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ORIGINAL RESEARCH

# Anti-VEGFs for Diabetic Macular Oedema: Analysis of Efficacy, Safety, and Cost of More Durable Therapies from a Dutch Societal Perspective

Sara W. Quist · Jeroen H. J. Paulissen · Izabella Lunk · Joao Carrasco · Marrit A. Woudstra · Michal Pochopien · Mateusz Nikodem · Catriona Crossan · Sankha Amarakoon · Freekje van Asten · Maarten J. Postma

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## ABSTRACT

***Introduction***: Frequent intravitreal injections of anti-vascular endothelial growth factors (VEGFs) for diabetic macular oedema (DMO) pose challenges for healthcare systems, patients, and society. This study assessed the efficacy, safety, resource utilization, and costs of anti-VEGFs from a Dutch societal perspective.

***Methods***: A systematic literature review and indirect treatment comparison (ITC) compared the efficacy and safety of aflibercept 8 mg with aflibercept 2 mg, ranibizumab, faricimab, and bevacizumab. A Markov model estimated lifetime costs for unilateral or bilateral DMO treatment over 5 years from a Dutch societal perspective. Break-even prices determined the cost-neutral price for each anti-VEGF compared to the least expensive option.

***Results***: The ITC found no significant differences in efficacy or safety among anti-VEGFs, leading to a cost-minimisation analysis. Over 5 years, the mean number of injections ranged from 15.0 (aflibercept 8 mg, flexible Q16 regimen) to 24.9 (bevacizumab, pro re nata regimen). Bevacizumab had the lowest 5-year per-patient cost (€80,315). Aflibercept 8 mg followed at €83,577, with a break-even price of €560 per injection (−23% vs. current price). Aflibercept 2 mg (fixed regimen), faricimab, and ranibizumab (treat-and-extend) required price reductions of 74%, 63%, and 71%, respectively, to match bevacizumab.

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S. W. Quist (✉) · J. H. J. Paulissen · M. J. Postma
Department of Health Sciences, University Medical Center Groningen, Groningen, The Netherlands
e-mail: s.w.quist@umcg.nl

S. W. Quist
Asc Academics, Groningen, The Netherlands

I. Lunk · J. Carrasco
Bayer AG, Basel, Switzerland

M. A. Woudstra
Bayer Pharmaceuticals, Hoofddorp, Netherlands

M. Pochopien
Clever Access, Cracow, Poland

M. Nikodem
Putnam PHMR, Cracow, Poland

C. Crossan
Putnam PHMR, London, UK

S. Amarakoon · F. van Asten
University Eye Clinic Maastricht, MUMC+, Maastricht, The Netherlands

M. J. Postma
Department of Economics, Econometrics and Finance, University of Groningen, Groningen, The Netherlands

***Conclusion*:** Despite similar efficacy and safety, differences in treatment burden were identified among the anti-VEGFs, with the more durable regimen of aflibercept 8 mg potentially reducing overall injection frequency compared to current care. Nevertheless, on the basis of current list prices, bevacizumab is the least expensive anti-VEGF for treating DMO. Aflibercept 8 mg, aflibercept 2 mg, faricimab, and ranibizumab could achieve cost-equivalence to bevacizumab if their medication prices were reduced by at least 23%, 74%, 63%, and 71%. These results could support future decision-making of healthcare providers and payers, encompassing aspects of medical costs, healthcare capacity use, and burden on patients as well as the healthcare system as a whole.

## PLAIN LANGUAGE SUMMARY

Diabetic macular oedema is a common eye condition that can cause vision loss. It is effectively treated with injections of anti-vascular endothelial growth factors (anti-VEGFs), but frequent injections can be a burden for patients and healthcare systems. This study analysed existing research to compare the effectiveness, safety, resource use, and healthcare and societal costs of different anti-VEGF treatments over 5 years. The results showed that all anti-VEGFs work equally well and have similar safety profiles. However, the number of required injections varied: aflibercept 8 mg required the fewest (15.0 over 5 years), while bevacizumab required the most (24.9 over 5 years). Despite needing more injections, bevacizumab was the cheapest option, costing €80,315 per patient in a lifetime with 5 year of treatment. Aflibercept 8 mg was slightly more expensive (€83,577) but could become cost-equivalent if its medication price dropped by 23%. Other anti-VEGFs would need even larger price reductions (63–74%) to match bevacizumab's cost. These findings highlight that while some treatments may reduce injection frequency, bevacizumab remains the least costly choice. This information can help healthcare providers and policymakers make better decisions about diabetic macular oedema treatment.

**Keywords:** Anti-VEGFs; Diabetic macular oedema; Cost-minimisation; Indirect treatment comparison

**Key Summary Points**

*Why carry out this study?*

The study aimed to compare the efficacy, safety, resource utilization and healthcare and societal costs of the more durable anti-VEGFs regimens with existing treatments.

*What was learned from the study?*

There were no significant differences in efficacy and safety identified between the more durable aflibercept 8 mg and other anti-VEGFs.

Treatment burden varied between anti-VEGFs, with aflibercept 8 mg in the flexible Q16 trial regimen requiring the least injections.

Bevacizumab was the least costly option and other anti-VEGFs could match bevacizumab's cost-effectiveness with medication price reductions.

These findings can guide healthcare providers and payers in optimizing DMO treatment decisions.

## INTRODUCTION

Currently, 537 million adults worldwide are living with diabetes, and its prevalence is expected to further increase by almost 20% by 2030 and 46% by 2045 [1]. A major complication of the disease is diabetic retinopathy, which may be accompanied by diabetic macular oedema (DMO) [2]. The global prevalence of DMO is estimated at 3.7% among patients with diabetes, with an annual incidence of 0.37% [2, 3]. In

2021, 1.2 million individuals in the Netherlands were affected by diabetes [4], which gives an estimate of 42,800 patients with DMO [5].

Patients with DMO experience an accumulation of excess fluid in their macular area. This accumulation may be attributed to a disruption of the blood-retinal barrier and inflammation, impacted by elevated vascular endothelial growth factor (VEGF) levels [6]. The macular pathology may result in distorted vision and potentially permanent vision loss. Consequently, DMO can considerably impact patients' daily activities and associated quality of life (QoL) [7]. Additionally, DMO imposes a substantial economic burden due to medical treatment costs and societal costs in the form of productivity losses and informal care [8].

In the Netherlands, once patients experience vision loss, the first-choice therapy consists of intravitreal injections with anti-VEGFs [9]. Anti-VEGF therapies block the VEGF protein, which drives abnormal blood vessel growth and leakage, improving vision in patients with DMO. Off-label bevacizumab was the first anti-VEGF to be used for the treatment of DMO, followed by ranibizumab, the first approved anti-VEGF demonstrating improved visual acuity (VA) in monthly administration frequency [10]. Subsequently, aflibercept 2 mg, brolucizumab, faricimab, and most recently aflibercept 8 mg were introduced, all demonstrating comparable efficacy profiles in several non-inferiority clinical trials and indirect treatment comparisons (ITCs) [9, 11–18].

