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Cost-Effectiveness of Treatments for Diabetic Macular Edema: Simulated Bevacizumab-First Step Therapy Versus Real-World Practice

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Abstract

Purpose: To compare the incremental cost-effectiveness of a clinical trial-simulated step-therapy versus real-world treatment for diabetic macular edema (DME). **Methods:** A theoretical Markov model (follow-up of 2 years and lifetime of 17 years) from the 2025 US societal perspective was used to compare the costs and cost-effectiveness between bevacizumab-first (Protocol AC) and real-world regimens from the Vestrum Health database. The modeling used mean characteristics from a reference case and analyzed low- and high-cost scenarios, total societal costs from formal and informal healthcare and non-healthcare sectors, and differences in utility (visual acuity outcomes) between arms. **Results:** Protocol AC bevacizumab-first in the reference case was 14% more expensive at 2 years, with a total adjusted societal cost of $69 850 versus $61 304 for real-world treatment. Although visual acuity gains were higher with Protocol AC, the incremental cost-utility ratio (ICUR) was $105 335/quality-adjusted life years (QALY) at 2 years and $151 032/QALY over 17 years, higher than most societal willingness-to-pay thresholds. In the low-cost scenario, Protocol AC was neither cost-saving nor cost-effective at 2 years (ICUR $82 283/QALY) but was cost-effective over 17 years (ICUR $591/QALY). In the high-cost scenario, Protocol AC was not cost-effective at 2 years (ICUR $219 420/QALY) or 17 years (ICUR $207 589/QALY). Probability sensitivity analysis showed that Protocol AC was more expensive in 87% of modeled scenarios and not cost-effective in 76%. **Conclusions:** Compared with real-world treatment, protocol AC bevacizumab-first treatment for DME was generally not cost-saving. Although better vision outcomes were achieved with bevacizumab-first, the protocol was generally not cost-effective due to greater treatment burdens.

Keywords

cost-effectiveness, diabetic macular edema, Protocol AC, Vestrum, real-world treatments

Introduction

The prevalence of diabetic macular edema (DME) has been increasing in the United States, and treatment with anti–vascular endothelial growth factor (anti-VEGF) injections in Medicare patients with DME rose from a frequency of 20.2% in 2009 to 47.6% in 2018.[1] Multiple anti-VEGF injection therapies are currently available. While bevacizumab (Avastin, Genentech Inc., San Francisco, CA) is the least expensive, there have been concerns, including its off-label use for eye diseases and its compounding and repackaging process,[2–4] which may be associated with an increased risk of inflammation, infection, and intravitreal silicone oil droplets.[5,6] In contrast, more expensive treatment options such as ranibizumab (Lucentis, Genentech, Inc.) and aflibercept (Eylea, Regeneron Pharmaceuticals, Inc.), along with more recent therapeutic options, are approved by the US Food and Drug Administration (FDA) for the treatment of DME[7,8] and have been shown to be cost-effective, with aflibercept being more effective than bevacizumab in the treatment of DME.[8,9]

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Many insurance companies have instituted requirements for step-therapy regimens, mandating the use of less expensive medications first, with authorization for more effective and more expensive treatments only if there is an inadequate treatment response. Such step-therapy regimens for DME typically require initiation of treatment with bevacizumab, allowing for a switch to FDA-approved options such as aflibercept only after failure has been documented.

Recently, the Diabetic Retinopathy Clinical Research Network (DRCR) reported the results from Protocol AC, a study in which a step-therapy approach for DME was simulated in a clinical trial setting by comparing outcomes between bevacizumab-first therapy (and a switch to aflibercept for under-responders) and aflibercept monotherapy. At 2 years, Protocol AC showed similar visual acuity outcomes between the 2 treatment arms,[10] and cost-effectiveness studies found that Protocol AC bevacizumab-first was more cost-effective than Protocol AC aflibercept monotherapy.[11,12] It should be noted though that those outcomes were achieved in a research environment requiring frequent clinic visits and injections, which may have diminished the impact of therapies of different efficacy and which are likely difficult to achieve in the real world, especially with younger, working-age patients with diabetes. Additionally, those cost analyses did not include the societal perspective or indirect costs, which comprise more than half of the total estimated costs from vision loss in the United States.[13]

In a prior analysis, the direct medical costs of Protocol AC bevacizumab-first in DME patients were compared with those in a real-world cohort of treatment-naive DME patients from the Vestrum Retinal Health database who were treated with anti-VEGF monotherapy.[14] That analysis found that Protocol AC was 40% more expensive than the real-world treatment. Although the real-world treatment did not improve visual acuity to the same extent as Protocol AC, the costs of real-world treatment were still 19% lower in a subcohort of patients whose vision outcomes matched those in the Protocol AC cohort, suggesting indirectly that Protocol AC is not more cost-effective than real-world strategies.

The purpose of this study was to determine the costs and cost-effectiveness of Protocol AC bevacizumab-first compared with real-world regimens from a US societal perspective, incorporating total societal costs and differences in visual acuity outcomes.

