Cost-Utility Analysis of VEGF Inhibitors for Treating Neovascular Age-Related Macular Degeneration

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• PURPOSE: To perform 11- and 2-year health care sector (ophthalmic) and societal cost perspective reference case, cost-utility analyses comparing bevacizumab, ranibizumab, and aflibercept monotherapies for neovascular age-related macular degeneration (NVAMD).

• DESIGN: Cost-utility analysis.

• METHODS: The authors performed 11-year and 2-year ophthalmic and societal cost perspective, cost-utility analyses comparing bevacizumab, ranibizumab, and aflibercept monotherapies for neovascular age-related macular degeneration (NVAMD). We employed patient utilities, bilateral outcomes, 2018 U.S. dollars, vision-related mortality, a Medicare fee schedule, and CATT (Comparison of Age-Related Macular Degeneration Treatments) study and VIEW (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD) trial. Cochrane data were also used. SETTING: Center for Value-Based Medicine. PATIENT/STUDY POPULATION: patients with NVAMD. INTERVENTION: Cost-utility analyses using published data. Data-modeled 10-year vision outcomes were modeled forward to year 11. MAIN OUTCOME MEASUREMENT: These included cost-utility ratios (CURs), costs, and quality-adjusted life-years (QALYs) gained. $100,00/QALY was considered the US cost-effectiveness upper limit.

• RESULTS: Bevacizumab and ranibizumab each conferred an 11-year, 1.339 QALY gain versus observation. Aflibercept conferred a 1.380 QALY gain. Aflibercept conferred greater QALY gain for less cost than ranibizumab but was not cost-effective compared to bevacizumab ($1,151,451/QALY incremental CUR). The average ophthalmic cost perspective CUR for bevacizumab was $11,033/QALY, $79,600/QALY for ranibizumab, and $44,801/QALY for aflibercept. Eleven-year therapies saved a 1.0 year-of-life loss without treatment from the 11.0-year life expectancy. Early treatment was 138%-149% more cost-effective than late treatment. Two-year therapy prevented a 1-month-of-life loss, and revealed bevacizumab, ranibizumab, and aflibercept conferred 0.141, 0.141, and 0.164 QALY gains, respectively, with corresponding average CURs of $40,371/QALY, $335,726/QALY, and $168,006/QALY, respectively.

• CONCLUSIONS: From an ophthalmic (medical) cost perspective, bevacizumab, ranibizumab, and aflibercept NVAMD monotherapies were all cost-effective over 11 years, with bevacizumab 6.21× more cost-effective than ranibizumab and 3.06× more cost-effective than aflibercept. Two-year modeling revealed bevacizumab was cost-effective, whereas ranibizumab and aflibercept were not. Early treatment was critical for obtaining optimal vision and cost-effectiveness, as is long-term follow-up and adherence to treatment. (Am J Ophthalmol 2020;218: 225–241. © 2020 Elsevier Inc. All rights reserved.)

U.S. FOOD AND DRUG ADMINISTRATION (FDA)-approved vascular endothelial growth factor-inhibitor (VEGF-I) monotherapies in the United States for treating neovascular age-related macular degeneration (NVAMD) include intravitreal ranibizumab (Lucentis, Genentech-Roche, South San Francisco, California; approved 2006),[1,2] intravitreal aflibercept (Eylea, Regeneron, Eastview, New York; approved 2011),[3,4] and intravitreal brolucizumab (Beovu, Novartis, Basel, Switzerland; approved 2019).[5] A fourth drug, bevacizumab (Avastin, Genentech-Roche, South San Francisco, California), has not been approved by the FDA but has been shown in a multicenter National Eye Institute-sponsored clinical trial to be therapeutically equivalent to ranibizumab and has assumed widespread acceptance within the vitreoretinal community.[6,7] Brolucizumab was not included in the present study because follow-up data were only available through 48 weeks.[5]

Ranibizumab for treating subfoveal NVAMD (n = 712),[1] treating predominantly classic NVAMD (n = 423),[2] a continuation of these 2 trials,[8] a large study comparing aflibercept and ranibizumab (n = 2,457),[3,4] the multicenter CATT (Comparison of Age-Related Macular Degeneration Treatments Trials) (n = 1,185) study comparing bevacizumab and ranibizumab,[6,7] meta-analyses comparing bevacizumab and ranibizumab, and

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ranibizumab and aflibercept,[9,10] Cochrane Database Systematic Reviews comparing aflibercept, bevacizumab and ranibizumab,[11,12] and a large U.S. database comparing aflibercept and ranibizumab[13] showed that monotherapy with each of the 3 VEGF-I drugs yielded similar vision results. Nonetheless, the longest randomized clinical trial portion of any study was 24 months.[1,2,4,7] A review of the bevacizumab, ranibizumab, and aflibercept therapy regimens using real-world data from 13,859 patients in the American Academy of Ophthalmology IRIS (Intelligent Research in Sight) registry[14] showed that monotherapy using each of the 3 VEGF-I drugs yielded equivalent vision results at 1 year. Although some studies have found minor discrepancies, adverse event profiles for the 3 drugs have also been shown to be similar.[3,6,8–14]

An American Academy of Ophthalmology Ophthalmic Technology Assessment Committee recently evaluated the 3 VEGF inhibitors for NVAMD.[15] Although the vision outcomes were similar among the drugs at 24 months, the Committee believed that longer term follow-up was needed.

The HORIZON (Open-Label Extension Trial of Ranibizumab for Choroidal Neovascularization Secondary to Age-Related Macular Degeneration) study[8] enrolled predominantly 2-year MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration)[1] and ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration)[2] patients to 2 additional years of as-needed ranibizumab therapy at the discretion of the investigator from months 25 to 48. The eyes receiving ranibizumab for 4 years averaged a mean letter gain of +2.0 from months 0 to 48 and a −0.1 letter for some patients followed 0-60 months.[14] The SEVEN-UP (Seven-Year Observational Update of Macular Degeneration Patients Post-MARINA/ANCHOR and HORIZON Trials) study,[16] noted that eyes treated with >11 injections of ranibizumab from month 49 to a mean of 7.3 years (88 months) gained a mean 3.9 letters according to Early Treatment Diabetic Retinopathy criteria over that time, whereas eyes receiving 6-10 post-HORIZON injections lost a mean of 6.9 letters. Combining the 2 sub-cohorts resulted in a loss of −0.6 letters from months 49 to 88 and a mean vision outcome of 20/63-2. The SEVEN-UP study was able to recall and examine 65 of 357 patients (18%) who completed the 2-year MARINA or ANCHOR trial, then the additional 2-year HORIZON follow-up study. More recent 10-year data for patients treated with 10 injections per year for 10 years in the study by Suner and associates[17] revealed a mean vision outcome of 20/63-2 from years 6-10, virtually identical to late SEVEN-UP study outcomes.

Cost-effectiveness analyses of each of the 3 medications in the treatment of NVAMD have been performed,[18–22] but the authors were unaware of a U.S. cost-effectiveness analysis comparing the 3 together. A recent study compared the long-term, historical drug costs of the more expensive ranibizumab and aflibercept versus bevacizumab.[23] The authors noted that, from 2008 to 2015 in the U.S. Medicare Fee-for-Service population, $13.8 billion would have been saved by Medicare and $3.5 billion would have been saved by patients if bevacizumab had been substituted for ranibizumab and aflibercept for NVAMD therapy.

These authors were unaware of any cost-utility analyses[18–22] comparing the use of bevacizumab, ranibizumab, and aflibercept monotherapy for NVAMD using 1) ophthalmic patient utilities, 2) bilateral treatment outcomes and costs, 3) an average, national Medicare Fee Schedule cost basis, 4) vision loss mortality data, and 5) ophthalmic (direct medical) and societal cost perspectives. Therefore, the current investigation was undertaken.