Although anti-VEGFs are effective, their use requires regular injection and monitoring visits, putting pressure on both the healthcare system and patients. Therefore, treatment strategies began focusing on the optimization of available resources and patient adherence and most guidelines started to recommend individualized therapy instead of fixed dosing and monitoring regimens [9, 19]. Initially, the pro re nata (PRN) regimen was introduced, in which patients receive more frequent injections at initiation (loading phase), followed by monitoring on a fixed monthly basis, and only receive injections when visual acuity or other anatomic indicators worsen [19]. Subsequently, a treat-and-extend (T&E) approach was introduced, where, after the loading phase, the intervals between injections are gradually extended according to the durability of the efficacy observed, which could prevent both under- and overtreatment [19].

Consequently, the focus of the more recently introduced anti-VEGFs has been on maintaining more durable personalized treatment regimens, which aim to reduce the frequency of injections by further increasing the mean interval between injections. The first authorized anti-VEGF injection, ranibizumab is approved in Europe in a 0.5 mg dose administered on a monthly basis (for 3 months or more as a loading phase), then potentially being extended up to 12-week intervals between injections as part of a T&E regimen [20]. Treatment with aflibercept 2 mg includes a loading phase of five monthly injections, followed by injections intervals up to 16 weeks [21]. Faricimab is a more recently available option that is administered with injection intervals up to 16 weeks, following loading phase of four monthly doses [14]. Bevacizumab, although recommended as first-line treatment of DMO, is not yet approved for the treatment of DMO by the European Medicines Agency. In clinical trials, it was solely studied in a monthly or PRN regimen [22]. Brolucizumab is approved in a loading phase of five doses every 6 weeks, followed by an 8 or 12 weekly injection, with potential to further extend from the second year of treatment [23]. Most recently, aflibercept 8 mg was approved, permitting an extension of treatment intervals up to 20 weeks after a loading phase of three monthly doses [15, 24]. Most anti-VEGFs have been compared and show similar efficacy, safety, and injection frequency [25, 26], but up to date, aflibercept 8 mg has only been shown to be non-inferior to aflibercept 2 mg in DMO, with no comparisons to other anti-VEGFs [15].

The Dutch treatment guideline focuses on optimizing medication costs, recommending off-label bevacizumab as a first-line anti-VEGF for patients with a VA above 69 Early Treatment of Diabetic Retinopathy Study (ETDRS) letters due to its low medication price and aflibercept 2mg or ranibizumab as second line. For patients with a VA below 69 letters, the treatment guideline recommends considering aflibercept 2 mg because of its greater effect on VA in this

subgroup [9]. At the time of writing, the DMO treatment guideline does not incorporate the treatment strategy regarding aflibercept 8 mg, brolucizumab, and faricimab. Brolucizumab is, however, included in the neovascular age-related macular degeneration (nAMD) treatment guideline, but as a result of concerns regarding its increased risk of intraocular inflammation, it is recommended as the last-line treatment in this guideline [27].

There is currently a 12.5-week waiting list for ophthalmic care in the Netherlands, and eye-related illnesses cost approximately one billion euros in total healthcare expenses [28, 29]. The more durable treatments with extended treatment intervals could alleviate healthcare burden, but ideally, without elevating the healthcare expenses [28, 29]. To understand the impact of the currently available and novel, more durable intravitreal anti-VEGFs for the treatment of DMO on Dutch healthcare and society, this study compares the efficacy, safety, resource burden, and societal costs among anti-VEGFs for treating patients with DMO in the Netherlands.

## METHODS

To analyse the Dutch treatment landscape in terms of resource use optimization, an indirect treatment comparison (ITC) was conducted, comparing efficacy and safety of the most recently introduced aflibercept 8 mg to the other anti-VEGFs. Previously, all anti-VEGFs have been evaluated for efficacy in visual acuity outcomes, safety, and injection frequency, either directly in head-to-head clinical trials [14, 30, 31] or indirectly through treatment comparisons with other anti-VEGFs [25, 26]. Overall, these treatments show similar effects, with significant differences between bevacizumab and other anti-VEGFs attributed to baseline characteristics or small and less than 5 ETDRS letters [25, 26, 30]. However, the most recent anti-VEGF, aflibercept 8 mg, has only been proved to be non-inferior to aflibercept 2 mg in a clinical trial and has not yet been compared to other anti-VEGFs [15]. An ITC was, therefore, required to inform the approach for an economic analysis (i.e. cost-minimisation analysis). The economic analysis compared the total societal and healthcare costs of all available anti-VEGFs.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

### Methodology of the Systematic Literature Review and Indirect Treatment Comparison

A systematic literature review (SLR) and an ITC were conducted to identify all the relevant data and evaluate the difference in treatment effect (i.e. mean change in BCVA and gain or loss of ≥ 10 letters), safety, and the average number of injections for different anti-VEGF treatments in DMO. The ITC comprised randomized clinical trials (RCTs) evaluating the impact of anti-VEGF treatment, identified through the SLR. The SLR and the ITC did not include brolucizumab since the current clinical guidelines/clinical recommendations position it at a latter line of treatment for nAMD because of safety concerns [12]. The network meta-analysis (NMA) approach was used for the ITC on the difference in mean change in BCVA, odds for gaining or losing ≥ 10 letters, and odds for total overall ocular and non-ocular adverse events (AEs) of aflibercept 8 mg versus other anti-VEGF therapies. The ocular analysis was performed on 1-year data, corresponding to the primary endpoint of most included clinical trials. The full methodology of the SLR and ITC are presented in Supplementary material 1. Details of the trial descriptions and the lists of measured ocular and non-ocular AEs included in the total AE outcomes are provided in Supplementary material 1, Tables S2 and S3.

The mean number of required injections was assessed by using a meta-analysis with a frequentist approach. For this analysis, the 2-year injection frequency for aflibercept 8 mg was obtained from early trial reports [24].

The ITC compared the outcomes for the anti-VEGFs in all regimens identified in the SLR. The economic analysis incorporated those regimen that came closest to T&E, meaning it focused on treatment regimens that are intended to reduce the treatment burden while

maintaining vision [19]. However, if a regimen comparable to T&E was not identified for a particular anti-VEGF, we included the available data of the remaining regimens. For aflibercept 8 mg, aflibercept 2 mg, ranibizumab, and faricimab a T&E or comparable regimen was found. This included a flexible Q16 regimen (with potential injection intervals up to 20–24 weeks in the second year) for aflibercept 8 mg, a T&E (with potential injection intervals up to 16 weeks) regimen for faricimab, and a T&E regimen (with potential injection intervals up to 12 weeks) for ranibizumab. For aflibercept 2 mg and bevacizumab a fixed Q8 and PRN regimen were included because of a lack of identified trials that studied a T&E or flexible regimen.

## Selection of Approach for Economic Analysis

The design of the economic analysis was dependent on the results of the ITC, which concluded that there is no statistically significant difference between aflibercept 8mg and the compared anti-VEGFs regarding their efficacy or safety profiles (details are described in Results, Figs. 1, 2, and 3), while numerical differences were suggested in the number of injections needed to achieve similar visual acuity levels. Given that the current ITC showed no significant differences in efficacy and comparable safety, and previous analyses also found similar efficacy across anti-VEGFs [25, 26, 30, 31], health-state transitions were equalized in the model, and a cost-minimisation approach was used to compare available anti-VEGF therapies.