Methods

Modeling and Cohorts

The cost-effective analysis was performed using a theoretical Markov model from the 2025 US societal perspective. The analysis followed the recommendations of the Second Panel on Cost-Effectiveness in Health and Medicine and the Consolidated Health Economic Evaluation Reporting Standards.[15] Specifically, we included formal healthcare sector costs (including the costs of direct medical care and adverse events), informal healthcare sector costs (including costs of patient time, unpaid caregiver time, and transportation), and non–healthcare sector costs of lost productivity (including lost productivity due to patient illness, lost caretaker productivity, and lost volunteer work), consumption (including the cost of glasses and refraction), and cost of social services (as from depression, injury, and skilled nursing facility stays). It was assumed that the treated eye was the better-seeing eye.

Institutional review board approval was not required for this study because the theoretical model did not involve human subjects or patient identifiers. The analyses adhered to the tenets of the Declaration of Helsinki and complied with all local and federal laws.

The costs and benefits of the Protocol AC bevacizumab-first arm were modeled based on published data from the DRCR Protocol AC.[10] Data for the real-world cohort were derived from the Vestrum Retinal Health database, comprising the electronic medical records of >1.8 million patients who were seen by more than 350 private practice retina specialists at more than 69 sites in 35 states (24% southeastern United States, 24% mid-Atlantic, 20% western, 12% southwestern, 8% northeastern, 7% Great Lakes, and 4% North Central regions). The majority of practices (65%) were in urban environments, while 32% were suburban and 3% were rural, although many practices had rural satellites not reflected in these demographics.

The inclusion and exclusion criteria used for patient selection in the Vestrum real-world cohort were modeled after those of Protocol AC. Specifically, the cohort comprised treatment-naive patients with DME and a baseline visual acuity between 20/50 and 20/320 who began treatment with anti-VEGF monotherapy starting in 2016; patients were excluded if they had a concurrent diagnosis of age-related macular degeneration, vascular occlusion, or myopic choroidal neovascularization before or during the 2-year follow-up period; if they had received intravitreal or periocular steroids prior to or during the study period; or if they had a history of focal laser therapy prior to or during the study period. The year 2016 was purposefully selected to best reflect unrestricted and informed physician drug choice, since the influence from the recently increased prevalence of insurance step-therapy requirements was minimized and we could account for the findings from DRCR Protocol T, published in 2015, which demonstrated that aflibercept was more effective than bevacizumab for DME treatment.[8]

For inputs of societal costs, the average employment rate for patients and caretakers, average number of sick days, and average salaries were derived from the US Bureau of Labor Statistics.[16–18] All costs and benefits were adjusted for inflation to 2025 US dollars and were discounted 3% per annum in order to reflect past and future costs being valued less than present costs. We utilized a reference case to model mean values or assumptions. Cost-effectiveness modeling also included both a low-cost scenario and a high-cost scenario with a range of assumptions (as detailed in the Appendix Methods and Appendix Table 1).

Probability Sensitivity Analyses

Probability sensitivity analyses were performed with Python,[19] using second-order Monte Carlo simulations repeated 100 000 times (see Appendix Methods for the ranges). Parameters were varied according to previously published available data;

otherwise, assumptions were as noted. In particular, parameter and methodological uncertainty were evaluated by varying the number and costs of visits, and structural uncertainty was assessed by varying the number of injections and non–healthcare-related costs (see Appendix Methods).

Two-Year Cost Analyses

Formal Healthcare Sector Costs

Direct medical costs at 2 years, including the costs of evaluation and management clinic visits, optical coherence tomography, intravitreal injections, and medications, in the Protocol AC and Vestrum real-world cohorts (Table 1) have been previously reported.[14]

When accounting for the cost of adverse events, the analysis restricted inclusion to the adverse event of endophthalmitis, being one of the most serious and costly complications of intravitreal injections, with a modeled incidence of 0.056% (range, 0.005%-0.009%) according to previously published reports.[20] Patients who developed endophthalmitis were treated with intravitreal injections of vancomycin and ceftazidime. In addition, vitreous cultures were obtained from these patients, and 28% (range, 18%-38%) had a pars plana vitrectomy.[21]

Informal Healthcare Sector Costs

Patient-time costs included the amount of time taken for work absences to receive care for DME, represented by lost wages. For the reference case, the median weekly salary, according to the US Bureau of Labor Statistics, was set at $1268 per week (range, $1097-$1442), and the number of sick days per year was based on that of the average worker after 5–10 years of service, a mean of 7 paid sick days (range, 0-10 days).[18] Moreover, for the reference case at the start of the model, the average employment rate was 64.1% (range, 56.7%-71.6%),[18] which was adjusted over time. Since patients without diabetes have been reported to take between 3.4 days and 8.7 sick days per year,[22] the analysis assumed that a mean of 6 annual sick days would be for non–diabetic retinopathy–related issues. The remaining sick day would be conservatively attributed in the analysis to the management of DME (and not to the remainder of care for systemic diabetes). However, in the low-cost and high-cost analyses, the number of paid sick days for diabetic retinopathy care was varied, ranging from 0 days to 8.7 days. It was assumed that the patient would take a full day off of work for each clinic visit, with a varying duration from half a day to 1.5 days.