SUBJECTS AND METHODS

REFERENCE CASE, OPHTHALMIC COST PERSPECTIVE AND SOcietal cost perspective, and average and incremental cost-utility analyses were performed for intravitreal bevacizumab therapy, ranibizumab therapy, and aflibercept therapy for the treatment of NVAMD. Wills Eye Hospital Institutional Review Board (IRB) approval was waived because no new patients were enrolled or identified patient data were used. The research adhered to the Declaration of Helsinki, and no state or federal regulations were violated.

A list of cost-utility analysis parameters is shown in Supplemental Table 1. Clinical study parameters are shown in Supplemental Table 2.[3,4,6-47]

The methodology used for this study has been described previously[18,27,28] and agrees with recommendations of the Second Panel on Cost-Effectiveness in Health and Medicine.[42] CATT data[6,7] were used for reference case analysis. CATT was a National Eye Institute-supported multicenter, randomized clinical trial comparing intravitreal bevacizumab and ranibizumab therapy for NVAMD therapy. VIEW (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD) 1 and 2 trial data,[3,4] modeled after ranibizumab trials,[1,2] (as was CATT[6,7]) were used to compare ranibizumab and aflibercept therapies.

- **VISION: 2-YEAR ANALYSIS:** According to clinical trials,[3,4,6,7] meta-analyses,[9,10] Cochrane Database Systematic Reviews,[11,12] a U.S. database,[13] and a large IRIS registry study,[14] the vision results of the 3 drugs under study were the same through the 24 months of randomized clinical trial data.

- **VISION: 11-YEAR ANALYSIS:** There were statistical differences at 2 years after baseline between the CATT drug cohorts that received monthly injections versus as-needed injections. Combining the ranibizumab and bevacizumab cohorts, there was a 24-month, 2.4 greater letter gain with monthly injections than with the as-needed injections

TABLE 1. Mean Visual Acuity Associated With VEGF Inhibitor Monotherapy and No Treatment for Subfoveal Choroidal Neovascularization[3–8,17,24,36]

Time	Bevacizumab, Ranibizumab, or Aflibercept Monotherapy	No Treatment (Control Cohort)
Baseline	20/63	20/63
One month	$20/50^{-1}$	$20/63^{-1}$
Three months	$20/50^{+2}$	$20/80^{+2}$
Six months	$40/40^{-2}$	$20/80^{-1}$
12 months	$20/40^{-1.5}$	$20/125^{-2}$
2 years	$20/40^{-1.5}$	20/200
3 years	$20/50^{+1}$	$20/250^{+1}$
4 years	$20/50^{-2}$	$20/250^{-2}$
5 years	$20/63^{-1}$	20/320
6 years	$20/63^{-2}$	20/400
7 years	$20/63^{-2}$	20/500
8 years	$20/63^{-2}$	$20/500^{-2}$
9 years	$20/63^{-2}$	$20/630^{+1}$
10 years	$20/63^{-2}$	20/630
11 years	$20/63^{-2}$	20/630
Treatment References for VISION		Control references for Vision
Years 0 to 2: CATT study[6,7] Years 3 to 5.0: CATT study[7] HORIZON trial[8] Australian 5-year study[24] Years 5.1 to 7.4: SEVEN-UP Study[16] Years 7.5 to 11: SEVEN-UP Study,[16] last observation carried forward Years 5-11: Suner et al.[17] 10-year, real-world, fixed-interval treatment—vision outcome, the same as in the SEVEN-UP study[16]		Years 0 to 2: CATT study[6,7] Years 3 to 11: Shah and Del Priore[36] meta-analysis of 6 Macular Photocoagulation Study trial control arms

NVAMD = neovascular age-related macular degeneration; VEGF = vascular endothelial growth factor.

($P = .046$).[7] The present authors therefore modeled the more visually favorable monthly injection regimen for bevacizumab and ranibizumab during the first 24 months after baseline treatment. Because it was noted in the VIEW trials that bimonthly aflibercept injections yielded vision outcomes equivalent to monthly aflibercept and ranibizumab injection results after 3 initial monthly injections, our study modeled half the administration frequency for aflibercept versus ranibizumab and bevacizumab after the first 24 months (Supplemental Table 2).[3,4,6,7]

For months 25-60 for ranibizumab and bevacizumab, vision results were modeled after the 5-year CATT study results, which were very similar to those of the HORIZON trial, an open-label extension of ranibizumab for the treatment of NVAMD,[8] and the 5-year follow-up, Australian retrospective review.[24] Averaging these results resulted in a 5-year outcome of 20/63-1.

The authors assumed that, during this period, aflibercept was administered with half the frequency of ranibizumab and bevacizumab. Table 1 shows the vision treatment results, their evidence-based vision basis, and the untreated control cohort vision results.[6,36]

From months 61-88 (years 5-7.4), vision results were modeled after the SEVEN-UP (post-MARINA/ANCHOR and HORIZON trials) study[16] for all 3 drugs. It should be noted that the authors biased against more favorable SEVEN-UP vision results by integrating data from the top 2 sub-cohort vision outcomes rather than just the top cohort of 11 or more injections; the latter was used to model VEGF-inhibitor-treated subjects in our cost-utility analysis. This amalgamation resulted in a letter loss of 0.6 from the end of year 5 to year 11, with a resultant vision of 20/63-2 during that time. From months 89-132, we used a last-observation-carried-forward model from the SEVEN-UP vision results at 88 months (7.4 years).[16] Months 61-132 were modeled with the 10-year treatment described in the study by Suner and associates,[17] with vision outcomes identical to those in SEVEN-UP through 88 months.[16]

After 5 years, the authors arbitrarily assumed that bevacizumab and ranibizumab were administered 3 times a year

TABLE 2. Conversion of Non-NVAMD Fellow Eyes of First-Eye Treatment Patients to NVAMD[43-47]

Time (beginning of year)	First-Eye Model Total: (Fellow Eye With Good Vision and no NVAMD)	Percent of Remaining Fellow Eyes in First-Eye Model Converting to NVAMD Over Time	Second-Eye Model (First Eye Already With NVAMD)
1 year	40.0%	0.0%	60.0%
2 years	30.9%	22.8%[43]	69.1%
3 years	25.4%	13.8%[43]	74.6%
4 years	22.9%	10.0%[44-47]	77.1%
5 years	20.6%	10.0%[44-47]	79.4%
6 years	18.5%	10.0%[44-47]	81.5%
7 years	16.7%	10.0%[44-47]	83.3%
8 years	15.0%	10.0%[44-47]	85.0%
9 years	13.5%	10.0%[44-47]	86.5%
10 years	12.2%	10.0%[44-47]	87.8%
11 years	11.0%	10.0% [44-47]	89.0%

NVAMD = neovascular age-related macular degeneration

TABLE 3. Reference Case, Eleven-Year, Individual, Patient Value (Quality-Adjusted Life Year) Gains Associated with VEGF Inhibitor Therapy for NVAMD (Percent Quality-of-Life Gains are in Parentheses)

Scenario	Bevacizumab QALY Gain (Value Gain)	Ranibizumab QALY Gain (Value Gain)	Aflibercept QALY Gain (Value Gain)
First-eye, 11-year model, QALY gain with mortality factored in	0.425 (8.3%)	0.425 (8.3%)	0.465 (9.0%)
Second-eye, 11-year model QALY gain with mortality factored in	1.948 (37.9%)	1.948 (37.9%)	1.990 (38.7%)
Combined-eye, 11-year model QALY gain with mortality treatment decrease factored in (60% 2nd-eye model + 40% 1st-eye model)	1.339 (26.1%)	1.339 (26.1%)	1.380 (26.9%)
Control cohort, 10.0-year model, QALY accrual with increased mortality factored in	5.099	5.099	5.099
Combined-eye model QALY gain with 10.0-year life expectancy	1.080 (21.1%)	1.080 (21.1%)	1.114 (21.7%)
QALY gain from increasing life expectancy from 10.0 years to 11.0 years, combined eye model	0.259 (5.0%)	0.259 (5.0%)	0.266 (5.2%)
Combined-eye, 2-year model with mortality factored in	0.141 (10.4%)	0.141 (10.4%)	0.157 (12.1%)

VEGF = vascular endothelial growth factor; NVAMD = neovascular age-related macular degeneration; QALY = quality-adjusted life-year. Note that QOL (quality-of-life) gains herein include conversion of the 1.0-year gain of life to QOL gain.

from years 6 to 8 and twice yearly from years 9 to 11 (Supplemental Table 2). Thus, 11 bevacizumab and ranibizumab injections were given after 4 years, the minimum number needed in SEVEN-UP[16] to obtain the best visual result. Aflibercept injections from years 3 to 11 were given half as often as ranibizumab and bevacizumab.