## Economic Analysis

### *Model Design*

The cost-minimisation model compared the societal and healthcare costs associated with the currently available anti-VEGFs, based on their respective resource use. A cost-minimisation analysis assumes an equivalent treatment effect and therefore excludes its consideration in the comparison [32]. Consequently, the analysis outcomes entailed costs associated with treatment (administration), diagnosis and monitoring, and impaired vision from a Dutch societal perspective for the treatment of two eyes. The analysis was performed with the use of a Markov model developed in Microsoft Excel (Version 2408, Microsoft Corporation, Redmond, WA, USA). The model outcomes were estimated for a lifetime horizon (i.e. 37 years). Since patients likely continue treatment beyond 24 months [30], study eyes (SEs) and affected fellow eyes (FEs) were treated with anti-VEGFs for a 5-year period in the model, in line with previous economic evaluations in DMO [33, 34]. Costs were discounted by 4% per year [35]. Furthermore, our economic analysis followed the Professional Society for Health Economics and Outcomes Research (ISPOR) Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist [36] (Supplementary material 2). Table 1 summarizes the most important model characteristics.

### *Model Structure*

The model estimated the costs of impaired vision and associated resource use of treatment of patients with DMO by simulating the progression and degression of a patient's BCVA of the SE and FE over their lifetime. The cycle length was set to 4 weeks aligned with the dosing and control regimens of all included treatments. A Markov model was employed to estimate patients' resource use based on the VA of their SE and FE (Supplementary material 3). VA health states were categorized by the number of the ETDRS letters the SE and FE could read. The VA health states were modelled independently for both SE and FE to reduce model complexity. VS1 represents normal vision and VA7 and VA8 represent a BCVA of 26–35 and 0–25 ETDRS letters read, respectively. Health state ranges were defined as 10-letter increments—except for the normal vision and VA8 state—as a change in vision of 10 ETDRS is considered clinically significant and is in line with clinical trial results [15, 37]. The model features a total of 65 health states: 64 for every combination of VA in both the SE and FE, and one absorbing health state representing death. As a result of the presumed equivalent treatment effect, patients transition

through the VA states with the same probability for all treatments, with the values from the PHOTON trial converted into 4-week probabilities [15]. Moreover, for all treatments, the discontinuation rate found in the PHOTON trial was used. The transition to death was based on Dutch population data regarding all-cause mortality [38]. Additionally, to account for the higher mortality risk of patients with DMO, a hazard ratio (HR) of 1.52 was applied to all patients in the model. To calculate an increase in mortality due to severe visual impairment, an HR of 1.54 was applied to patients who have their SE or FE in VA7 or VA8. Lastly, all patients had the same yearly risk for bilateral involvement, based on previous NICE submissions [39, 40]. The transition probabilities and discontinuation rates are presented in Supplementary material 4. We assumed that the management of blood sugar was equally effective across the RCTs that were used for aflibercept 8 mg and its comparators and therefore the transition of patients was independent of this.

### *Patient Characteristics*

Patient characteristics are presented in Table 2. Patients' age, gender, and initial VA were based on the PHOTON trial ($N$=658) [15]. The percentage of bilateral patients at baseline was based on previous National Institute for Health and Care Excellence (NICE) submissions and was validated by Dutch clinical experts.

### *Treatment and Treatment Regimens*

The model compared aflibercept 8 mg to aflibercept 2 mg, bevacizumab 1.25 mg, faricimab 6 mg, and ranibizumab 0.5 mg using the regimens and associated injection and monitoring frequencies found in the ITC (Table 3 and Supplementary material 5). In line with the Dutch treatment guideline, a T&E regimen was included for ranibizumab and faricimab, in which treatment intervals of the patients are shortened or extended according to the disease activity of the patient after the loading doses [9]. In the T&E regimen of faricimab, treatment intervals could be extended up to 16 weeks after the loading phase of four monthly injections. In the T&E regimen of ranibizumab, treatment intervals could be extended up to 12 weeks after three monthly loading injections. The flexible Q16 arm with treatment intervals up to 20–24 weeks of the PHOTON trial was used for aflibercept 8 mg [15, 41]. The flexible Q16 regimen was comparable to the T&E regimen, but it started with a 16-weekly interval after the loading dose of only three monthly injections, with a possibility of being subsequently shortened to 8 or 12 weeks, based on disease activity in the first year, and extended up to 20–24 weeks after the first year [24]. For aflibercept 2 mg no clinical trial with T&E regimen met the inclusion criteria and therefore a fixed Q8 regimen was used, in which patients received an injection every 8 weeks after the loading dose of five monthly injections [41]. The SLR solely identified a PRN regimen for the off-label bevacizumab, in which patients visited the hospital for monthly monitoring and received an intravitreal injection as needed. Given the lack of data in the third year and thereafter, it was assumed that in year 3, the injections were equal to year 2. To avoid long-term extrapolation, in years 4 and 5, all patients received two injections per year. This was a conservative assumption in line with previous health technology assessment submissions and the low treatment frequency seen in long-term studies [30, 39]. In the case of bilateral disease, it was assumed that 50% of the injection visits overlapped.

### *Costs*

Following Dutch guidelines, we incorporated costs within the healthcare system (i.e. medical costs) and societal costs (i.e. costs for patients and caregivers and productivity losses) in our model [35] (Table 4). All costs were indexed to January 2024, using Dutch indexation data [42].

***Costs Within the Healthcare System*** Costs within the healthcare system included costs of treatment, administration, monitoring, AEs, and reduced VA (Table 4). Treatment costs were based on the list prices per injection (i.e. vial or pre-filled syringe). For each administration, the costs of an intravitreal injection were assumed. Additionally, patients were regularly monitored with the monitoring frequency based on the

included regimen (Table 2). At treatment initiation, diagnosis consisted of a spectral domain optical coherence tomography (SD-OCT) and fundus fluorescein angiography (FFA). For each following monitoring visit, disease activity was assessed with an SD-OCT [9, 43]. Costs related to AEs were based on Dutch declaration data [44] (Supplementary material 6). Costs associated with a reduced VA were included in the model as health state costs and depended on the VA of both the SE and FE, including home care, residential care, and the increased risk of depression [45]. To account for the costs of depression, a risk of developing mild, moderate, or severe depression was included per VA health state [46]. The depression treatment costs were based on the Dutch treatment guidelines for depression [47]. Table 4 summarizes the costs per health state and Supplementary material 6 provides an overview of all the different cost inputs.

***Societal Costs*** Societal costs included costs for patients and caregivers (i.e. informal care and fuel costs) and productivity losses. Productivity losses were incorporated for patients under the retirement age (i.e. 67 years) [35, 48]. We accounted for short-term losses due to injection and monitoring visits and short-term losses due to reduced productivity at work, which were corrected for long-term losses due to reduced vision (Supplementary material 6). The short-term losses were valued at the hourly wage for the duration of the visit (including travel time) or the duration of reduced productivity and corrected for the average labour force per VA health state. The hourly rate and vacancy data stem from Dutch statistics from 2022 [48]. Our model factored in the informal care costs associated with injection and monitoring visits, as well as the additional assistance required as a result of decreased visual acuity (Supplementary material 6). Hours of informal care were valued with the home care replacement rate (i.e. opportunity costs informal care). Travel costs were incorporated for each injection and monitoring visit, and travel distances to the hospital were based on the Dutch guideline for economic evaluation [35].

