Healthcare Resource Utilization and the Economic Burden of Neovascular Age-Related Macular Degeneration: A Systematic Literature Review

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OBJECTIVE

To perform a systematic literature review (SLR) to assess the healthcare utilization and economic burden associated with neovascular age-related macular degeneration (nAMD) and its treatment

CONCLUSIONS

nAMD and anti-VEGF therapies were associated with a substantial cost burden to society and healthcare systems

The cost of nAMD treatment with anti-VEGF therapy increased with worsening vision

Among studies comparing the cost-effectiveness of anti-VEGF therapies, bevacizumab was more cost-effective than ranibizumab and aflibercept

Our results suggest that nAMD management can benefit from newer therapies offering more durable vision maintenance, ultimately reducing injection burden and the cost of re-treatment

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INTRODUCTION

- Age-related macular degeneration (AMD) is a neurodegenerative disease that affects the macula, which is responsible for sharp central vision[1]
- Neovascular age-related macular degeneration (nAMD), also known as wet AMD, is an advanced stage of AMD wherein abnormal blood vessels grow into the macula and leak blood and fluid, causing scarring and the rapid and permanent loss of central vision[1–3]
  - The prevalence of nAMD increases sharply with age, from < 1% in patients aged 65–74 years to 8.5% in patients aged ≥ 85 years[3]
- Current treatment options for nAMD include anti-vascular endothelial growth factor (VEGF) agents such as aflibercept, ranibizumab, and brolucizumab, which are typically administered once a month for the first few months by intravitreal injection[2,3]

METHODS

- Biomedical publication and health technology assessment (HTA) databases were searched for literature on cost-utility, cost-effectiveness, cost-benefit, cost-minimization, and cost-consequence of anti-VEGF therapy for the treatment of patients with nAMD
  - Electronic databases included: Embase, Medline, Cochrane, National Health Service Economic Evaluation Database, the HTA Database, EconLit, and Ichushi Web
  - A search of the 'grey literature' was also performed, in which conference proceedings and HTA body websites were manually reviewed
- Literature search results were screened for inclusion by two independent reviewers using population, intervention, comparator, outcome, and study design criteria (**Table 1**)
  - Disagreements were resolved by a third reviewer
- The Drummond checklist[4] was used to assess the quality of the economic evaluations included in the SLR

Table 1. Inclusion Criteria for the SLR

Criterion	Parameters
Population	• **Included:** patients with nAMD/wet AMD • **Excluded:** patients with nAMD/wet AMD and another ocular comorbidity not in the scope of the current SLR, and with separate data not available for either of the indications
Intervention	• Anti-VEGF therapies
Comparator	• Any intervention • An intervention of interest used as a monotherapy
Outcomes	• Costs, resource use, and cost-effectiveness
Study design	• Cost, cost-effectiveness, cost-benefit, cost-minimization, cost-consequence, and resource use evaluations
Timeframe	• Database inception to July 2023

AMD, age-related macular degeneration; HTA, health technology assessment; nAMD, neovascular age-related macular degeneration; SLR, systematic literature review; VEGF, vascular endothelial growth factor.
Note: In the original SLR, HTA documents reported in the native language of the HTA body were translated using online translation tools.

RESULTS

- **Table 2** summarizes the electronic databases, conference proceedings, and coverage years assessed in this study

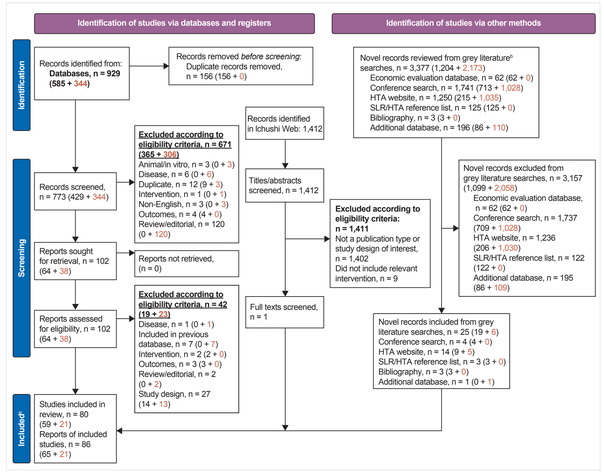
Table 2. Databases Assessed and Coverage Years

Criterion	Database or Conference Proceeding	Coverage Years
Electronic databases	Embase	1947–July 2023
	Medline	1966–July 2023
	Cochrane	1908–July 2023
	NHS-EED	1994–March 2015
	HTAD	1989–March 2018
	EconLit	1886–July 2023
	Ichushi Web[a]	1903–June 2018
Conference proceedings (original and updated SLR)	EURETINA Congresses	2015[b]–2022
	AAO	2015[b]–2022
	ISPOR: Annual European Congresses	2015[b]–2022
	ISPOR: Annual International Congresses	2016–2023
	ISPOR: Asia Pacific Congresses	2016–2022[c]
Conference proceedings (updated SLR)	ISPOR: Asia Pacific Congresses	2020[b]–2022
	ARVO	2019–2023
	The Retina Society	2019–2022