• **CONTROL COHORT:** For controls, the authors used 2-year, MARINA,[1] and ANCHOR[2] sham-treatment, ranibizumab trial data for the 2-year analysis,[1,2] followed by a Shah and Del Priore[36] Lineweaver-Burke plot meta-analysis of the natural history of untreated NVAMD for years 3 to 11 in the 11-year analysis. Shah and Del Priore[36] integrated the untreated control cohort vision results from 6 previous, randomized clinical trials. Those authors found that mean vision in a cohort correlates highly with the time since the development of NVAMD.[36] The visual acuities at specific times are shown in Table 1.

• **COST-UTILITY ANALYSIS:** The reference case herein was based primarily upon the ophthalmic cost perspective cost-utility ratio (CUR) which was calculated by dividing the

TABLE 4. Eleven-Year and Two-Year Direct Ophthalmic Medical Costs Per VEGF-I Monotherapy-Treated Baseline Patient in 2018 U.S. Real Dollars[29-31]

National Average Medicare Fee Schedule Costs				
Entity (2018 U.S. Nominal $ Cost per 1 Service)	Medicare HCPSC #	Bevacizumab (1.25 mg/Dose)	Ranibizumab (0.5 mg/dose)	Aflibercept (2.0 mg/Dose)
Initial eye examination ($154)	92,004	$154	$154	$154
Office examination ($129)	92,014	$2,066	$2,066	$6,226
Optical coherence tomography ($42)	92,134	$2,593	$2,593	$2,593
Fundus photographs ($58)	92,250	$114	$114	$114
Fluorescein angiography ($88)	92,235	$173	$173	$173
Intravitreal injection ($104)	67,028	$4,879	$4,879	$2,423
Drug ASP cost[a]	See below	$3,717	$87,727	$45,005
Adverse events	NA	$11	$11	$6
Bevacizumab	J9035	$789	–	–
Ranibizumab	J2778	–	$1,870	–
Aflibercept	J0178	–	–	$1,936
Eleven-year model				
Total cost per treated baseline eye	NA	$13,565	$97,573	$56,546
Direct ophthalmic medical cost per fellow eye converting to NVAMD	NA	$1,207	$9,009	$5,266
Total direct ophthalmic medical cost per average patient	NA	$14,772	$106,582	$61,811
Bilateral drug cost/direct ophthalmic medical cost per average patient	NA	27.4%	89.7%	79.3%
Two-year model				
Total cost per treated second-eye model eye	NA	$5,526	$45,961	$25,584
Direct ophthalmic medical cost per fellow eye converting to NVAMD	NA	$410	$3,395	$1,972
Total direct ophthalmic medical cost per treated first-eye model eye patient	NA	$5,937	$49,356	$27,557
Total direct ophthalmic medical cost per weighted average of first-eye model eye (40%) and second-eye model eyes (60%)[6]	NA	$5,690	$47,319	$26,377

VEGF-I = vascular endothelial growth factor inhibitor; HCPSC = Healthcare Common Procedure Coding System; ASP = Medicare Part B Average Sales Price;[29] NA = not applicable; NVAMD = neovascular age-related macular degeneration.

Note that the costs are discounted at 3% annually.

[a]2018 Part B Medicare Average Sales Prices:[29] Bevacizumab HCPCS = J9035, $79 per dose; Ranibizumab HCPCS = J9035, $1,870 per dose; Aflibercept HCPCS = J0178, $1,936 per dose.

ophthalmic direct medical costs expended for an intervention by the quality-adjusted life-years (QALYs) gained. The cost-utility methodology was similar to that used in other value-based medicine ophthalmic cost-utility analyses using patient utilities, an average national Medicare Fee Schedule, and a 3% annual discount rate for QALY outcomes and costs (the last recommended by the Second Panel on Cost-Effectiveness in Health and Medicine[42]). The time tradeoff utilities were obtained from a visual utility database of 1,400 ophthalmic patient interviews. The utilities have been validated,[48] are reproducible,[49] correlated most highly with vision in the better-seeing eye,[50–54] and are typically unaffected by comorbidities,[55–57] sex,[50–54] age,[50–54] ethnicity,[58] and Western country of origin.[58–60] They are generally, but not always, unaffected by the underlying cause of vision loss.[38,61]

The authors also integrated newer data for vision-related mortality into the current analysis (see Mortality below).[39]

A combined-eye model cost basis was used.[18,27,28,38] This model included a weighted average of first-eye and second-eye models.[18,27,38] The second-eye model assumes that the first eye already has vision loss from NVAMD or another cause. Thus, patient value gain begins immediately at the time of initiation of therapy in the second eye.

With the first-eye model, it is assumed that the fellow eye has good vision.[38] We have been unable to demonstrate a significant improvement in quality-of-life (QOL) when vision improves in 1 eye (e.g., 20/200 to 20/63 or 20/63

TABLE 5. Eleven-Year Societal Costs (2018 U.S. Real Dollars) Associated With VEGF-I Therapy for an NVAMD Individual (in 2018 Real U.S. Dollars)

Costs	Bevaciz.	Ranibiz.	Afliber.
Drug cost per injection[29]	$79	$1,936	$1,870
Direct ophthalmic medical costs expended	$14,772	$106,582	$61,811
Systemic costs added by saving 1.0 years of life: extending life expectancy from 10.0 to 11.0 years		+$24,800	
Societal costs accrued against direct ophthalmic medical costs			
Systemic costs added by saving 1.0 year of life: extending life expectancy from 10.0 to 11.0 years		$24,800	
Direct ophthalmic medical costs saved			
Low vision services[33]		−$12,118	
Subtotal		−$12,118	
Direct nonophthalmic medical costs saved			
Injury costs[32]		−$1,607	
Depression costs[32]		−$4,108	
Subacute nursing facility costs[32]		−$6,263	
Yet unidentified Medicare costs[32]		−$39,797	
Nursing home costs[32]		−$23,744	
Subtotal		−$75,519	
Direct nonmedical (caregiver) costs saved			
Inside activities of daily living[33]		−$138,051	
Outside activities of daily living[33]		−$18,038	
Transportation costs[33]		−$38,964	
Residence costs[33]		−$83,593	
Subtotal		−$276,646	
Indirect medical costs saved			
Wage lost[34,35]		−$25,471	
Volunteer costs[33]		−$7,497	
Subtotal		−$32,969	
Total (nonophthalmic direct medical, direct nonmedical and indirect medical costs saved, including systemic costs added by treatment saving 1 year of life)		−$372,452	

	Bevaciz.	Ranibiz.	Afliber.
Total societal costs (direct medical, direct nonmedical, and indirect medical costs)	−$357,680	−$265,870	−$310,641

Costs include treatment in fellow eyes that develop NVAMD over the 11-year model.
Note that negative costs are costs returned to society for the direct ophthalmic medical costs expended.
VEGF-I = vascular endothelial growth factor inhibitor; NVAMD = neovascular age-related macular degeneration; Bevaciz. = bevacizumab; Ranibiz. = ranibizumab; Afliber. = aflibercept.

to 20/40) and the fellow eye has normal vision.[27,38] In that instance, QALYs are gained when the second eye with good vision eventually converts to NVAMD and is treated. The authors have modeled using CATT data[6] showing that 60% of cases at baseline underwent second-eye treatment (second-eye model) and that 40% had the first eye treated (first-eye model), with good vision at baseline in the fellow eye. With the first-eye model, fellow eyes were treated if they converted from atrophic AMD to NVAMD over the 2- or 11-year model (Table 2). With the first-eye model, QALY gains were assumed to occur only when second eyes were treated for conversion for NVAMD and experienced decreased vision.

