants and providers: Yes.	No: ITT analysis not performed; uneven loss to follow-up (25% vs 13%).	No: adverse events only reported for patients completing 1-year follow-up visit. Data on minor adverse events not reported.	No: not powered to detect differences (original goal sample size was calculated to be 135, while actual enrollment was only 28, with only 22 analyzed).	High
VIEW 1; Heier 2012[43]	Unclear: "Consecutively enrolled patients were assigned to treatment groups on the basis of a	Yes: central allocation by an interactive voice response system.	Assessors: Yes Participants: Yes Providers: No, an unmasked investigator performed the	Yes: acceptable and equal loss to follow-up (7.1%); missing values imputed using last observation carried forward (LOCF) approach. "Full Analysis	Unclear: all outcomes pre-specified in ClinicalTrials.gov protocol; however, confidence intervals	Unclear: funded by manufacturer.	Low

Author, Year; Trial name	**Sequence generation:** Was the allocation sequence adequately generated?	**Allocation concealment:** Was allocation adequately concealed?	**Blinding:** Was knowledge of the allocated intervention adequately prevented during the study?	**Incomplete outcome data:** Were incomplete outcome data adequately addressed?	**Selective outcome reporting:** Are reports of the study free of suggestion of selective outcome reporting?	**Other sources of bias:** Was the study apparently free of other problems that could put it at a high risk of bias?	**Overall assessment of potential for bias:** Low/Unclear/High
	predetermined central randomization scheme with balanced allocation," but unclear what the "randomization scheme" entailed.		injection, but this was unlikely to have introduced bias	set" only included randomized patients who received any study medication and had a baseline and at least 1 post-baseline BCVA assessment; however, 99.4% of randomized patients were included in this analysis.	or *P*-values not reported for all outcomes.		
VIEW 2; Heier 2012[43]	Unclear: "Consecutively enrolled patients were assigned to treatment groups on the basis of a predetermined central randomization scheme with balanced allocation," but unclear what the "randomization scheme" entailed.	Yes: allocation managed by an interactive voice response system	Assessors: Yes Participants: Yes Providers: No, an unmasked investigator performed the injection, but this was unlikely to have introduced bias	Yes: acceptable and equal loss to follow-up (10.2%); missing values imputed using last observation carried forward (LOCF) approach. "Full Analysis set" only included randomized patients who received any study medication and had a baseline and at least 1 post-baseline BCVA assessment; however, 96.9% of randomized patients were included in this analysis.	Unclear: all outcomes pre-specified in ClinicalTrials.gov protocol; however, confidence intervals or *P*-values not reported for all outcomes.	Unclear: funded by manufacturer.	Low
Diabetic Macular Edema (DME) Trials							
DRCR.net (Protocol T); Wells 2016[46,47]	Yes: performed at the DRCR.net study website (computer-generated) in	Yes: central randomization at the DRCR.net study website.	Assessors: Yes. Participants and providers: Yes.	Yes: 7% lost to follow-up (similar between groups). Primary analysis used ITT; used Markov chain Monte Carlo method of multiple	Yes: all outcomes pre-specified in the protocol are reported.	Yes	Low

Author, Year; Trial name	**Sequence generation:** Was the allocation sequence adequately generated?	**Allocation concealment:** Was allocation adequately concealed?	**Blinding:** Was knowledge of the allocated intervention adequately prevented during the study?	**Incomplete outcome data:** Were incomplete outcome data adequately addressed?	**Selective outcome reporting:** Are reports of the study free of suggestion of selective outcome reporting?	**Other sources of bias:** Was the study apparently free of other problems that could put it at a high risk of bias?	**Overall assessment of potential for bias:** Low/Unclear/High
	permuted blocks and with stratification according to study site and visual acuity in the study eye.			imputation to impute missing data (sensitivity analyses with different approaches for handling missing data produced similar results). There was no imputation for missing data in secondary analyses.			
Ekinci 2014[30]	Unclear: randomization method not reported.	Unclear: allocation concealment method not reported.	Assessors: Unclear, not reported. Participants and providers: Unclear, not reported.	No: excluded 15 participants after randomization due to adverse events; not reported by randomization group.	Unclear: protocol or registration number not provided.	Yes: either made an error reporting ranibizumab dose, or used an atypical dose (one tenth of typical dose).	High
Nepomuceno 2013[31]	Yes: computer-generated sequence. However, if both eyes were eligible for treatment, one eye received randomized treatment and the contralateral eye received the other anti-VEGF agent.	Unclear: not reported.	Assessors: Yes. Participants and providers: Yes.	Unclear: incomplete data not reported. Analyses were not ITT.	No: change in BCVA was listed as the primary outcome but was not clearly reported for week 48. Outcomes were reported based on at what timepoint there were significant differences.	No: sample size calculation was based on power to detect a difference of 50um between groups in central subfield thickness, and might have been underpowered to detect clinically meaningful differences in BCVA. Also, since 15 patients were treated with both treatments (one in each eye), there was possible crossover that could obscure differences in effects between the drugs.	High

Author, Year; Trial name	**Sequence generation:** Was the allocation sequence adequately generated?	**Allocation concealment:** Was allocation adequately concealed?	**Blinding:** Was knowledge of the allocated intervention adequately prevented during the study?	**Incomplete outcome data:** Were incomplete outcome data adequately addressed?	**Selective outcome reporting:** Are reports of the study free of suggestion of selective outcome reporting?	**Other sources of bias:** Was the study apparently free of other problems that could put it at a high risk of bias?	**Overall assessment of potential for bias:** Low/Unclear/High
Macular Edema due to Central Retinal Vein Occlusion (CRVO) or Branch Retinal Vein Occlusion (BRVO) Trials							
CRAVE; Rajagopal 2015[32]	No: reported using centralized, computer-generated random table for assignments, but an additional 9 patients included in the study who were not randomized to treatment due to financial hardship and were instead assigned to the bevacizumab group.	Unclear: states that "assistance programs were used to defray any financial hardship, but if it could not be eliminated, then the patient was assigned to the bevacizumab arm," which could have introduced bias in allocation.	No: patients, technicians, and examining physicians were not masked to treatment.	Unclear: ITT using LOCF was used for analyses. 25% loss-to-follow-up, but reasons were not reported.	Yes: protocol published on ClinicalTrials.gov, all outcomes pre-specified are reported.	Unclear: power of the study was calculated for anatomical change (their primary outcome) of 50 μm, not BCVA, so it is unknown whether the study was powered to detect differences in BCVA. Original enrollment planned for 150 patients, but only 98 were randomized.	High
MARVEL; Narayanan 2015[36]	Unclear: "randomised...in a 1:1 ratio in block sizes of 6," but process of selecting the blocks was not specified.	Unclear: not reported.	Assessors: Unclear Participants: Unclear Providers: Yes Study is described as "double-masked" but does not specify blinding of outcome assessors (other than at baseline) or patients.	Yes: ITT analyses using LOCF to impute for missing data; 90% completed the study (reasons for not completing NR).	Unclear: a trial registration number was provided but the protocol was unavailable.	Effectiveness of randomization is unclear: *P*-values not reported for baseline characteristics, and the ranibizumab group had a much higher proportion of females (60% vs 32%)	Unclear

APPENDIX C. PEER REVIEW COMMENTS AND AUTHOR RESPONSES

Question Text	Reviewer Number	Comment	Response
Are the objectives, scope, and methods for this review clearly described?	1	Yes	Noted, thank you.
	2	Yes	Noted, thank you.
	3	Yes	Noted, thank you.
	4	Yes	Noted, thank you.
	5	Yes	Noted, thank you.
	6	Yes	Noted, thank you.
Is there any indication of bias in our synthesis of the evidence?	1	No	Noted, thank you.
	2	No	Noted, thank you.
	3	No	Noted, thank you.
	4	No	Noted, thank you.
	5	No	Noted, thank you.
	6	No	Noted, thank you.
Are there any published or unpublished studies that we may have overlooked?	1	No	Noted, thank you.
	2	No	Noted, thank you.
	3	No	Noted, thank you.
	4	No	Noted, thank you.
	5	No	Noted, thank you.
	6	No	Noted, thank you.
Additional suggestions or comments can be provided below. If applicable, please indicate the page and line numbers from the draft report.	2	Excellent report I do have one concern about the DME results and the overall conclusion drawn. Page 32 lines 21-30 shows aflibercept to have statistically significant superiority to bevacizumab with mean improvement in vision at 12 months and still with increased improvement but not statistically significant at 24 months. This was also true for those with lower baseline BCVA for the aflibercept versus ranibizumab on page 33 lines 7-17. These were deemed "not clinically significant" presumably due to the lack of statistical significance at 24 months yet in both the mean visual acuity improvement was still higher in the aflibercept group. The final conclusions on page 69 should likely reflect this consistent superior	We have changed “clinically significant” to “clinically meaningful” throughout the report and have clarified our definition in the Data Synthesis section of the Methods. A clinically meaningful difference often has a greater threshold than statistical significance, as it is related to whether the difference is substantial and noticeable to the patient and relevant to clinical practice. We determined the clinically meaningful difference between drugs to be 5 or more ETDRS letters (i.e., one line) in consultation with our ophthalmologist authors. Since the difference in mean change in BCVA between aflibercept and bevacizumab (and aflibercept and ranibizumab on the following page)

Question Text	Reviewer Number	Comment	Response
		improvement in VA at 12 months for aflibercept and improvement still yet not reaching statistical significance at 24 months. (This is stated in the table on page 62 line 56-60.	was less than 5 letters, this difference was not considered clinically meaningful. However, we revised the language in the paragraph about the subgroup with lower baseline BCVA, since the difference between groups was 6.5 letters. The final conclusion paragraph was also revised slightly to reflect the benefit seen with aflibercept in this study.
	2	In the comparative of cost-effectiveness section, although the literature only shows cost comparison data for multi-dosed vials of bevacizumab to the other two agents, the VA does not multi-dose the vial. Instead it is one 4cc vial per patient. Perhaps this should be mentioned either under this sub-section or in the Research Gaps/Future research section and that there is no cost comparative literature available when bevacizumab is not compounded. The cost-effectiveness will be reduced somewhat with this scenario but still likely superior to the two other agents. This could alternatively be mentioned in the Research Gaps/Future Research section on page 68.	This point was included in the Limitations section (second paragraph), but a sentence was added to the cost-effectiveness section (Key Question 3) as well. A clarification of this point was also added to the Executive Summary.
	3	Findings form this analysis were not unexpected and confirms what is known about this topic	Noted.
	3	p.19 typo regarding bevacizumab dose; should read 1.25mg Trials used standard recommended doses of the drugs unless otherwise indicated (aflibercept 2.0 mg; bevacizumab 0.5 mg; ranibizumab 0.5 mg for AMD and BRVO/CRVO, and 0.3 mg for DME).	Thank you, this has been corrected.
	3	For the tables discussing costs, consider adding a footnote that pricing is based on wholesale costs and not VA costs	The term “compounded” as well as a footnote was added to the Summary of Evidence table when talking about the cost of bevacizumab to clarify that the cost was for compounded bevacizumab, which is not currently available at the VHA.
	4	Although not clearly defined in the key questions, the treatment burden for patients is an important consideration. For example, when comparing aflibercept to bevacizumab in the treatment of AMD, the report mentions the fact that in the fixed interval dosing phase of the VIEW trials, the visual results were comparable between aflibercept given bimonthly and ranibizumab given monthly, although this result is not used in the interpretation of the results. The fact that aflibercept can be given less frequently is an important consideration for both patient and physician.	Thank you, we agree that this is an important consideration. While we had already included a statement to this effect in the Limitations section, we have added some language to the Discussion section to help further address this issue. We also added a brief statement to the Results section about the comparable visual acuity results between these two groups, although the cost implications are unclear since this was not explored by the trial.
	4	The report mentions that in the DRCR.net protocol discussing the	Our definition of a clinical significant or meaningful