### *Break-Even Price*

After determining the per-patient costs, we calculated the break-even medication price per injection for each anti-VEGF treatment relative to the cheapest option. The break-even price is the price at which a more expensive anti-VEGF treatment becomes cost-neutral compared to the cheapest anti-VEGF. To determine the break-even price per injection, the difference between the total cost of the cheapest anti-VEGF and the total cost (excluding medication costs) of the other anti-VEGF drugs was calculated. This difference was then divided by the number of required injections.

### *Sensitivity and Scenario Analyses*

The impact of individual model parameters on the incremental costs was evaluated in deterministic sensitivity analysis (DSA) by varying them over their confidence intervals. Additionally, several scenario analyses were performed to assess the impact of general model settings, including the impact of using a healthcare payer's perspective (i.e. excluding societal costs), varying the discount rate, and a 3-year time horizon. Moreover, since the ITC did not include clinical trials that examine a flexible or T&E regimen for aflibercept 2 mg and bevacizumab, additional scenarios were performed to identify the impact of the injection frequency of these deviating regimens. For bevacizumab, a PRN regimen was used, involving regular monitoring visits rather than monitoring at each injection. To assess the impact, two scenarios were performed: one where bevacizumab's monitoring visits coincided with injections, and another where its treatment regimen matched that of ranibizumab as bevacizumab demonstrated clinical non-inferiority to ranibizumab in one of the included clinical trials for a similar treatment frequency [30]. For aflibercept 2 mg a fixed Q8 regimen was used based on the ITC, which did not allow for extension of treatment intervals. Consequently, an alternative scenario was performed where injection frequency was based on a small non-randomized single-arm trial, excluded from the SLR as a result of its structure, which investigated a T&E regimen for

aflibercept 2 mg [21]. In this scenario, the injection frequency of aflibercept 2 mg was 7.0 in the first year and 4.4 in the second and third year.

### *Probabilistic Cost-Effectiveness Analysis*

While a cost-minimisation approach is appropriate given the lack of significant difference in clinical outcomes of included anti-VEGFs that was demonstrated in the ITC, the approach may not always align with local reimbursement guidelines [49–51]. To substantiate our cost-minimisation approach and present the impact of the estimated treatment effects on the robustness of cost-effectiveness results, we additionally performed a cost-effectiveness analysis. In the cost-effectiveness analysis, the progression of patients through the model was adjusted by the treatment outcomes found in the ITC. Besides incremental costs, which were based on the resource use per treatment, incremental quality-adjusted life-years (QALYs) and BCVA at the end of model duration were determined. The same model structure was used as in the cost-minimisation model. Additional parameters including utility values and their calculation method, odds ratios per treatment, and risk for AEs are presented in Supplementary material 7. To demonstrate the uncertainty surrounding the results, we focused on the outcomes of the probabilistic sensitivity analysis, in which input parameters were varied by their respective distributions (i.e. normal, beta, gamma, Dirichlet) across 1000 simulations.

## RESULTS

### Indirect Treatment Comparison

The NMA did not indicate any significant differences, based on 1-year data, in the mean change in BCVA or the odds of patients gaining 10 or more letters when aflibercept 8 mg was compared to all other anti-VEGFs across all available regimens (Figs. 1 and 2). Additionally, there were no differences found in odds of non-ocular and ocular adverse events of aflibercept 8 mg compared to aflibercept 2 mg, faricimab, and ranibizumab across all available regimens (Fig. 3). However, when compared to bevacizumab, aflibercept 8 mg had a significantly lower odds for ocular adverse events and there were no significant differences in odds for non-ocular adverse events. Details of the clinical trials included for the NMA as well as the network plots are presented in Supplementary material 1. A meta-analysis, performed with 2-year data, identified required injection frequency over 2 years varying from 8.4 for aflibercept 8 mg to 15.3 for bevacizumab (Table 3).

### Economic Analysis

Based on the mostly non-significant differences in treatment effect and safety, a cost-minimisation analysis was performed. Among the included anti-VEGFs, a patient treated with bevacizumab incurs the lowest costs after up to 5 years of treatment within a lifetime horizon (i.e. €80,315) (Table 5). Aflibercept 8 mg follows with a total cost of €83,577, which implies that a per-injection price of €560 is needed to be cost-equivalent to bevacizumab. Aflibercept 2 mg in a fixed Q8 regimen is more expensive than the anti-VEGFs in personalized regimens, costing €96,564 per patient. The break-even price for aflibercept 2 mg in a fixed Q8 regimen versus bevacizumab in a PRN regimen is calculated at €186 per injection. Vision loss is the largest proportion of the costs, but as a result of the assumption of equal treatment effects, these costs are equal across all treatments. The largest differences in anti-VEGFs are found in medication and administration costs. Owing its low medication price, bevacizumab incurs the lowest medication costs, amounting to €577 over a treatment period of up to 5 years. However, bevacizumab's relatively high injection frequency resulted in the highest administration costs of all anti-VEGFs, amounting to €12,659. In contrast, aflibercept 8 mg has higher medication costs (i.e. €14,463 over up to 5 years) but considerably lower administration costs (i.e. €7455 over up to 5 years). Additionally, aflibercept 8 mg induces lower costs for monitoring, outpatient visits, productivity losses, informal care, and travel.