The authors did not use a methodology that has been noted by some[37] that decreases the interventional utility gain in individuals who are elderly or have disabilities,

TABLE 6. Two-Year Societal Costs (2018 U.S. Real Dollars) Associated With VEGF-I Therapy for NVAMD

Costs	Bevaciz.	Ranibiz.	Afliber.
Direct ophthalmic medical costs expended (see Table 4)	$5,690	$47,319	$26,377
Systemic costs added by saving one month of life: extending model expectancy from 23 months to 24 months		+$1,407	
Direct ophthalmic medical costs saved			
Low vision services[33]		−$827	
Subtotal		−$827	
Direct nonophthalmic medical costs saved			
Injury costs[32]		−$867	
Depression costs[32]		−$1281	
Subacute nursing facility costs[32]		−$1,941	
Yet unidentified Medicare costs[32]		−$5,899	
Nursing home costs[32]		−$1,451	
Subtotal		−$11,440	
Direct nonmedical (caregiver) costs saved			
Inside activities of daily living[33]		−$13,533	
Outside activities of daily living[33]		−$874	
Transportation costs[33]		−$6,155	
Residence costs[33]		−$8,573	
Subtotal		−$29,135	
Indirect medical costs saved			
Wage loss[34,35]		$0	
Volunteer costs[33]		−$1,206	
Subtotal		−$1,206	
Total (non-ophthalmic direct medical, direct nonmedical, and indirect medical costs saved		−$41,211	

	Bevaciz.	Ranibiz.	Afliber.
Total 2-year societal costs (direct medical, direct nonmedical, and indirect medical costs)	−$35,521	$6,108	−$14,834

Costs include treatment in fellow eyes that develop NVAMD over the 2-year model.
Note that negative costs are costs returned to society for the direct ophthalmic medical costs expended.
VEGF-I = vascular endothelial growth factor inhibitor; NVAMD = neovascular age-related macular degeneration; Bevaciz. = bevacizumab; Ranibiz.= ranibizumab; Afliber. = aflibercept.

thus biasing against these groups. That methodology has little chance of becoming public policy in the United States.

Using the ophthalmic cost perspective, the direct ophthalmic costs expended typically result in a positive CUR because the ophthalmic direct medical costs expended generally exceed ophthalmic direct medical costs saved (e.g., low-vision costs). Use of a societal cost perspective more commonly has a negative CUR because the direct ophthalmic medical costs expended are much more likely to be exceeded by the costs saved (caregiver costs, medical costs such as trauma and depression, wage loss prevented, and others). Thus, the overall costs associated with the intervention are negative.[27] A negative CUR can also be encountered when one intervention dominates another, meaning that it delivers greater QALY gain for less cost than the comparator intervention.

• **PATIENT VALUE:** Improvement in QALY and/or Length of Life Gains: Mean vision measurements in the VEGF-I cohorts and control cohorts each year were converted to utility format, ranging from a utility of 0.80 for 20/40 vision in the better-seeing eye to 0.538 associated with 20/630 vision, to calculate the yearly QALY accrual associated with therapy versus none (Table 3).[50,51] The QALY loss from adverse events was

TABLE 7. Eleven-Year Model, Incremental Cost-Utility Ratios in $/QALY Associated With VEGF-Inhibitor Monotherapy for NVAMD (2018 Real U.S. Dollars)

Incremental Cost-Utility Ratios			
11-Year Model	Bevacizumab vs. Ranibizumab	Aflibercept vs. Ranibizumab	Aflibercept vs. Bevacizumab
Ophthalmic Cost Perspective	Ophthalmic Cost Perspective	Ophthalmic Cost Perspective	Ophthalmic Cost Perspective
Combined-eye model	NA	−$1,091,976/QALY (Aflibercept dominant)	$1,147,293/QALY
Societal cost perspective	Societal cost perspective	Societal cost perspective	Societal cost perspective
Combined-eye model	NA	−$1,091,976/QALY (Aflibercept dominant)	$1,147,293/QALY

VEGF = vascular endothelial growth factor; NA = not applicable; QALY = quality-adjusted life-year.

The direct ophthalmic cost perspective $/QALY, or cost-utility ratio, = dollars expended per quality-adjusted life-year gained,. Minus cost-utility ratios simply indicate that the VEGF inhibitor therapy dominates no treatment or another therapy because it generates greater patient value gain (QALYs) and is less expensive than observation or the other therapy.

subtracted from the total QALY accrual in each treated eye. Adverse events included cases of endophthalmitis per 1,756 intravitreal injections,[6,7] 1 day of post-injection ocular discomfort (utility = 0.89) and 2 days of post-injection ocular erythema (utility = 0.96). The 11-year QALY loss from adverse events was 0.070 QALY per eye in the bevacizumab and ranibizumab cohorts and 0.035 QALY per eye in the aflibercept cohort receiving fewer intravitreal injections. For the 2-year model, the respective adverse event QALY losses were 0.065 per eye and 0.032 per eye. Systemic adverse events, such as death and cardiovascular events, were not considered due to the similar incidence rates among the 3 drugs and the uncertainty as to whether they exceeded those found in an age-matched population without NVAMD.[3,4,6–15]

• **MORTALITY:** Christ and associates[39] calculated the risk of premature death associated with vision loss in the better-seeing eye (Supplemental Table 3). Their comprehensive methodology and statistical analysis are well described in a study of 2,520 ophthalmic patients with baseline ages of 65-84 years and 20-year follow-up in the Salisbury Eye Evaluation Study. Referent to 20/20 vision with a hazard ratio of 1.0 for the chance of dying within 8 years, the hazard ratio for 20/40 vision was 1.03, 1.08 for 20/80, and 1.18 for 20/200. The calculation by Christ and associates in our present study demonstrated that, for 20/630 vision, the hazard ratio was 1.33. Thus, there is a 33% higher chance that someone with 20/630 vision will die within 8 years than a person with 20/20 vision. When the annual mean vision changes between the present cohorts treated with VEGF-I and those of the control cohort were analyzed (Table 1) and correlated with the hazard ratios, the mean treated patient in each of the bevacizumab, ranibizumab, and aflibercept cohorts had a life expectancy of 11.0 years, whereas the mean person in the untreated control cohort was calculated to have a mean life expectancy of 10.0 years. Thus, VEGF-inhibitor monotherapy resulted in the prevention of approximately 1.0 year of life lost for the average untreated NVAMD patient, a 0.259 QALY gain for bevacizumab and ranibizumab and a 0.266 QALY gain for aflibercept, each consisting of 19.2% of the total QALY gains, respectively, of 1.339 and 1.380, respectively. In the 2-year model, VEGF-inhibitor therapy prevented 1 month of life loss over 2 years while gaining 8.1% of the total bevacizumab and ranibizumab QALY gains and 6.6% of the QALY gain associated with aflibercept therapy.

• **COSTS:** The ophthalmic direct medical costs (paid by insurers and patient out-of-pocket dollars) were taken directly from the 2018 national average Medicare fee schedule (Table 4).[29–31] Although only 1 eye was enrolled in the clinical trials studied,[3–7] the authors also included the costs associated with treating fellow eyes with atrophic AMD (age-related macular degeneration) that converted to NVAMD with the same drug during the 11-year (Table 5) and 2-year (Table 6) models to simulate clinical practice. The direct nonophthalmic medical costs were taken from a study by Javitt and associates,[32] and the direct nonmedical costs (caregiver costs) were taken from a study by Brown and associates,[33] and the indirect medical costs were taken from Brown and associates,[33] The U.S. Bureau of Labor Statistics,[34] and the Household Economic Studies from the US Census Bureau.[35] Direct nonmedical, or caregiver, costs included 27% for paid caregivers and 73% for unpaid caregivers,[33] similar to what has been noted by others.[40]

All non-2018 nominal dollar amounts were converted to 2018 U.S. real dollars by using the Consumer Price Index for All Urban Consumers (CPI-U).[62] The U.S. city average all-items index was used for nonmedical costs such as transportation, activities of daily living, and residence-related costs. The U.S. city average, medical care index, which included provider and hospital medical care services and medical care commodities such as drugs, equipment, and supplies, were used for conversion of entities such as depression costs, trauma costs, and facility costs.