Question Text	Reviewer Number	Comment	Response
		treatment of DME, the [*a priori*] subgroup analysis (emphasis mine) of patients with 20/50 or worse vision provides evidence that aflibercept results in better visual outcomes at 12 months than both bevacizumab and ranibizumab (although this improvement is lost at 24 months). This is an important point that should not be glossed over. The difference in visual outcomes in the study overall was driven by the patients with worse vision, at least in part because of a ceiling effect in the group with better starting vision (i.e. vision cannot be better than 20/20). A 7 letter difference between aflibercept and bevacizumab is indeed clinically significant (almost 2 lines of Snellen visual acuity). The conclusion that bevacizumab and aflibercept are equivalent in this context is erroneous. Even when considering the fact that the visual benefit decreases after 24 months, there is an important clinical benefit to having an additional year of better vision, even if this cannot be shown in terms of QALY or cost effectiveness.	difference in mean change in BCVA between drugs was clarified in the Methods section (5 or more ETDRS letters). We also revised this part in the Results to clarify the fact that aflibercept had a significant advantage over bevacizumab and ranibizumab at 12 months in the subgroup of patients with lower baseline BCVA. We added text to the Summary of Evidence table and Summary sections to clarify these findings as well.
	5	The report is comprehensive and includes all major RCTs on this topic. The report questions were adequately addressed.	Noted, thank you.
	6	We had three responses from field ophthalmologists. The points in all three comments are similar and captured in this comment: "The following finding for DME pts should be highlighted a bit more as an important finding: “These differences between aflibercept and both bevacizumab and ranibizumab were slightly more pronounced, but still clinically insignificant, in a subgroup analysis of patients with lower baseline BCVA.”	This statement was clarified in the text to highlight the fact that aflibercept had a clinically meaningful advantage over bevacizumab in this subgroup at 12 months. Similar statements have been added to summary statements throughout the draft.
	6	Also, the following phrase needs to be clarified: “While few differences between agents were seen for most AEs, previous trials and systematic reviews have shown that patients treated with anti-VEGF agents are at higher risk for serious systemic AEs, including death and cerebrovascular accidents.” I assume the latter clause was from the systemic use NOT intraocular use. This needs to be made clearer.	In fact, this sentence is referencing data from systematic reviews comparing intravitreal anti-VEGF agents to sham/placebo or other treatments (such as laser therapy), which show an increased risk for some systemic AEs associated with intravitreal anti-VEGF. The wording in this sentence was revised to clarify this. A more detailed discussion of this evidence can be found in the last paragraph of the “Summary of the Evidence” section in the Discussion (immediately before the Limitations section).

APPENDIX D. DETAILED DATA ABSTRACTION

Abbreviations Used in Appendix D

Abbreviation	Term
AE	Adverse event
AMD	Age-related macular degeneration
B	Bevacizumab
BCVA	Best-corrected visual acuity (represented in ETDRS letters unless otherwise indicated)
BRVO	Branch retinal vein occlusion
CI	Confidence interval
CFT	Central foveal thickness
CMT	Central macular thickness
CNV	Choroidal neovascularization
CRT	Central retinal thickness
CRVO	Central retinal vein occlusion
CST	Central subfield thickness
DME	Diabetic macular edema
EQ-5D	European Quality of Life-5 Dimensions
ETDRS	Early Treatment of Diabetic Retinopathy Study
FA	Fluorescein angiogram
G	Group (G1 = Group 1)
GMR	Geometric mean ratio
HbA1c	Hemoglobin A1c
HR	Hazard ratio
HTN	Hypertension
IOP	Intraocular pressure
IQR	Interquartile range
ITT	Intention-to-treat
logMAR	Logarithm of the Minimal Angle of Resolution
LS	Least squares
MacDQoL	Macular Disease-dependent Quality of Life
MacTSQ	Macular Disease Treatment Satisfaction Questionnaire
MI	Myocardial infarction
N	Number
NCT	National Clinical Trial register number (ClinicalTrial.gov)
NEI VFQ-25	25-item National Eye Institute Visual Functioning Questionnaire
NR	Not reported
NS	Not significant
OCT	Optical coherence tomography
OR	Odds ratio
PDT	Photodynamic therapy
PRN	*Pro re nata* (“as needed”)
QOL	Quality of life

Abbreviation	Term
R	Ranibizumab
PRP	Panretinal photocoagulation
RR	Relative risk
RVO	Retinal vein occlusion
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
TIA	Transient ischemic attack
VEGF	Vascular endothelial growth factor
US	United States

Trials in Patients with Choroidal Neovascularization Secondary to Age-Related Macular Degeneration (AMD)

Study	**Biswas 2011[33]**	**BRAMD; Schauwvlieghe 2016[45]**	**CATT; Martin 2012[41,42]**
• *Follow-up* • *Country* • *NCT or ID number* • *Funding*	• 18 months • India • NR • None ("Source of Support: Nil.")	• 12 months • the Netherlands • Trialregister.nl NTR1704 • The Netherlands Organisation for Health Research and Development; Dutch health insurance companies	• 24 months • US • NCT00593450 • National Eye Institute
Objective	To determine and compare the efficacy and safety of intravitreal ranibizumab and bevacizumab in treatment of choroidal neovascular membrane due to AMD.	To compare the effectiveness of bevacizumab and ranibizumab in the treatment of exudative AMD.	To assess the relative efficacy and safety of ranibizumab and bevacizumab and to determine whether PRN regimen would compromise long-term visual acuity, as compared with a monthly regimen.
Population/ Condition	Choroidal neovascular membrane secondary to AMD.	Primary or recurrent sub- or juxtafoveal CNV secondary to AMD.	Previously untreated active CNV due to AMD
Population Character-istics (baseline)	Age: 63.9 years (SD NR) Male: 48% (B vs R: 56% vs 41%) Mean BCVA: 57.5 (B vs R: 56.80 vs 58.19) Mean CMT: 286.2 μm Occult choroidal neovascular membrane: 44%	Age: 78 years (SD 7) Male: 44% Mean BCVA: 60 (SD 13) Mean CRT: 378 μm (SD 115)	Age: 79.2 years (SD 7.5) Male: 38.2% White: 98.6% Mean BCVA: 60.6 (SD 13.5) Mean foveal thickness: 460 μm (SD 187)
Main Inclusion Criteria	Patients aged more than 50 years; patients with baseline BCVA 35-70; all cases of CNV with classic and occult lesions; all cases of subfoveal and juxtafoveal CNV; cases with active leakage pattern; baseline CMT ≥250 μm.	Age ≥60 years; primary or recurrent sub- or juxtafoveal CNV secondary to AMD; total area of CNV of < 12 disc areas; BCVA 20-78 letters.	Age ≥50 years; presence in the study eye (one eye per patient) of previously untreated active CNV due to AMD (leakage on FA and subretinal or intraretinal fluid on OCT); visual acuity 20/25 to 20/320 on electronic visual-acuity testing; CNV or sequela of the CNV involving the center of the fovea.
Main Exclusion Criteria	Previous treatment for CNV in either eye; macular scarification; coexisting other ocular pathology (like advanced cataract, high myopia, chorio-retinal atrophic	The patient was labelled as a poor-responder and treatment was changed to the other drug if at any visit after the third injection there was a drop in BCVA of >10 letters	Previous treatment in the study eye; previous treatment with intravenous bevacizumab or concurrent use of systemic anti-VEGF agents; any concurrent intraocular condition in the

Study	**Biswas 2011[33]**	**BRAMD; Schauwvlieghe 2016[45]**	**CATT; Martin 2012[41,42]**
	patches, diabetic retinopathy, glaucoma); one-eyed patients; history of ocular surgery within last 6 months; history of cerebrovascular accident and MI.	compared to baseline and there was clear evidence of active CNV or leakage by qualitative OCT and/or FA assessment or at least two of the following signs of leakage on OCT: CRT >300 μm, intraretinal cysts or subretinal fluid any time after the third injection.	study eye (*eg*, cataract or diabetic retinopathy) that could either require medical or surgical intervention during the 2 year follow-up period; active or recent (within 4 weeks) intraocular inflammation; current vitreous hemorrhage in the study eye.
Intervention vs Comparator • *Schedule* • *Co-Intervention/ Rescue Treatment*	**G1:** Bevacizumab 1.25 mg **G2:** Ranibizumab 0.5 mg • **Schedule** (both groups): monthly for 3 months; retreatment afterwards based on OCT or BCVA changes (increase in CMT of >100 μm after the initial 3 injections in or fall in BCVA by >5 letters). • Full aseptic measures on 3 consecutive months	**G1:** Bevacizumab 1.25 mg **G2:** Ranibizumab 0.5 mg • **Schedule** (both groups): Administered monthly.	**G1:** Bevacizumab 1.25 mg monthly **G2:** Ranibizumab 0.5 mg monthly **G3:** Bevacizumab 1.25 mg PRN **G4:** Ranibizumab 0.5 mg PRN • **Schedule**: Monthly regimens were given an injection every 28 days; PRN regimens were given one initial injection and then only when signs of active CNV were present (fluid on OCT, new or persistent hemorrhage, decreased visual acuity as compared with the previous examination, or dye leakage or increased lesion size on FA). Patients in the monthly groups were re-randomized at 12 months to either continue with monthly injections or switch to PRN (study drug not changed). • At the discretion of the investigator, topical antibiotic was used 4 times a day for 3 days (including day of injection).
N	120 G1: 60 (50 analyzed) G2: 60 (54 analyzed)	332 (327 analyzed) G1: 166 G2: 166	1208 (1105 analyzed at 12 months, 1030 analyzed at 24 months) G1: 286 G2: 301 G3: 300 G4: 298
Visual Outcomes (ETDRS chart unless otherwise indicated); Functional Status/QOL Outcomes	**G1 vs G2** • Mean change in BCVA: -12 months: 0.52 vs 3.22; *P*=.463 -18 months: 3.96 vs 3.56; *P*=.563 • Mean BCVA achieved: -12 months: 57.32 vs 61.41 -18 months: 60.76 vs 61.74 • Proportion of participants gaining/losing BCVA letters from baseline: -Gaining >15 letters: 12% vs 26% -Gaining >5 letters: 32% vs 33% -Maintaining BCVA (≤5 letters change): 60% vs 56% -Losing >5 letters: 8% vs 11% -Losing >15 letters: 0% vs 4%	**G1 vs G2** • Mean change in BCVA: 5.1 (SD 14.1) vs 6.4 (12.2); *P*=.37 • Mean BCVA achieved: 65.0 (SD 19.0) vs 66.4 (SD 15.8); *P*=.37 • Proportion of participants gaining/losing BCVA letters from baseline: -Gaining ≥15 letters: 24% vs 19% -Maintaining BCVA (<15 letters change): 65% vs 76% -Losing ≥15 letters: 11% vs 5% • Number of switchers: 6% vs 5%	**G1 vs G2 vs G3 vs G4** • Mean change in BCVA -12 months: 8.0 (SD 16) vs 8.5 (SD 14) vs 5.9 (SD 16) vs 6.8 (SD 13); *P*=.16 ◦Longitudinal regression model, estimated mean change: 7.3 (SE 0.8) vs 7.2 (SE 0.7) vs 6.1 (SE 0.7) vs 6.4 (SE 0.6); *P*=.53 -24 months: 7.8 (SD 15.5) vs 8.8 (SD 15.9) vs 5.0 (SD 17.9) vs 6.7 (SD 14.6); *P*=.21 between drugs ◦Longitudinal regression model, estimated mean change: 0.7 letters (95% CI, -0.9 to 2.3), *P*=.41 • Mean BCVA achieved: -12 months: 68.4 (SD 18.2) vs 68.8 (SD 17.7) vs 66.5 (SD 19.0) vs 68.4 (SD 16.4); *P*=.45 -24 months: 68.2 (SD 16.1) vs 68.5 (SD 18.9) vs 66.0 (SD 19.9) vs 68.5 (15.3); *P*=.17 between drugs