Unpaid caregiver-time costs included the caregiver's uncompensated time used to help care for the patient, provide transportation, and accompany the patient to clinic visits. Initially, ~89% of patients (range, 49.7% to 92.7%) were assumed to have an accompanying caretaker;[23,24] over time, the percentage of patients with caretakers or drivers was further varied, depending on the degree of vision improvement. It was assumed that the caretaker had a similar number of paid sick days, of which half would be available for helping the patient, and the caretaker would be absent from work for a full day for each clinic visit, which ranged from 0.75 days off to 1.25 days off per visit to account for extra transportation and caretaker time. In the reference case, the initial age of the caretaker, based on the demographics of an average caretaker in the United States, was assumed to be 54 years, the caretaker's median weekly salary was assumed to be $1336,[25] and the average employment rate was set at 78.9%;[17] the median weekly salary was varied from $1192 to $1356, and the employment rate was varied from 8.4% to 81.9% in the probability sensitivity analyses, to reflect potential differences in the gender, age, and ethnicity of the caretaker. Similar to the patient, the caretaker salary and employment rate decreased over time. Transportation costs were assumed to be $32.98 per visit (range, $13.32 to $46.30) based on previously published data.[26]

Non–Healthcare Sector Costs

The cost of lost productivity in this model was the value of the resources that the patient would have generated at work had they not had an illness affecting their job performance. Lost productivity was calculated using the human capital approach instead of the friction cost approach, since it was assumed that patients would be absent from work for less than 1 contiguous month at a time, thereby making it less likely they would be replaced by another worker. The total productivity cost included the lost productivity from absenteeism and from presenteeism (resulting from decreased output and early retirement due to impaired vision). The full retirement age was assumed to be 67 years.[27] Patients with moderate-to-severe vision loss were assumed to have 30% loss of productivity[28,29] and early retirement based on previously published estimates, and mild vision loss was assumed to decrease productivity by 20%, varied by 10% in the probability sensitivity analyses. According to the World Health Organization definitions, mild vision loss was defined as visual acuity between 6/12 and 6/18 (approximate Snellen equivalent of 20/40 to 20/60), moderate vision loss as visual acuity worse than 6/18 but better than 6/60 (approximate Snellen equivalent 20/63 to 20/200), and severe vision loss as visual acuity worse than 6/60 (Snellen equivalent 20/200).[30] The median productivity multiplier of 1.44 (range 1.00 to 1.61) was used in the reference case to account for the effects of a lost worker in a group setting.[31]

The costs of lost productivity from the caregiver were similarly calculated. However, the caretakers were assumed to have no visual impairment and therefore no associated loss of work productivity while at work or in early retirement. Calculations for the cost of lost volunteer work, consumables, and social services are detailed in Appendix Table 2.

Utilities

Visual acuity was converted to the associated time-tradeoff utilities in order to determine the incremental cost-utility ratio (ICUR), using the following previously published formula: utility = 0.374 * (visual acuity in better seeing eye) + 0.514.[32,33] The time-tradeoff method for determining utilities was modeled from patient feedback on how many years of their

Table 1. Model Parameters From Years 1–2 and Years 3–17 in the Anti-VEGF Treatment Cohorts of Patients With Diabetic Macular Edema.[a]

Parameter	Protocol AC Bevacizumab-First	Real-World
Annual Clinic Visits (mean n)		
Years 1–2	12 (first year), 10.5 (second year)	8.3 (first year), 5.4 (second year)
Years 3–17	10.5	5.4
Intravitreal Injections (mean n)		
Total (years 1–2)	16.1 (10 first year, 6.1 second year)	8.6 (5.5 first year, 3.1 second year)
Total per year (years 3–17)	6.1	3.1
Anti-VEGF mix at end of year 2	30% bevacizumab, 70% aflibercept	42% bevacizumab, 45% aflibercept, 13% ranibizumab
Mean Best Corrected Visual Acuity (ETDRS letters; approximate Snellen equivalent)		
Baseline	60; ~20/63	54; ~20/80
At 2 years	73; ~20/40	60; ~20/63
At 17 years	68; ~20/44	58; ~20/70
Productivity Loss and Early Retirement due to Visual Impairment (% of patients)	30 (year 1), 20 (years 2–17)	30 (years 1–17)

Abbreviation: anti-VEGF, anti–vascular endothelial growth factor.
[a]Parameters from years 1–2 were from actual Protocol AC or Vestrum data, while parameters from years 3–17 were based on the listed assumptions and were varied in the analyses.

remaining lives they would theoretically be willing to trade in order to achieve a perfect health state (value of 1), then subtracting the portion of years traded by the years left to live from 1.[16] Death was equated to a utility value of 0, and bilateral no light perception was equated to a utility value of 0.26.[34] The quality-adjusted life years (QALYs) gained were determined by multiplying the improved utilities by the duration of benefit,[32,33] minus the cost of complications. The ICUR was determined by dividing the difference in costs between the 2 treatment regimens by the difference in QALYs gained over the time horizon, discounted 3% per annum.