• **SENSITIVITY ANALYSES:** Deterministic sensitivity analysis assesses the model outcome, resulting from changing 1 input parameter (one-way sensitivity analysis), 2 parameters simultaneously (two-way sensitivity analysis), and so forth. These analyses often involve variables in which investigators have the least confidence and/or those for which changes can cause dramatic changes in outcomes.

RESULTS

UNLESS OTHERWISE INDICATED, REFERENCE CASE RESULTS are reported for an ophthalmic cost perspective and a societal cost perspective cost-utility analysis, each using a combined-eye model, QALY gains, and treatment-associated costs in treated eyes and fellow eyes with atrophic AMD that converted to NVAMD over the 2- and 11-year time periods.

• **PATIENT VALUE GAIN:** The overall, 11-year QALY (patient value) gains for the drugs were similar for bevacizumab, ranibizumab, and aflibercept (Table 3), differing only because the QALY loss due to adverse events was less in the aflibercept cohort because fewer intravitreal injections were administered (Supplemental Table 2). The combined-eye model QALY gain per individual in the bevacizumab and ranibizumab cohorts was 1.339, correlating with a 26.1% improvement in patient value (QALY gain). The visual gain during the first 10.0 years provided (21.1%/26.1% =) 80.8% of the total value (QALY) gain, and the extra 1.0 year of life added by therapy provided (5.0%/26.1% =) 19.2% of the patient value gain. The combined-eye model QALY gain in the aflibercept cohort was 1.380. The first 10.0 years also provided 80.8% of patient value (QALY) gain, and the last 1.0 year provided 19.2%. The 2-year model revealed total value (QALY) gains over no therapy of 10.4% for bevacizumab and ranibizumab and 12.1% over no therapy for aflibercept.

• **COSTS:** The 11-year direct ophthalmic medical costs of VEGF-I therapy are shown in Table 4. The combined-eye model, bilateral, total direct ophthalmic medical cost was $14,772 for bevacizumab therapy, $106,582 for ranibizumab therapy, and $61,811 for aflibercept therapy. The respective 2-year model costs were $5,690, $47,319, and $26,377.

The 11-year societal costs are listed in Table 5. Low-vision costs accrued against the direct ophthalmic VEGF therapy costs. The nonophthalmic direct medical costs were the same at −$75,519 for each of the 3 drugs and accrued against the direct ophthalmic medical costs because they related to interventions obviated by better vision. More than 50% of these costs came from preventing

TABLE 8. Two-Year Model, Cost-Utility Ratios of the VEGF Inhibitors for Neovascular Age-Related Macular Degeneration (2018 U.S. Real Dollars)

Incremental Cost-Utility Ratios (Combined-Eye Model)

Models	Direct Ophthalmic Cost Perspective				Societal Cost Perspective			
Aflibercept vs. Comparator	Incr. cost	Incr. QALY gain	Incr. value gain	Incr. $/QALY	Incr. cost	Incr. QALY gain	Incr. value gain	Incr. $/QALY
Aflibercept vs bevacizumab	$20,687	0.016	Afl. 1.7% greater	$1,292,938	$20,687	0.016	Afl. 1.7% greater	$1,292,928
Aflibercept vs ranibizumab	Aflibercept dominant				Aflibercept dominant			

Average Cost-Utility Ratios (Combined-Eye Model)

Drug	Direct Ophthalmic Cost Perspective				Societal Cost Perspective			
	Direct oph. med. Costs	QALY Gain	% Value Gain	$/QALY	Societal Costs	QALY Gain	% Value Gain	$/QALY
Bevacizumab	$5,690	0.141	10.4%	$40,355	−$35,521	0.141	10.4%	−$251,922
Ranibizumab	$47,319	0.141	10.4%	$335,596	$6,108	0.141	10.4%	$43,319
Aflibercept	$26,377	0.157	12.1%	$168,006	−$14,835	0.157	12.1%	−$94,484

VEGF = vascular endothelial growth factor; Direct oph. med. costs = Direct ophthalmic medical costs; Afl = aflibercept; Incr. = incremental; QALY = quality-adjusted life-year; VEGF-I = vascular endothelial growth factor inhibitor.

Domination indicates that one drug confers great patient value (QALY gain) for less cost than its comparator drug. Negative costs are those returned to society for the direct ophthalmic medical costs expended. Negative cost-utility ratios indicate that there is a net return of dollars to society from the intervention.

yet unidentified interventions associated with poorer vision that Medicare would pay for without VEGF-I therapy.[32]

The 11-year direct nonmedical costs, which are alternatively listed as caregiver costs, are also the same for each drug at −$267,646.[33] The contributing direct nonmedical costs are listed in Table 5. Inside activities of daily living costs comprised 50% of caregiver costs.

The 11-year, indirect medical costs, primarily wage loss, were also the same for each drug at −$32,969. With better vision from VEGF-I monotherapy, more people were able to work and volunteer. The wage costs were calculated assuming an age-matched population of 8.1% of people over 75 years of age who were working as the standard for numbers of people gainfully employed.[34] Those with severe difficulty seeing (<20/200), however, earned a median $2,564 per month (98% that of a nondisabled person) but were only 47% as likely to be employed as people without disabilities.[35]

The 2-year model societal costs, excluding the direct ophthalmic medical costs, totaled −$41,211 for each drug (Table 6).

• **INCREMENTAL COST-UTILITY RATIOS:** The 11-year model ophthalmic cost perspective and societal cost perspective, incremental CURs comparing aflibercept to bevacizumab were both $1,147,273/QALY (Table 7), much higher than the informal CUR of $100,000/QALY often used as an upper limit of cost-effectiveness in the United States[18,27,63,64] and the 3× Gross Domestic Product per capita ($200,868/QALY in 2020) upper limit recommended by the World Health Organization (WHO).[28] Aflibercept was more effective than ranibizumab because it provided greater patient value gain (QALY gain) for less cost than ranibizumab, with average incremental and societal incremental CURs of −$1,091,976/QALY. Thus, if therapy is started with bevacizumab and switching drugs is necessary, aflibercept is the next drug of choice, rather than ranibizumab. An incremental CUR comparing bevacizumab to ranibizumab cannot be calculated because both deliver the same QALY gain.

The 2-year model incremental average and societal CURs comparing aflibercept to bevacizumab were both $1,292,938/QALY (Table 8). Again, aflibercept was more effective than ranibizumab. Aflibercept was again the drug of choice if bevacizumab could not be used.

• **AVERAGE COST-UTILITY RATIOS:** The reference case, 11-year model, average CURs versus no therapy associated with each of the 3 drugs are shown in Table 9. With the ophthalmic cost perspective, using only direct ophthalmic medical costs in the numerator, the combined-eye CURs were $11,033/QALY for bevacizumab therapy, $79,600/QALY for ranibizumab, and $44,801/QALY for aflibercept. Comparing CURs for cost-effectiveness, the authors divided the difference in 2 CURs by the lesser CUR to quantify the relative cost- effectiveness of the less expensive intervention

TABLE 9. Eleven-Year Model, Average Cost-Utility Ratios in $/QALY Associated With VEGF-Inhibitor Monotherapy for NVAMD (2018 Real U.S. Dollars)

Average Cost-Utility Ratios			
11-Year Model	Bevacizumab	Ranibizumab	Aflibercept
Ophthalmic Cost Perspective	Ophthalmic Cost Perspective	Ophthalmic Cost Perspective	Ophthalmic Cost Perspective
Combined-eye model, reference Case	$14,772/1.339 = $11,033/QALY	$106,582/1.339 = $79,600/QALY	$61,811/1.380 = $44,801/QALY
Societal cost perspective	Societal cost perspective	Societal cost perspective	Societal cost perspective
Combined-eye model	−$357,680/1.339 = −$267,124/QALY	−$265,870/1.339 = −$198,558/QALY	$310,641/1.380 = −$225,102/QALY

VEGF = vascular endothelial growth factor; the direct ophthalmic cost perspective $/QALY, or cost-utility ratio, = dollars expended per quality-adjusted life-year gained; VEGF = vascular endothelial growth factor; NA = not applicable.