Study	**Biswas 2011[33]**	**BRAMD; Schauwvlieghe 2016[45]**	**CATT; Martin 2012[41,42]**
			• Proportion of participants gaining/losing BCVA letters from baseline: -12 months: ◦Gaining ≥15 letters: 31.3% vs 34.2% vs 28.0% vs 24.9%; *P*=.09 ◦Gaining 5-14 letters: 37.0% vs 31.7% vs 33.2% vs 36.1% ◦Maintaining vision (≤4 letters change): 18.9% vs 21.8% vs 26.3% vs 21.8% ◦Losing 5-14 letters: 6.8% vs 6.7% vs 8.5% vs 8.1% ◦Losing ≥15 letters: 6.0% vs 5.6% vs 8.5% vs 4.6%; *P*=.29 -24 months (patients treated with same dosing regimen for entire 2 years): ◦Gaining ≥15 letters: 31.8% vs 32.8% vs 28.3% vs 30.7% ◦Gaining 5-14 letters: 27.9% vs 36.6% vs 31.5% vs 29.5% ◦Maintaining vision (≤4 letters change): 24.0% vs 16.4% vs 19.5% vs 23.5% ◦Losing 5-14 letters: 8.5% vs 7.5% vs 9.2% vs 9.1% ◦Losing ≥15 letters: 7.8% vs 6.7% vs 11.6% vs 7.2% • Proportion of participants achieving Snellen equivalent of 20/40 or better (>68 ETDRS letters) at 24 months: 60.5% vs 67.9% vs 62.1% vs 63.3%
Anatomic Outcomes (reported in μm unless otherwise indicated)	**G1 vs G2** • Mean change in CMT from baseline: -12 months: -26.44 vs -27.59; *P*=.283 -18 months: -37.96 vs -44.70; *P*=.281 • Percentage of patients showing improvement in CMT: 60% (mean 78.73 μm) vs 63% (mean 96.5 μm) • Percentage of patients showing deterioration in CMT: 40% (mean 41.4 μm) vs 37% (mean 56.6 μm)	**G1 vs G2** • Mean change in CRT: -131 (SD 129) vs -138 (SD 117); *P*=.31 • Subretinal fluid and intraretinal cysts absent on OCT: 44% vs 59%; *P*=.020	**G1 vs G2 vs G3 vs G4** • Mean change in total foveal thickness: -12 months: -164 (SD 181) vs -196 (SD 176) vs -152 (SD 178) vs -168 (SD 186); *P*=.03 -24 months: -180 (SD 196) vs -190 (SD 172) vs -153 (SD 189) vs -166 (SD 190); *P*=.38 between drugs • Fluid absent on OCT: -12 months: 26.0% vs 43.7% vs 19.2% vs 23.9%; *P*<.001 -24 months: 30.2% vs 45.5% vs 13.9% vs 22.3%; *P*=.0003 between drugs
Harms/Adverse Event (AE) outcomes (in study eye)	**G1 vs G2** Minor complications: 11.1% vs 7.3%	**G1 vs G2** • ≥1 serious AE: 21.1% vs 22.3%; *P*=.87 • Number of AEs: 256 vs 299; *P*=.48 *Systemic AEs:* • Death due to serious AE: 0.6% vs 0.6%; *P*=.6818 • Cardiac disorders: 2.5% vs 3.7% • Gastrointestinal disorders: 1.2% vs 1.2%	**G1 vs G2 vs G3 vs G4** *Ocular AEs:* • Endophthalmitis: 1.2% vs 0.7%; *P*=.38 • Pseudo-endophthalmitis: 0.2% vs 0.2%; *P*=1.00 *Systemic AEs:* • ≥1 serious AEs: 39.9% vs 31.7%; *P*=.004; adjusted RR 1.30 (95% CI, 1.07 vs 1.57), *P*=.009 • All-cause death: 6.1% vs 5.3%; *P*=.62 • Arterial thrombotic events: 5.0% vs 4.7%: *P*=.89

Study	**Biswas 2011[33]**	**BRAMD; Schauwvlieghe 2016[45]**	**CATT; Martin 2012[41,42]**
			-Nonfatal stroke: 1.4% vs 1.3%; *P*=1.00 -Nonfatal MI: 1.2% vs 1.5%; *P*=.80 -Vascular death: 2.4% vs 2.0%; *P*=.70 • Venous thrombotic events: 1.7% vs 0.5%; *P*=.054 • HTN: 0.7% vs 0.5%; *P*=.72 • Cardiac disorders: 10.6% vs 7.8%; *P*=.11 • Gastrointestinal disorders: 4.8% vs 1.8%; *P*=.005 • AEs not previously associated with anti-VEGF treatment (*eg*, arterial thrombotic events, systemic hemorrhage, congestive heart failure, venous thrombotic events, HTN, and vascular death): 34.5% vs 28.4%; *P*=.02
Cost and Burden Outcomes	**G1 vs G2** • Mean number of injections: 4.3 vs 5.6	NR	**G1 vs G2 vs G3 vs G4** • Mean number of injections : -12 months (max 13): 11.9 (SD 1.2) vs 11.7 (SD 1.5) vs 7.7 (SD 3.5) vs 6.9 (SD 3.0); *P*=.003 between PRN groups -24 months (max 26): 23.4 (SD 2.8) vs 22.4 (SD 3.9) vs 14.1 (SD 7.0) vs 12.6 (SD 6.6); *P*=.01 between PRN groups • Average cost of drug per patient in US dollars (based on per-dose cost of $50 for bevacizumab and $2,000 for ranibizumab): -12 months: 595 vs 23,400 vs 385 vs 13,800 -24 months: 1,170 vs 44,800 vs 705 vs 25,200
Notes; Subgroup Analyses	• **Subgroup analyses:** -Ranibizumab: Mean change in BCVA at 18 months, whole group vs predominantly classic subgroup: 3.55 vs 5.24 -Bevacizumab: Mean change in BCVA at 18 months, whole group vs predominantly classic subgroup: 3.96 vs 5.4	Non-inferiority trial	• "The data and safety monitoring committee recommended that data for 23 patients at one study center be excluded because of serious protocol noncompliance, so analyses included only the 1185 patients who were enrolled at the remaining 43 centers in the analyses." • At 12 months, treatment decisions by study ophthalmologists were consistent with the retreatment protocol for 2336/3268 examinations (71.5%) in the group assigned to ranibizumab PRN and for 2328/3133 examinations (74.3%) in the group assigned to bevacizumab PRN. • Re-randomization: At 12 months, patients initially assigned to monthly treatment retained their drug assignment but were reassigned randomly to either monthly or as-needed treatment. However, 24-months results recorded here only for patients treated with the same dosing regimen for 2 years.

Study	**GEFAL; Kodjikian 2013[34]**	**IVAN; Chakravarthy 2013[27,37,38]**	**LUCAS; Berg 2015[39,40]**
• *Follow-up* • *Country* • *NCT or ID number* • *Funding*	• 12 months • France • NCT01170767 • French Ministry of Health; French Health Insurance System	• 24 months • UK • ISRCTN 92166560 • UK National Institute for Health Research Health Technology Assessment programme	• 24 months • Norway • NCT01127360 • Oslo University Hospital
Objective	To evaluate the relative efficacy and safety profile of bevacizumab versus ranibizumab intravitreal injections for the treatment of neovascular AMD.	To compare the efficacy and safety of ranibizumab and bevacizumab intravitreal injections to treat neovascular AMD; to estimate the effectiveness of discontinuous versus continuous treatment regimens; and to estimate the cost-effectiveness of the alternative treatment strategies.	To compare the efficacy and safety of bevacizumab versus ranibizumab when administered according to a treat-and-extend protocol for the treatment of neovascular AMD.
Population/ Condition	Active subfoveal neovascular AMD.	Active previously untreated neovascular AMD with neovascular lesion involving the center of the fovea.	Previously untreated active neovascular AMD.
Population Character-istics (baseline)	Age: 79.2 years (SD 7.1) Male: 33.7% Mean BCVA: 55.2 (SD 14.0)	Age: 77.7 years Male: 40% Mean BCVA: 61.4 (SD 15.3) More participants in the bevacizumab group than the ranibizumab group had a history of angina (17% vs 11%).	Age: 78.3 years (SD 7.9) Male: 32.5% Mean BCVA: 61 (SD 13.5) Mean CRT: 364.5 μm History of MI (B vs R): 5.6% vs 11.9%; *P*=.021
Main Inclusion Criteria	Patients aged >50 years with BCVA between 20/32 and 20/320 (Snellen equivalent) measured on the ETDRS chart at a distance of 4 m; active subfoveal neovascular AMD; and total CNV area <12 optic disc areas.	Adults ≥50 years old with previously untreated neovascular AMD in the study eye and BCVA ≥25 letters on the ETDRS chart and a foveal neovascular lesion. Participants without a subfoveal (within 200 μm) neovascular component were eligible if subretinal fluid or serous pigment epithelial detachment was subfoveal.	Age ≥50 years; previously untreated active neovascular AMD in one eye; BCVA between 20/25 and 20/320.
Main Exclusion Criteria	Eyes with subfoveal fibrosis or atrophy; retinal pigment epithelial tear involving the macula; subretinal hemorrhage involving the center of the fovea (>50% of total CNV area); previous treatment with intraocular anti-VEGF or intravenous bevacizumab therapy; history or presence of intraocular inflammation or infection; and uncontrolled systemic HTN despite medical treatment; etc.	Lesions comprising >50% fibrosis or blood (to avoid including inactive or advanced disease); greatest linear diameter >6000 μm; ≥8 diopters of myopia; thick blood involving the center of the fovea; previous treatment (argon laser within 6 months, PDT or a VEGF inhibitor to the study eye); other active ocular disease causing concurrent vision loss.	Pigment epithelial detachments with no associated intraretinal or subretinal edema and lesions comprising more than 50% blood or fibrosis.
Intervention vs Comparator • *Schedule* • *Co-Intervention/ Rescue Treatment*	**G1:** Bevacizumab 1.25 mg **G2:** Ranibizumab 0.5 mg • **Schedule** (both groups): monthly for 3 months; retreatment afterwards based on OCT or BCVA changes (loss of 5 letters from the previous visit with no	**G1:** Ranibizumab 0.5 mg (monthly or PRN) **G2:** Bevacizumab 1.25 mg (monthly or PRN) • **Schedule**: All groups received injections monthly for 3 months. Groups in the monthly regimen were treated monthly thereafter. Participants randomized to the PRN groups were not retreated after 3 months unless prespecified clinical and OCT criteria for	**G1:** Bevacizumab 1.25 mg **G2:** Ranibizumab 0.5 mg • **Schedule** (both groups): A "treat-and-extend" protocol was employed. Patients were examined and injected every 4 weeks until no signs of active AMD were found. If there were no signs of active neovascular disease, a

Study	**GEFAL; Kodjikian 2013[34]**	**IVAN; Chakravarthy 2013[27,37,38]**	**LUCAS; Berg 2015[39,40]**
	obvious atrophy or subretinal fibrosis and fluid on OCT; active exudation on OCT [subretinal fluid unless stable since the last 3 monthly injections, macular edema with intraretinal fluid, or increase in CST of ≥50 µm compared with the previous examination]; increased CNV area or persistence of leakage on angiography since previous visit; or new or persistent subretinal or intraretinal macular hemorrhage).	active disease were met (any subretinal fluid, increasing intraretinal fluid, or fresh blood; uncertainty about these criteria and BCVA had drop of ≥10 letters; or fluorescein leakage >25% of the lesion circumference or expansion of CNV). If retreatment was needed, a further cycle of 3 doses delivered monthly was delivered.	new injection was given and the period to the next treatment was extended by 2 weeks at a time, up to a maximum interval of 12 weeks. Recurrent disease was defined as any fluid on OCT, new or persistent hemorrhage or dye leakage, or increased lesion size on FA. If examination showed any sign of recurrence, the interval was shortened by 2 weeks at a time, until the disease was considered to be inactive. • The protocol allowed for withdrawal of patients defined as nonresponders, with the intention of offering patients alternative treatments if available.
N	501 G1: 191 G2: 183	628 (610 analyzed) G1: 323 (314 analyzed) G2: 305 (296 analyzed)	441 (431 analyzed) G1: 220 (213 analyzed) G2: 221 (218 analyzed) Patients who developed wet AMD in the nonstudy eye received the same drug in both eyes (31 patients in G1 and 25 patients in G2).
Visual Outcomes (ETDRS chart unless otherwise indicated); Functional Status/QOL Outcomes	**G1 vs G2** • Mean change in BCVA: 4.82 (SD 14.85) vs 2.93 (SD 15.09); *P*=.4200 • Mean BCVA achieved: 59.44 (SD 18.52) vs 58.70 (SD 19.82); *P*=.8632 • Proportion of participants gaining/losing BCVA letters from baseline: -Gaining ≥15 letters: 20.4% vs 21.3%; *P*=.8318 -Gaining ≥5 letters: 54.5% vs 49.7%; *P*=.3607 -Losing ≥5 letters: 20.9% vs 24.6%; *P*=.4001 -Losing ≥15 letters: 8.9% vs 9.8%; *P*=.7562	**G1 vs G2** • Mean change in BCVA -12 months: 6.4 (SD 12.8) vs 4.7 (SD 12.5); weighted mean difference -1.66 (95% CI, -3.83 to 0.50) -24 months: 4.9 (SD 15.0) vs 4.1 (SD 13.5); weighted mean difference -0.80 (95% CI, -3.26 to 1.66) • Mean BCVA achieved: -12 months: 69.1 (SD 15.7) vs 66.2 (SD 17.1) -24 months: 67.8 (SD 17.0) vs 66.1 (SD 18.4); mean difference -1.37 (95% CI, -3.75 to 1.01); *P*=.26 • Proportion of participants gaining/losing BCVA letters from baseline: -12 months: ◦Gaining ≥15 letters: 23% vs 16% ◦Gaining 5-14 letters: 33% vs 31% ◦Losing 5-14 letters: 10% vs 14% ◦Losing ≥15 letters: 5% vs 4% -24 months: ◦Gaining ≥15 letters: 24% vs 16% ◦Gaining 5-14 letters: 32% vs 34% ◦Losing 5-14 letters: 12% vs 12% ◦Losing ≥15 letters: 9% vs 9% • Bailey-Love Near Word Visual acuity chart, logMAR: -Mean at 12 months: 0.57 (SD 0.38) vs 0.62 (SD 0.41); GMR 0.92 [95% CI, 0.84 to 1.00]; *P*=.058	**G1 vs G2** • Mean change in BCVA (ITT analysis): -12 months: 7.8 vs 8.0; mean difference 0.2 (95% CI, -2.2 to 2.5), *P*=.550 -24 months: 7.8 vs 7.5; mean difference -0.3 (95% CI, -3.2 to 2.7), *P*=.873 • Mean BCVA achieved: -12 months: 67.2 (SD 17) vs 69.6 (SD 15.1); *P*=.148 -24 months: 68.0 (SD 17.0) 67.2 (SD 19.1); *P*=.690 • Proportion of participants gaining/losing BCVA letters from baseline: -12 months: ◦Gaining ≥15 letters: 25.5% vs 26.7% ◦Gaining ≥5 letters: 36.4% vs 40.6% ◦Maintaining vision (<4 letters change): 25.5% vs 23.0% ◦Losing ≥5 letters: 8.7% vs 5.3% ◦Losing ≥15 letters: 3.8% vs 4.3% -24 months: ◦Gaining ≥15 letters: 29.9% vs 29.1% ◦Gaining 5-14 letters: 34.7% vs 34.3% ◦Maintaining vision (≤4 letters