Lifetime Costs

While the primary analysis of this study focused on Protocol AC and Vestrum real-world data over the 2-year clinical trial duration, a secondary analysis further extrapolated the data over the patient's lifetime, modeled over a time span of 17 years (Table 1). It was assumed that 5.6% of patients per year would switch from bevacizumab to an FDA-approved therapy, similar to the Intelligent Research In Sight (IRIS) registry data.[35,36] The costs of the drugs were varied by 25% and the percentage of the FDA-approved medications used was varied by 10% to account for the wider variability in pricing of newer medications in the probability sensitivity analyses. The employment rates, productivity, and wages for the patient and caretaker decreased with age, in accordance with data from the Bureau of Labor Statistics.[37] Patients with diabetes were assumed to have a 1.71-point to 2.42-point higher relative risk of death than the general population (1.3% to 4.6% more deaths per year in patients ages 60 to 80 years).[38,39]

In the reference case in both treatment arms, the patient was assumed to continue to receive the same number of injections in years 3–17 as were received in year 2,[40] with treatment intervals similar to the discontinuation and decreased injection intervals found in prior studies.[35,41–43] In the low-cost analysis in years 3–17, however, the average number of injections and clinic visits was decreased to 3 per year for both the Protocol AC and Vestrum real-world cohorts, and in the high-cost analysis, it was assumed that the clinic visits and injections were 10% higher than that of the reference case.

Based on the outcomes observed in the 5-year Protocol T extension study, the visual acuity gains were assumed to decline by ~36.4% in the Vestrum real-world treatment group over the remaining modeled lifetime.[44] In the reference case in the Protocol AC group, the visual acuity loss was assumed to be half as much as that in the Vestrum real-world treatment reference case and therefore needed only half as many drivers/caretakers. In the low-cost scenario, the visual acuity loss and the number of caretakers/drivers in the Protocol AC group were equal to those in the Vestrum group over time, as the number of injections in the Protocol AC patients decreased. In the high-cost scenario, patients in the Protocol AC group, who received a greater number of injections over time, were assumed to maintain their visual acuity gains.

Results

The reference case for the Protocol AC bevacizumab-first arm was a 61-year-old man with a mean best corrected visual acuity of 60 ETDRS letters (approximate Snellen equivalent 20/63) at baseline, which improved to 73 ETDRS letters (Snellen ~20/40) after administration of 16.1 bevacizumab injections and 22 visits over 2 years.[10] In the Vestrum real-world scenario, the reference case was a 61-year-old man with a mean best corrected visual acuity of 54 ETDRS letters (Snellen ~20/80) at baseline, which improved to 60 ETDRS letters (Snellen ~20/63) at 2 years after administration of 8.6 injections of anti-VEGF monotherapy over 13.8 visits.[10]

Table 2. Total Adjusted Societal Costs By Sector For the Reference Case in the Anti-VEGF Treatment Cohorts.[a]

	2 years		17 years	
Sector	Protocol AC Bevacizumab-First	Real-World	Protocol AC Bevacizumab-First	Real-World
Formal Healthcare Sector Costs				
Health				
Direct Medical Costs (US $)	21,414	12,948	146,953	70,717
Adverse Events (n)	6	4	52	28
Informal Healthcare Sector Costs (US $)				
Health				
Patient-Time Costs/Lost Wages	3,332	1,902	13,626	6,647
Unpaid Caregiver-Time Costs	2,905	921	14,878	921
Transportation Costs	742	452	5,731	3,018
Non–Healthcare Sector Costs (US $)				
Productivity				
Patient Costs	48,426	50,833	140,002	136,084
Caretaker Costs	5,869	3,587	39,870	21,027
Lost Volunteer Work	770	770	6,160	6,160
Consumption Costs (US $)				
Glasses and Refraction	650	650	5,525	5,525
Social Services Costs (US $)				
Depression, Injury, ± Skilled Nursing Facility	117	156	1,288	1,327
Total Societal Cost (US $)	69,850	61,304	238,839	176,217
Total QALYs Gained	0.13	0.047	0.58	0.17
ICUR (US $/QALY)[b]	105,335		151,032	

Abbreviations: anti-VEGF, anti–vascular endothelial growth factor; ICUR, incremental cost-utility ratio; QALY, quality-adjusted life years.
[a]Costs were discounted 3% per annum and adjusted for inflation to 2025 US dollars, and QALYs gained were adjusted for adverse events.
[b]Difference in costs per QALYs gained versus real-world treatment.

As previously reported, the 2-year mean direct cost (in 2022 US dollars) in the Protocol AC group was $18,952, and the 2-year mean direct cost in the Vestrum real-world group was $11,459.[14] In our analysis, these reported costs were adjusted to 2025 US dollars and discounted 3% per annum (Table 2). In the reference case in the Protocol AC bevacizumab-first arm, the total adjusted 2-year societal cost, including both direct and indirect healthcare costs to the patient, healthcare sector costs, and society costs, was modeled at $69,850 (Table 2), which was 14% more than the total adjusted 2-year societal cost for the Vestrum real-world reference case ($61,304) (Figure 1, A and B). In the low-cost scenario, the total adjusted societal cost was $50,883 for Protocol AC, which was 13% higher than the Vestrum cohort (total adjusted societal cost $44,875). In the high-cost scenario, Protocol AC societal cost ($103,902) was 23% higher than that for the Vestrum group ($84,318) (Appendix Table 2).