Minus cost-utility ratios simply indicate that the VEGF-inhibitor therapy dominates no treatment or another therapy because it generates greater patient value gain (QALYs) and is less expensive than observation or the other therapy.

[Relative cost effectiveness of less expensive drug = (higher CUR − lower CUR)/lower CUR].

For example, the difference in CURs between ranibizumab ($79,600/QALY) and bevacizumab ($11,033/QALY) was $68,567/QALY. Dividing the $68,567/QALY difference by the lower CUR of $11,033/QALY revealed that bevacizumab was [($79,600/QALY-$11,033/QALY)/$11,033/QALY =)] 6.21 × (621%) more cost-effective than ranibizumab. Substituting the aflibercept CUR of $44,801/QALY, the relative cost-effectiveness of bevacizumab versus aflibercept is ($44,801-$11,033)/$11,033 =) 3.06× (316%) greater than that associated with aflibercept. Therefore, it is 3.06× more cost-effective than aflibercept. The CUR associated with ranibizumab ($79,600/QALY) is 0.78× (78%) greater, or $34,799 greater, than the $44,801/QALY CUR associated with aflibercept, indicating that aflibercept is 78% ($34,799/$44,801) more cost effective than ranibizumab. With the societal cost perspective, all CURs were negative, respectively at −$267,124/QALY, −$198,558/QALY, and −$225,102/QALY. The negative CURs indicated a net return of dollars to society.

The 2-year model, ophthalmic cost perspective, average CURs (Table 8) were, $40,355/QALY for bevacizumab therapy, $335,596/QALY for ranibizumab and $168,006/QALY for aflibercept, with only bevacizumab cost-effective with an upper limit of cost-effectiveness of $100,000/QALY. With the societal cost-perspective, the average CURs were, respectively, −$251,922/QALY, $43,319/QALY and −$94,484/QALY.

SENSITIVITY ANALYSIS

ONE-WAY DETERMINISTIC, SENSITIVITY ANALYSES WERE performed for the 11- and 2-year models. More detailed data and explanations are in Supplemental Section 4.

• **EARLY TREATMENT VS. LATE TREATMENT:** According to Boyer and associates data,[41] early treatment (baseline vision of 20/40-20/80) in the 11-year model resulted in a 1.484 QALY gain, a 29.1% patient value gain for bevacizumab and ranibizumab, respectively. Early treatment with aflibercept yielded a 1.519 QALY gain and a 29.9% patient value gain. The order of favorable cost-effectiveness remained bevacizumab > aflibercept > ranibizumab.

Late treatment (baseline vision <20/160) with a final vision outcome of 20/250+1, demonstrated a 0.587 QALY gain for bevacizumab or ranibizumab, an 11.7% patient value gain. Late aflibercept therapy yielded a 0.622 QALY gain, a 12.5% patient value gain. Cost-effectiveness order was unchanged.

The early treatment and late treatment, average, ophthalmic cost perspective, CURs for bevacizumab were $9,957/QALY and 25,152/QALY, for ranibizumab were $71,840/QALY and $181,481/QALY, and for aflibercept were $40,697/QALY and $99,296/QALY.

• **DECREASING TREATMENT VISION AFTER YEAR 2 TO 20/80:** After 24-month randomized data, we modeled treatment vision at 20/80 thru 11 years. The ophthalmic cost perspective CURs for the 20/80 scenario were: bevacizumab = $12,192QALY, ranibizumab = $87,966/QALY, and aflibercept = $49,582/QALY.

• **DECREASING TREATMENT VISION AFTER YEAR 2 TO 20/200:** The ophthalmic cost perspective CURs were: bevacizumab = $24,212/QALY, ranibizumab = $174,694/QALY, and aflibercept = $95,815/QALY.

• **TREATING THE SECOND EYE AFTER FIRST-EYE TREATMENT:** By 5 years, 20% of treated eyes in CATT deteriorated to a vision of less than or equal to 20/200.[7] Treating the second eye decreased the chance of a final visual result of less than or equal to 20/200 in the better-seeing eye from 20% to 4% (20% × 20%). The ophthalmic cost perspective CURs of treating second eyes with the VEGF-I agents were bevacizumab = $11,813/QALY, ranibizumab = $88,174/QALY, and aflibercept = $51,540/QALY.

• **DOUBLING THE AFLIBERCEPT INJECTIONS:** Doubling the aflibercept injections to match the number of bevacizumab and ranibizumab injections made no difference in the cost-effectiveness order.

• **DECREASING THE AFLIBERCEPT INJECTIONS:** In May 2019, FDA-approved aflibercept labeling stated, "Although not as effective as the recommended every 8 week dosing regimen, the FDA approved giving aflibercept injections every 3 months after 1 year of effective therapy."[65] When aflibercept was given with one-third the frequency of bevacizumab and ranibizumab after year 2, the end of the randomized trial, the cost-effectiveness drug order remained unchanged. The aflibercept CUR improved 17.4% from $44,801/QALY to $36,863/QALY.

• **DOUBLING THE VEGF-I INJECTIONS FROM YEARS 6 TO 8 FROM 3×/YEAR TO 6×/YEAR AND FROM YEARS 9 TO 11 FROM 2×/YEAR TO 4×/YEAR:** Bevacizumab therapy and aflibercept therapy remained cost-effective with an upper cost-effectiveness limit of $100,000/QALY, whereas ranibizumab therapy was borderline cost-effective at $100,600/QALY.

• **TRIPLING OF VEGF-I INJECTIONS FROM YEARS 6 TO 8 FROM 3×/YEAR TO 9×/YEAR AND FROM YEARS 9 TO 11 FROM 2×/YEAR TO 6×/YEAR:** Bevacizumab therapy and aflibercept therapy remained cost-effective, while ranibizumab therapy is over the cost-effectiveness limit at $131,459/QALY.

• **DECREASING RANIBIZUMAB AND AFLIBERCEPT DRUG PRICES TO MATCH THE COST-EFFECTIVENESS OF BEVACIZUMAB ($11,033/QALY):** To match bevacizumab's cost-effectiveness, the price of aflibercept per injection needed

to decrease to $107, a 94.5% decrease from $1936, while the price of ranibizumab needed to decrease to $79, a 95.8% decrease from $1,870.

• **ASSUMING NO TREATMENT EFFECT UPON LONGEVITY:** Integrating the $24,800 systemic medical cost saved if a person aged 88-89 years dies 1.0 year prematurely,[66] the CUR of bevacizumab increases by 196%, ranibizumab by 27% and aflibercept by 47%.

• **ELEVEN-YEAR FIXED INTERVAL INJECTION MODEL:** With the Suner and associates model,[17] using 10 injections/year for 11 years and a vision outcome of 20/63-2, the respective 11-year costs for bevacizumab, ranibizumab and aflibercept therapy were $24,213, $200,455 and $101,109, while the respective CURs were $19,041/QALY, $160,621/QALY and $76,336/QALY.

• **TREAT-AND-EXTEND THERAPY:** In a treat-and-extend (T-E) model,[67–70] 49.1 injections were given to first-treated eyes over 11 years versus 51.2 in the present bevacizumab and ranibizumab reference cases. The T-E model also resulted in 17 fewer office visits. The respective, bilateral, 11-year therapeutic costs for bevacizumab, ranibizumab and aflibercept were $11,792, $98,853 and $56,744, respectively, whereas the respective CURs were $8,793/QALY, $73,716/QALY and $41,059/QALY.

