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Direct and indirect healthcare costs of ocular diseases in Italy: a literature review on glaucoma, diabetic retinopathy, and macular degeneration

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Parole chiave: Glaucoma; Retinopatia diabetica; Degenerazione maculare legata all'età; Costi sanitari; Salute pubblica

Abstract

Background. *Glaucoma, diabetic retinopathy, and age-related macular degeneration impose substantial economic burdens on healthcare systems due to their high prevalence and chronic nature. Nevertheless, comprehensive Italian data is limited. This study aims to collect Italian evidence on the economic impact of these conditions to support more effective healthcare planning.*

Study Design. *Systematic review.*

Methods. *A systematic literature search was conducted in accordance with PRISMA guidelines across PubMed, Scopus, Web of Science, and EMBASE databases. Studies reporting cost evaluations of managing glaucoma, diabetic retinopathy, and age-related macular degeneration in Italy were included. Direct, indirect and non-medical costs were considered.*

Results. *The review included 23 studies exhibiting considerable heterogeneity in timeframes, regions, and economic evaluation approaches. For glaucoma, annual direct costs ranged from €788.70 for early-stage cases to €8,368.51 for advanced cases requiring surgery. Annual costs associated with diabetic retinopathy ranged from €4,050 to €5,799 per patient, depending on disease severity and treatment approach. The financial burden of age-related macular degeneration varied considerably, with costs ranging from €1,399.20 for early-stage cases to €3,973.30 for advanced stages. Although non-medical and indirect costs, such as lost productivity and caregiving expenses were less frequently assessed, they represented a significant contributor to the overall financial burden.*

Conclusions. *This study highlights the substantial economic burden ocular diseases place on the Italian healthcare system. Early intervention and preventive strategies could reduce the long-term costs of managing diabetic retinopathy and age-related macular degeneration. Further research into indirect costs and cost-effective interventions is necessary to support more efficient healthcare resource allocation.*

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Introduction

Many of the developed and developing countries are facing an unprecedented and rapid rise in the number of elderly people, leading to profound health and economic consequences (1). As Italy faces a rapidly ageing population, with individuals aged 65 and older expected to account for 35.9% of the population by 2050 (2), the country must confront the increasing prevalence of age-related chronic diseases, including ocular conditions such as glaucoma, diabetic retinopathy (DR), and age-related macular degeneration (AMD) (3). They are among the most common eye diseases leading to blindness and visual impairment in Italy and other developed countries (4,5).

These diseases not only impair vision and diminish quality of life (6) but also restrict opportunities for education and employment (7,8). Furthermore, the diagnosis and management of these chronic conditions impose a considerable financial burden on the National Healthcare Service (NHS). In Italy, it is estimated that approximately 550,000 individuals have been diagnosed with glaucoma; this corresponds to about 2% prevalence in population aged ≥40 years (9). DR is one of the most common complications of diabetes mellitus (DM) (10) and the leading cause of blindness in the working-age population (11,12). However, there is a lack of comprehensive data on the prevalence and incidence of legal blindness among diabetic patients, exacerbated by the absence of a national registry for individuals with DM. Epidemiological studies indicate that at least 30% of the diabetic population in Italy is affected by retinopathy, though significant regional heterogeneity exists (13). AMD also presents a major public health challenge. While recent Italian data on AMD incidence are limited, European studies estimate that among individuals aged 60 years and older, the prevalence of early or intermediate AMD is approximately 25.3%, and the prevalence of any late-stage AMD is around 2.4% (14).

The economic impact of these ocular diseases is multifaceted, encompassing both direct costs, such as medical treatment and hospital care, and non-medical and indirect costs, including lost productivity and caregiver expenses (7,15). Despite some available data, comprehensive national cost figures are fragmented and difficult to access. This lack of detailed and up-to-date information hinders effective healthcare planning and the optimal allocation of resources.

Given that the prevalence of glaucoma, DR, and AMD is expected to rise in the coming years, posing a significant burden on healthcare systems globally, the objective of this review is to provide a comprehensive and up-to-date overview of the direct and indirect healthcare costs associated with these conditions in Italy. The primary objectives are to provide an in-depth overview of the economic burden these ocular diseases impose on the Italian NHS, to identify gaps in the current knowledge, and to suggest areas for future research. By critically evaluating the available data, this review seeks to inform healthcare policy and resource allocation, ultimately contributing to the improved management of these increasingly prevalent ocular conditions within the context of Italy's ageing population.

Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD CRD42024572796.

Literature search strategy

The literature search was conducted on PubMed/MEDLINE, Scopus, Web of Science (WoS), and EMBASE on July 24, 2024. Moreover, grey literature was also consulted to detect any potentially relevant articles. Additionally, manual searches were performed by reviewing the bibliographic citations. The search aimed to answer the question: "What are the current direct and indirect healthcare costs associated with managing glaucoma, diabetic retinopathy, and macular degeneration in Italy, and how have these costs evolved over time?". The search strategy combined Medical Subject Headings (MeSH) terms and title/abstract keywords. For glaucoma, diabetic retinopathy, and AMD, terms such as 'cost evaluation,' 'economic burden,' and 'Italy' were employed. The full search strategy, developed for each database, is available in supplementary table 1.

Eligibility criteria

Studies were selected based on the PEOS framework: Population (P), Exposure (E), Outcome (O), and Study design (S). Eligible studies were those involving patients with glaucoma, diabetic retinopathy, or age-related macular degeneration (population), and assessing the economic evaluations related to these ocular diseases, including direct,

non-medical and indirect (outcome), associated to the treatment and management of these diseases (exposure). Primary outcomes included cost data related to disease management (direct, indirect and non-medical costs). Secondary outcomes included the economic impact of different stages of disease severity and treatment modalities. In this review, we included both observational studies (cohort studies, case-control studies, cross-sectional studies) and economic evaluations employing simulation models and administrative database analyses, to enable a comprehensive mapping of cost dimensions. The search was restricted to studies published in Italian and English. Supplementary table 2 provides a detailed description of the criteria.

Study selection and data extraction

The study selection process was conducted in two stages. First, titles and abstracts of all identified records were screened independently by two reviewers using predefined eligibility criteria. Full-text articles of potentially eligible studies were then retrieved and assessed for inclusion. Discrepancies were resolved through discussion or by consulting a third reviewer. The study selection process was documented using a PRISMA flow diagram.

Data were extracted using a standardized template in Microsoft Excel (Microsoft Excel® for Microsoft 365 MSO, Redmond, WA, USA, 2019). The extracted data included: first author, year of publication, region where the study took place, time period, study design, ocular pathology, study type, study objective, sample size, age, sex and incidence and prevalence of included ocular diseases; data collection methods, follow-up, cost calculation methods, cost perspective, funding sources and main results, including average cost per patient, cost breakdown, sensitivity analysis, and cost-effectiveness results. Lastly, funding sources were also collected.

The data extraction template was piloted on three randomly selected studies to ensure consistency and reliability among the reviewers. Data extraction was performed independently by two reviewers, and discrepancies were resolved through discussion.

Quality assessment

The risk of bias in the included studies was assessed independently by two reviewers using the Newcastle-Ottawa Scale (NOS). This scale is specifically designed for evaluating the quality of non-randomized studies, such as cohort and case-control studies. The NOS assesses studies based on three main domains: selection of study groups, comparability of groups, and ascertainment of the outcome of interest. Each study is scored on a star system, with higher scores indicating lower risk of bias. The reviewers carefully examined each domain, assigning stars according to predefined criteria. To ensure a rigorous quality assessment of economic evaluations and simulation models included in this review, we applied the CHEERS checklist (Consolidated Health Economic Evaluation Reporting Standards). This tool was selected for its emphasis on transparency and adequacy in reporting, specifically addressing key components such as the validity of economic assumptions and the accuracy of modeling frameworks employed within each study. Additionally, the quality of the economic model was assessed using the ISPOR-SMDM Modeling Good Research Practices guidelines, covering 6 core domains: model transparency, structural assumptions, data sources and validation, internal consistency and validity, uncertainty and sensitivity analyses, and contextual relevance of model outcomes. Each domain was evaluated qualitatively for adequacy, partial adequacy, or inadequacy based on model rigor, data reliability, and alignment with real-world healthcare decision-making. Discrepancies between the reviewers' assessments were resolved through discussion, and if consensus could not be reached, a third senior reviewer was consulted to make the final decision. This thorough assessment process ensured a rigorous evaluation of the methodological quality of the included studies.