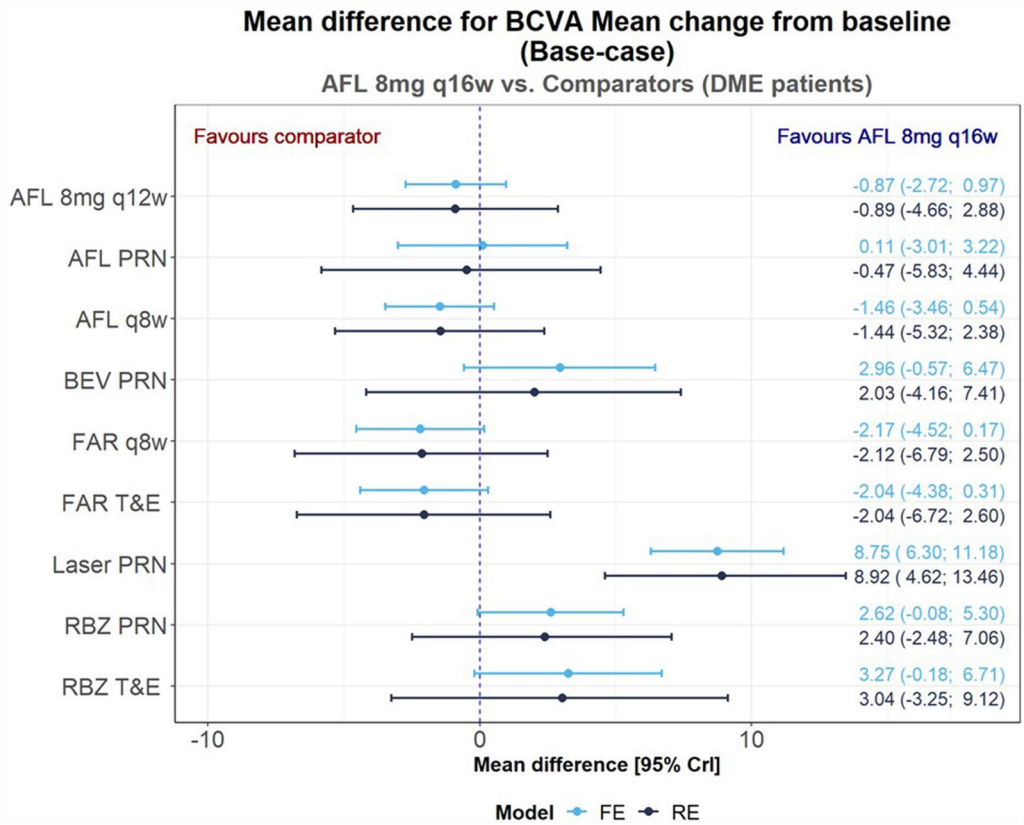


**Fig. 1** Forest plot for odds ratio for comparison aflibercept 8 mg q16 (flexible regimen up to 20–24 weeks) vs comparators for mean change for BCVA. *BCVA* best-correct visual activity, *CRI* credibility intervals, *DMO* diabetic macular oedema, *FE* fixed effect, *PRN* pro re nata, *RE* random effect, *T&E* treat-and extend

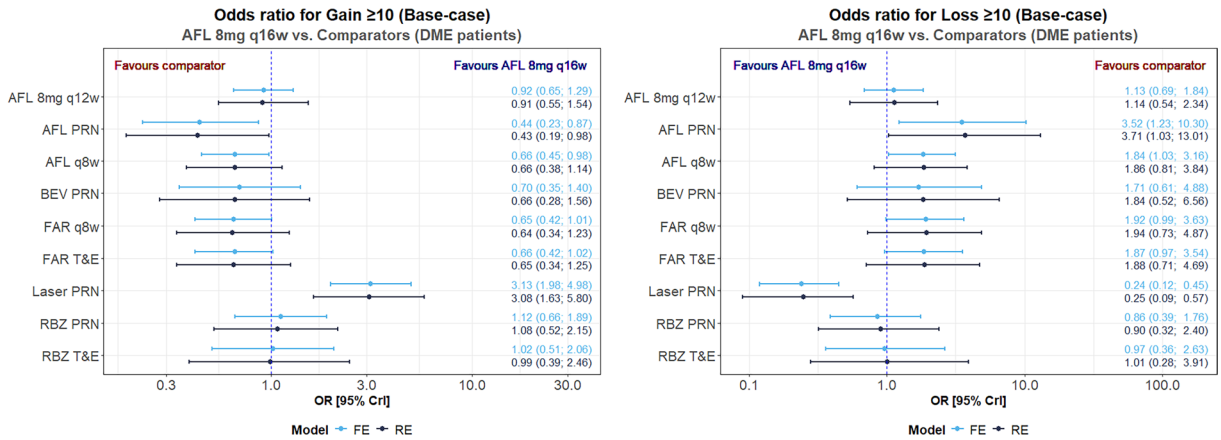


**Fig. 2** Forest plot for odds ratio for comparison aflibercept 8 mg q16 (flexible regimen up to 20–24 weeks) vs comparators for odds for gaining or losing ≥ 10 letters. *BCVA* best-correct visual activity, *CRI* credibility intervals, *DMO* diabetic macular oedema, *FE* fixed effect, *PRN* pro re nata, *RE* random effect, *T&E* treat-and extend

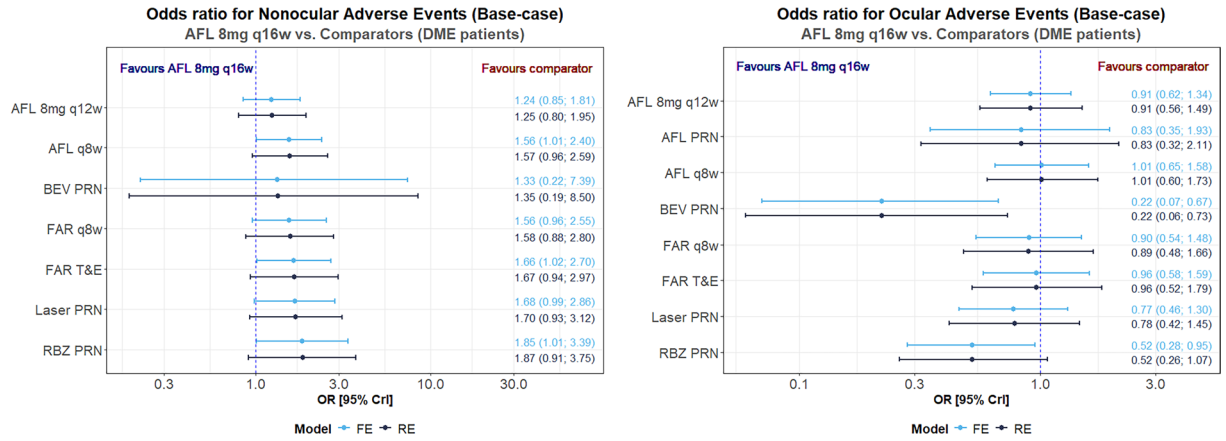


**Fig. 3** Forest plot for odds ratio for comparison aflibercept 8 mg q16 (flexible regimen up to 20–24 weeks) vs comparators for odds for non-ocular and ocular adverse events. *BCVA* best-correct visual activity, *CRI* credibility intervals, *DMO* diabetic macular oedema, *FE* fixed effect, *PRN* pro re nata, *RE* random effect, *T&E* treat-and extend

**Table 1** Model characteristics and outcomes

| | **Input** |
|---|---|
| Model characteristics | |
| Population | Patients with DMO |
| Treatment (regimens) | Aflibercept 8 mg (Flexible Q16 with intervals up to 20–24 weeks)<br>Aflibercept 2 mg (fixed Q8)<br>Bevacizumab (PRN)<br>Faricimab (T&E with intervals up to 16 weeks)<br>Ranibizumab (T&E with intervals up to 12 weeks) |
| Time horizon | Up to 5-year treatment (discontinuation assumed)<br>Lifetime impact of visual impairment (i.e. 37.7 years) |
| Perspective | Dutch societal |
| Discounting | 4% costs |
| Model outcomes | |
| Primary outcomes | Medication costs<br>Administration costs<br>Monitoring costs<br>Vision loss costs<br>Costs related to productivity losses<br>Costs related to informal care |
| Sensitivity analyses | Scenario analyses<br>One-way sensitivity analysis<br>Probabilistic cost-effectiveness results |

*DMO* Diabetic macular oedema, *PRN* pro re nata, *T&E* treat-and-extend

**Table 2** Patient characteristics

| | Input | Source |
|---|---|---|
| Mean age, years [SD] | 62.3 [10.4] | PHOTON trial [15] |
| Proportion female, % | 39.1% | PHOTON trial [15] |
| Mean BCVA, unit [SD] | 62.5 [10.86] | PHOTON trial [15] |
| Proportion treatment-naïve[a], % | 56% | PHOTON trial [15] |
| Mean CRT, unit [SD] | 454.0 (129.5) | PHOTON trial [15] |
| Bilateral involvement | 46.5% | TS346, assumption, and clinical expert opinion [40] |

*BCVA* best-correct visual acuity, *CRT* central retinal thickness, *ETDRS* Early Treatment Diabetic Retinopathy Study, *SD* standard deviation