The discounted incremental QALYs gained over 2 years in the Protocol AC bevacizumab-first arm compared to the Vestrum real-world treatment arm were modeled at 0.081, adjusted for adverse events. Therefore, the Protocol AC bevacizumab-first arm reference case had an ICUR of $105,335/QALY at 2 years (Table 2). In the low-cost scenario, the modeled ICUR for the Protocol AC bevacizumab-first arm was $82,283/QALY, and the high-cost ICUR was $219,420/QALY (Appendix Table 2).

Over a 17-year horizon, continuing Protocol AC would result in 35% greater costs compared with the Vestrum real-world treatment in the reference case ($238,389 versus $176,217, respectively; cost difference $62,172). For the reference case, the QALYs gained were 0.412 (range 0.263–0.584), with a modeled reference ICUR of $151,032/QALY. In the low-cost scenario, in which the number of injections and clinic visits decreased to an average of 3 per year in both the Protocol AC and Vestrum real-world groups, we observed that the Protocol AC bevacizumab-first treatment was not cost-saving and was slightly more expensive than the Vestrum real-world treatment (cost difference $156), but the ICUR in the Protocol AC group had decreased to $591/QALY (Appendix Table 3). In the high-cost scenario, Protocol AC was more expensive than the Vestrum real-world treatment (cost difference $121,398) over the 17-year modeled lifetime, with an ICUR of $207,589/QALY (Appendix Table 3).

The probability sensitivity analyses revealed that the Protocol AC bevacizumab-first treatment was not cost-saving and was more expensive than the Vestrum real-world treatment in 87% of modeled lifetime scenarios and was not cost-effective in 76%, even with significant variations in the number of injections, clinic visits, treatment costs, and other parameters. The greatest factors impacting the total societal costs were the cost of medications and the indirect medical costs such as patient salary and productivity losses, which were dependent on the number of clinic visits and injections.

Discussion

Step-therapy protocols for the treatment of retinal diseases such as DME have been increasingly mandated by insurance carriers. To the authors' knowledge, there are currently no real-world studies

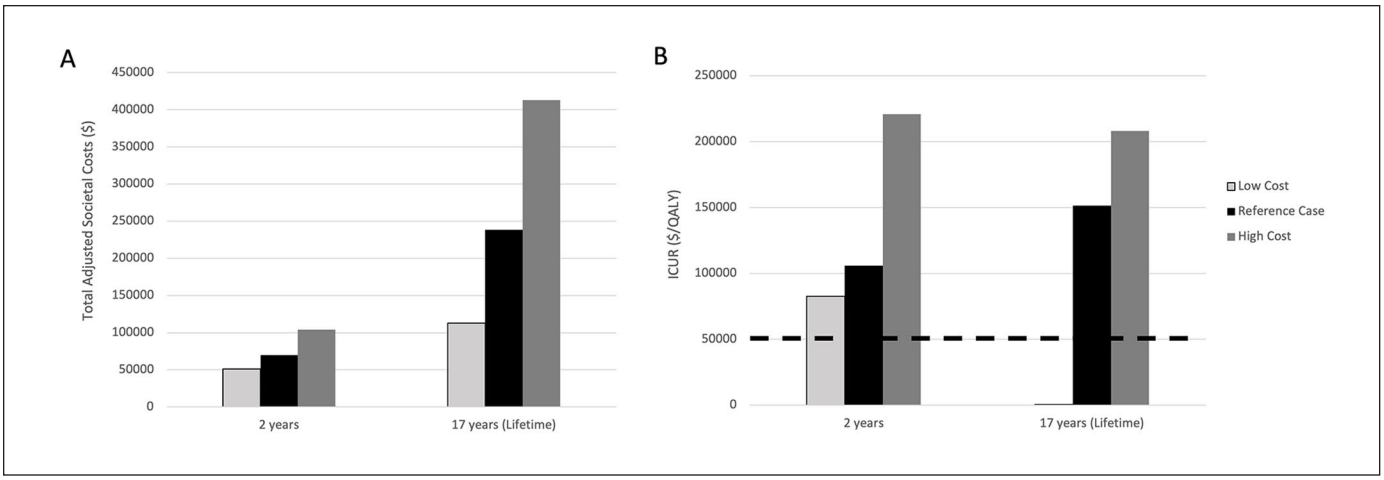

Figure 1. (A) Total Adjusted Societal Costs over Time. In the reference case, over two years, Protocol AC bevacizumab-first would be 14% more expensive than real-world treatments, and over a patient's lifetime, Protocol AC bevacizumab-first would be 35% more expensive. (B) Incremental Cost-Effectiveness of Protocol AC vs. Real-World Treatments. Over the course of 2 years, the incremental cost-utility ratio (ICUR) for Protocol AC bevacizumab-first was above the societal willingness-to-pay threshold of $50,000/QALY (marked by the horizontal dashed line) for the low-cost, reference, and high-cost scenarios and would therefore not be considered cost-effective compared to real-world treatments. Over a patient's lifetime, Protocol AC remained not cost-effective in the reference and high-cost scenarios but not the low-cost scenario.