• **MODELING VARIABLES HIGHER AND LOWER:** Increasing and decreasing the costs or the QALY gain of one drug or each drug by 20% did not change the cost-effectiveness order of bevacizumab > aflibercept > ranibizumab.

• **TWO-WAY SENSITIVITY ANALYSIS CHANGING QALY GAINS AND COSTS BY 20%:** Cost-effectiveness order was maintained at bevacizumab > aflibercept > ranibizumab, the only exception being that decreasing ranibizumab cost by 20% and increasing QALY gain increased by 20% yielded a CUR ($53,067/QALY) more favorable than aflibercept ($67,186/QALY) when its cost increased by 20% and QALY gain decreased by 20%.

• **TWO-YEAR MODEL:** Ophthalmic cost perspective, early treatment, average CURs were $23,440/QALY, $195,002/QALY and $96,687/QALY. Late treatment bevacizumab/ranibizumab QALY gains were each 0.004, while that for aflibercept was 0.037. The respective average CURs were $1,422,542/QALY, $11,829,821/QALY and $712,891/QALY.

DISCUSSION

THE PRESENT INCREMENTAL COST-UTILITY ANALYSES demonstrated that aflibercept therapy was more effective than ranibizumab therapy because it was less costly and delivered slightly greater patient value. Aflibercept therapy delivered slightly greater patient value than bevacizumab as well but was far from cost-effective versus bevacizumab due to its considerably higher cost. Nonetheless, if bevacizumab cannot be used, the present data suggested aflibercept is the next drug of choice.

Average cost-utility analyses demonstrated that the 26%-27% patient value gains associated with bevacizumab, ranibizumab, and aflibercept therapy were considerable due to gains in QOL and length-of-life. These gains were higher than those seen with many non-ophthalmic therapies.[28] The QALY gain in these previous combined-eye model on ranibizumab NVAMD therapy was 10.4%.[18] The greater QALY component gain herein was due to use of a long-term, untreated NVAMD control cohort that demonstrated continued long-term visual deterioration in untreated NVAMD eyes.[36] The inclusion of increased mortality as vision decreased in untreated eyes[39] also contributed approximately 20% to the overall QALY gain in our 11-year model herein, although less than half that in the 2-year model. Vision mortality-relevant data[39] have been used previously for cataract surgery cost-utility analysis.[63]

The patient value gains associated with use of the bevacizumab, ranibizumab, and aflibercept differed nominally (26.1% quality-of-life gain with bevacizumab and ranibizumab versus 26.9% with aflibercept) due to greater adverse event QALY loss associated with a mean 51.2 intravitreal injections in the bevacizumab and ranibizumab primary eye cohorts, versus a mean 25.6 injections in the aflibercept cohort.

• **COST-EFFECTIVENESS:** The reference case, ophthalmic cost perspective, average CURs for each drug differed dramatically due to the drug cost differentials (Tables 4 through 6 and 9). Using an informal U.S. upper limit of cost-effectiveness (cost-utility) of $100,000/QALY,[28] the 11-year model, bevacizumab, ophthalmic cost perspective, average CUR was cost-effective at $11,033/QALY, ranibizumab was still cost-effective at $79,600/QALY, and aflibercept was intermediate at $44,801/QALY. With the 2-year model, the respective CURs were $40,355/QALY, $335,596/QALY and $169,006/QALY, suggesting that ranibizumab and aflibercept therapy were not cost-effective. Using the WHO upper limit of 3× GDP/capita (U.S. 2018 $187,554/QALY) aflibercept therapy became cost-effective. Using an upper cost-effectiveness limit of £30,000 ($39,600 US dollars in December 2018) used by NICE (National Institute for Health and Care Excellence in the U.K.),[28] only bevacizumab was cost-effective with the ophthalmic cost perspective, 11-year model. Importantly, with the 11-year societal cost perspective, the average CURs for all 3 drugs were all cost-effective by any standard. (Table 9). A list of the upper limits of cost-effectiveness is shown in Supplemental Section 5.

With the 2-year model, ophthalmic cost perspective, average CURs comparing treatment to no treatment (Table 8), only bevacizumab was cost-effective at $40,355/QALY. The analogous societal, 2-year cost perspective results revealed all 3 drugs were cost-effective, with bevacizumab and aflibercept demonstrating negative CURs.

It has been suggested by the Second Panel on Cost-Effectiveness in Health and Medicine[42] that cost-utility reference case analyses be performed using 2 variants, 1 variant using health care sector costs (herein direct ophthalmic medical costs) and the second variant using direct medical costs with all relevant associated societal costs.[42] This study performed both. Many analyses, however, do not use both recommended cost perspectives.[42]

Societal costs included the excess direct Medicare medical costs associated with different levels of vision loss,[32] age-adjusted wage loss associated with different levels of vision loss,[33–35] and personal costs related to caregivers (activities of daily living, transportation, residence change), loss of volunteering, low vision devices and others, which were acquired directly from a large cohort of patients with age-related macular degeneration and different levels of vision loss in the better-seeing eye.[33]

• **EARLY VERSUS LATE VEGF-I-TREATMENT:** Neither early nor late treatment changed the relationship that incremental aflibercept therapy was more effective than ranibizumab therapy and that aflibercept therapy was not more cost effective than bevacizumab therapy. Earlier treatment, however, delivered markedly greater patient value than late treatment (Supplemental Material, Section 4).[41] With early therapy, the 11-year, ophthalmic cost perspective, average CUR of each of the 3 drugs was cost-effective, whereas late therapy with ranibizumab (average CUR of $181,481/QALY) was not cost-effective, late aflibercept therapy (average CUR of $99,296/QALY) was borderline cost-effective, and late bevacizumab therapy remained cost-effective (CUR = $25,152/QALY).[28]

Two-year model, ophthalmic cost-perspective, average, early treatment CURs demonstrated that (Supplemental Material, Section 4) bevacizumab therapy was cost-effective (CUR = $23,440/QALY), aflibercept was marginally so (CUR = $96,687/QALY), and ranibizumab therapy was not cost-effective (CUR = $195,002/QALY). Late therapy was very expensive, with CURs ranging from >$700,000/QALY with aflibercept therapy to $11.8 million/QALY for ranibizumab therapy.

Marked differences in the 11-year, average, ophthalmic cost perspective CURs showed that bevacizumab and ranibizumab were 153% more cost effective when given early than late, and early aflibercept therapy was 144% more cost-effective than late therapy (Supplemental Material, Section 4). These numbers emphasize the importance of detecting and treating new cases of NVAMD as early as possible.[41]

• **UNILATERAL AND BILATERAL THERAPY:** Patient utilities[42–58] have demonstrated that second-eye model, average, ophthalmic cost perspective CURs are more favorable than those associated with the first-eye model. In essence, greater patient value gain accrues when treating the second eye if first-eye vision has already been lost than accrues from treating the initial eye if the fellow eye vision is good.[18,27,28,63] Both 11-year, ranibizumab ($/QALY = $282,577/QALY), and aflibercept ($/QALY = $150,038/QALY) ophthalmic cost perspective, first-eye model, average CURs (Supplemental Material, Section 4) exceeded the cost-effectiveness upper limit of $100,000/QALY.

