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

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Prepared by:
Evidence-based Synthesis Program (ESP) Center
Portland VA Health Care System
Portland, OR
Devan Kansagara, MD, MCR, Director

Investigators:
Principal Investigator:
Allison Low, BA

Contributing Investigators:
Devan Kansagara, MD, MCR
Michele Freeman, MPH
Rochelle Fu, PhD
Kavita Bhavsar, MD
Ambar Faridi, MD
Karli Kondo, PhD
Robin Paynter, MLIS

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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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EXECUTIVE SUMMARY

INTRODUCTION

Visual impairment is a common problem among Veterans and results in significant reduction in quality of life. Diseases commonly responsible for substantial losses in visual acuity include neovascular ("wet") age-related macular degeneration (AMD), diabetic macular edema (DME), and central or branch retinal vein occlusion (CRVO or BRVO). While the etiologies of these diseases are complex, all are driven at least in part by vascular endothelial growth factors (VEGFs). This has led to the development of several drugs called anti-VEGF agents designed to block these factors and thus limit their damage to the eye. The most commonly used anti-VEGF agents—aflibercept, bevacizumab, and ranibizumab—have been shown to slow and even reverse the vision loss typically seen in patients with AMD, DME, BRVO, and CRVO. The comparative effectiveness, harms, and costs of these drugs are unclear.

METHODS

Data Sources and Searches

We searched Ovid MEDLINE to December 11, 2015 and PubMed, Elsevier EMBASE, and Ovid EMB Reviews to February 2, 2016. Grey literature sources included trial registries, regulatory agencies, conference proceedings, and Scientific Information Packet requests from pharmaceutical manufacturers. We identified additional articles by reviewing bibliographies of relevant studies and reviews.

Study Selection

Reviewers screened titles and abstracts for relevance, and potentially eligible articles were independently reviewed against inclusion criteria at the full-text level by 2 reviewers. The anti-VEGF agents of interest were aflibercept, bevacizumab, and ranibizumab. We included trials directly comparing 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, anatomic outcomes from optical coherence tomography [OCT], functional status, quality of life, harms, or costs). For data on costs, we also considered cohort and validated modeling studies that reported costs in the United States (US).

Data Abstraction and Quality Assessment

One investigator abstracted key study characteristics and outcome data and a second investigator checked entries for accuracy.

Data Synthesis and Analysis

Two reviewers independently assessed the quality of each study using published criteria and assigned a rating of low, unclear, or high risk of bias (ROB).

We qualitatively synthesized all data; our primary outcomes of interest were related to visual acuity changes and harms, but we also abstracted data for other outcomes such as anatomic changes. Based on discussion with experts, we felt a difference between treatment groups of less than 5 letters (one line) in mean change in best-corrected visual acuity (BCVA) using the Early

Treatment of Diabetic Retinopathy Study (ETDRS) chart was not likely to be clinically meaningful.

We also conducted meta-analyses to pool the findings from trials according to drug comparison and clinical condition on 2 measures of visual acuity: mean change from baseline in BCVA using the ETDRS chart, and percentage of participants gaining 15 or more ETDRS letters from baseline. Meta-analyses for mean change in BCVA was performed using the mean differences in score from baseline to follow-up between treatments; we used the mean difference between arms reported by the trial when available. For the percentage of patients gaining 15 or more letters, we used risk ratios to generate a combined estimate. We used the profile-likelihood random-effects model for all analyses and assessed statistical heterogeneity among the studies using Cochran's chi-square test and the I^2 statistic.

We assessed the overall strength of evidence of the body of literature for each outcome and assigned a rating of high, moderate, low, or insufficient according to published criteria.

RESULTS

Of 6,350 total citations screened, we reviewed 127 at the full-text level and included 16 trials: 11 for AMD, 3 for DME, and 2 for BRVO or CRVO. The main findings are summarized in the **Table**.

Overall, we did not find consistent, clinically meaningful differences in efficacy or harms between the agents. However, the strength of evidence supporting these findings varied considerably according to clinical condition and the drugs being compared. Patients with AMD were the best-studied population, and the most commonly compared agents were bevacizumab and ranibizumab.

Among patients with AMD, we found consistent, high-strength evidence from 9 randomized controlled trials (RCTs) of no difference between bevacizumab and ranibizumab in mean BCVA improvement at 12 months (pooled mean difference -0.218 letters [95% CI, -1.431 to 0.995] in 7 RCTs) or 24 months (-0.126 letters [95% CI, -1.033 to 0.781] in 3 RCTs). Similarly, there was moderate-strength evidence of no difference between these drugs in the proportion of patients gaining 15 or more letters (relative risk [RR] 0.930 [95% CI, 0.804 to 1.075] at 12 months; RR 0.835 [95% CI, 0.630 to 1.107] at 24 months). Two trials comparing aflibercept to ranibizumab provided low-strength evidence of no difference between the drugs in the proportion of patients gaining 15 or more letters; however, the evidence was insufficient for mean change in BCVA because of inconsistent results between the trials. Trials reported low rates of serious ocular adverse events in AMD patients and no differences were reported between drugs (moderate-strength evidence). Systemic adverse events occurred slightly more often in these trials, but rates were also similar between groups (moderate-strength evidence for intravitreal bevacizumab compared to ranibizumab; low-strength evidence for intravitreal aflibercept compared to ranibizumab). No studies compared the effectiveness or harms of aflibercept to bevacizumab in this population.