Study	GEFAL; Kodjikian 2013[34]	IVAN; Chakravarthy 2013[27,37,38]	LUCAS; Berg 2015[39,40]
		-Mean at 24 months: 0.55 (SD 0.39) vs 0.61 (SD 0.42); GMR 0.94 (95% CI, 0.85 to 1.04), *P*=.23 • Median change from baseline on Belfast Reading Speed chart: -Median at baseline: 36.9 (IQR 15.6 to 65.3) vs 35.0 (IQR 14.0 to 69.6) -Median at 12 months: 57.5 (IQR 23.4 to 94.4) vs 51.8 (IQR 11.5 to 94.6) -Median at 24 months: 50.9 (IQR 22.8 to 93.7) vs 52.5 (IQR 9.7 to 90.6); mean difference -1.34 (95% CI, -8.29 to 5.61), *P*=.70 • Pelli-Robson Contrast Sensitivity chart (letters): -Mean change from baseline at 12 months: 2.1 (SD 4.9) vs 2.1 (SD 5.0) -Mean change from baseline at 24 months: 1.5 (SD 5.9) vs 1.7 (SD 5.1); mean difference 0.21 (95% CI, -0.62 to 1.04), *P*=.62. • Median months from randomization to first treatment failure: 4.9 (IQR 3.2 to 14.0) vs 5.1 (IQR 3.7 to 16.8); HR 1.13 (95% CI, 0.94 to 1.36); *P*=.18. • EQ-5D Utility Index (higher score = better utility): -Median change at 12 months: -0.12 (IQR -0.24 to 0.00) vs -0.13 (IQR -0.26 to 0.00) -Median change at 24 months: -0.15 (IQR -0.27 to 0.00) vs -0.15 (IQR -0.27 to 0.00); score of 1 (“perfect health”) OR 0.89 (95% CI, 0.64 to 1.25), *P*=.51 • MacDQoL [disease-specific QOL index] (lower score = less impact on QOL): -Median at 12 months: -1.27 (IQR -2.76 to -0.36) vs -1.18 (IQR -3.14 to -0.39) -Median at 24 months: -1.45 (IQR -2.77 to -0.27) vs -1.39 (IQR -2.73 to -0.41); GMR 1.05 (95% CI, 0.78 to 1.42), *P*=.74 • MacTSQ treatment satisfaction index (higher score = higher treatment satisfaction): -Median at 12 months: 66.00 (IQR 61.00 to 69.00) vs 66.00 (IQR 59.50 to 69.00) -Median at 24 months: 66.00 (IQR 61.50 to 70.00) vs 65.00 (IQR 60.00 to 69.00); OR 0.79 (95% CI, 0.54 to 1.16), *P*=.23	change): 18.0% vs 19.2% ◦Losing 5-14 letters: 9.6% vs 7.0% ◦Losing ≥15 letters: 7.8% vs 10.5%
Anatomic Outcomes (reported in µm unless otherwise indicated)	**G1 vs G2** • Intraretinal and subretinal fluid absent on OCT: 50.5% vs 58.2%; *P*=.14 • Change in CST from baseline: -94.96 (SD 132.78) vs -107.23 (SD 103.25); *P*=.27 • Pigment epithelial	**G1 vs G2** • Mean change in total thickness at the fovea at 24 months: -146.9 (SD 177.4) vs -133.8 (SD 205.0); GMR 0.96 (95% CI, 0.90 to 1.03), *P*=.24 • Fluid absent on OCT at 24 months: 50% vs 41%; OR 0.72 (95% CI, 0.50 to 1.02), *P*=.065	**G1 vs G2** • Mean change in CRT plus subfoveal fluid: -12 months: -108 (SD 102) vs -111 (SD 96); mean difference 3 (95% CI, -16 to 22); *P*=.265. -24 months: -111 (SD 116) vs -112 (SD 105); mean difference 1 (95% CI , -22 to 20), *P*=.923

Study	**GEFAL; Kodjikian 2013[34]**	**IVAN; Chakravarthy 2013[27,37,38]**	**LUCAS; Berg 2015[39,40]**
	detachment on OCT: 33.2% vs 30.6%; 0.596		• Fluid absent on OCT (intraretinal or subretinal): -12 months: 47.0% vs 65.2%; *P*<.001 -24 months: 55.1% vs 72.1%; *P*<.001
Harms/Adverse Event (AE) outcomes (in study eye)	**G1 vs G2** • ≥1 serious AE: 12.6% vs 12.1%; *P*=.8757 • Withdrawn due to AE: 2.8% vs 2.9% *Ocular AEs:* • Eye disorders: 0.8% vs 2.1%; *P*=.2791 • Amaurosis fugax: 0% vs 0.4% • Retinal artery occlusion: 0.4% vs 0% • Subretinal hematoma: 0.4% vs 0.8% • Vitreous hemorrhage: 0% vs 0.4% • Endophthalmitis: 0% vs 0.4% • Retinal detachment: 0% vs 0% • Traumatic cataract: 0% vs 0% *Systemic AEs:* • ≥1 systemic serious AE: 12.2% vs 10.0%; *P*=.4510 • Death: 0.8% vs 1.3%; *P*=.6818 • Arterial thrombotic events: -MI: 0.4% vs 0.4%; *P*=1.0 -Stroke: 0% vs 0%; *P*=1.0 • Venous thrombotic events: -Pulmonary embolism: 0.4% vs 0.0%; *P*=1.0 -Phlebitis: 0% vs 0%; *P*=1.0 • TIA: 0% vs 0%; *P*=1.0 • HTN: 0.4% vs 0.8%; *P*=.6189 • Gastrointestinal disorder: 2.3% vs 2.3%; *P*=.994	**G1 vs G2** • ≥1 serious AE: 28.3% vs 27.7% • Withdrawals due to serious AEs: 1.3% vs 1.9% *Ocular AEs:* • ≥1 ocular AE: 2.0% vs 2.5% • Endophthalmitis: 0% vs 0% • Retinal detachment: 0% vs 0.3% • Retinal hemorrhage: 0% vs 0.3% • Retinal pigment epithelial tear: 0.3% vs 1.0% • Traumatic cataract: 0.3% vs 0.3% • Vitreous hemorrhage: 0.3% vs 0% • RVO: 0% vs 0.3% • Uveitis: 0.3% vs 0% • Infection: 0.3% vs 0.0% *Systemic AEs:* • ≥1 serious systemic AE: 27.0% vs 25.8%; OR 0.96 (95% CI, 0.66 to 1.39), *P*=.82 • All-cause death: 5.1% vs 4.8%; OR 0.96 (95% CI, 0.46 to 2.02), *P*=.91 • Any vascular event, heart failure, or all-cause death: 9.5% vs 12.1%; OR 1.36 (95% CI, 0.80 to 2.29); *P*=.25 • Arterial thrombotic event: 3.4% vs 4.1%; OR 1.24 (95% CI, 0.53 to 2.86) -Non-fatal MI: 1.4% vs 1.3% -Non-fatal stroke: 1.0% vs 1.9% -Vascular death: 1.4% vs 1.0% • Heart failure: 0.7% vs 2.2% • Arterial thrombotic event or heart failure: 4.1% vs 6.4%; OR 1.69 (95% CI, 0.80 to 3.57), *P*=.16 • Venous thrombotic events: 1.4% vs 1.0% • TIA: 0.3% vs 0.3% • Hospitalized for angina: 1.0% vs 2.2% • Cardiac disorders: 6.4% vs 6.4% • Gastrointestinal disorders: 3.0% vs 1.0%; OR 0.31	**G1 vs G2** • Withdrawal due to AE: 7.3% vs 4.1% *Ocular AEs:* • Endophthalmitis: 0.5% vs 0%; *P*=.499 • Pseudo-endophthalmitis: 1.4% vs 0%; *P*=.123 • Macular hemorrhage: 1.4% vs 0.0%; *P*=.123 • Retinal tear: 0.5% vs 0%; *P*=.499 • Pigment epithelial rupture: 0.5% vs 0%; *P*=.499 • Acute glaucoma: 0.5% vs 0%; *P*=.499 *Systemic AEs:* • ≥1 serious systemic AE: 29.1% vs 30.3%; *P*=.778 • All-cause death: 6.8% vs 5.9%; *P*=.687 • Arterial thrombotic events: 4.1% vs 6.3%; *P*=.289 -Nonfatal MI: 1.4% vs 4.1%; *P*=.080 -Nonfatal stroke: 1.4% vs 1.8%; *P*=1.0 -Vascular death: 1.4% vs 0.9%; *P*=.685 • Venous thrombotic events: 0% vs 1.4%; *P*=.248 • TIA: 1.4% vs 0%; *P*=.123 • HTN: 0.9% vs 0.9%; *P*=1.0 • Cardiac disorder: 5.5% vs 8.6%; *P*=.197 • Gastrointestinal disorder: 3.2% vs 5.0%; *P*=.341
Cost and Burden Outcomes	**G1 vs G2** • Mean number of injections: 6.8 (SD 2.7) vs 6.5 (SD 2.4); *P*=.39 • Patients requiring monthly injections: 4.2% vs 1.6%; *P*=.14	**G1 vs G2** • Median number of treatments: 18 (IQR 11 to 23) vs 19 (IQR 12 to 23)	**G1 vs G2** • Mean number of injections: -12 months: 8.9 (SD 2.6) vs 8.0 (SD 2.3); *P*=.001 -24 months: 18.2 vs 16.0; mean difference 1.2 (95% CI, -3.4 to -1.0), *P*≤.001 Average treatment interval in weeks: 6.5 vs 7.6 • Proportion of patients receiving

Study	GEFAL; Kodjikian 2013[34]	IVAN; Chakravarthy 2013[27,37,38]	LUCAS; Berg 2015[39,40]
			injections at treatment interval: -4 weeks: 27% vs 20%; *P*=.002 -12 weeks: 10% vs 17%; *P*=.002
Notes; Subgroup Analyses	Non-inferiority trial	4 exclusions (3 patients wrong drug injected; 1 patient was not treatment naïve). • **Subgroup Analyses:** No statistically significant differences were found for the drug or treatment regimen comparisons (*P*≥.26) for the following subgroup analyses: baseline BCVA in fellow eye, baseline retinal angiomatous proliferation, baseline lesion, baseline CNV size, baseline BCVA, hemorrhage was present at baseline, study eye ≥5 letters better than in the fellow eye at baseline.	• Non-inferiority study • All 9 patients from 1 study center were excluded because of serious protocol violations, and 1 patient was excluded after a serious retinal and vitreous hemorrhage a few days after inclusion.