Data Synthesis

Given the expected high variability in study methodologies, cost definitions, and publication years, we chose to conduct a qualitative synthesis of the data rather than a meta-analysis. Our qualitative approach enables us to retain the diversity of findings across time periods, highlighting cost patterns and areas of heterogeneity without imposing potentially confounding adjustments. This choice aligns with the primary objective of this review: to map the range of direct, indirect and non-medical costs associated with ocular diseases in Italy, rather than to provide a pooled estimate that may not accurately reflect the variability across settings and times. Therefore, a narrative synthesis of the included studies was conducted, summarizing the study characteristics, cost data, and economic impacts. The results were tabulated and presented in text, with key findings illustrated in tables and figures.

Results

Study selection

A total of 304 articles were retrieved, of which 77 in PubMed/MEDLINE, 80 in Scopus, 100 in EMBASE and 47 in Web of Science. After removing duplicates, 165 studies were screened for eligibility by evaluating titles and abstracts, resulting in 45 studies selected for full-text assessment. Following this assessment, 23 studies (16-38) were included in the descriptive analysis. Figure 1 illustrates the study selection process.

Descriptive characteristics of included studies

The 23 studies included in this systematic review span various timeframes, regions, and ocular conditions, providing a broad perspective on the economic evaluations of glaucoma, DR, and AMD in Italy. Most studies (13/23, 57%) (17-20,24-27,29,31,32,35,38) cover focused on an observation period between 2000 and 2010, with a smaller proportion (35%) conducted after 2010 (16,22,23,28,30,33,34,36,37). The geographical distribution of the studies was diverse, with some offering regional insights and others presenting national data. Approximately 30% of studies (16,17,19,24,26,31,38) included international evaluations, providing a comparative lens across different healthcare systems.

Glaucoma was the most studied condition, representing 48% of the total studies (11 out

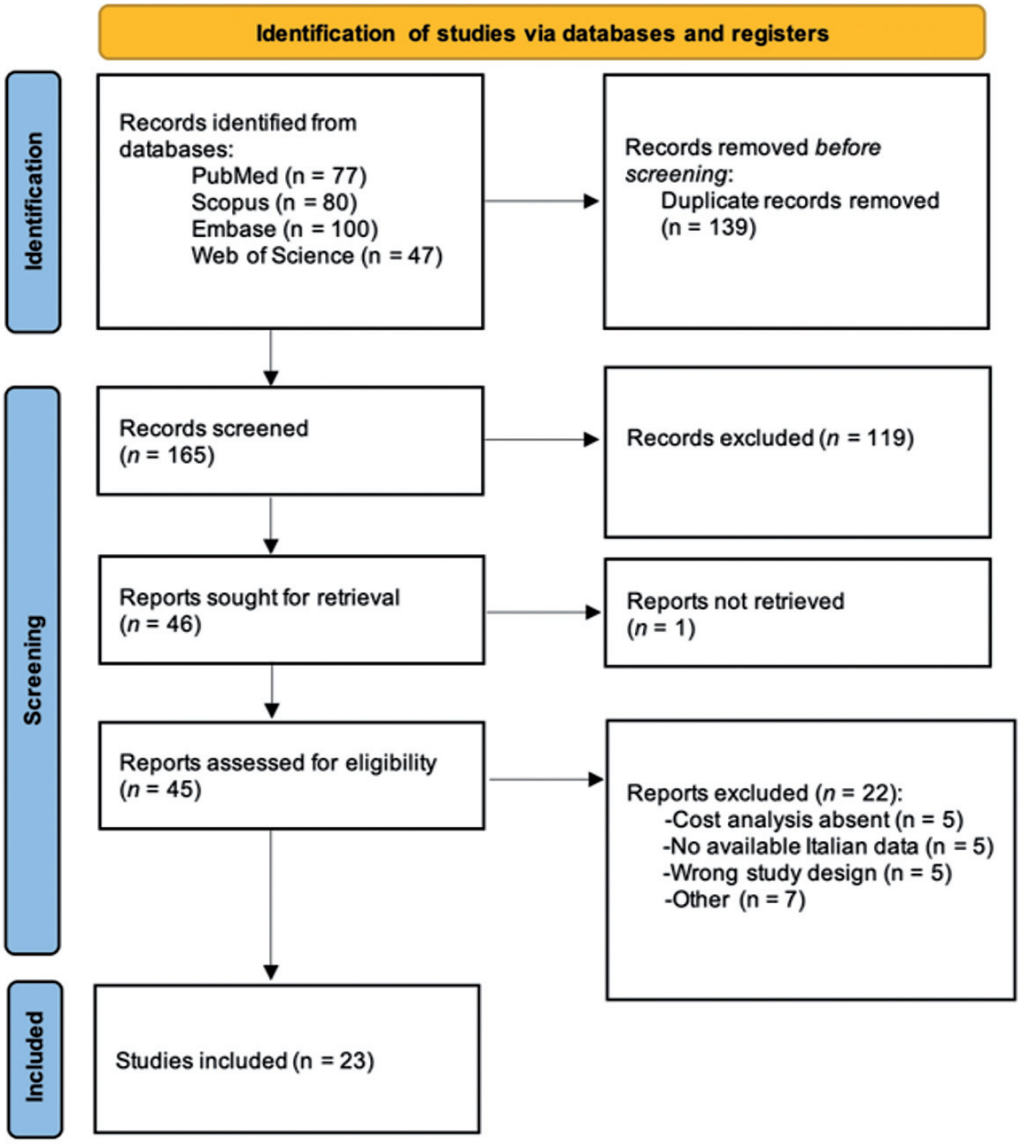

Figure 1 - Flow diagram depicting the screening process.

of 23), (18,19,21,22,26,27,29-31,34,38), while DR (28,35,36) and AMD accounted for 35% each (16,17,20,23,25,32,33,37). One study (24) encompassed at least two of these conditions.

Regarding cost assessment, the majority (35%, 8 out of 23) (16,17,20,25,29,31,37,38) focused on direct or indirect cost analysis, with an emphasis on resource utilization in the management of these chronic conditions. Cost-effectiveness analyses were employed in 22% of the studies (5 out of 23) (21,26,27,35,36) particularly for assessing treatment modalities and prevention strategies. Screening programs for DR were evaluated for their economic impact in 22% of the studies (5 out of 23) (24,28,32,35,36), with most highlighting the potential cost savings from early detection. Importantly, the assessment of costs in these studies primarily focused on direct costs, with 91% (21 out of 23) concentrating on expenses related to medical care, such as treatment and hospitalizations (16,18-31,33-38).Only two studies comprehensively assessed both direct and indirect costs, highlighting a gap in the literature regarding the broader economic burden, including loss of productivity and caregiver expenses (17,32). Descriptive characteristics of the included studies are provided in Table 1.

Overall, the descriptive characteristics of these studies demonstrate a focus on direct medical costs, particularly in relation to advanced disease stages, with a noticeable underrepresentation of indirect cost assessments. This emphasizes the need for future research to address the comprehensive economic impact of these ocular diseases, particularly as Italy's aging population continues to grow.