demonstrating benefits and/or evaluating the consequences of step therapy in the real-world management of retinal disease. In a 2023 survey of more than 1,000 retina specialists, almost 90% of US respondents reported being given step-therapy protocols, with greater than half of the US respondents reporting patient dissatisfaction, lack of vision improvement, or lack of anatomic improvement, and nearly half of respondents noting worsening vision and worsening anatomy resulting from step-therapy protocols.[45]

DRCR Protocol AC was a clinical trial designed to simulate a step-therapy program, comparing DME patients treated with bevacizumab first (and a switch to aflibercept for under-responders) versus aflibercept monotherapy. Although the trial demonstrated similar vision outcomes over 2 years, these outcomes were achieved with aggressive initial monthly treatment protocols. The frequent visits and treatments in Protocol AC would likely minimize any differences associated with drugs of different efficacy, and this treatment burden, which is standard in a clinical trial setting, would likely not be achievable in the real world, particularly for a population of younger, working-age patients with diabetes. In a follow-up from Protocol AC, the DRCR Retina Network evaluated the cost-effectiveness of the bevacizumab-first arm versus the aflibercept-monotherapy arm. A 47.4% cost savings with use of bevacizumab-first versus aflibercept monotherapy was identified, and the authors concluded that the bevacizumab-first approach may confer "substantial cost savings on a societal level."[11] Although DRCR demonstrated that cost savings could be achieved in a clinical trial setting comparing an aggressive regimen of bevacizumab-first versus an aggressive regimen of aflibercept monotherapy, real-world savings should only be considered if the same regimens were to be applied in a real-world setting. In a previous analysis comparing the cost of Protocol AC with actual real-world utilization, modeling showed that the bevacizumab-first arm of Protocol AC had a higher cost (40% higher) than real-world treatment regimens, even when vision outcomes were matched.

In order to comprehensively capture the direct and indirect costs of DME anti-VEGF treatments, the current model included total societal costs, which included lost productivity related to vision loss from absenteeism, presenteeism, and early retirement. The Protocol AC group, in which patients received treatment more frequently, had a higher cost of absenteeism from work. The Vestrum real-world treatment group, in which patients had a greater degree of visual impairment secondary to lower vision gains, had a higher cost of presenteeism, or decreased value of their work while at their job. The higher initial treatment burden and higher direct and indirect costs when the patient and caretaker were of working age, and presumably more productive, outweighed the greater vision benefits of Protocol AC bevacizumab-first compared to real-world treatments in the reference case. Furthermore, the majority of the Protocol AC bevacizumab-first patients did eventually switch to the more expensive treatments over time.[10]

In the current analysis, the total societal cost of Protocol AC bevacizumab-first was modeled at ~14% higher than the real-world costs from the Vestrum real-world treatment over 2 years. When extrapolated over 17 years, Protocol AC bevacizumab-first was 35% more expensive than real-world therapies in the reference case. The probability sensitivity analyses found that Protocol AC was not cost-saving and was frequently more expensive than Vestrum real-world therapies in a wide range of scenarios.

The ICUR ratios factored in costs as well as vision outcomes, modeled through QALYs. While there is no standard societal willingness-to-pay threshold in the United States, interventions with ICURs below $50,000/QALY are often

considered cost-effective.[46] For comparison, the UK National Institute for Health and Care Excellence identified £20,000–£30,000/QALY (~$25,000–$38,000/QALY) as an acceptable threshold.[47] Protocol AC bevacizumab-first therapy would therefore not be considered cost-effective compared to real-world therapies from the Vestrum database in the reference case at 2 years or 17 years ($105,335/QALY and $151,032/QALY, respectively). Similarly, the high-cost scenarios would not be cost-effective at either 2 years or 17 years, despite preserving visual acuity with a higher sustained number of injections. When the average number of injections was decreased to 3 per year for both arms in the low-cost scenario, Protocol AC was still 14% more expensive over a patient's lifetime, but Protocol AC could be considered cost-effective under this scenario. The variability in the costs and probability of the ICUR being below the societal willingness-to-pay threshold reflected the inherent challenges in models based on assumptions where the impact of various costs compounded over a longer time horizon.

There are inherent limitations to the current analysis. Many of these, such as the limitations of comparing clinical trial data to real-world data harvested from an electronic medical record dataset, have been discussed in a prior study comparing direct costs between Protocol AC and the real world.[14] For example, the rationale for drug selection in the real world could not be ascertained based on electronic medical record data. An important follow-up analysis would be to compare real-world treatment regimens based on step therapy with treatments based on physician choice, but this could not be performed from an analysis of a large database that did not identify the rationale for starting with bevacizumab first. The Vestrum real-world treatment regimen likely reflected a combination of factors, including insurance mandates, financial constraints and copays, drug availability, pharmacy formularies, practice setting, and physician choice. Furthermore, the data for the real-world cohort were derived from a large electronic database, which represents a diverse physician population but is limited to private practices in the US. In addition to not capturing treatment regimens chosen by physicians in academic settings, it is unclear if the Vestrum database is representative of the national distribution of practice type, practice ownership, extent of resource-limited settings, and other factors of potential consequence. Further analyses to account for differences in utilization by practice type, location, and other factors would be valuable but outside the scope of this study.