Study	**MANTA; Krebs 2013[35]**	**Scholler 2014[29]**	**Subramanian 2010[26]**
• *Follow-up* • *Country* • *NCT or ID number* • *Funding*	• 12 months • Austria • NCT00710229 • Austrian Ophthalmologic Society, Ludwig Boltzmann Institute of Retinology and Biomicroscopic Lasersurgery	• 12 months • Austria • Unclear (registration numbers provided appear to be for a different trial) • NR	• 12 months • US • ISRCTN 73359806 • VA Boston Healthcare System
Objective	To examine whether bevacizumab is inferior to ranibizumab with respect to maintaining/improving visual acuity.	To evaluate the number of needed injections within one year of treatment.	To compare bevacizumab to ranibizumab for treatment of AMD in terms of visual and anatomic outcomes.
Population/ Condition	Active primary or recurrent subfoveal lesion with CNV secondary to AMD.	Active previously untreated neovascular AMD	Symptomatic CNV affecting the foveal center secondary to AMD
Population Character-istics (baseline)	Age: 77.2 years (SD 8.0) Male: 36.3% Mean BCVA: 56.7 (SD 13.3)	Age: 80.1 years (SD 6.7) Male: 29.1% Mean BCVA: 58.0 (SD 11.7) Mean CRT: 422 μm (SD 124)	Age: 78.6 years Male: 95% Caucasian: 100% Mean BCVA (B vs R): 34.9 (range 12-60) vs 32.7 (range 4-66); *P*=.80 Classic or predominantly classic CNV (B vs R): 20% vs 14%
Main Inclusion Criteria	Treatment naive patients >50 years with active primary or recurrent subfoveal lesion with CNV secondary to AMD; BCVA using ETDRS 20/40 to 20/320. If both eyes were eligible for inclusion in the present study, the eye that showed more progression (loss of distance acuity) based on the local investigator's assessment was included.	Age ≥50 years; neovascular AMD verified by fluorescence angiography; BCVA between 20/40 and 20/320.	Age >50 years; presence of a symptomatic CNV (confirmed by intravenous fluorescein angiogram and OCT) affecting the foveal center; baseline BCVA ≥20/400.
Main Exclusion Criteria	Prior treatment with any intravitreal drug or verteporfin PDT in the study eye; prior treatment with systemic bevacizumab or any intravitreal drug; subfoveal fibrosis or atrophy in the study eye >50%; active intraocular inflammation; acute or recurrent infectious conjunctivitis; history of MI and/or stroke.	Previous AMD treatment; previous systemic bevacizumab treatment; vision impairing cataract or other ophthalmologic disease like glaucoma, active inflammation, diabetic retinopathy, etc.	Previous treatment for wet AMD within the past year; presence of subretinal hemorrhage >50% of the size of the lesion on FA; presence of advanced glaucoma; history of malignant or uncontrolled HTN, intraocular inflammation, or history of thromboembolic phenomena.
Intervention vs Comparator • *Schedule* • *Co-Intervention/ Rescue Treatment*	**G1:** Bevacizumab 1.25 mg **G2:** Ranibizumab 0.5 mg • **Schedule** (both groups): monthly for 3 months; retreatment afterwards based on OCT or BCVA changes (BCVA loss of ≥5 letters with OCT or fluorescein angiographic evidence of fluid in the macula; an increase in CRT ≥100 μm; new macular hemorrhage; new area of classic CNV; or evidence of persistent fluid on OCT ≥1 month after the previous injection).	**G1:** Bevacizumab 1.25 mg **G2:** Ranibizumab 0.5 mg • **Schedule** (both groups): monthly for 3 months; retreatment afterwards based on OCT or BCVA changes (loss of BCVA of ≥5 letters with OCT evidence of fluid in the macula; increase in CRT of ≥100 μm; new area of AMD; new macular hemorrhage; persistent fluid on OCT ≥1 month after the previous injection).	**G1:** Bevacizumab (dose not reported) **G2:** Ranibizumab (dose not reported) • **Schedule** (both groups): monthly for 3 months; retreatment afterwards based on OCT or BCVA changes and clinical examination (qualitative increase in intraretinal or subretinal fluid by OCT; if any significant worsening of visual acuity or increase in fluid or hemorrhage present on clinical examination, a repeat FA was administered with possible re-injection based on the results). • Patients were treated with topical antibiotics for 4 days after injection.
N	317 G1: 154 G2: 163	55 (number analyzed unclear) G1: 29 G2: 26	28 (22 analyzed) G1: 20 (15 analyzed) G2: 8 (7 analyzed)

Study	**MANTA; Krebs 2013[35]**	**Scholler 2014[29]**	**Subramanian 2010[26]**
Visual Outcomes (ETDRS chart unless otherwise indicated); Functional Status/QOL Outcomes	**G1 vs G2** • Mean change in BCVA: 4.9 vs 4.1; *P*=.78 • Mean BCVA achieved: 62.2 (95% CI, 60.1 to 64.3) vs 60.7 (95% CI, 58.7 to 62.8) • Proportion of participants gaining/losing BCVA letters from baseline (all estimated from graph): -Gaining ≥15 letters: 23% vs 21%; *P*=.42 -Gaining ≥5 letters: 58% vs 53%; *P*=.31 -Losing ≥5 letters: 21% vs 21%; *P*=.11 -Losing ≥15 letters: 5% vs 6%; *P*=.23	**G1 vs G2** • Mean BCVA achieved: 64.75 (SD 17.03) vs 59.12 (SD 16.64); mean difference 5.5, *P*=.631 • Proportion of participants losing ≥15 letters from baseline: 6.9% vs 7.7%	**G1 vs G2** • Mean change in BCVA: 7.6 vs 6.3; *P*=.74 • Mean BCVA achieved: 42.5 (SD 13.7) vs 39.0 (SD 10.1); *P*=.5 • Proportion of participants gaining/losing BCVA letters from baseline: -Gaining ≥15 letters: 33% vs 14% -Gaining ≥5 letters: 60% vs 57% -Losing ≥5 letters: 27% vs 14% -Losing ≥15 letters: 0% vs 14% *NOTE: BCVA measured using ETDRS at 2 m instead of recommended 4 m; vision was recorded in the same, consistent fashion for all study subjects.
Anatomic Outcomes (reported in μm unless otherwise indicated)	**G1 vs G2** • Mean change in CRT (corrected values): -86.3 vs -89.9; *P*=.81	**G1 vs G2** • Mean CRT: 350.47 (SD 102.84) vs 315.67 (SD 65.86); *P*=.088	**G1 vs G2** • Mean change in CMT: -50 vs -91; *P*=.29
Harms/Adverse Event (AE) outcomes (in study eye)	**G1 vs G2** • Total number of AEs: 19 (12.3%) vs 15 (9.2%); *P*=.37 *Ocular AEs:* 0 (0%) vs 0 (0%); *P*=1.0 *Systemic AEs:* • Death: 3 (1.9%) vs 2 (1.2%); *P*=.61 • Vascular disorders: -Heart attack: 3 (1.9%) vs 2 (1.2%); *P*=.61 -Stroke: 1 (0.6%) vs 1 (0.6%); *P*=.94 -Mesenteric artery occlusion: 1 (0.6%) vs 0 (0%); *P*=.30 • Non-vascular disorders: -Infection: 3 (1.9%) vs 3 (1.8%); *P*=.94 -Injury or procedural complication: 2 (1.3%) vs 3 (1.8%); *P*=.70 -Surgical or medical procedure: 1 (0.6%)vs 0 (0%); *P*=.30 -Any system organ class: 3 (1.9%) vs 2 (1.2%); *P*=.61	**G1 vs G2** *Ocular AEs:* • Subretinal bleeding: 0% vs 7.7% *Systemic AEs:* • TIA: 0% vs 3.8%	No major ocular AEs or systemic AEs reported in any subjects who completed the one-year follow-up visit. Minor AEs (*eg*, subconjunctival hemorrhage, transient post-injection pain, and elevated IOP) data not reported. No reports of anterior chamber inflammation, vitreous hemorrhage, retinal detachment, endophthalmitis, or systemic AEs in patients completing one-year follow-up.
Cost and Burden Outcomes	**G1 vs G2** • Mean number of re-treatments: 6.1 (SD 2.8) vs 5.8 (SD 2.7); *P*=.26	**G1 vs G2** • Mean number of injections: 5.80 (SD 2.28) vs 5.00 (SD 1.67); *P*=.084	**G1 vs G2** • Mean number of injections: 8 (range 3-8) vs 4 (3-6); *P*=.001
Notes; Subgroup Analyses	Non-inferiority approach (power calculated assuming 7 letter increase in BCVA with ranibizumab and no change in BCVA with bevacizumab). The study was not powered to determine AEs of statistical significance.		• VA Boston Healthcare System Hospital. • Inclusion criteria amended from BCVA 20/40 to 20/200, to BCVA ≥20/400. • BCVA measured at 2 m instead of recommended 4 m because of exam room size; vision was recorded in the same, consistent fashion for all study subjects.

Study	**VIEW 1; Heier 2012[43]**	**VIEW 2; Heier 2012[43]**	**VIEW 1 and VIEW 2 combined 96-week results; Schmidt-Erfurth 2014[44]**
• Follow-up *• Country* *• NCT or ID number* *• Funding*	• 12 months • US and Canada • NCT00509795 • Regeneron Pharmaceutical and Bayer HealthCare	• 12 months • Europe, the Middle East, Asia-Pacific, and Latin America • NCT00637377 • Regeneron Pharmaceutical and Bayer HealthCare	•22 months • US, Canada, Europe, the Middle East, Asia-Pacific, and Latin America • NCT00509795 and NCT00637377 • Regeneron Pharmaceutical and Bayer HealthCare
Objective	To compare monthly and every-2-month dosing of intravitreal aflibercept injection with monthly ranibizumab in patients with neovascular AMD.	To compare monthly and every-2-month dosing of intravitreal aflibercept injection with monthly ranibizumab in patients with neovascular AMD.	To compare monthly and every-2-month dosing of intravitreal aflibercept injection with monthly ranibizumab in patients with neovascular AMD.
Population/ Condition	Active subfoveal CNV lesions or juxtafoveal lesions with leakage affecting the fovea, secondary to AMD.	Active subfoveal CNV lesions or juxtafoveal lesions with leakage affecting the fovea, secondary to AMD.	Active subfoveal CNV lesions or juxtafoveal lesions with leakage affecting the fovea, secondary to AMD.
Population Character-istics (baseline)	Age: 78 years (SD 8.0) Male: 41.2% White: 96.6% Baseline BCVA: 55.1 (SD 13.1) Predominantly classic lesion: 26.5%; Minimally classic lesion: 34.1%; Occult lesion: 38.3%	Age: 73.9 years (SD 8.7) Male: 44.5% White: 72.8% Baseline BCVA: 52.4 (SD 13.9) Predominantly classic lesion: 25.8%; Minimally classic lesion: 35.3%; Occult lesion: 38.4%	Age: 75.9 years (SD 8.6) Male: 42.8% White: 84.7% Baseline BCVA: 53.8 (SD 13.6)
Main Inclusion Criteria	Age ≥50 years; active subfoveal CNV lesions (any subtype) secondary to AMD, or juxtafoveal lesions with leakage affecting the fovea; CNV comprising ≥50% of total lesion size; BCVA between 73 and 25 letters (20/40 to 20/320 Snellen equivalent).	Age ≥50 years; active subfoveal CNV lesions (any subtype) secondary to AMD, or juxtafoveal lesions with leakage affecting the fovea; CNV comprising ≥50% of total lesion size; BCVA between 73 and 25 letters (20/40 to 20/320 Snellen equivalent).	Age ≥50 years; active subfoveal CNV lesions (any subtype) secondary to AMD, or juxtafoveal lesions with leakage affecting the fovea; CNV comprising ≥50% of total lesion size; BCVA between 73 and 25 letters (20/40 to 20/320 Snellen equivalent).
Main Exclusion Criteria	Prior treatment for AMD (including investigational agents or anti-VEGF therapy) in study eye.	Prior treatment for AMD (including investigational agents or anti-VEGF therapy) in study eye.	Prior treatment for AMD (including investigational agents or anti-VEGF therapy) in study eye.
Intervention vs Comparator *• Schedule* *• Co-Intervention/ Rescue Treatment*	**G1:** Aflibercept 2.0 mg every 4 weeks **G2:** Aflibercept 0.5 mg every 4 weeks **G3:** Aflibercept 2.0 mg every 8 weeks (after 3 initial doses every 4 weeks) **G4:** Ranibizumab 0.5 mg every 4 weeks **• Schedule**: Patients were seen every 4 weeks and given either active treatment or a sham injection depending on randomization group (*ie*, G3 received sham every other visit).	**G1:** Aflibercept 2.0 mg every 4 weeks **G2:** Aflibercept 0.5 mg every 4 weeks **G3:** Aflibercept 2.0 mg every 8 weeks (after 3 initial doses every 4 weeks) **G4:** Ranibizumab 0.5 mg every 4 weeks **• Schedule**: Patients were seen every 4 weeks and given either active treatment or a sham injection depending on randomization group (*ie*, G3 received sham every other visit).	**G1:** Aflibercept 2.0 mg every 4 weeks for first 52 weeks, capped PRN thereafter **G2:** Aflibercept 0.5 mg every 4 weeks for first 52 weeks, capped PRN thereafter **G3:** Aflibercept 2.0 mg every 8 weeks (after 3 initial doses every 4 weeks) for first 52 weeks, capped PRN thereafter **G4:** Ranibizumab 0.5 mg every 4 weeks for first 52 weeks, capped PRN thereafter **• Schedule** for follow-up phase (weeks 52-96): required a switch of all regimens from fixed monthly or every 2 months regimen to a variable regimen requiring at least quarterly dosing (capped PRN); interim injections allowed based on an assessment of anatomic and visual parameters.
N	1217 G1: 304 G2: 304	1240 G1: 313 G2: 311	2457 G1: 617 G2: 615