[a]All included patients were not treated with macular laser photocoagulation or intravitreal anti-VEGFs 3 months prior to treatment

**Table 3** Overview of included regimens, injection frequencies, and monitoring frequencies based on the outcomes of the ITC

| Treatment | Regimen[a] | Mean injection frequency (mean monitoring frequency)[b] | | | | | |
|---|---|---|---|---|---|---|---|
| | | Year 1 | Year 2 | Year 3 | Year 4–5 | Total | Trials in ITC |
| Aflibercept 8 mg | Flexible Q16 (with intervals up to 20–24 weeks) | 5.8 (4.8) | 2.6 (2.6) | 2.6 (2.6) | 2.0 (2.0) | 15.0 | PHOTON [15, 25] |
| Aflibercept 2 mg | Fixed Q8 | 8.5 (7.5) | 4.9 (4.9) | 4.9 (4.9) | 2.0 (2.0) | 22.3 | PHOTON, KESTREL, KITE RHINE, VISTA, VIVID, VIVID-EAST, YOSMITE [14–18] |
| Bevacizumab 1.25 mg | PRN | 9.7 (12) | 5.6 (12) | 5.6 (12) | 2.0 (2.0) | 24.9 | PROTOCOL-T [30, 55] |
| Faricimab 6 mg | T&E (with intervals up to 16 weeks) | 8.3 (7.3) | 3.8 (3.8) | 3.8 (3.8) | 2.0 (2.0) | 19.9 | YOSMITE RHINE [14, 18] |
| Ranibizumab 0.5 mg | T&E (with intervals up to 12 weeks) | 7.0 (6.0) | 5.8 (5.8) | 5.8 (5.8) | 2.0 (2.0) | 22.6 | RETAIN [20] |

*ITC* indirect treatment comparison, *PRN* pro re nata, *T&E* treat-and-extend

[a]The regimens were based on the optimal regimens that were identified in the ITC, meaning that they required the lowest number of injections for effective treatment

[b]All injection frequencies were corrected to a time period of 52 weeks

### *Scenario Analysis*

The scenario analysis assessed the impact of several model assumptions based on the deterministic outcomes (Table 6). The conclusions remained consistent over all scenarios, with bevacizumab being the least expensive treatment option and aflibercept 8 mg the second least expensive. In a 3-year time horizon, the break-even price of aflibercept 8 mg compared to bevacizumab increased to €710 per injection, and when the treatment regimen of bevacizumab is assumed to be equal to ranibizumab, the break-even price of aflibercept 8 mg reduced to €312 per injection. Using a T&E regimen for aflibercept 2 mg results in the third lowest total costs per patient (i.e. €93,289 for a 5-year treatment period in a lifetime horizon), ranking after bevacizumab and aflibercept 8 mg. For aflibercept 2 mg in a T&E regimen to be cost-equal to bevacizumab, its medication price would have to be €253 per injection.

### *Deterministic Sensitivity Analysis*

Supplementary material 8 presents the incremental costs of aflibercept 8 mg versus comparators that were found in the DSA. The analysis shows that—compared to aflibercept 2 mg, faricimab, and ranibizumab—aflibercept 8 mg remains cost-saving for all parameter variations. Compared to bevacizumab, aflibercept 8 mg is more expensive across all cost distributions. Parameters with major impact on outcomes included injection frequencies, medication costs, and administration costs.

### *Probabilistic Cost-Effectiveness Analysis*

Supplementary material 9 presents the outcomes of the probabilistic cost-effectiveness analysis comparing aflibercept 8 mg versus other anti-VEGFs. The presented scatter plots illustrate the distribution of data points across all four quadrants of the cost-effectiveness plane, meaning that as well as positive as negative incremental QALYs and costs were identified in the analysis. This spread can be caused by the insignificant and small differences found in the ITC.

## DISCUSSION

Our analysis aimed to support treatment decision-making in the use of anti-VEGFs for DMO by evaluating treatment efficacy and resource use through an ITC that compared the most recently introduced aflibercept 8 mg with the other anti-VEGFs and assessing the associated economic impact from a societal perspective using a cost-minimisation analysis. Despite continuous innovation, no significant differences in the efficacy or safety profiles of the therapies were detected in our ITC and previous trials [14–18]. Aflibercept 8 mg, the newest addition to the landscape, was found to be comparable to aflibercept 2 mg, faricimab, ranibizumab, and bevacizumab in change from baseline BCVA during the first year of treatment. Occurrence of ocular and non-ocular adverse events with aflibercept 8 mg was also not different from aflibercept 2 mg, faricimab, and ranibizumab, while statistically lower than that of bevacizumab. Even though it was not possible to compare injection numbers statistically because of the differences in study protocols regarding pre-defined regimens, a meta-analysis of available evidence demonstrated that, within its clinical trial, aflibercept 8 mg could achieve comparable efficacy with fewer injections than the other anti-VEGFs.

Medication costs and injection frequency and associated resource use were the main cost drivers in the cost-minimisation analysis. The maximum identified injection frequency was 24.9 injections over up to 5 years for bevacizumab in a PRN regimen, while the minimum was 15.0 injections over up to 5 years for aflibercept 8 mg in a flexible Q16 (up to 20–24 weeks) regimen. Nevertheless, on the basis of list prices, the current standard of care bevacizumab resulted in the lowest total costs due to its low medication price (i.e. €80,315 per patient over a lifetime horizon). Bevacizumab was followed by aflibercept 8 mg, which induced total costs of €83,577 per patient over a lifetime horizon, and

**Table 4** Overview of all included cost parameters within the healthcare system and for patients and caregivers

| Costs within the healthcare system: costs due to reduced vision | | | | | | | | | Source |
|---|---|---|---|---|---|---|---|---|---|
| | VA1 (SE) | VA2 (SE) | VA3 (SE) | VA4 (SE) | VA5 (SE) | VA6 (SE) | VA7 (SE) | VA8 (SE) | |
| VA1 (FE) | | | | | | | €3097 | €3097 | Weighted average of home care, residential care, and depression (Supplementary material 6) |
| VA2 (FE) | | | | €218 | €218 | €218 | €3315 | €3315 | |
| VA3 (FE) | | | | €518 | €518 | €518 | €3614 | €3614 | |
| VA4 (FE) | | €218 | €518 | €1100 | €1099 | €1099 | €4196 | €4196 | |
| VA5 (FE) | | €218 | €518 | €1100 | €1099 | €1099 | €4196 | €4196 | |
| VA6 (FE) | | €218 | €518 | €1100 | €1099 | €1099 | €4196 | €4196 | |
| VA7 (FE) | €3097 | €3315 | €3614 | €4196 | €4172 | €4172 | €4242 | €4242 | |
| VA8 (FE) | €3097 | €3315 | €3614 | €4196 | €4172 | €4172 | €4242 | €6527 | |

| | Input | Source |
|---|---|---|
| Adverse event | | |
| Cataract (nuclear and subcapsular) | €1217 | Weighted average of Dutch DBC codes 070401009, 070401008, 079699011 |
| Retinal detachment | € 2882 | Weighted average of Dutch DBC codes 079799011, 079799005, 079799002 |
| Retinal artery occlusion/retinal vascular disorder | €1065 | Dutch DBC code: 079799004 |
| Vitreous haemorrhage | €2882 | Weighted average of Dutch DBC codes 079799011, 079799005, 079799002 |
| Intraocular pressure | €854 | Proportion treated with medication vs. surgery or laser surgery redacted from TA824<br>Medication (50% of patients)<br>Weighted average of:<br>Postaglandins, Beta blockers, alpha-2-agonists,<br>Additional therapy (50% of patients):<br>Laser surgery: 070601009<br>Surgery simple: 070601004<br>Surgery advanced: 070601002 |
| Diabetic retinopathy | €1065 | Dutch DBC code: 079799004 |
| Other costs within the healthcare system | | |
| Aflibercept 8 mg (per injection) | €724 | Z-index (list price) |
| Aflibercept 2 mg (per injection) | €724 | Z-index (list price) |
| Bevacizumab (per dosage of hospital preparation) | €17 | Based on hospital preparation [52, 53] |
| Faricimab (per injection) | €730 | Z-index (list price) |