Demographic characteristics of the included population

This systematic review included studies with sample sizes ranging from 83 (18) to 18,161 (34) patients. The mean age of participants ranged from 58.6 years (35) to 77 years (17). The reviewed studies reported the prevalence of AMD ranging from 0.2% (33) in younger age groups to 13% (25) in older populations. The prevalence of DR among diabetic populations was approximately 29%, with an annual incidence between 2% and 6% (28). In Lombardy, 81% of diabetic patients, an estimated 36,780 individuals in 2014, were affected by DME (23). The prevalence of glaucoma in the Italian population aged 40 and over was approximately 2%. (22). Results are summarized in Table 1.

Table 1 - Descriptive characteristics of the included studies and demographic characteristics of the included population

Author and year (ref)	Region	Time period	Study design	Ocular pathology	Study type	Study objective	Sample size	Sex and age	Incidence and prevalence
Albrecht M et al, 2018 (16)	San Raffaele Hospital, Milan, Lombardy	2013 - 2015	Observational retrospective study	AMD, DME	Drug utilization and cost analysis of intravitreal anti-VEGF treatments (Ranibizumab and Aflibercept)	Evaluate the drug utilization patterns and associated direct costs of intravitreal anti-VEGF treatments in a real-world setting	2,117 patients (AMD: 60.5%, DME: 23.4%, mCNV: 7.1%, RVO: 9%)	Mean age: 69.9; 54.4% female	NA
Bandello F et al, 2008 (17)	France, Germany, Italy	2004	Cross-sectional observational study	AMD	Cost analysis	Investigate the costs of exudative AMD in patients actively treated at ophthalmology referral centers in France, Germany, and Italy	360 patients (France: 120, Germany: 126, Italy: 114)	Mean age: 77 years; 60% female	Prevalence in Italy: 1.1% in rural southern regions
Christensen TL et al, 2005 (18)	Italy (national level)	2005	Markov modelled pharmacoeconomic analysis	Glaucoma	Cost-minimization analysis	Analyze the costs and cost-savings of bimatoprost 0.03% as an alternative to filtration surgery for glaucoma patients in Italy over a 4-year period	83 adult patients with uncontrolled glaucoma scheduled for filtration surgery	Mean age: 66 years (± 11 years)	NA

(Segue Tab. 1)

De Natale R et al, 2011 (19)	France, Germany, Italy, Spain, UK	1995 - 2006	Longitudinal prescription analysis	Glaucoma	Prescription and economic impact analysis	Compare the evolution of prostaglandin analog and beta-blocker prescriptions across 5 European countries and evaluate the impact of healthcare regulations on glaucoma treatment costs and outcomes	Glaucoma-treated patients from various European databases	NA	NA
Denti C et al, 2002 (20)	Italy (national level)	1998	Observational retrospective study	AMD	Cost analysis of AMD from the payer's perspective	Evaluate the direct costs of patients affected by AMD in Italy from the perspective of the payers	497 patients divided into six subgroups: new and previous drusen, new and previous geographic atrophy, new and previous CNV	Mean age: 74 years	NA
Fea AM et al, 2021 (21)	Italy (national level)	NA	Cost-utility analysis	Glaucoma	Cost-effectiveness study comparing trabecular microbypass stents (iStent inject®) with cataract surgery vs. cataract surgery alone	Assess the cost-effectiveness of the iStent inject® device combined with cataract surgery compared to cataract surgery alone in patients with mild-to-moderate glaucoma	Patients with mild-to-moderate glaucoma in need of cataract surgery	Mean age: 64.7 years	Approximately 1 million individuals in Italy, with about 4500 new cases of blindness due to glaucoma registered each year
Ferrario L et al, 2020 (22)	Italy (national level)	2020	Economic sustainability analysis	Glaucoma	Economic evaluation of the XEN gel stent device for glaucoma treatment	Define economic sustainability of XEN gel stent in clinical practice across Italian regions, comparing costs with reimbursement tariffs	Approximately 550,000 glaucoma patients in Italy, representing 2% of the population over 40 years old	NA	550,000 people in Italy (2% of over 40 population)
Foglia E et al, 2017 (23)	Lombardy	2014 - 2015	Budget impact analysis	DME	Economic evaluation comparing alternative technologies to Ranibizumab	Evaluate the economic benefits of introducing additional alternative technologies for DME treatment in the Lombardy Region healthcare system	Patients with DME in Lombardy Region	NA	Diabetes prevalence in Lombardy: 5.40%. DME prevalence rate: 6.81%. Estimated 36,780 individuals with DME in 2014.
Gandjour A et al, 2002 (24)	France, Germany, Italy, The Netherlands, Sweden, Switzerland, and the UK)	2000 - 2001	European multicentre observational assessment	DR	Cost and quality comparison of preventive services for Type 2 diabetes mellitus	Evaluate potential differences in the process quality and costs of preventing secondary complications in patients with Type 2 diabetes mellitus across 7 European countries	Data from 188 European physician practices, assessing services for one hypothetical average patient and real patients	Aged 65 or younger	NA
Garattini L et al, 2004 (25)	Italy (Northern and Central)	1998 - 99	Multicenter, prospective 1-year study	AMD	Cost analysis of AMD in hospital ophthalmology departments	Calculate the resource utilization and direct medical costs of AMD in Italian hospital ophthalmology departments	476 patients, classified into three prognostic groups: Drusen: 23.7%, Geographic atrophy: 16.4%, CNV: 59.9%	Aged over 50 years	AMD affects adults from the age of 50 years, with higher prevalence in older age groups; almost 5% prevalence in those aged 75–84 years; 13% prevalence in those aged 85 or over

Holmstrom S et al, 2006 (26)	France, Germany, Italy, Spain, UK	2005	Cost-effectiveness analysis using a pharmacoeconomic model	Glaucoma	Cost-effectiveness analysis	Evaluate the cost-effectiveness of bimatoprost, latanoprost, and timolol in treating glaucoma in 5 European countries	Patients with primary open-angle glaucoma	Aged 18 years and older	NA
Hommer A et al, 2008 (27)	Europe (Italy, Spain, UK, Norway, Sweden)	2007	Cost-effectiveness analysis using a decision analytic model	Glaucoma	Cost-effectiveness analysis	Compare the cost-effectiveness of fixed-combination therapies (bimatoprost/timolol, travoprost/timolol, and latanoprost/timolol) in the treatment of glaucoma	Patients with open-angle glaucoma	NA	NA
Invernizzi A et al, 2016 (28)	Milan (Lombardy)	2012 - 2013	Single-center, single-blind observational study	DR	Feasibility and cost analysis of telemedical DR screening	Assess the feasibility of a telemedical approach for DR screening in the Italian population and to evaluate the advantages/disadvantages compared to standard slit-lamp funduscopic examination	1,281 patients with type 2 diabetes; 61% male	Mean age: 65.69 ± 12.64 years	Prevalence of DR in the diabetic population: approximately 29%; yearly incidence of DR: approximately 2%-6% l
Koleva D et al, 2006 (29)	Emilia-Romagna, Friuli-Venezia Giulia, Lombardy, Piedmont, Veneto, Lazio, Tuscany, Abruzzo, Apulia, Calabria, Sardinia, Sicily	2003	Multicenter observational study	Glaucoma	Cost analysis of glaucoma	Analyze the resource utilization and costs of glaucoma (staged by severity) in Italian ophthalmology departments	Patients with: Glaucoma: (273) or advanced Glaucoma (204)	65.1 years overall; 48.9% female	NA
Lazzaro C et al, 2023 (30)	Italy (national level)	NA	Cost-utility analysis	Glaucoma	Economic evaluation using a cost-utility analysis	Evaluate the cost-utility of STN1013001 compared to other latanoprost formulations	patients with glaucoma	57.60 years (range: 33.00;82.00)	Prevalence of open-angle glaucoma: 1.4%
Lee PP et al, 2007 (31)	USA, Europe (France, Germany, Italy, UK)	1995 - 2003	Retrospective medical chart reviews	Glaucoma	Cost analysis based on disease stage	Evaluate and compare treatment patterns, outcomes, and costs of glaucoma care in the United States and Europe	Total sample: 345 patients (151 US, 194 Europe)	Mean age: US: 66.3 years, Europe: 64.7 years US: 57.6% female, Europe: 47.9% female	US: glaucoma prevalence estimated at 2.47 million Americans in 2000 Italy: 1.4% of the population estimated to have glaucoma, with 540,000 undiagnosed cases
Muscio A et al, 2011 (32)	Italy (national level)	2005	Simulation and cost-benefit analysis	AMD, Glaucoma, DR	Economic impact analysis	Assess the financial effects of efficient prevention programs in Italy, providing empirical evidence that government investments in visual care prevention could reduce public spending.	Total number of blind individuals in Italy: 362,000 Blind individuals younger than 65 years: 61,000 Blind individuals in working age (15 – 64 years old): 56,000	Primarily individuals aged 15 to 64 years for working-age population and those older than 75 years	NA