Study	**VIEW 1; Heier 2012[43]**	**VIEW 2; Heier 2012[43]**	**VIEW 1 and VIEW 2 combined 96-week results; Schmidt-Erfurth 2014[44]**
	G3: 303 G4: 306	G3: 313 G4: 303	G3: 616 G4: 609
Visual Outcomes (ETDRS chart unless otherwise indicated); Functional Status/QOL Outcomes	**G1 vs G2 vs G3 vs G4** • Mean change in BCVA: 10.9 (SD 13.8) vs 6.9 (SD 13.4) vs 7.9 (SD 15.0) vs 8.1 (SD 15.3); LS mean difference: G1 vs G4: 3.15 (95% CI, 0.92 to 5.37), *P*=.0054; G2 vs G4: -0.80 (95% CI, -3.03 to 1.43), *P*=.4793; G3 vs G4: 0.26 (95% CI, -1.97 to 2.49), *P*=.8179 • Proportion of participants gaining/losing BCVA letters from baseline: -Maintaining BCVA (losing <15 letters, LOCF): 95.1% vs 95.0% vs 94.4% vs 93.8% -Gaining ≥0 letters (losing no letters): 83.6% vs 78.1% vs 79.7% vs 78.9% -Gaining ≥15 letters: 37.5% vs 24.9% vs 30.6% vs 30.9%; LS mean difference: G1 vs G4: 6.58 (95% CI, -0.98 to 14.14), *P*=.1042; G2 vs G4: -6.00 (95% CI, -13.17 to 1.16), *P*=.1037; G3 vs G4: -0.36 (95% CI, -7.74 to 7.03), *P*=.93 • Proportion achieving BCVA 20/40 or better: 45.7% vs 34.9% vs 37.9% vs 34.5% • Mean change in total NEI VFQ-25 score: 6.7 (SD 13.5) vs 4.5 (SD 11.9) vs 5.1 (SD 14.7) vs 4.9 (SD 14.0); LS mean difference: G1 vs G4: 1.28 (95% CI, -0.73 to 3.28), *P*=.2090; G2 vs G4: -0.67 (95% CI, -2.69 to 1.35), *P*=.5128; G3 vs G4: -0.60 (95% CI, -2.61 to 1.42), *P*=.5579	**G1 vs G2 vs G3 vs G4** • Mean change in BCVA: 7.6 (SD 12.6) vs 9.7 (SD 14.1) vs 8.9 (SD 14.4) vs 9.4 (SD 13.5); LS mean difference: G1 vs G4: -1.95 (95% CI, -4.10 to 0.20), *P*=.076; G2 vs G4: -0.06 (95% CI, -2.24 to 2.12), *P*=.955; G3 vs G4: -0.90 (95% CI, -3.06 to 1.26), *P*=.4131 • Proportion of participants gaining/losing BCVA letters from baseline: -Maintaining BCVA (losing <15 letters): 94.5% vs 95.3% vs 95.4% vs 94.8% -Gaining ≥0 letters (losing no letters): 78% vs 83.1% vs 81.7% vs 79% -Gaining ≥15 letters: 29.4% vs 34.8% vs 31.4% vs 34.0%; LS mean difference: G1 vs G4: -4.57 (95% CI, -12.02 to 2.88), *P*=.229; G2 vs G4: 0.78 (95% CI, -6.91 to 8.46), *P*=.843; G3 vs G4: -2.65 (95% CI, -10.18 to 4.88), *P*=.490 • Proportion achieving BCVA 20/40 or better: 32.7% vs 32.4% vs 27.5% vs 35.7% • Mean change in total NEI VFQ-25 score: 4.5 (SD 15.0) vs 5.1 (SD 13.7) vs 4.9 (SD 14.7) vs 6.3 (SD 14.8); LS mean difference: G1 vs G4: -2.79 (95% CI, -4.90 to -0.68), *P*=.0097; G2 vs G4: -0.93 (95% CI, -3.07 to 1.20), *P*=.3917; G3 vs G4: -1.95 (95% CI, -4.07 to 0.17), *P*=.0717	**G1 vs G2 vs G3 vs G4** • Mean change in BCVA at 22 months: 7.6 vs 6.6 vs 7.6 vs 7.9 • Proportion of participants gaining/losing BCVA letters from baseline: -Maintaining vision (losing <15 letters): 92.2% vs 91.5% vs 92.4% vs 91.6% -Gaining ≥15 letters : 31.2% vs 28.1% vs 33.4% vs 31.6%
Anatomic Outcomes (reported in μm unless otherwise indicated)	**G1 vs G2 vs G3 vs G4** • Mean change in CNV area (mm^2): -4.6 (SD 5.5) vs -3.5 (SD 5.3) vs -3.4 (SD 6.0) vs -4.2 (SD 5.6); LS mean difference: G1 vs G4: -0.33 (95% CI, -1.04 to 0.38), *P*=.3575; G2 vs G4: 0.71 (95% CI, -0.01 to 1.42), *P*=.0507; G3 vs G4: 0.86 (95% CI, 0.15 to 1.58), *P*=.0173. • Mean change in CRT: -116.5 (SD 98.4) vs -115.6 (SD 104) vs -128.5 (SD 108.5) vs -116.8 (SD 109) • Proportion with dry retina (no	**G1 vs G2 vs G3 vs G4** • Mean change in CNV area (mm^2): -6.0 (SD 6.1) vs -4.2 (SD 6.1) vs -5.2 (SD 5.9) vs -4.2 (SD 5.9); LS mean difference: G1 vs G4: -1.18 (95% CI, -1.98 to -0.38); G2 vs G4: -0.17 (95% CI, -0.63 to 0.97); G3 vs G4: -0.73 (95% CI, -1.53 to 0.07) • Mean change in CRT: -156.8 (SD 122.8) vs -129.8 (SD 114.8) vs -149.2 (SD 119.7) vs -138.5 (SD 122.2) • Proportion with dry retina (no	**G1 vs G2 vs G3 vs G4** • Mean change in CRT at 22 months: -128 vs -113 vs -133 vs -128 • Proportion with retinal fluid absent on OCT: 54.4% vs 44.6% vs 50.1% vs 45.5%

Study	**VIEW 1; Heier 2012[43]**	**VIEW 2; Heier 2012[43]**	**VIEW 1 and VIEW 2 combined 96-week results; Schmidt-Erfurth 2014[44]**
	cystic intraretinal edema or subretinal fluid on OCT): 64.8% vs 56.7% vs 63.4% vs 63.6%	cystic intraretinal edema or subretinal fluid on OCT): 80.3% vs 63.9% vs 71.9% vs 60.4%	
Harms/Adverse Event (AE) outcomes (in study eye)	**G1-3 (all aflibercept groups) vs G4** • Withdrawal due to AE: 12 (1.3%) vs 4 (1.3%) *Ocular AEs:* • Patients with ≥1 serious ocular AE: 16 (1.8%) vs 10 (3.3%) • Endophthalmitis: 3 (0.3%) vs 3 (1.0%) • Retinal hemorrhage: 2 (0.2%) vs 2 (0.7%) • Increased IOP: 41 (4.5%) vs 22 (7.2%) • Treatment-emergent serious retinal detachment: 1 (0.1%) vs 0 (0%) • Treatment-emergent serious cataract: 1 (0.1%) vs 0 (0%) *Systemic AEs:* • Serious systemic or nonocular AEs: 141 (15.5%) vs 57 (18.8%) • Any arterial thrombotic event: 15 (1.6%) vs 5 (1.6%) -Vascular death: 5 (0.5%) vs 1 (0.3%) -Nonfatal MI: 6 (0.7%) vs 4 (1.3%) -Nonfatal stroke: 4 (0.4%) vs 0% • HTN: 82 (9.0%) vs 29 (9.5%) • Venous thromboembolic event: 1 (0.1%) vs 1 (0.3%) • Congestive heart failure: 4 (0.4%) vs 2 (0.7%) • Gastrointestinal perforation or fistula: 0 (0%) vs 0 (0%) • Nonocular hemorrhagic event: 7 (0.7%) vs 1 (0.3%)	**G1-3 (all aflibercept groups) vs G4** • Withdrawal due to AE: 23 (2.5%) vs 2 (0.7%) *Ocular AEs:* • Patients with ≥1 serious ocular AE: 20 (2.2%) vs 9 (3.1%) • Endophthalmitis: 0% vs 0% • Retinal hemorrhage: 4 (0.4%) vs 1 (0.3%) • Increased IOP: 54 (5.9%) vs 19 (6.5%) • Treatment-emergent serious retinal detachment: 2 (0.2%) vs 1 (0.3%) • Treatment-emergent serious cataract: 2 (0.2%) vs 1 (0.3%) *Systemic AEs:* • Serious systemic or nonocular AEs: 111 (12.2%) vs 26 (8.9%) • Any arterial thrombotic event: 17 (1.9%) vs 5 (1.7%) -Vascular death: 4 (0.4%) vs 1 (0.3%) -Nonfatal MI: 9 (1.0%) vs 2 (0.7%) -Nonfatal stroke: 4 (0.4%) vs 2 (0.7%) • HTN: 81 (8.8%) vs 29 (10.0%) • Venous thrombotic events: 0 (0%) vs 0 (0%) • Congestive heart failure: 1 (0.1%) vs 1 (0.3%) • Gastrointestinal perforation or fistula: 2 (0.2%) vs 0 (0%) • Nonocular hemorrhagic event: 3 (0.3%) vs 0 (0%)	**G1-3 (all aflibercept groups) vs G4** • Withdrawal due to AE by 22 months: 75 (4.1%) vs 16 (2.6%) *Ocular AEs:* • ≥1 serious ocular AE: 65 (3.6%) vs 26 (4.4%) • Endophthalmitis: 5 (0.3%) vs 5 (0.8%) • Retinal detachment: 3 (0.2%) vs 3 (0.5%) • Retinal hemorrhage: 13 (0.7%) vs 4 (0.7%) • Retinal pigment epithelial tear: 4 (0.2%) vs 1 (0.2%) • Cataract: 11 (0.6%) vs 1 (0.2%) • Increased IOP: 3 (1.6%) vs 1 (0.2%) • Any intraocular inflammatory response: 15 (0.8%) vs 9 (1.5%) • Posterior capsule opacification: 0 (0%) vs 2 (0.3%) *Systemic AEs:* • ≥1 serious systemic or nonocular AE: 437 (24.0%) vs 146 (24.5%) • Arterial thrombotic event: 60 (3.3%) vs 19 (3.2%) ◦Nonfatal MI: 25 (1.4%) vs 12 (2.0%) ◦Nonfatal stroke: 13 (0.7%) vs 5 (0.8%) ◦Vascular death: 24 (1.3%) vs 3 (0.5%) • Congestive cardiac failure: 16 (0.9%) vs 5 (0.8%) • Coronary artery disease: 8 (0.4%) vs 5 (0.8%) • Atrial fibrillation: 23 (1.3%) vs 5 (0.8%) -TIA: 17 (0.9%) vs 1 (0.2%) -Cerebrovascular accident: 14 (0.8%) vs 4 (0.7%) -Death: 52 (2.8%) vs 16 (2.7%)
Cost and Burden Outcomes	NR	NR	**G1 vs G2 vs G3 vs G4** • Mean number of injections at week 96: 16.0 (SD 3.2) vs 16.2 (SD 4.0) vs 11.2 (SD 2.9) vs 16.5 (SD 2.7) • Mean number of injections from week 52-96 (PRN schedule): 4.1 (SD 1.8) vs 4.6 (SD 2.2) vs 4.2 (SD 1.7) vs 4.7 (SD 2.2); *P*<.0001 G1 vs G4; *P*<.0001 G3 vs G4
Notes; Subgroup Analyses	Non-inferiority study. Not powered to detect differences in rare but serious intraocular complications (*eg*, endophthalmitis).	Non-inferiority study. Not powered to detect differences in rare but serious intraocular complications (*eg*, endophthalmitis).	