**Table 4** continued

| | Input | Source |
|---|---|---|
| Ranibizumab (per injection) | €637 | Z-index (list price) |
| Administration of intravitreal injection | €460 | DBC: 079799020 |
| Monitoring visit | €95 | DBC: 079699010 |
| SD-OCT screening | €48 | Declaration code: 039823 |
| Diagnosis visit (visit + SD-OCT + FFA) | €190 | DBC: 079699011 |
| Costs for patients and caregivers | | |
| Wage per hour | €31.30 | Dutch costing manual [35] |
| Average visit duration | 1.5 h | Time at hospital and for traveling |
| Average working hours per week | 33.1 | Statistics Netherlands [48] |
| Average workforce (Age 55–65) | 67.3% | Statistics Netherlands [48] |
| Reduced workforce due to vision loss | Depends on VA | Supplementary material 6 |
| Reduced productivity at work due to vision loss | Depends on VA | Supplementary material 6 |
| Opportunity costs of caregiver | €14 | Dutch costing manual [35] |
| % of patients accompanied by caregiver during hospital visit | 80% | Assumption, validated with medical expert |
| Average hours of informal care per week | Depends on VA | Supplementary material 6 |
| Average distance to the hospital (km) | 7 | Dutch costing manual [35] |
| Average costs per km | €0.25 | Dutch costing manual [35] |

*DBC* diagnosis treatment combination, *FE* fellow eye, *FFA* fluorescein angiography, *km* kilometre, *SD-OCT* spectral domain optical coherence tomography, *SE* study eye, *VA* visual acuity

a medication price of €560 (i.e. 23% reduction from current list price) per injection to be cost-equal to bevacizumab. To be cost-equal to bevacizumab, aflibercept 2 mg in a fixed Q8 regimen required a medication price of less than €186 per injection, faricimab in a T&E regimen less than €269 per injection, and ranibizumab less than €183 per injection.

Currently, the waiting list for ophthalmic care in the Netherlands is 12.5 weeks, and the total healthcare costs of eye-related illnesses amount to approximately one billion euros [28, 29]. With the constantly increasing number of patients, DMO management needs to focus on the optimization of care in terms of healthcare capacity use, burden of treatment, and costs. Frequent hospital visits place a burden on both facility capacities and the patient and caregivers who need to accompany them to each injection visit leading to productivity losses. The costs of DMO treatment, therefore, involve direct healthcare costs as well as considerable societal costs. Our analysis showed that while bevacizumab can help manage direct medication costs, the more durable clinical trial treatment regimen of aflibercept 8 mg has the potential to reduce pressure and costs related to administration, productivity losses, and informal care.

As the ITC showed no significant differences in mean change in BCVA between aflibercept 8 mg and other anti-VEGFs and previous analyses came to similar findings across the other anti-VEGFs [25, 26, 30, 31], we excluded the treatment effect from the base case analysis and followed a cost-minimisation approach. Even though we chose a cost-minimisation approach,

former cost analyses on anti-VEGFs often used a cost-effectiveness approach [33, 34], and some health technology assessment (HTA) bodies recommend the use of a cost-effectiveness analysis even with convincing evidence of similar outcomes [49–51]. Therefore, we performed an additional probabilistic cost-effectiveness analysis, which showed the uncertainty around the incremental QALYs and costs due to the insignificant differences in treatment effects, which may lead to unrepresentative incremental cost-effectiveness ratios and conclusions. Therefore, contrary to some HTA bodies and previous studies, we suggest that for future (reimbursement) analyses a cost-minimisation approach for treatments with comparable or non-inferior treatment effect is most suitable.

Although they provide comprehensive comparison of treatment effect, safety, and resource use, the SLR and the ITC introduce some limitations. The SLR included trials that incorporated a photocoagulation rescue laser in their treatment regimen [16]. This laser is used to reduce DMO, thereby decreasing central retinal thickness and potentially impacting BCVA. Although the methods of an ITC partly account for discrepancies in trial designs and treatment factors, it might have inaccurately estimated the observed BCVA of patients in those regimens. Additionally, the clinical trials included in our SLR spanned over a decade. In recent years, reducing treatment frequency has become increasingly important in the field and thus clinical trial design. Consequently, older trials may not have prioritized reducing injection frequency, potentially leading to higher frequencies.

In addition to the limitations of the SLR and ITC, our cost-minimisation model has some limitations due to limited data and assumptions. Firstly, the impact of blood glucose management was excluded from the model, even though the progression of DMO is strongly affected by the blood glucose levels of patients [6]. This simplification is not expected to impact model outcome as variations in glucose level management will not differ significantly across treatment arms and is therefore also uncommon in DMO modelling studies. Secondly, we assumed that the injection frequency in year 3 was equal to year 2, and all anti-VEGFs were administered twice a year during years 4 to 5, in line with the long-term data of the PROTOCOL-T study [30]. However, this is likely a conservative assumption, as a real-world study in nAMD indicates that the injection frequency of bevacizumab and ranibizumab for long-term treatment is slightly higher than aflibercept 2 mg [54]. The more durable treatment regimens aim to extend treatment intervals, and consequently decrease the injection frequency in year 3 even further. Given the major impact of injection frequency on our outcomes, this could possibly lead to an overestimation of the costs of the treatments with more durable regimens.