[a]The Japanese database "Ichushi Web" was only searched for the economic modeling SLR. It was not searched as part of the SLR update, per the original SLR, as this is not a standard requirement of HTA submissions. [b]2016 for cost and resource use/health-state utility values reviews. [c]Only for cost and resource use/health-state utility values reviews.
AAO, American Academy of Ophthalmology; ARVO, Association for Research in Vision and Ophthalmology; EURETINA, European Society of Retina Specialists; HTA, health technology assessment; HTAD, Health Technology Assessments Database; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; NHS EED, National Health Service Economic Evaluation Database; SLR, systematic literature review.

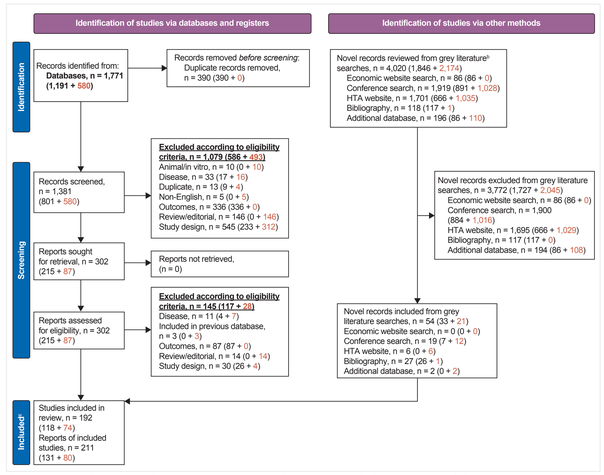
- For the economic modeling review, a total of 929 records were retrieved by the electronic database searches, with a further 3,377 records identified in grey literature (**Figure 1**)
  - A total of 773 unique records from electronic database searches were screened for eligibility based on titles and abstracts, of which 102 were selected for full-text review
  - A total of 61 records from electronic database searches and 25 records identified in grey literature met all eligibility criteria and were included in the qualitative synthesis
- For the cost and resource use review, a total of 1,771 records were retrieved by the electronic database searches, with a further 4,020 records identified in grey literature (**Figure 2**)
  - A total of 1,381 unique records from electronic database searches were screened for eligibility based on titles and abstracts, of which 302 were selected for full-text review
  - A total of 157 records from electronic database searches and 54 records identified in grey literature met all eligibility criteria and were included in the qualitative synthesis
- Characteristics of the 80 studies are summarized in **Figure 3**
  - In total, 64 studies reported a cost-utility analysis, 6 reported a cost-minimization analysis, and 13 reported a cost-benefit analysis, based on improved visual acuity or vision years (**Figure 3A**)
  - Studies were conducted across 21 countries. Most of the studies were conducted in the US (n = 17) and UK (n = 14), followed by Canada (n = 9) (**Figure 3B**). Country was not reported in one study
  - In the economic modeling evidence review, ranibizumab was included in more analyses than any other intervention (**Figure 3C**)
- The economic evaluations included in the SLR were generally judged to be of good quality
  - Reporting of study design was generally good, the research question was stated in all but one study, and the form of economic evaluation was stated in 74 of 80 studies
  - All studies gave a full or partial answer to the study question, and the conclusions followed from the data reported in all 80 studies
- Based on economic evaluation outcomes comparing the cost-effectiveness of anti-VEGF therapies, bevacizumab and brolucizumab were found to be more cost-effective than ranibizumab and aflibercept (**Figure 4**)
- From both a societal and healthcare system perspective, nAMD was associated with substantial cost and resource use burden (**Table 3**)
  - Mean societal ophthalmic costs were significantly higher in patients with mild to very severe vision loss compared to those with no or negligible vision loss
    - The mean 12-month "societal" ophthalmic cost (direct medical, direct nonmedical, and indirect medical) for the overall study cohorts, with mild to very severe vision loss, was significantly higher at $39,910 per capita (*P*<.001) compared with the control cohort, with no or negligible vision loss ($6,116 per capita)
  - Treatment of nAMD with anti-VEGF therapies was associated with substantial treatment costs at 12 and 24 months
    - At 12 months, treatment-naïve patients with nAMD had comparable injection cost with ranibizumab and aflibercept ($11,351 vs $10,702, *P*=.06); similar trends were reported at 24 months ($16,286 vs $16,666, *P*=.690)
- Of note, this study was based on clinical trial data and does not include real-world data; therefore, the results may not be representative of current resource use in clinical practice

Figure 1. PRISMA Diagram – Economic Modeling Review[a]