Perrone V et al, 2022 (33)	The Marches, Lombardy, Calabria, Apulia, Lazio	2010 - 2017	Observational retrospective cohort study	AMD	Pharmaco-utilization of anti-VEGF drugs and cost analysis	Analyze pharmaco-utilization of anti-VEGF drugs and healthcare costs in AMD and other ocular diseases patients in Italy	Patients with anti-VEGF prescriptions	Aged ≥50 years	Prevalence of AMD (both wet and dry): between 0.2% and 5.6% in Europe, with 2.1% in Italy. Worldwide, 30–50 million people are affected by AMD
Perrone V et al, 2023 (34)	Apulia, Campania, Umbria, Lazio, Veneto	2010 - 2021	Observational retrospective study	Glaucoma	Real-world analysis	Evaluate characteristics, therapeutic paths, and economic burden of glaucoma patients treated with ophthalmic drops in Italy using real-world data	18,161 glaucoma patients	Mean age: 66.6 years; 56% female	Prevalence: 0.67% among study population, estimated 550,000 individuals in Italy
Porta M et al, 1999 (35)	Turin (Piedmont)	1993 - 94	Observational retrospective study	DR	Cost-effectiveness analysis of screening and treatment approaches	Analyze and compare the costs of screening and treating sight-threatening diabetic retinopathy in three different clinical settings	2,040 patients (Centre A: 493; Centre B: 500; Centre C: 1,076)	Mean ages: Centre A: 58.6 years, Centre B: 62.7 years, Centre C: 60.3 years Females: Centre A: 50.7%, Centre B: 51.4%, Centre C: 49.6%	Prevalence: DR: Centre A: 58.2%, Centre B: 74.7%, Centre C: 64.3%; Background DR: Centre A: 29.2%, Centre B: 12.3%, Centre C: 18.9%; Proliferative DR: Centre A: 1.2%, Centre B: 1.3%, Centre C: 3.4%
Scarpa G et al, 2016 (36)	Treviso (Veneto Region)	2012	Prospective study	DR	Cost-effectiveness analysis	Evaluate the feasibility and cost-effectiveness of a screening programme for DR using a nonmydriatic fundus camera in Treviso	498 diabetic patients in Ponzano, Treviso (340 accepted for screening)	Mean age: 68 years; 45% females	Prevalence of diabetes in Ponzano: 10%. Prevalence of DR among screened: 13%
Scuteri D et al, 2019 (37)	Calabria	2014 - 2017	Observational retrospective study	DR, AMD	Pharmacoutilization and cost analysis	Assess prevalence of DR and AMD, and pharmacoeconomic impact of ranibizumab treatment	Patients receiving clinical observation at "Mater Domini" University Hospital: 377 patients with AMD 183 patients with DR 185 patients with DME	Females: AMD: 51.2% (193/377), DR: 32.8% (60/183), DME: 26.5% (49/185), RVO: 49.6% (62/125)	NA
Traverso CE et al, 2005 (38)	Austria, France, Germany, Italy, UK	1995 - 2003	Multinational long-term observational study	Glaucoma	Cost analysis of glaucoma treatment based on disease severity	Estimate resource utilization and direct medical costs associated with long-term management of glaucoma of different severities in 5 European countries	194 patients with diagnoses of glaucoma, normal tension glaucoma, ocular hypertension, or glaucoma suspect	Mean age: 64.7 years (SD 12.1)	Prevalence: Italy: Approximately 50,000 people visually handicapped by glaucoma, 540,000 over 40 years had glaucoma, half undiagnosed Germany: Glaucoma third leading cause of blindness (1.6/100,000), 22.8/100,000 in those aged 75 and older

AMD: Age-related macular degeneration; DR: Diabetic retinopathy; DME: Diabetic Macular Edema; EU: European, UK: United Kingdom; USA: United States of America. AMD: Age-related macular degeneration; DR: Diabetic retinopathy; DME: Diabetic Macular Edema; mCNV: myopic Choroidal Neovascularization; RVO: Retinal Vein Occlusion; SD: Standard Deviation; anti-VEGF (Anti-Vascular Endothelial Growth Factor).

Methodological approaches and funding sources in health economic evaluations

The studies included in this review employed various data collection methods. Administrative databases and registries were utilized in 30% of the studies (7 out of 23) (16,19,22,33,34,36,37), while 23% of the studies (6 out of 23)(17,20,25,27,28,35) relied on patient interviews and medical records (Table 2).

The follow-up durations exhibited considerable variation, ranging from 1 day to 36 years, with most studies (39%, 9 out of 23)(18–20,23–25,31,36,38) having a follow-up period of 1 to 5 years. Notably, two studies(17,32) did not include any follow-up period, as they were cross-sectional or simulation-based analyses.

Cost calculation methods were classified into three categories: bottom-up microcosting (35% of the studies)(17,18,20,24–27,29), Activity-Based Costing (ABC)(13%)(22,34,36) and Markov models (11.5%) (21,30). Additionally, a subset of studies (16,19,23,28,31-33,35,37,38) adopted a hybrid approach, integrating unit costs derived from tariffs or national pricing lists with the aforementioned methodologies. Regarding cost perspectives, most of the studies (87%, 20 out of 23) (16,18-22,24-31,33-38) were conducted from the National Health System (NHS) perspective. Most studies (65%, 13 out of 23) (16-18,21,24-27,29,31,33,34,38) reported external financial support, predominantly from pharmaceutical companies. The quality assessment using the NOS is presented in Table 2, while the results of the CHEERS checklist assessment and ISPOR evaluation are detailed in Supplementary Tables 3a and 3b.

Direct Costs

Glaucoma

The analysis of the literature on the direct costs of glaucoma revealed substantial variability influenced primarily by disease severity and the complexity of required medical interventions. Reported annual costs per patient range from approximately €788.7 for early-stage glaucoma to €8,368.51 for cases involving advanced surgical procedures such as the iStent inject combined with cataract surgery (21). Surgical interventions, particularly trabeculectomy and filtration surgery, emerged as the most significant cost drivers, with expenses reaching up to €2,121 for a single filtration surgery (18). Medication costs also play a substantial role, especially with treatments like

Table 2 - Methodological approaches and funding sources of included studies, and quality assessment.