Does that mean the first eye to develop NVAMD should not be treated or that the second eye to develop NVAMD should not be treated if the first had NVAMD and has been treated? We believe not. Some patients can have a good result in 1 eye and poor result in the other with the same treatment for unclear reasons. To deny treatment can deprive a patient of better depth perception, increase patient anxiety, and facilitate a poorer long-term visual outcome with its inherent increase in costs. Furthermore, 20% of treated eyes in CATT had 5-year vision of less than or equal to 20/200.[7] Assuming both eyes react independently to therapy, treating both eyes theoretically reduces the incidence of bilateral legal blindness from 20% if only one eye with bilateral NVAMD is treated to (20% × 20% =) 4% if both eyes with active NVAMD are treated.[7]

Although it may seem that fear of intravitreal injections plays a prominent role in therapeutic choices, data suggest there is no statistical difference in mean patient utility outcomes when intravitreal injections are given every 4 weeks or every 8 weeks.[71]

• **ELEVEN-YEAR VS. TWO-YEAR MODELS:** In the 11-year model, more costs were spent early, and the QALY gain was greater in years 3-11 than in the first 2 years because vision in untreated eyes continued to deteriorate. Thus, the 2-year model was less cost-effective than the 11-year model. Only bevacizumab was cost-effective with the ophthalmic cost perspective 2-year model, whereas all 3 drugs were cost-effective in the 11-year model. Nonrandomized CATT,[7] HORIZON,[8] and 5-year Australian study[24] data provide additional treatment data through year 5, as does the Shah and Del Priore Lineweaver-Burke meta-analysis[36] modeling untreated NVAMD. We suspect that undertreatment from years 3 to 5 may have played a role in the visual deterioration seen during this time with the 3 VEGF-inhibitors,[7,8] especially because participants who returned for SEVEN-UP[16] follow-up had better long-term vision outcomes with more injections. Suner and associates' 10-year data[17] and Peden and associates' data[72] suggest the same. Of course, this could also just mean that those with better vision outcomes were more likely to return for follow-up.[7] Although 11-year

randomized data may give more reliable results,[15] it is doubtful that long-term randomized trials for the three drugs herein will be sponsored due to cost, as well as new drugs and novel delivery systems under development.

• **COMPARISONS TO CATARACT SURGERY:** The cost-utility of U.S. cataract surgery has been analyzed with similar methodology to NVAMD herein.[63] The respective ophthalmic CURs of bevacizumab, ranibizumab, and aflibercept of $11,033/QALY, $79,600/QALY and $44,801/QALY considerably exceed the $1,007/QALY CUR for first-eye cataract surgery,[68] although all interventions are cost-effective. Mean QOL gain from NVAMD therapy herein was 26.5%, versus 34.2% for first-eye cataract surgery,[63] all excellent compared to interventions across medicine.[57]

• **POTENTIAL LIMITATIONS:** Our most pronounced limitation is the lack of 11-year randomized trial data. Our 2-year model outcome data, however, directly modeled CATT treatment results[73] and MARINA[1] placebo cohort outcomes in the 24-month clinical trials. Only bevacizumab, however, was cost-effective in our ophthalmic cost perspective, 2-year model.

The 11-year model is encouraging due to the fact that the SEVEN-UP study,[16] with a mean 7.4-year follow-up data for ranibizumab-treated NVAMD patients found the mean vision outcome to be 20/63-1 in patients treated with 6 to >11 injections between years 4 and 7.4. This vision was carried forward in a last-observation-carried-forward model for the 3 drugs. The real-world study by Suner and associates[17] noted a 10-year vision gain of 11.3 letters over baseline in a cohort treated every 4 to 8 weeks with fixed interval VEGF-I therapy for 10 years, supporting the SEVEN-UP data that more aggressive treatment can result in more reasonable long-term mean vision (20/63-2) versus no treatment (20/630).The Second Panel on Cost-Effectiveness in Health and Medicine recommends longer cost-utility modeling versus the present 2-year modeling.[42]

As-needed therapy and treat-and-extend therapy were not emphasized because increasing data suggested that greater frequency of treatment for a longer-term results in a better long-term vision outcome in the real world.[17] T-E methodology was modeled in the Sensitivity Analysis, and it was slightly more cost effective than the present reference case.[6,7,16,41,67–70] One study with 5-year T-E data actually had more injections over the 5 years than the mean CATT 5-year eye study due to higher numbers of injections in years 3 to 5.[67]

The data analyzed herein came from patients with NVAMD. Thus, the outcomes are not generalizable to other conditions treated with VEGF-I agents such as background and proliferative diabetic retinopathy, branch retinal vein occlusion, and central retinal vein occlusion. It should also be noted that data from 200 patients' societal costs associated with NVAMD taken from predominantly the northeast U.S. are not necessarily applicable to other areas of the country.

Switching of drugs was not modeled in the analysis because this is arbitrary at the current time and because of the generally agreed upon similarity in visual outcomes with each of the 3 drugs.

We did not compare previous NVAMD therapies such as laser photocoagulation intravitreal pegaptanib or photodynamic therapy with verteporfin as comparators for an incremental cost-utility analysis because VEGF-inhibitor therapy delivered 3.2× the QALY gain from photodynamic therapy (8.1% patient value), 4.4× the QALY gain from pegaptanib therapy (5.9% patient value gain), and 5.9× the QALY gain associated with subfoveal laser photocoagulation (4.4% patient value gain).[64] Thus, the older therapies are rarely used.

• **CLINICAL APPLICATIONS:** The data gains herein demonstrated that bevacizumab, aflibercept, and ranibizumab were all cost-effective for treating NVAMD with the health care sector (direct ophthalmic medical cost) reference case. With the societal reference case, they were cost-effective, with their negative CURs indicating they returned substantial dollars to society. If bevacizumab cannot be used, the next drug in line is aflibercept, which confers greater patient benefit for lesser cost than ranibizumab. Treatment with each of the 3 VEGF-I agents studied preserves 1.0 year of life in the mean 11-year life expectancy that otherwise would have been reduced to 10.0 years due to vision loss. The 2-year model showed bevacizumab therapy was considerably less cost-effective than with the 11-year model, while aflibercept and ranibizumab therapy were not cost-effective with the 2-year model. The authors believe, however, that the 11-year model, especially with newer data,[17] most closely approximates the real-world clinical scenario.

The eleven-year ophthalmic cost perspective, average cost-utility, reference case QALY gains of 26.1% for bevacizumab and ranibizumab, and 26.9% for aflibercept versus a do-nothing approach are slightly less than the early treatment, respective QALY gains of 29.1% for bevacizumab and ranibizumab, and 29.8% for aflibercept versus no treatment This difference equates to 11.5% and 10.8% relative increases over the reference case.

Late treatment confers long-term 11.7% and 12.5% QALY gains over no therapy, respectively. Thus, early bevacizumab and ranibizumab therapy confer 149% [29.1%-11.7%)/11.7%] greater QALY gain and are 149% more cost-effective than late therapy. Early aflibercept therapy confers 138% [29.8% − 12.5%)/12.5%] greater QALY gain and is 138% more cost-effective than late therapy.

In the 2-year model, late treatment, ophthalmic cost perspective, average CURs are not cost effective at $1,422,542/QALY for bevacizumab, $11,289,821 for ranibizumab and $712,891 for aflibercept.

CONCLUSIONS

BEVACIZUMAB, RANIBIZUMAB, AND AFLIBERCEPT THERAPY for NVAMD conferred similar, considerable patient value (QALY) gain and were all cost-effective by a commonly used U.S. cost-effectiveness threshold. Nonetheless, the cost-effectiveness of bevacizumab therapy was found to be approximately 7× that of ranibizumab therapy and 4× that of aflibercept therapy with an 11-year ophthalmic (health care) cost perspective, cost-utility model. Aflibercept therapy was not incrementally cost-effective versus bevacizumab therapy but was more cost-effective than ranibizumab therapy and, thus, was the next drug of choice when bevacizumab could not be used. Early treatment is critical because it conferred 149% greater QALY gain and was 153% more cost-effective than late treatment with bevacizumab therapy and ranibizumab therapy. Early treatment for aflibercept was also critical because it conferred 138% greater QALY gain and was 144% more cost-effective than late treatment. An 11-year cost-utility model was considerably more cost-effective than a 2-year model because the direct ophthalmic medical costs accrued were greater during the first two years of therapy and the QALY gain accrued was greater during the latter half of the 11-year model.

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