Trials in Patients with Diabetic Macular Edema (DME)

Study	**DRCR.net (Protocol T); Wells 2016[46-48]**	**Ekinci 2014[30]**	**Nepomuceno 2013[31]**
• *Follow-up* • *Country* • *NCT or ID number* • *Funding*	• 24 months • US • NCT01627249 • National Institutes of Health. Regeneron Pharmaceuticals provided the aflibercept at no cost, and Genentech provided the ranibizumab at no cost for the study.	• 12 months • Turkey • NR • NR ("The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter")	•11 months (48 weeks) • Brazil • NCT01487629 • São Paulo Research Foundation, Fundação de Apoio ao Ensino, Pesquisa e Assistência do Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo
Objective	To compare intravitreal aflibercept, bevacizumab, and ranibizumab for the treatment of DME involving the center of the macula and causing vision impairment.	To compare the effects of bevacizumab and ranibizumab on visual acuity and foveal thickness in macular edema due to diabetic retinopathy.	To compare visual acuity and spectral-domain OCT outcomes associated with intravitreal bevacizumab versus ranibizumab for the management of DME.
Population/ Condition	DME involving the macular center	Clinically significant DME	DME with central involvement
Population Character-istics (baseline)	Age: 60.6 years (SD 10) Male: 54% White: 65% Black/African American: 16% Hispanic: 16% Mean BCVA: 64.8 (SD 11.3) Type 2 diabetes: 90.6% (mean duration 17 years) Mean HbA1c: 7.7 Mean CST: 412 μm (SD 130)	Age: 66.5 years (SD 11.5) Male: 36% Mean BCVA, B vs R (Snellen chart): 0.22 (SD 0.11) vs 0.24 (SD 0.12) Mean foveal thickness, B vs R: 483.8 (SD 126) vs 489.8 (SD 141) Mean duration of diabetes: 15.5 years (SD 3.3) Mean HbA1c level: 7.3 (SD 0.6)	Age: 63.8 years (SE 8.9) Male: 45% White: 70% Mean BCVA (logMAR, B vs R): 0.63 (SE 0.06) vs 0.60 (SE 0.05); *P*=.680 Baseline CST (B vs R): 451 μm (SE 22) vs 421 μm (SE 23); *P*=.406 Mean duration of DME: 3.1 years Mean duration of diabetes: 16 years Mean HbA1c: 8.6 (SD 1.6) Moderate or severe nonproliferative diabetic retinopathy: 60% Diabetic retinopathy treated with PRP ≥6 months before enrollment: 40%
Main Inclusion Criteria	≥18 years of age; type 1 or 2 diabetes; at least one eye with a BCVA letter score of 78 to 24 and center-involved DME on clinical examination and OCT according to protocol-defined thresholds; and received no anti-VEGF treatment within the previous 12 months.	Clinically significant DME (CMT >300 μm), as found through FA and OCT evaluations and dilate fundus examination, after 1-year follow-up period.	Center-involved DME, defined as a CST >300 μm on OCT, despite ≥1 session of macular laser photocoagulation performed at least 3 months previously; BCVA between 0.3 logMAR (Snellen equivalent: 20/40) and 1.6 logMAR (Snellen equivalent: 20/800).
Main Exclusion Criteria	Substantial cataract; significant renal disease; unstable medical status including blood pressure, cardiovascular disease, and glycemic control; MI, other acute cardiac	Patients who received intravitreal treatment at another center; PRP, grid	Vitreomacular traction on OCT; history of glaucoma or ocular HTN; systemic

Study	**DRCR.net (Protocol T); Wells 2016[46-48]**	**Ekinci 2014[30]**	**Nepomuceno 2013[31]**
	event requiring hospitalization, stroke, TIA, or treatment for acute congestive heart failure within 4 months of randomization.	or focal laser photocoagulation application within 6 months; intraocular surgery within 6 months; acute ocular infection, stroke, MI, uncontrolled HTN, pregnancy, renal failure and cataract formation during the follow-up period.	corticosteroid therapy; any condition that might preclude follow-up throughout the study period; last anti-VEGF or steroid treatment >6 months before enrollment.
Intervention vs Comparator • *Schedule* • *Co-Intervention/ Rescue Treatment*	**G1:** Aflibercept 2.0 mg **G2:** Bevacizumab 1.25 mg **G3:** Ranibizumab 0.3 mg • **Schedule** (all groups): Administered every 4 weeks unless visual acuity was 20/20 or better with a CST below the eligibility threshold and there was no improvement (≥5 letters or ≥10% decrease in thickness) or worsening in response to the past two injections. • The use of pre-injection or post-injection antibiotics was at the investigator's discretion. Laser photocoagulation therapy (focal, grid, or both) was initiated at or after the 24-week visit for persistent DME. Treatment for DME other than the randomly assigned anti-VEGF agent or laser therapy was permitted if a study eye met the criteria for treatment failure.	**G1:** Bevacizumab 1.25 mg **G2:** Ranibizumab 0.05 mg* (*possible reporting error, as typical dose is 0.3 mg) • **Schedule** (both groups): Administered monthly for 3 months. An additional 3 monthly injections were applied if the CMT was >275 µm or if there was an increase in BCVA of ≥3 letters compared with baseline. After the 6th intravitreal injection, if the CMT >275 µm or if there was an increase in BCVA of ≥2 letters, additional intravitreal injections were performed until stable visual acuity was obtained. • Topical antibiotics 4 times daily for 1 week.	**G1:** Bevacizumab 1.5 mg **G2:** Ranibizumab 0.5 mg • **Schedule** (both groups): Administered monthly if CST was >275 µm. -Randomization of both eyes: If both eyes were eligible for treatment and the patient agreed to treat both eyes with anti-VEGF therapy, 1 eye received the randomized treatment and the contralateral eye received the other anti-VEGF agent on the next day. • Focal/grid laser photocoagulation could be used as rescue therapy (at the discretion of ophthalmologist) after 3 injections if there was not a reduction in CST of ≥10% or an increase in BCVA of ≥5 letters compared with baseline; or patient could receive injections for an additional 3 consecutive visits. • Patients were instructed to instill 1 drop of 0.3% ciprofloxacin into the injected eye 4 times daily for 1 week after the procedure.
N	660 G1: 224 G2: 218 G3: 218	100 G1: 50 G2: 50	48 (63 eyes); 45 (60 eyes) analyzed G1: (32 eyes) G2: (28 eyes) *15 patients with bilateral DME received bevacizumab in one eye and ranibizumab in the other eye.
Visual Outcomes (ETDRS chart unless otherwise	**G1 vs G2 vs G3** • Mean change in BCVA -12 months: 13.3 (SD 11.1) vs 9.7 (SD 10.1) vs 11.2 (SD 9.4); *P*<.001 for G1 vs G2, *P*=.03 G1 vs G3, *P*=.12 G2 vs G3	**G1 vs G2** • BCVA achieved (Snellen chart): 0.38 (SD 0.12) vs 0.39 (SD 0.11); *P*=NS	**G1 vs G2** • Mean BCVA improvement at 48 weeks (logMAR): 0.23 (SD 0.02) vs 0.29 (SD 0.04) • Mean BCVA achieved

Study	**DRCR.net (Protocol T); Wells 2016[46-48]**	**Ekinci 2014[30]**	**Nepomuceno 2013[31]**
indicated); Functional Status/QOL Outcomes	-24 months: 12.8 (SD 12.4) vs 10.0 (SD 11.8) vs 12.3 (SD 10.5); *P*=.02 for G1 vs G2, *P*=.47 G1 vs G3, *P*=.11 G2 vs G3 • Proportion of participants gaining/losing BCVA letters from baseline: -12 months: ◦Gaining ≥15 letters: 42% vs 29% vs 32%; *P*=.028 for G1 vs G2, *P*=.068 G1 vs G3, *P*=.51 G2 vs G3 ◦Gaining ≥10 letters: 63% vs 52% vs 59%; *P*=.021 for G1 vs G2, *P*=.25 G1 vs G3, *P*=.15 G2 vs G3 ◦Losing ≥10 letters: 2% vs 3% vs 1%; *P*=.83 for all comparisons ◦Losing ≥15 letters: 1% vs 1% vs 1%; *P*=.98 for all comparisons -24 months: ◦Gaining ≥15 letters: 39% vs 35% vs 37%; *P*=.70 for all comparisons ◦Gaining ≥10 letters: 62% vs 54% vs 59%; *P*=.22 for G1 vs G2, *P*=.51 G1 vs G3, *P*=.50 G2 vs G3 ◦Losing ≥10 letters: 4% vs 6% vs 2%; *P*=.49 for G1 vs G2, *P*=.39 G1 vs G3, *P*=.15 G2 vs G3 ◦Losing ≥15 letters: 2% vs 3% vs 2%; *P*=.84 for all comparisons • Mean BCVA achieved: 77.8 (SD 11.5) vs 74.6 (SD 14.5) vs 77.1 (SD 12.4) • *Mean change in BCVA according to baseline visual acuity, see Notes; Subgroup Analyses row below*		(logMAR): 0.36 (SE 0.05) vs 0.34 (SE 0.04); *P*=.1886 • Proportion of participants gaining BCVA letters from baseline: -Gaining ≥15 letters: 39% vs 48%; *P*=NS -Gaining ≥10 letters: 61% vs 68%; *P*=NS
Anatomic Outcomes (reported in µm unless otherwise indicated)	**G1 vs G2 vs G3** • Mean change in CST: -12 months: -169 (SD 138) vs -101 (SD 121) vs -147 (SD 134); *P*<.001 for G1 vs G2, *P*=.036 G1 vs G3, *P*<.001 G1 vs G2 -24 months: -171 (SD 141) vs -126 (SD 143) vs -149 (SD 141); *P*<.001 for G1 vs G2, *P*=.08 G1 vs G3, *P*<.001 G2 vs G3	**G1 vs G2** • Mean foveal thickness: 342.3 (SD 121) vs 339.3 (SD 121); *P*=NS	**G1 vs G2** • Mean CST at 48 weeks: 329.7 (SE 19.3) vs 280.9 (SE 12.6); *P*=.4865 • Maximum mean CST reduction: -126 (SE 25) at week 48 vs -136 (SE 23) at week 44; *P*=NS
Harms/Adverse Event (AE) outcomes (in study eye)	**G1 vs G2 vs G3** *Ocular AEs:* • Endophthalmitis: 0 (0%) vs 1 (0.5%) vs 0 (0%); *P*=.66 • Inflammation: 6 (2.7%) vs 3 (1.4%) vs 4 (1.8%); *P*=.69 • Retinal detachment: 2 (0.9%) vs 2 (0.9%) vs 1 (0.9%); *P*=1.0 • Retinal tear: 1 (0.4%) vs 1 (0.5%) vs 1 (0.5%); *P*=1.0 • Vitreous hemorrhage: 15 (6.7%) vs 17 (7.8%) vs 10 (4.6%); *P*=.37 • Injection-related cataract: 3 (1.3%) vs 2 (0.9%) vs 0 (0%); *P*=.38 • IOP elevation: 39 (17.4%) vs 27 (12.4+V12%) vs 35 (16.5%); *P*=.31 *Systemic AEs:* • Serious AE: 88 (39.3%) vs 81 (37.2%) vs 82 (37.6%); *P*=.90 • Vascular events: 12 (5.4%) vs 17 (7.8%) vs 26 (11.9%); *P*=.047	• "Patients with acute ocular infection (endophthalmitis after intravitreal injection, n=3), stroke, MI (n=2), uncontrolled HTN (n=4), renal failure (n=1) and cataract formation during follow-up period (n=4) were excluded from the study." (not reported by group) • "No complications, like IOP rise or arterial HTN was observed in patients in the study as a result of intravitreal bevacizumab and ranibizumab injections."	**G1 vs G2** (percentages based on number of eyes) • Clinically significant cataract progression: 1 (3%) vs 0 (0%) • Transient vitreous hemorrhage after an acute posterior vitreous detachment: 1 (3%) vs 0 (0%) • Endophthalmitis: 0 (0%) vs 2 (7%) • Increased blood pressure: 0 (0%) vs 1 (4%) • Transient worsening of renal function: 1 patients receiving both treatments