Author and year	Data Collection Methods	Follow-Up	Cost Calculation Methods	Cost Perspective	Funding Sources	Quality Assessment
Albrecht M et al, 2018 (16)	The AIFA anti-VEGF monitoring registry and the reimbursement files from local health authorities	Median follow-up 224 days, (1 to 1,448 days)	Based on the number of injections and associated drug expenditures	NHS	Novartis Farma S.p.A.	Selection: 3/4 Comparability: 0/2 Outcome: 3/3 Total Score: 6/9
Bandello F et al, 2008 (17)	Patient interviews and medical records	None (cross-sectional study)	Medical costs based on national tariffs and market prices non-medical costs estimated from market prices and national tariffs	Societal perspective	Alcon France SA, Rueil-Malmaison, France	Selection: 3/4 Comparability: 0/2 Outcome: 3/3 Total Score: 6/9
Christensen TL et al, 2005 (18)	RCT and Delphi panel of Italian ophthalmologists	4 years	Unit costs obtained from Italian chart and tariffs review and pharmacy website; 3% discount rate applied	NHS	Allergan Inc.	Reported in Supplementary table 3b
De Natale R et al, 2011 (19)	IMS Health, UK-GPRD, and the Padova region pharmaceutical service	Longitudinal analysis from 1995 to 2006	Prescription data from various national and regional databases	NHS	None declared	Reported in Supplementary table 3a
Denti C et al, 2002 (20)	Patient records and billing information from seven centers	Retrospective analysis covering the trimester before patient enrollment (1999-2000)	Detailed analysis of direct costs based on tariffs of medical services and hospitalizations	NHS and patients	None declared	Selection: 3/4 Comparability: 1/2 Outcome: 3/3 Total Score: 7/9
Fea AM et al, 2021 (21)	Published literature, randomized clinical trials	Lifetime horizon adopted in the analysis	Costs calculated using a Markov model with four health states and a one-month cycle, considering only direct healthcare costs from the Italian NHS perspective	NHS	Glaukos	Reported in Supplementary table 3b

Ferrario L et al, 2020 (22)	Activity-Based Costing, data from various stages of patient care	Single follow-up ophthalmic visit	Activity-Based Costing	NHS	None declared	Reported in Supplementary table 3b
Foglia E et al, 2017 (23)	Real-life data from clinical practice, fine-tuned with the support of clinicians using Delphi methodology	12, 24, and 36 months	Based on number of injections and additional procedures	Lombardy Regional Healthcare Service	None declared	Reported in Supplementary table 3b
Gandjour A et al, 2002 (24)	Patient charts/medical records and estimates from physician offices	From May 2000 to February 2001	Bottom-up microcosting approach using reimbursement fees as unit costs in countries with detailed fee-for-service schedule (Germany, Italy, Switzerland)	NHS	German Ministry of Health	Selection: 3/4 Comparability: 1/2 Outcome: 3/3 Total Score: 7/9
Garattini L et al, 2004 (25)	Prospective data collection using a standardized questionnaire completed by ophthalmologists	1-year follow-up of patients	Costs calculated using NHS tariffs for consultations and diagnostic tests	NHS	Novartis Ophthalmics	Selection: 3/4 Comparability: 1/2 Outcome: 3/3 Total Score: 7/9
Holmstrom S et al, 2006 (26)	RCTs and a pharmacoeconomic model	1 year	Costs of medication and ophthalmologist visits included; other costs assumed equal among alternatives	NHS	Allergan R&D Europe	Reported in Supplementary table 3b
Hommer A et al, 2008 (27)	Retrospective analysis of clinical trial data	3 months	Medication costs based on 2007 market prices inclusive of VAT Clinical visit costs from national databases	NHS	Allergan R&D Europe	Reported in Supplementary table 3b
Invernizzi A et al, 2016 (28)	Routine diabetes visits and patient interviews	1 year	Based on minimum wage of a reading center reader and depreciation of the DRS	NHS	None declared	Selection: 3/4 Comparability: 0/2 Outcome: 3/3 Total Score: 6/9
Koleva D et al, 2006 (29)	Routine clinical practice data collected by ophthalmologists using predesigned questionnaires	1-year follow-up of patients	Micro-costing study in 5 centers, direct costs, and NHS tariffs for diagnostic tests, laser, and surgical interventions	NHS	Novartis Farma and Pharmacia Italia SpA	Selection: 3/4 Comparability: 1/2 Outcome: 3/3 Total Score: 7/9
Lazzaro C et al, 2023 (30)	Clinical studies and health economic modeling	5-year horizon with a 1-year cycle	Based on a Markov model with a 5-year horizon and 1-year cycle	NHS	Santen GmbH, München, Germany	Reported in Supplementary table 3b
Lee PP et al, 2007 (31)	Retrospective chart review with data abstraction by trained researchers	Minimum of 5 years continuous follow-up	Unit costs from publicly available health resource costing, reimbursement, or tariff sources Costs to the healthcare system, not out-of-pocket expenses for patients	NHS	Allergan, Inc.	Selection: 3/4 Comparability: 1/2 Outcome: 3/3 Total Score: 7/9
Muscio A et al, 2011 (32)	National statistics, labor economics, tax authorities, and interviews with representatives of IAPB Italia Onlus	None (simulation study)	Three-stage approach: Calculation of aggregate costs, estimation of individual average costs, simulation in capital budgeting	Societal perspective	None declared	Reported in Supplementary table 3b
Perrone V et al, 2022 (33)	Administrative databases	At least 12 months to 3 years	Using DRG tariffs and Italian NHS purchase prices	NHS	Novartis Farma S.p.A.	Selection: 3/4 Comparability: 1/2 Outcome: 3/3 Total Score: 7/9
Perrone V et al, 2023 (34)	Administrative databases	From index date to end of data availability or death	Activity-Based Costing	NHS	Allergan SpA, an AbbVie company	Selection: 3/4 Comparability: 0/2 Outcome: 3/3 Total Score: 6/9

Porta M et al, 1999 (35)	Case notes, patient questionnaires, hospital records	1993-1994, follow-up until Jun 1995	Data from three diabetes clinics in Turin	NHS and patients	None declared	Selection: 3/4 Comparability: 1/2 Outcome: 3/3 Total Score: 7/9
Scarpa G et al, 2016 (36)	Primary and secondary diagnosis databases, hospitalizations, drugs, and healthcare procedures	1 year	Activity-based costing analysis andbudget impact analysis; 2015 Italian Outpatients and Hospital Admissions Reimbursement Tariffs; NHS price list	NHS	None declared	Selection: 3/4 Comparability: 0/2 Outcome: 3/3 Total Score: 6/9
Scuteri D et al, 2019 (37)	Ophthalmology ward database	January 2014 to June 2017	Based on the number of ranibizumab injections	NHS	None declared	Selection: 3/4 Comparability: 0/2 Outcome: 3/3 Total Score: 6/9
Traverso CE et al, 2005 (38)	Retrospective chart review	Minimum 5 years	Unit costs from national sources: France (PMSI), Germany (EBM and GOA), Italy (CEIS), UK (NHS costing manual)	NHS	Allergan Inc.	Selection: 3/4 Comparability: 1/2 Outcome: 3/3 Total Score: 7/9

AIFA: Agenzia Italiana del Farmaco; anti-VEGF (Anti-Vascular Endothelial Growth Factor; NHS: National Health Service; RCT: Randomized Controlled Trial; IMS Health: Information Medical Statistics Health; UK-GPRD: United Kingdom General Practice Research Database; VAT: Value-Added Tax; DRS: Diabetic Retinopathy Study; DRG: Diagnosis-Related Group; IAPB Italia Onlus: International Agency for the Prevention of Blindness, Italian branch; PMSI: Programme de Médicalisation des Systèmes d'Information (France); EBM: Einheitlicher Bewertungsmaßstab (Germany); GOA: Gebührenordnung für Ärzte (Germany); CEIS: Centro di Economia Internazionale e Sviluppo (Italy).

bimatoprost, which, although more cost-effective over time compared to surgery, still represents a significant ongoing expense (27). Furthermore, managing complications, such as stent obstruction, adds additional financial burden, with costs reported at €1,522 per incident (21). Notably, the analysis revealed a clear correlation between increasing disease severity and rising costs, particularly in advanced stages where the need for frequent hospitalizations and complex treatments drives expenses upwards to €1,054.9 annually (29). Results are summarized in Table 3.