Moreover, as a result of a lack of trials studying the T&E regimen identified in the SLR, a PRN regimen for bevacizumab and a fixed Q8 weekly for aflibercept 2 mg were used. A PRN regimen requires monthly monitoring visits and there is a risk for undertreatment due to delay in intravitreal injections resulting in a reduced BCVA. With the use of a PRN regimen, the injection frequency could deviate from the current clinical practice, and we might have overestimated the monitoring frequency of bevacizumab. Two scenarios were performed to assess the impact of this assumption. In the first, the monitoring frequency for bevacizumab was set equal to its injection frequency. In the second, bevacizumab's regimen was matched to that of ranibizumab. In both scenarios, the per-patient costs of bevacizumab decreased, underscoring the significant influence of treatment regimens and the selection of clinical trials on our model outcomes. To address the overestimation in injection frequency in the fixed Q8 used for aflibercept 2 mg, an additional scenario was performed using the injection frequency identified in a small single-arm non-randomized trial studying a T&E regimen. With these numbers, aflibercept 2 mg became the second most expensive treatment option, requiring a medication price below €253 per injection to be less costly than bevacizumab. Since administration costs were a major cost driver, discrepancies between clinical trials might have impacted model results. Although the DSA showed similar conclusions across the entire parameter ranges, it would be beneficial to conduct a cost-minimisation analysis once long-term real-world evidence becomes available

**Table 5** Base case results of the cost-minimisation analysis

| | Aflibercept 8 mg flexible Q16 (up to 20–24 weeks) | Aflibercept 2 mg fixed Q8 | Bevacizumab PRN | Faricimab T&E (up to 16 weeks) | Ranibizumab T&E (up to 16 weeks) |
|---|---|---|---|---|---|
| Costs related to the healthcare system | | | | | |
| Medication | €14,463 | €21,865 | €577 | €19,770 | €19,311 |
| Administration | €7455 | €11,267 | €12,659 | €10,101 | €11,311 |
| Outpatient visits | €1768 | €2555 | €4435 | €2314 | €2564 |
| Diagnosis and monitoring | €1077 | €1472 | €2415 | €1351 | €1476 |
| AEs | €149 | €149 | €149 | €149 | €149 |
| Vision loss costs | €56,973 | €56,973 | €56,973 | €56,973 | €56,973 |
| Costs within society | | | | | |
| Productivity losses | €586 | €1116 | €1810 | €1014 | €1119 |
| Informal care | €1051 | €1083 | €1203 | €1014 | €1084 |
| Travel costs | €55 | €83 | €94 | €75 | €84 |
| Total costs | €83,577 | €96,564 | €80,315 | €92,797 | €94,072 |
| Break-even price compared to bevacizumab | €560 (−23%) | €186 (−74%) | N/A | €269 (−63%) | €183 (−71%) |

*AE* adverse event, *PRN* pro re nata, *T&E* treat-and-extend

to reduce the uncertainty associated with using only clinical trial data.

Overall, our study provides a comprehensive overview of the treatment effect, safety, resource use, and associated costs of anti-VEGF treatment. The ITC showed no difference in the treatment effect of anti-VEGFs, and by using a cost-minimisation approach we were able to compare the anti-VEGFs, without confounding by treatment effects. The cost-minimisation results show the considerable impact of DMO on healthcare and societal costs, the productivity losses experienced by patients and their families, and the crucial role of injection frequency in this burden. Moreover, all sensitivity and scenario analyses support the base-case finding, confirming that bevacizumab is the least expensive treatment option and aflibercept 8 mg is next most next at the current list price.

## CONCLUSION

Despite similar efficacy and safety, differences in treatment burden were identified among the anti-VEGFs based on data from clinical trials. Aflibercept 8 mg demonstrated higher durability, potentially reducing overall injection frequency compared to current care and therefore offering lower burden on patients and healthcare providers. Nevertheless, on the basis of current list prices, bevacizumab in a PRN regimen is the least expensive anti-VEGF for the treatment of DMO. Aflibercept 8 mg, aflibercept 2 mg, faricimab, and ranibizumab could achieve cost-equivalence to bevacizumab with potential discounts on medication prices starting at 23%, 74%, 63%, and 71% respectively. These results could support future decision-making of healthcare providers and payers, encompassing aspects of medical costs, healthcare capacity use, and

**Table 6** Outcomes of the scenario analysis

| | Aflibercept 8 mg flexible Q16 (up to 20–24 weeks) | Aflibercept 2 mg Q8 | Bevacizumab PRN | Faricimab T&E (up to 16 weeks) | Ranibizumab 0.5 T&E (up to 12 weeks) |
|---|---|---|---|---|---|
| Base case | | | | | |
| Total costs | €83,577 | €96,564 | €80,315 | €92,797 | €94,072 |
| Break-even price | €560 (− 23%) | €186 (− 74%) | N/A | €269 (− 63%) | €183 (− 71%) |
| Scenario 1: Healthcare perspective | | | | | |
| Total costs | €81,885 | €94,282 | €77,208 | €90,659 | €91,785 |
| Break-even price | €490 (− 32%) | €159 (− 78%) | N/A | €233 (− 68%) | €156 (− 75%) |
| Scenario 2: 10% discounting on costs and effects | | | | | |
| Total costs | €58,912 | €70,921 | €56,214 | €67,538 | €68,459 |
| Break-even price | €573 (− 21%) | 187 (− 74%) | N/A | 270 (− 63%) | 189 (− 70%) |
| Scenario 3: 0% discounting on costs and effects | | | | | |
| Total costs | €117,954 | €131,605 | €114,204 | €127,537 | €129,088 |
| Break-even price | €550 (− 24%) | €188 (− 74%) | N/A | €271 (− 63%) | €182 (− 72%) |
| Scenario 4: 3-year time horizon | | | | | |
| Total costs | €30,519 | € 42,810 | €30,310 | €39,245 | €40,722 |
| Break-even price | €710 (− 2%) | €213 (− 71%) | N/A | €315 (− 47%) | €211 (− 67%) |
| Scenario 5: Bevacizumab's monitoring frequency is equal to its injection frequency | | | | | |
| Total costs | €83,577 | €95,564 | €77,352 | €92,797 | €94,072 |
| Break-even price | €412 (− 43%) | €87 (− 88%) | N/A | €160 (− 68%) | €85 (− 87%) |
| Scenario 6: Bevacizumab's treatment regimen is equal to ranibizumab's treatment regimen | | | | | |
| Total costs | €83,577 | €95,564 | €75,356 | €92,797 | €94,072 |
| Break-even price | €312 (− 57%) | €22 (− 97%) | N/A | 86 (− 88%) | 20 (− 97%) |
| Scenario 7: Aflibercept 2 mg's is based on single-arm non-randomized trial studying a T&E regimen [21] | | | | | |
| Total costs | €83,577 | €93,289 | €80,315 | €92,797 | €94,072 |
| Break-even price | €560 (− 23%) | €253 (− 65%) | N/A | €269 (− 63%) | €183 (− 71%) |

*PRN* pro re nata, *QALYs* quality-adjusted life-years, *TE* treat-and-extend

burden on patients as well as the healthcare system as a whole.

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***Data Availability.*** Most data used during this study are included in this published article/as supplementary information files. Remaining data used during the current study are available from the corresponding author on reasonable request.

### *Declarations*

***Conflict of Interest.*** Sara Quist and Jeroen Paulissen were employees of Asc Academics during this research, which was funded by Bayer. Jeroen Paulissen is now employed by Daiichi Sankyo Nederland B.V. Izabella Lunk, Joao Carrasco, and Marrit Woudstra were an employee of Bayer during the conduct of this research. Michal Pochopien was an employee of Clever Access the conduct of this research, which was funded by Bayer. Mateusz Nikodem and Catriona Crossan were employees of Putnam during the conduct of this research, which was funded by Bayer. Sankha Amarakoon conducted consultancy work for Bayer, Novartis, Horuspharma, and Roche. Freekje van Asten has no conflict of interest to declare. Maarten Postma has received grants and honoraria from various pharmaceutical companies (unrelated to this work) and holds stocks and advisory roles in PAG BV, Health-Ecore, and Asc Academics (all in Groningen, the Netherlands).

***Ethical Approval.*** This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.



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