The current model purposefully selected 2016 for initiation of treatment in the real-world analysis to account for the likely increased real-world aflibercept utilization following the 2015 publication of DRCR Protocol T results, which demonstrated superiority of aflibercept for DME treatment,[8] while minimizing the effect of more recent step-therapy mandates by insurance carriers. The model normalized all costs to current values by adjusting for inflation to 2025 US dollars, with discounting of 3% per annum. Importantly, modeling analyses required assumptions when actual data were not available. For example, the study assumed that the treated eye was the better-seeing eye; however, having even 1 eye with poor visual function can adversely affect activities of daily living and productivity.[48,49] Estimates on productivity loss can vary depending on the methodology used and the patient and caretaker demographics, salary, and employment; these values were varied in the sensitivity analyses. The QALYs gained were based on a previously published formula in order to provide a precise value and be more conservative in the estimates, but there may be variations based on newer vision utility tables. There are few long-term follow-up studies available evaluating the effects of DME anti-VEGF treatment over a patient's lifetime, so the lifetime modeling would be further subject to assumptions without data. These assumptions are inherently subject to imprecision, whose effects would compound over a longer time horizon. The current analysis sought to address some of these limitations by modeling both a low-cost and high-cost scenario, in addition to using a reference case. Additionally, a probability sensitivity analysis modeled the range of parameters and assumptions even further and supported the robustness of the model.

Our cost-effectiveness analyses show that the total societal costs and direct medical costs of Protocol AC bevacizumab-first were higher than for real-world treatments from the Vestrum database. Although the simulated clinical trial patients achieved better vision outcomes than in the real world, they required more frequent visits and treatments. The current model found that the Protocol AC bevacizumab-first treatment regimen was not cost-saving and was often more expensive than current real-world treatments from the Vestrum database. If the 1.1 million patients estimated to have DME in the United States were switched from real-world DME treatment to a Protocol AC bevacizumab-first regimen, the 2-year additional cost would be $10 billion, and the 17-year additional cost would be $69 billion. Clearly, there are important economic considerations associated with increasing anti-VEGF use. However, in the real world, highly trained retina specialists incorporate both their expertise and clinical judgment in personalizing the treatment regimen for each individual patient. Protocols that interfere with physician choice should be thoroughly considered and evaluated before implementation.

Appendix Methods

The modeled inputs were derived from previously published data when possible. For direct medical costs, the cost of imaging and clinical visits were varied based on locality and facility and non-facility fees. The mean average wholesale acquisition cost of the longer-acting anti-VEGF medications was $775.20 for ranibizumab 0.3mg, $1806 for aflibercept 2mg, and $69.72 for bevacizumab. The mean cost was used in the analyses, varied by 25% in the probability sensitivity analyses. The proportion of the most expensive medications were varied by 10%.

To estimate the cost of endophthalmitis, the average wholesale price from Lexi-Comp Online database (Hudson, Ohio: Lexi-Comp, Inc.) of topical prednisolone ($105.60) and topical moxifloxacin ($185.95) was used, with prices varied by 25% in

the PSAs. It was assumed that patients would have 6 ± 2 extra clinical visits within the 90-day global period; approximately 28%[21] would undergo a pars plana vitrectomy (CPT 67036, $858, ambulatory surgery center facility fee of $2080, and anesthesia fees of $142). The costs were varied based on facility, non-facility, and non-facility limiting charges in the PSAs. The QALY was adjusted for the mean vision loss caused by endophthalmitis and varied by 10% in the PSAs.[20]

The cost of lost volunteer work was the amount of volunteer work the patient or caretaker would have performed if the patient did not have an illness. According to the US Census Bureau and AmeriCorps, Americans volunteered an average of 4.1 billion hours yearly, and the US population was estimated to be 331.9 million; the mean hourly cost of housework of $15.35 was used to calculate the average cost of volunteer work per hour lost per patient,[50–52] which was equally attributed to all modeled groups; it was assumed that both patients and caretakers did not volunteer as a result of the patient's disease.

Consumption was limited to glasses and refraction, which were equally attributed to both groups. A refraction cost was modeled at $50 (range for sensitivity analysis: $37.5-95)[53] and new glasses at $275 (range for sensitivity analysis: $95-520).[54]

The cost of social services included the cost of depression, injury, and SNF stays from vision loss. According to a prior report, the average yearly cost for patients with moderate vision loss in 2003 due to depression was $397.10 and from non-ocular injury was $268.10,[55] with an incidence of 10.9% (range for sensitivity analysis: 7.7-15.2%)[56] in those with visual impairment and 6.8% (95% CI, 5.8-7.8) without vision impairment.[56] The real-world group with moderate vision loss was assumed to have the higher incidence of depression and injury, and the Protocol AC group was assumed to have the lower incidence. The cost of SNF for patients with moderate-to-severe vision loss was based on adjusted values from a 2003 report of $602,[55] and it was assumed that patients with mild vision loss had half the risk of needing a SNF.