Diabetic retinopathy

Direct costs for DR include all diagnostic tests for detecting the disease, follow-up costs, and medical therapies to control and prevent progression, including laser therapy. Early diagnosis significantly impacts cost estimates, with screening campaign costs relatively low but potentially influencing future avoidable costs (ranging between Italian Lira (ItL) 64,857 and 86,044) (35). Screening programs conducted within specialized diabetes clinics were notably more cost-effective compared to those involving external ophthalmologists, with standardized costs per 1,000 screenings ranging from ItL 65,916 to ItL 81,545, depending on the center (35). The implementation of fundus photography screening, at €4.45 per session, proved to be a cost-saving alternative to standard funduscopic examination (€7.90 per session), thereby enhancing screening efficiency and reach (28). Including cost-effectiveness analyses of screening interventions in this review highlights the crucial role of prevention in the overall management of DR. Screening programs not only help improve patient health by enabling early intervention but also yield substantial financial benefits by averting the progression to severe stages of the disease, which would incur higher treatment costs. For instance, comprehensive screening programs significantly outperformed the "do nothing" strategy, yielding savings of €271,543.32 (–13.71%) by reducing the incidence of blindness and associated healthcare costs (36). Treatment with Anti-Vascular Endothelial Growth Factor (anti-VEGF) agents, particularly ranibizumab, represented a major cost driver, with per-patient annual costs decreasing from €5,799.84 in 2014 to €4,050.00 in 2017, reflecting reduced treatment frequencies (37) .

Age-related macular degeneration

Direct costs for AMD include expenses for ophthalmological visits, in-depth ocular exams (e.g.,

Table 3 - Summary of the main results for each included study

Disease Type	Author and Year	Cost Breakdown	Sensitivity Analysis	Average cost per patient
AMD	Albrecht M et al, 2018	Drug costs and injections	Monocentric design limits generalizability: differences in approval times may affect treatment	AMD: €2,787-2,899, DME: €3,010-3,231
	Bandello F et al, 2008	Medical costs (Consultations, Examinations, Hospitalizations, Medications, Treatments), Non-medical costs (Visual aids/services, Paid assistance, Transportation)	Costs vary significantly by severity level	€3,001.50 (Total Costs); Range: Level 1: €1,399.20 – Level 4: €3,973.30
	Denti C et al, 2002	Medical costs, non-medical costs	NA	€33,371 - €968,060 (depending on the scenario)
	Foglia E et al, 2017	Drug costs, diagnostic tests, specialist visits, procedure costs for injections	Various retreatment rates and market shares analyzed	First Year: €1,562 (Bevacizumab) – €4,276 (Aflibercept); Over 36 months: €7,042 (Dexamethasone)
	Garattini L et al, 2004	Specialist consultations, diagnostic procedures, hospitalizations, laser therapy, medications	NA	Drusen: €158.1; Geographic atrophy: €147.9; CNV: €540.1
	Muscio A et al, 2011	Healthcare costs for screening and treatment vary depending on disability progression	Simulation: varying disability levels	Scenario 1: €871.41 (glaucoma), €1,169.04 (AMD), €291.53 (diabetic retinopathy), €1,575.16 (cataracts)
	Perrone V et al, 2022	Drug prescriptions; hospitalizations; outpatient specialist services; diagnostic tests	NA	2014: €5799.84; 2015: €3284.01; 2016: €3212.84
	Scuteri D et al, 2019	Intravitreal injections, drug costs, procedure costs	NA	2014: €5,799.84; 2015: €5,388.77; 2016: €4,759.56; 2017: €4,050.00
DR	Gandjour A et al, 2002	Preventive care for Type 2 diabetes	NA	€282.50 (5 years)
	Invernizzi A et al, 2016	Fundus photography, standard funduscopic exam	NA	Fundus Photography: €4.45 per session; Standard Funduscopic Exam: €7.90 per session
	Porta M et al, 1999	Screening costs, total costs of treated patients	Sensitivity to prevalence and cost structure	Screening: €64,857 – €86,044 (ItL per person/year); Treated patients: €1,131,594 – €1,879,827 (ItL/year)
	Scarpa G et al, 2016	Screening Phases, Ranibizumab + Laser Therapy, Dexamethasone	Variation in screening attendance and examination rates	NA

Glaucoma	Christensen TL et al, 2005	Visit to ophthalmologist, filtration surgery, beta-blocker, bimatoprost	Transition probabilities, varying time horizons	After 1 year: €3,566 (surgical) vs. €1,576 (bimatoprost); After 4 years: Bimatoprost costs 19.6% less than surgery
	De Natale R et al, 2011	Medication and treatment persistence	NA	NA
	Fea AM et al, 2021	Surgeries, medications, adverse events	One-way deterministic and probabilistic sensitivity analyses performed	iStent inject® + Cataract Surgery Group: €8,368.51 per patient per year; Cataract Surgery Alone Group: €7,134.71 per patient per year
	Ferrario L et al, 2020	XEN Gel Stent Surgery, day hospital, trabeculectomy	NA	XEN Gel Stent Surgery: €2,297.99; Day Hospital: €1,653.59; Trabeculectomy: €1,236.44
	Gandjour A et al, 2002	Preventive care for Type 2 diabetes	NA	€282.50 (5 years)
	Holmstrom S et al, 2006	Medication costs, ophthalmologist visit	Results robust across ±10% variation	€284.34 per year (Timolol + Bimatoprost)
	Hommer A et al, 2008	Medications per month, ophthalmologist visits	Varying discontinuation rates, medication unit costs	€116.66 (BT or TT) -€119.36 (LT) for 3 months
	Koleva D et al, 2006	Drugs, ophthalmologic consultations, diagnostic tests, hospital admissions	NA	€572 (Ocular Hypertension) - €1,054.9 (Advanced Glaucoma)
	Lazzaro C et al, 2023	Drug costs, diagnosis, follow-up, management, health states over 5 years	One-way, Probabilistic and scenario sensitivity analyses	+€57.60 over 5 years (STN1013001 vs. Latanoprost)
	Lee PP et al, 2007	Surgery vs. non-surgery; medication vs. no medication	NA	€2,943.83 per year (all stages of glaucoma)
	Perrone V et al, 2023	Drug expenditure, hospitalizations, outpatient services	One-way, probabilistic, and scenario-based sensitivity analyses	Costs from 2010 to 2021: €1,725 (2010) - €1,950 (2021)
	Traverso CE et al, 2005	Office visits, glaucoma exams, visual fields, glaucoma surgeries, cataract extractions, medications	NA	Stage 0: €153; Stage 1: €386; Stage 2: €421; Stage 3: €669; Stage 4: €791; Stage 5: €712

AMD: Age-related Macular Degeneration; DME: Diabetic Macular Edema; NA: Not Applicable

angiography), hospitalization, emergency room visits, and specific therapies (photocoagulation, photodynamic therapy, and innovative drugs). The annual per-patient costs reflect the intensity of care required, showing a 4% increase from 2014 to 2015, primarily driven by the frequency of intravitreal injections, which averaged approximately four per patient per year (16). The severity of AMD is a critical determinant of cost, as highlighted by Bandello et al (17), where annual costs range significantly from €1,399.2 for less severe cases to €3,973.3 for advanced stages, indicating that disease progression substantially inflates healthcare expenditures. Direct medical costs, particularly for hospitalizations, surgeries, and laser therapies, represent the bulk of the expenses, with surgical cases incurring costs as high as €2,843.10 per patient (20). Choroidal Neovascularization (CNV) further exacerbates costs, with associated annual expenses reaching €540.1 per patient, underscoring the financial impact of this complication (25). Additionally, economic models suggest that without effective blindness prevention strategies, the total annual costs for AMD could escalate significantly, potentially reaching €24,741.13 per patient in cases of total disability (32). Pharmacological management, particularly with anti-VEGF therapies such as ranibizumab, constitutes a substantial part of these costs. However, a reduction in treatment frequency has been linked to a decrease in per-patient costs, from €5,799.84 in 2014 to €4,050.00 in 2017, indicating the potential for cost savings with optimized treatment protocols (37) .