Study	**DRCR.net (Protocol T); Wells 2016[46-48]**	**Ekinci 2014[30]**	**Nepomuceno 2013[31]**
	-Nonfatal MI: 7 (3.1%) vs 3 (1.4%) vs 6 (2.8%) -Nonfatal stroke: 2 (0.9%) vs 6 (2.8%) vs 11 (5.0%) -Vascular death (from any potential vascular or unknown cause): 3 (1.3%) vs 8 (3.7%) vs 9 (4.1%) • All-cause death: 5 (2%) vs 13 (6%) vs 11 (5%); *P*=.12 • Hospitalization: 77 (34.4%) vs 71 (32.6%) vs 73 (33.5%); *P*=.93 • Gastrointestinal: 67 (29.9%) vs 64 (29.4%) vs 60 (27.5%); *P*=.85 • Renal and urinary disorder events: 50 (22.3%) vs 46 (21.1%) vs 35 (16.1%); *P*=.22 • HTN: 39 (17.4%) vs 27 (12.4%) vs 44 (20.2%); *P*=.08		
Cost and Burden Outcomes	**G1 vs G2 vs G3** • Median number of injections: -12 months: 9 (IQR 8 to 11) vs 10 (IQR 8 to 12) vs 10 (IQR 8 to 11); *P*=.045 for overall comparison -24 months: 15 (IQR 11-17) vs 16 (IQR 12-20) vs 15 (IQR 11-19); *P*=.08 for overall comparison • Laser photocoagulation performed at least once: -12 months: 37% vs 56% vs 46%; *P*<.001 for overall comparison -24 months: 41% vs 64% vs 52%; *P*<.001 for G1 vs G2, *P*=.04 G1 vs G3, and *P*=.01 G2 vs G3	**G1 vs G2** • Mean number of injections: 5.1 (SD 0.74) vs 6.5 (SD 0.85); *P*<.05	**G1 vs G2** • Mean number of injections: 9.84 (SEM 0.55) vs 7.67 (SEM of the mean 0.60); *P*=.005 • Rescue therapy: -Eyes meeting rescue therapy criteria: 9 vs 4; *P*=.042 -Patients receiving rescue laser therapy: 1 (1 eye) vs 1 (1 eye) -Patients receiving rescue anti-VEGF therapy: 8 (8 eyes) vs 3 (3 eyes)
Notes; Subgroup Analyses	When the other (nonstudy) eye required anti-VEGF treatment (129 participants in the aflibercept group [58%], 122 participants in the bevacizumab group [56%], and 121 participants in the ranibizumab group [56%]), the agent that was used was the same as that used for the study eye. • **Subgroup Analyses: G1 vs G2 vs G3** Subgroup analyses based on baseline visual acuity (<69 vs 69-78 letters) -Patients with letter score <69 at baseline: ◦Mean change in BCVA at 12 months (n=102 vs n=102 vs n=101): 18.9 (SD 11.5) vs 11.8 (SD 12.0) vs 14.2 (SD 10.6); *P*<0.001 for G1 vs G2, *P*=.003 G1 vs G3, *P*=.21 G2 vs G3 ◦Mean change in BCVA at 24 months (n=98 vs n=92 vs n=94): 18.1 (SD 13.8) vs 13.3 (SD 13.4) vs 16.1 (SD 12.1); *P*=.02 for G1 vs G2, *P*=.18 G1 vs G3, *P*=.18 G2 vs G3 -Patients with letter score 78-69 at baseline: ◦Mean change in BCVA at 12 months (n=106 vs n=104 vs n=105): 8.0 (SD 7.6) vs 7.5 (SD 7.4) vs 8.3 (SD 6.8); *P*=.69 for all comparisons ◦Mean change in BCVA at 24 months (n=103 vs n=93 vs n=97): 7.8 (SD 8.4) vs 6.8 (SD 8.8) vs 8.6 (SD 7.0); *P*=.51 for G1 vs G2, *P*=.51 G1 vs G3, *P*=.31 G2 vs G3 The relative treatment effect on CST also varied according to initial visual acuity (*P*<0.001).	Excluded patients with certain AEs during follow-up (acute ocular infection, stroke, MI, uncontrolled HTN, pregnancy, renal failure and cataract formation)	If both eyes were eligible for treatment and the patient agreed to treat both eyes with anti-VEGF therapy, 1 eye received the randomized treatment and the contralateral eye received the other anti-VEGF agent on the next day; thus, if an eye was randomized to the ranibizumab group, the contralateral eye was allocated to the bevacizumab group. • **Subgroup Analyses:** A multivariate analysis comparing BCVA and CST outcomes between the bevacizumab and ranibizumab groups, taking into account number of injections, baseline BCVA, and CST, demonstrated a statistically significant influence of baseline BCVA on follow-up BCVA (*P*<.001) but no other significant differences between groups (*P*=.051) across follow-up time (*P*=.490) regarding these 2 outcomes.

Trials in Patients with Macular Edema due to Central Retinal Vein Occlusion (CRVO) or Branch Retinal Vein Occlusion (BRVO)

Study	**CRAVE; Rajagopal 2015[32]**	**MARVEL; Narayanan 2015[36]**
• *Follow-up* • *Country* • *NCT or ID number* • *Funding*	• 6 months • US • NCT01428388 • Barnes Retina Institute	• 6 months • India • CTRI/2012/ 01/003120 (Clinical Trials Registry-India) • Brian Holden Eye Research Center, L.V. Prasad Eye Institute, Hyderabad, India
Objective	To compare efficacy of monthly treatment with bevacizumab or ranibizumab for macular edema due to RVO.	To assess the efficacy and safety of intravitreal bevacizumab compared with ranibizumab in the treatment of macular edema due to BRVO.
Population/ Condition	Macular edema secondary to RVO (60% of patients with branch RVO or hemi-RVO, 40% with central RVO)	Center-involving macular edema due to BRVO
Population Characteristics (baseline)	Age: 71.5 years (SD 8.6) Male: 44.9% Mean BCVA (logMAR): 0.745 (SD 0.42)	Age: 51.7 years (SD 8.6) Male: 54.6% (B vs R: 68.4% vs 40.5%) Mean BCVA: 54.4 (SD 12.2) Mean CRT: 469 μm (SD 138)
Main Inclusion Criteria	Age ≥50 years; diagnosis of RVO in the past 9 months, BCVA of 20/40 to 20/320 (Snellen) in study eye (regardless of relative afferent pupillary defect); and CFT >250 μm on OCT.	Age ≥18 years; center-involving macular edema due to BRVO of <9 months duration; minimum CRT of 250 μm in the central subfield on spectral domain OCT); BCVA of 20/40 to 20/320 (73 to 24 letters) in the study eye.
Main Exclusion Criteria	History of intraocular surgery in the study eye including pars plana vitrectomy (but not including uncomplicated cataract surgery) within 60 days; any intravitreal injections within 12 weeks; prior RVO; history of PRP within 3 months of study onset or anticipated within 4 months after study onset; history of cerebrovascular event or MI within 3 months.	Prior episode or bilateral manifestation of RVO; previous panretinal laser photocoagulation or macular laser photocoagulation in the study eye; decrease in BCVA due to causes other than BRVO; history or presence of AMD (dry or wet form); use of intraocular or periocular corticosteroids in the study eye within the previous 3 months; previous treatment with anti-VEGF drugs in the study eye.
Intervention vs Comparator • *Schedule* • *Co-Intervention/ Rescue Treatment*	**G1:** Bevacizumab 1.25 mg **G2:** Ranibizumab 0.5 mg • **Schedule** (both groups): Patients received monthly injections for 6 months • Patients were eligible for rescue therapy with focal/grid laser or steroid at any point in the study, at the physician's discretion. Enrolled patients could receive PRP when needed at the discretion of the treating physician	**G1:** Bevacizumab 1.25 mg **G2:** Ranibizumab 0.5 mg • **Schedule** (both groups): Injection at baseline followed by PRN (met one of following retreatment criteria: >50 μm increase in CRT compared with the thinnest previous measurement; new or persistent cystoid retinal changes or sub-retinal fluid on OCT; loss of ≥5 letters from the best previous BCVA measurement in conjunction with any increase in CRT; increase in BCVA of ≥5 letters between the current and months recent visits). • Subjects were eligible to receive modified macular grid laser photocoagulation at 12 weeks if the following prespecified criteria were met: >50 μm increase in CRT compared with the thinnest previous measurement, and persistent diffuse edema ≥250 μm in CRT. Whenever laser photocoagulation was performed, an anti-VEGF injection was also administered
N	98* G1: 49* G2: 49 *Includes 9 patients who were not randomized but were assigned to bevacizumab for financial reasons.	75 G1: 38 G2: 37
Visual Outcomes	**G1 vs G2**	**G1 vs G2**

Study	**CRAVE; Rajagopal 2015[32]**	**MARVEL; Narayanan 2015[36]**
(ETDRS chart unless otherwise indicated); Functional Status/QOL Outcomes	• Mean change in BCVA (logMAR, using Snellen chart): 0.33 (SD 0.45) vs 0.34 (SD 0.33); *P*=.38 • Proportion of participants gaining ≥0.3 logMAR units from baseline: 71.4% vs 70.6%; *P*=.94	• Mean change in BCVA: 15.55 vs 18.08; mean difference: -2.5 letters (95% CI, -8.0 to 5.0), *P*=.74 • Mean BCVA achieved: 71.7 (SD 10.0) vs 70.9 (SD 13.4) • Proportion of participants gaining ≥15 letters from baseline: 57.8% vs 59.4%; *P*=1.0 • Proportion of participants achieving BCVA >20/40 (Snellen equivalent): 68.4% vs 62.2%
Anatomic Outcomes (reported in μm unless otherwise indicated)	**G1 vs G2** • Mean change in CFT: -212.6 (SD 234.8) vs -243.8 (SD 204.2); *P*=.72 • Proportion of participants achieving CFT <275 μm (estimated from graph): 65% vs 67%; *P*=1.0 • Fluid absent on OCT: 56.3% vs 51.4%; *P*=.81	**G1 vs G2** • Mean change in CRT: -212.7 (SD 234.8) vs -177.1 (SD 204.2); *P*=.34
Harms/Adverse Event (AE) outcomes (in study eye)	"No instances of ophthalmic serious AEs including endophthalmitis, noninfectious uveitis, retinal detachment, retinal tear, or traumatic cataract were encountered. Injection site pain and irritation were the most AEs. One patient died from complications of pneumonia. No patients suffered MI or cerebrovascular accident during the study."	**G1 vs G2** *Ocular AEs:* • Epiretinal membrane: 7.9% vs 0% • Progression of cataract: 7.9% vs 5.4% • Elevated IOP: 2.6% vs 0% • Developed a BRVO in the fellow eye: 0% vs 2.7% • Endophthalmitis: 0% vs 0% *Systemic AEs:* • Systemic arterial HTN: 5.3% vs 8.1% • Hospitalization (for fractured foot and fever): 0% vs 5.4%
Cost and Burden Outcomes	NR	**G1 vs G2** • Mean number of injections: 3.0 (SD 1.4) vs 3.2 (SD 1.5) • Received rescue grid laser photocoagulation: 21.0% vs 10.8%; *P*=.34 • Received sector laser photocoagulation due to the development of neovascularization in retina: 2.6% vs 5.4%
Notes; Subgroup Analyses	• "Assistance programs were used to defray any financial hardship, but if it could not be eliminated, then the patient was assigned to the bevacizumab arm (9 patients)." • "No patient departed from the protocol to receive rescue therapy, and none required PRP." It is unclear if this means that no patients received rescue therapy with focal/grid laser or steroid according to the protocol. • **Subgroup Analyses:** No differences between treatment groups were observed among BRVO or CRVO subsets in CFT changes (BRVO: *P*=.37; CRVO: *P*=.92) or change in BCVA (BRVO: *P*=.15; CRVO: *P*=.73).	Non-inferiority trial