In trials comparing anti-VEGF treatments for DME, we found moderate-strength evidence that bevacizumab and ranibizumab had similar effects on mean BCVA change (mean difference -1.190 letters [95% CI, -2.889 to 0.509] in 3 RCTs) and percentage of patients gaining

15 or more letters (RR 0.871 [95% CI, 0.670 to 1.133] in 2 RCTs) after 12 months of treatment; furthermore, one RCT assessing 24-month outcomes also found no difference between the drugs.

One large trial provided low-strength evidence of a small benefit with aflibercept over bevacizumab in mean BCVA change and percentage of patients gaining at least 15 letters from baseline at both 12 and 24 months; this benefit with aflibercept was likely clinically important (≥ 5 letter difference) at 12 months in a subgroup of patients with lower baseline BCVA. The same trial also provided low-strength evidence of a small short-term benefit for aflibercept compared to ranibizumab in mean BCVA change at 12 but not 24 months, and low-strength evidence of no difference between the drugs regarding the proportion of patients gaining 15 or more letters at either timepoint. In a subgroup analysis of patients with lower baseline BCVA, the differences between aflibercept and ranibizumab were slightly more pronounced, but the absolute relative improvement still fell below our pre-determined measure of a clinically meaningful difference. In the DME trials overall, there was low- to moderate-strength evidence (depending on drug comparison) of no difference in rates of ocular adverse events between agents. Regarding systemic adverse events, one trial reported more arterial thrombotic events in patients treated with intravitreal ranibizumab compared to aflibercept (low-strength evidence); otherwise, no differences were reported between drugs (low-strength evidence).

Two small short-term trials comparing bevacizumab to ranibizumab in patients with BRVO or CRVO provided insufficient evidence from which to draw conclusions about effectiveness or harms.

Overall, based on the available data on treatment costs, frequency of injections, and direct cost data from 2 comparative trials and one long-term cost model, treatment with compounded bevacizumab (not currently available within the VHA) is associated with considerably lower costs than treatment with the other 2 agents. No trials evaluated the comparative costs of non-compounded bevacizumab to other anti-VEGF agents.

DISCUSSION

Our findings are consistent with the comparative effectiveness and harms of anti-VEGF agents reported in other recent systematic reviews and meta-analyses. Our exploratory meta-analyses combining patient populations also found no significant differences in visual acuity between drugs despite increased power. Within trials, potential reasons for variability in individual treatment response (indicated by large standard deviations) include factors such as age, time to treatment initiation, genetics, severity of disease, and baseline visual acuity, wherein less improvement is seen in patients starting treatment with higher BCVA scores due to a possible ceiling effect. While few differences between agents were seen for most adverse events, previous trials and systematic reviews have shown that patients treated with intravitreal anti-VEGF agents are at a higher risk for some serious systemic adverse events (compared to patients receiving sham injections or other treatments).

Research Gaps/Future Research

More research is needed to determine the comparative effectiveness of aflibercept and its potential for less-frequent dosing schedules. Very limited evidence was found in patients with BRVO or CRVO; currently ongoing large clinical trials will help fill current research gaps for

these conditions. Future studies should include quality of life and functional status outcomes, and follow patients for longer periods of time.

Conclusions

No clear, consistent, clinically meaningful differences between anti-VEGF drugs were found for most effectiveness and harms outcomes. Aflibercept may provide a greater visual acuity benefit than the other agents among patients with low baseline visual acuity over the short-term, but the longer-term findings are unclear and more trials assessing the effects of aflibercept are needed. Compounded bevacizumab treatment is likely to be the most cost-effective of the 3 drugs. In choosing amongst these drugs, clinicians may also need to consider factors such as patient preference, individual treatment response, convenience, and distance to facility.

Table. 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 2-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 arm (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 Veterans Health Administration (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.

ABBREVIATIONS TABLE

Abbreviation	Term
AHRQ	Agency for Healthcare Research and Quality
AMD	Age-related macular degeneration
BCVA	Best-corrected visual acuity
BRAMD	Bevacizumab to Ranibizumab in Patients with Exudative Age-Related Macular Degeneration trial
BRVO	Branch retinal vein occlusion
CATT	Comparison of AMD Treatments Trials
CI	Confidence interval
CMT	Central macular thickness
CNV	Choroidal neovascularization
CRAVE	Comparison of Anti-VEGF Agents in the Treatment of Macular Edema from Retinal Vein Occlusion Trial
CRT	Central retinal thickness
CRVO	Central retinal vein occlusion
CST	Central subfield thickness
DME	Diabetic macular edema
DRCR.net	Diabetic Retinopathy Clinical Research Network
EQ-5D	European Quality of Life-5 Dimensions
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDA	Food and Drug Administration
GEFAL	French Study Group Avastin versus Lucentis for Neovascular AMD trial
IQR	Interquartile range
ITT	Intention-to-treat
IVAN	Inhibition of VEGF in Age-related choroidal Neovascularisation trial
logMAR	Logarithm of the Minimal Angle of Resolution
LS	Least squares
LUCAS	Lucentis Compared to Avastin Study
MacDQoL	Macular Disease-dependent Quality of Life
MacTSQ	Macular Disease Treatment Satisfaction Questionnaire
MANTA	Multicenter Anti-VEFG Trial in Austria
MI	Myocardial infarction
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
PRN	*Pro re nata* (“as needed”)
QALY	Quality-adjusted life-years
QOL	Quality of life
RCT	Randomized controlled trial
ROB	Risk of bias

RR	Relative risk
RVO	Retinal vein occlusion
SD	Standard deviation
SE	Standard error
TIA	Transient ischemic attack
US	United States
VEGF	Vascular endothelial growth factor
VHA	Veterans Health Administration
VIEW	VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD Trial