Denti et al (20) separately evaluated private healthcare costs in macular degeneration (out-of-pocket costs for private visits and over-the-counter medications), with annual private visit expenses averaging €29.90 (14% of the total) and medications at €8.60 (4.1% of the total). Garattini et al. (25) estimated the average annual private expenditure for a macular degeneration patient at €51.70. Results are summarized in Table 3.

Non-medical costs and indirect costs

Non-medical costs for all pathologies were analyzed by two studies, including expenses for visual aid devices, insurance assistance, housing adaptation, transportation, and social assistance.

Bandello et al (17) provided a comprehensive analysis of both medical and non-medical expenses, demonstrating the escalating financial impact as the disease progresses. Non-medical costs refer to expenses incurred by patients that are not directly related to medical treatments. These costs include out-of-pocket expenses for vision aids, transportation, and support services. Notably, the study revealed that non-medical costs, such as those associated with social security and other out-of-pocket expenses, varied markedly with disease severity. For instance, patients with better visual acuity (Best Eye (BE) ≥20/40) incurred non-medical costs up to €1,745.10, contributing to a total annual cost of €3,761.90 per patient. In contrast, in more advanced stages (BE <20/40, Worst Eye (WE) <20/200), non-medical costs were slightly lower at €1,539.30, yet the total annual cost per patient reached €3,973.30. This suggests that while non-medical costs may decrease slightly in later stages, the overall financial burden remains high, due to the increasing medical costs.

Muscio et al (32) further expanded on this by simulating the broader economic impact of AMD through various hypothetical scenarios, particularly focusing on the costs associated with the absence of effective blindness prevention programs. Their findings indicated that as AMD progresses, the non-medical costs and indirect costs - including social security payments, tax allowances, and productivity losses - can escalate significantly. In a scenario of partial disability, the total indirect costs were calculated to be €24,741.13 annually, with substantial contributions from social security expenses and productivity losses. This analysis underscores the critical role of indirect costs in the overall economic assessment of AMD, highlighting the necessity for comprehensive management strategies that address both direct and indirect financial impacts. Table 3 provides a summary of the results from the analysis.

Studies' quality assessment

The quality assessment of the studies reviewed indicates a generally robust methodological approach. Overall, the total scores ranged from 5 to 7 (out of 9 maximum points), with 9 studies (16,17,19,22,23,28,34,36,37) scoring 6 and 11 studies (18,20,24–27,29,31,33,35,38) achieving 7 points, suggesting that, while most of the studies had solid methodological quality, there is room for improvement in comparability and selection criteria.

Most of the studies (20 out of 23) (16–20,22–29,31,33–38) got a good rating for how participants were selected, scoring 3 out of 4. However, the scores for how well the studies handled confounding factors varied more. Half of the studies (10 studies) didn't

control for these factors well and scored 0 out of 2 (16,17,19,22,23,28,30,34,36,37), while the other half (12 studies) did a better job and scored 1 out of 2(18,20,21,24–27,29,31,33,35,38). The Outcome Score was consistently high, with all 23 studies receiving 3 out of 3, demonstrating strong and reliable outcome measurements. Results of quality assessment are reported in Table 2.

Discussion

Main Results

This systematic review aimed to evaluate the economic burden of three major ocular diseases: glaucoma, diabetic retinopathy, and age-related macular degeneration. The review included a total of 23 studies. Our findings underscore the significant variability in direct, indirect and non-medical costs associated with these conditions, influenced primarily by disease severity, treatment modalities, and the healthcare settings in which patients are managed. These findings underscore the complex economic burden that these ocular diseases impose on the Italian NHS and highlight critical areas where targeted interventions could potentially yield significant cost savings.

Most of the studies were conducted between 2000 and 2010, primarily in northern Italian regions (Piedmont, Lombardy, and Veneto). Despite this heterogeneity, costs ranged from approximately €788.7 per year (29) (direct costs for managing early-stage uncomplicated glaucoma) to €24,741.13 per year (32) (including both direct and indirect costs for diabetic retinopathy with visual disability).

Due to the significant variability in cost estimates, diagnostic methods, and therapeutic approaches among the included studies, calculating an average cost for the three conditions is methodologically unreliable. Consequently, any average cost evaluation would likely be an oversimplification, and the interpretation of these data should be cautious. The only reliable comprehensive costs derived were those for individual conditions or blindness, a common outcome of all three diseases.

The analysis of glaucoma-related costs highlighted substantial variability, with annual direct costs ranging from approximately €788.70 (29) for early-stage glaucoma to over €8,368.51 (21) for advanced cases requiring surgical interventions. Surgical procedures, particularly trabeculectomy and filtration surgery, are identified as major cost drivers, with individual surgeries costing up to €2,121(18). Additionally, medication costs, especially for drugs like Bimatoprost, represent a significant ongoing financial burden, although they may be more cost-effective in the long run compared to surgical options (18). This finding is consistent with other studies (38–40) that have documented the high costs associated with long-term medication use in glaucoma management. The variability in costs also reflects the diversity of treatment regimens and the progression rates of the disease. The clear correlation between increasing disease severity and rising costs emphasizes the importance of early intervention and effective disease management strategies to minimize the economic impact (17,32,38). Effective cost management strategies should focus on optimizing pharmacological therapies and considering the cost-benefit ratio of early surgical interventions.

For DR, the direct costs are a significant component of the overall expenses for managing diabetes, given its nature as a complication of the primary disease. They are predominantly linked to diagnostic tests, ongoing monitoring, and treatment interventions such as laser therapy. Early diagnosis and regular screening play crucial roles in mitigating these costs by preventing the progression of the disease. The costs associated with anti-VEGF treatments, particularly ranibizumab, have been shown to decrease over time, reflecting reduced treatment frequencies and improved management protocols (37). Despite these reductions, the treatment of DR remains a significant financial burden on the healthcare system, underscoring the need for cost-effective preventive measures. Indeed, the cost of screening programs for DR is relatively low compared to the long-term costs associated with disease progression. Several studies from the dataset provide valuable insights into the economic benefits of early detection. The standardized costs for 1,000 screenings ranged from ItL 65,916 to ItL 81,545, depending on the center, illustrating the economic advantage of centralized, specialized care in comparison to external ophthalmologists. In terms of screening technologies, fundus photography, priced at €4.45 per session, emerged as a cost-saving alternative to traditional funduscopic exams, which cost €7.90 per session.

Regarding glaucoma, Christensen *et al* (18) conducted a cost-minimization analysis at a national level in Italy, showing that early intervention through screening can be highly cost-effective, particularly in specialized diabetes clinics. In particular, De Natale *et al* (19) found that implementing systematic screening

could reduce healthcare costs by €271,543.32 (a 13.71% reduction), primarily by decreasing the incidence of blindness and the high costs associated with late-stage disease management. These findings strongly support the prioritization of early detection programs for both DR and glaucoma. In summary, the data from the included studies illustrate that investing in early screening programs, especially those utilizing cost-effective methods like fundus photography, can lead to substantial long-term savings. Policymakers should focus on expanding such programs to achieve both economic benefits and improved patient outcomes by preventing the progression of diabetic retinopathy and its associated complications.

Similar results for AMD were found by Denti *et al* (20), who analysed the direct costs of ocular pathologies in Italy, suggesting that the introduction of more efficient screening methods could significantly reduce overall screening costs, while extending the reach of preventive care. Moreover, comprehensive screening programs have been shown to yield significant cost savings over a "do nothing" approach. Annual per-patient costs have been observed to increase from €2,787 to €2,899 (16) with the frequency of intravitreal injections being a significant factor. Advanced stages of AMD, particularly those involving CNV, are associated with markedly higher costs, reaching up to €3,973.3 (17) per patient annually. The financial impact of AMD is further exacerbated by the high costs of hospitalizations, surgeries, and specialized treatments such as laser therapies. The findings suggest that while the introduction of anti-VEGF therapies has provided a means of managing the disease, the overall cost burden remains substantial, particularly in advanced stages of AMD.