Appendix Table 1. Ranges used in the High and Low Scenarios. Both groups were assumed to switch from bevacizumab to the more expensive aflibercept at the same rate of 5.6% per year, but the real-world cohort had a higher initial proportion on bevacizumab in the reference case than the Protocol AC group. The costs and benefits were then discounted 3% per annum. The ranges listed were used in the low and high-cost analyses, but the ranges used in probability sensitivity analyses were even wider.

	Protocol AC Bevacizumab First		Real-World	
	Low Cost	High Cost	Low Cost	High Cost
Clinical Visits				
# Annual Clinical Visits year 1	11	13	7.3	9.3
# Annual Clinical Visits year 2	9.5	11.5	4.4	5.94
# Annual Clinical visits years 3-17	3	11.55	3	5.94
Injections				
# Injections year 1	9	11	5.5	10.2
# Injections year 2	5.1	6.71	3	3.41
# Injections years 3-17	3	6.71	3	3.41
% bevacizumab year 1	44%	36%	46%	38%
% bevacizumab year 2	33%	27%	44%	36%
% bevacizumab years 3-17	14-33%	11-25%	18-41%	15-33%
Productivity Loss from Visual Acuity				
Years 1-17	18-27%	22-33%	27%	33%

Appendix Table 2. Total Adjusted Societal Costs over 2 years. The low and high-cost scenarios were detailed, with additional ranges tested in the probability sensitivity analyses.

		Protocol AC		Real-World	
Sector		Low Cost	High Cost	Low Cost	High Cost
Formal Health Care Sector Costs					
Health	*Direct Medical Costs*	18,863	36,116	11566	17394
	Adverse Events	2	18	1	14
Informal Health Care Sector Costs					
Health	*Patient Time-Costs/ Lost Wages*	852	5808	274	2924
	Unpaid Caregiver-Time Costs	1764	5026	802	2342
	Transportation Costs	273	1137	156	706

(continued)

Appendix Table 2. (continued)

Sector		Protocol AC		Real-World	
		Low Cost	High Cost	Low Cost	High Cost
Non-Health Care Sector Costs					
Productivity	*Patient Lost Productivity*	35,215	65,699	37580	67636
	Caretaker Lost Productivity	3,530	8,571	2029	5294
	Cost of Lost Volunteer Work	693	847	693	847
Consumption	*Glasses and Refraction*	265	1,230	265	1230
Social Services	*Depression, injury, ± skilled nursing facility*	97	488	130	651
Totals	*Total Adjusted Societal Costs*	50,883	103,902	42,875	84,318
QALYs	*QALYs gained*	0.12	0.14	0.042	0.052
ICUR	*Difference in Costs per QALYs gained*	82,283	219,420		

Appendix Table 3. Total Adjusted Societal Costs over 17 years. The total adjusted societal costs included discounting 3% per annum and accounting for deaths over time.

Sector		Protocol AC		Real World	
		Low Cost	High Cost	Low Cost	High Cost
Formal Healthcare Sector Costs					
Health	*Direct Medical Costs*	46,189	267,821	55,668	120,220
	Adverse Events	9	176	10	109
Informal Health Care Sector Costs					
Health	*Patient Time-Costs/ Lost Wages*	852	31,628	274	16,959
	Unpaid Caregiver-Time Costs	2,319	37,806	1,357	12,080
	Transportation Costs	863	8,820	745	4,657
Non-Healthcare Sector Costs					
Productivity	*Patient Lost Productivity*	78,172	230,428	80,537	217,513
	Caretaker Lost Productivity	12,279	66,617	8,952	35,735
	Cost of Lost Volunteer Work	5,544	6,776	5,544	6,776
Consumption	*Glasses and Refraction*	2,253	10,455	2,253	10,455
Social Services	*Depression, injury, ± skilled nursing facility*	1,071	5371	1,104	5,534
Totals	*Total Adjusted Societal Costs*	112,642	411,995	112,487	290,833
QALYs	*QALYs gained*	0.42	0.77	0.15	0.19
ICUR	*Difference in Costs per QALYs gained*	591	207,589		

Ethical Approval

The analyses adhered to the tenets of the Declaration of Helsinki and complied with all local and federal laws.

Statement of Informed Consent

This article does not contain any studies with human or animal participants. As no human participants were included, informed consent was not required.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article:
Dr. Grewal is a consultant to Genentech and Regeneron.
Dr. Niles is a consultant to Regeneron.
Dr. Kolomeyer is a consultant to Alimera, Apellis, Genentech, and Regeneron, and has been a speaker for Biogen, Genentech, IvericBio/Astellas, and Regeneron.
Dr. Hahn is on the advisory boards of Adverum, Alimera, Eyepoint, and Genentech, is a consultant to Adverum, Eyepoint, and Genentech, and has been a speaker for Eyepoint and Genentech.
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