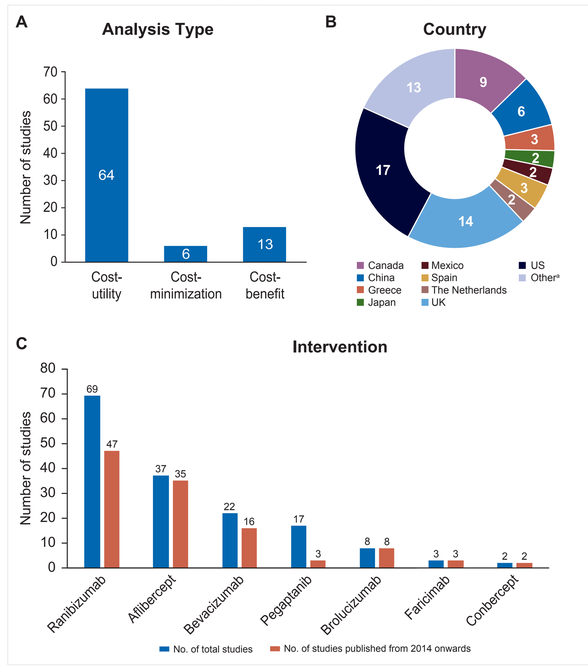
[a]The total number of studies identified includes the number identified in the original SLR and the updated SLR (red text). [b]The grey literature consisted of conference proceedings and HTA body websites, which were manually reviewed. [c]The literature search resulted in the inclusion of 80 studies; a total of 86 reports of included studies are noted as some studies were reported in multiple publications.
HTA, health technology assessment; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

Figure 2. PRISMA Diagram – Cost and Resource Use Review[a]



[a]The total number of studies identified includes the number identified in the original SLR and the updated SLR (red text). [b]The grey literature consisted of conference proceedings and HTA body websites, which were manually reviewed. [c]The literature search resulted in the inclusion of 192 studies; a total of 211 reports of included studies are noted as some studies were reported in multiple publications.
HTA, health technology assessment; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

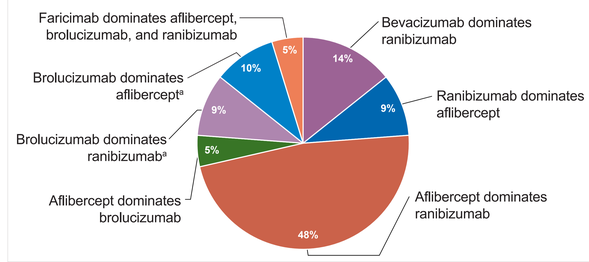
Figure 3. Study Characteristics by Analysis Type (A), Country (B), and Intervention (C)



[a]One study each in Argentina, Australia, Brazil, Czech Republic, Europe, Finland, France, Germany, Italy, Russia, Scotland, Sweden, and Turkey.

Figure 4. Economic Modeling Review

Results of studies comparing cost-effectiveness of anti-VEGF therapies (n = 16)



[a]The estimated market share of brolucizumab in 2022 (3.56%) is lower than ranibizumab (24.01%) and aflibercept (14.95%)[5]

Table 3. nAMD is Associated with Substantial Cost and Resource Use Burden on Healthcare Systems

Study	Country	Overview	Key Findings at 12 Months
Johnston et al 2013[6]	USA	• This was a US administrative claims database study conducted between November 2011 and April 2013	• The mean total healthcare expenditure was reported to be $19,484 in the aflibercept group and $14,241 in the ranibizumab group in the 12-month analyses • At 12 months, the mean expenditure on intravitreal injections was $11,052 in the aflibercept group and $11,342 in the ranibizumab group
Brown et al 2016[7]	USA	• Total societal ophthalmic costs associated with nAMD dramatically increase as vision in the better-seeing eye decreases – Study cohort 1 (mild VL): $20,339 – Study cohort 4 (severe VL): $82,984; *P*<.001 • In this study, 90% of patients received anti-VEGF inhibitor injections	• The mean 12-month "societal" ophthalmic cost (direct medical, direct nonmedical[a], and indirect medical) for the overall study cohorts[b] was significantly higher at $39,910 per capita (*P*<.001) compared with the control cohort[c] ($6,116 per capita) – Among the cost categories, direct nonmedical costs were the highest ($26,765), followed by direct medical costs ($8,642), and indirect medical costs ($4,503)
Kiss et al 2020[8]	USA	• Real-world cost for ranibizumab and aflibercept drugs at 12 and 24 months are reported in this study	• At 12 months, treatment-naïve patients with nAMD had comparable injection costs with ranibizumab and aflibercept ($11,351 vs $10,702, *P*=.06)

[a]Direct nonmedical costs were primarily related to caregiver costs and included transportation costs, activities of daily living costs inside and outside the home, residence costs, and child care costs for medical visits. [b]Study cohort (mild to very severe vision loss). [c]Control cohort (no or negligible vision loss).
nAMD, neovascular age-related macular degeneration; VEGF, vascular endothelial growth factor; VL, vision loss.

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