No data are available in the literature for the average cost per patient for the three conditions combined, making such evaluations impossible. The only available data pertain to the aggregated annual costs for "Diseases of Social Importance" (as defined by the World Health Organization (WHO) in 2006, including cataracts) in Italy, estimated by Muscio *et al* (32). This study calculated indirect costs from social security benefits, mobility subsidies, civil service assistance, and productivity loss, amounting to approximately €6.48 billion annually. This includes 44% for medical care (direct costs), 16% for social security subsidies, 2% for tax deductions, 1% for education costs, 5% for other benefits, and 32% for productivity loss.

The review also revealed considerable non-medical costs associated with all the three ocular diseases, encompassing expenses for visual aids, insurance assistance, housing adaptations, transportation, and social aids. Two key studies (17,32) provide insights into these costs, particularly for AMD, approaching from different perspectives and methodologies. Bandello *et al* (17) demonstrated that non-medical costs vary significantly with disease severity, with total annual costs per patient ranging from €3,761.9 to €3,973.3, depending on the stage of AMD. Muscio *et al*.'s (32) simulation study emphasizes the potential for significant increases in indirect costs as the disease progresses to more severe stages. The scenarios they modelled demonstrate how, in the absence of effective preventive measures, indirect costs such as social security payments and productivity losses could escalate dramatically, especially in cases of partial or total disability. The study estimated that total indirect costs could reach as high as €24,741.13 annually in cases of total disability, driven primarily by social security payments and productivity losses. These findings underscore the importance of considering both direct and indirect costs in the economic assessment of ocular diseases, as the latter can substantially contribute to the overall financial burden. Addressing these costs requires a comprehensive approach that includes support for visual aids, social services, and workplace adaptations to maintain productivity and quality of life for affected individuals.

The studies included in this review cover a wide temporal range, each reflecting different healthcare policies, diagnostic technologies, and economic contexts relevant to their specific periods. Attempting to harmonize or adjust these costs to a common base year would risk losing the nuances and temporal trends inherent to each study.

Interpretation of results, practical implications, future research

The management of glaucoma, DR, and AMD in Italy largely aligns with protocols established across the entire European Union. A detailed overview of approved medications and treatment strategies, reported in Supplementary Table 3, highlights the reliance on long-term treatments such as topical eye drops for glaucoma (e.g., Bimatoprost, Latanoprost, Timolol) and anti-VEGF agents for DR and AMD (e.g., Ranibizumab, Aflibercept, Bevacizumab). These therapies, while effective, require sustained administration and frequent monitoring, contributing significantly to the direct medical costs, particularly in outpatient settings. The introduction of newer agents such as Brolucizumab (Beovu) and Faricimab

(Vabysmo) for AMD reflects advancements in treatment options, potentially impacting both the costs and frequency of treatments due to varying maintenance phases. Additionally, therapies like Verteporfin (Visudyne) used in photodynamic therapy for specific AMD subtypes offer distinct approaches that may influence cost structures due to their combination of intravenous drug administration and laser activation, demanding specialized care.

Given that these chronic conditions require long-term treatment, the cumulative cost of care—both direct (e.g., medication, monitoring) and indirect (e.g., loss of productivity, caregiver burden)—is substantial. This further underscore the need for healthcare systems to consider patient-specific factors such as comorbidities and the potential for more intensive outpatient monitoring, as they may increase the resource utilization and associated costs. In this perspective, European countries, the three conditions under review are considered priorities at European level (41). Epidemiologically, in 2020, an estimated 596 million people had distance vision impairment worldwide, of whom 43 million were blind. However, encouragingly, more than 90% of people with vision impairment have a preventable or treatable cause with existing highly cost-effective interventions. By 2050, population ageing, growth, and urbanisation might lead to an estimated 895 million people with distance vision impairment, of whom 61 million will be blind (42). Action to prioritise eye health is needed now.

Despite the expected increase in the frequency of these conditions and associated disorders, underdiagnosis of ocular issues, particularly in the elderly, remains a significant problem, leading to blindness (32). According to INPS (Istituto nazionale della previdenza sociale, in English National Institute for Social Security) data, in 2023, there were 108, 416 blind individuals in Italy, with a markedly uneven distribution (e.g., Sicily with 14,244 blind individuals, prevalence 2.96‰; Lombardy with 12.535, prevalence 1.26‰) (43). These data refer to individuals with absolute or partial blindness (visual acuity not exceeding 1/20 in both eyes with correction) recognized by the Italian social security institution (INPS), making them eligible for pensions and allowances (44–46). Social security costs are significant because, for all three analyzed conditions, annual direct costs for disease management are substantially lower than indirect costs. Indirect costs mainly stem from social security interventions and productivity loss. Disabilities during working age significantly increase these costs, particularly for diabetic retinopathy, the leading cause of vision loss in working-age individuals in industrialized countries (ages 20-65) (47).

Regarding diabetes, WHO projects a 54% increase in cases in industrialized countries between 2000 and 2030 (48). In Italy, diabetes has been on the rise, with prevalence and incidence expected to continue increasing in those over 30 years old. Without preventive measures, diabetes and diabetic retinopathy will remain major problems in Italy and worldwide, where patient education and healthcare providers' training are crucial for risk management. Implementing secondary prevention campaigns is also highly effective in reducing costs and improving public health (28).

These primary and secondary prevention initiatives are strongly recommended (49), especially considering the Italian demographic trend, with an increasing elderly population (23.2% over 65 today, expected to reach 35% by 2050). The aging population will raise the average age from 45.7 years in 2020 to 49.7 years in 2040, alongside an increase in elderly individuals living alone, potentially increasing care needs. As demonstrated by Muscio et al. (32), early diagnosis through screening can reduce both disability risk and disease management costs, estimating a 9-34% reduction of the €4.376 billion annually spent by the Italian government on medical care, social security subsidies, tax deductions, education costs, and other benefits related to visual disability.

These findings highlight the growing economic burden posed by glaucoma, DR, and AMD in Italy. As the aging population grows, the financial strain on the NHS will intensify. Addressing these costs will require innovative healthcare strategies, particularly in preventive care and the optimization of treatment protocols to mitigate long-term expenses. Nevertheless, given the high costs associated with advanced disease stages, prioritizing early detection and preventive measures, such as regular screenings and patient education, could substantially reduce the financial burden on the NHS. Overall, the success of ocular prevention interventions depends on the availability, accessibility, affordability, and acceptability of dedicated services. Future research should focus on identifying barriers to these interventions and providing evidence on the economic burden of the reviewed conditions.

Limitations and strengths

Several limitations of this review should be considered before generalizing the results. The

included studies are heterogeneous in objectives and cost evaluation methodologies, making comparisons challenging. Many studies (57%, 13 out of 23) (17–20,24–27,29,31,32,35,38) were published before 2010 and considering medical advancements in diagnostic protocols and new therapies, the data might no longer be current. The possibility of drug price changes, inflation, and purchasing power should also be considered. Additionally, one study (35) performed before 2000 reported costs in Italian Lira or ItL instead of Euro (EUR, €). Moreover, systematic reviews are subject to several common limitations. One relevant issue is the heterogeneity of included studies, which can differ widely in design, population characteristics, and methodologies, making result comparison challenging. Additionally, publication bias may occur when studies with positive outcomes are more likely to be published, potentially skewing the review's findings. The quality of evidence can be compromised by biases present in the primary studies, and the reliance on available literature may result in the exclusion of relevant data. These limitations must be acknowledged to ensure accurate interpretation of results and informed decision-making.

However, a strength of this research lies in its rigorous methodology, allowing the inclusion of 23 studies only. In the absence of updated and specific publications on this topic in Italy, this report provides a first attempt to evaluate the direct, indirect and non-medical costs of three major causes of visual disability and blindness in industrialized countries.

Conclusions

Considering the Italian epidemiological context, with an expected increase in the frequency of the three reviewed conditions in the general and elderly populations, a similar growth in direct and indirect costs can be anticipated. The review successfully highlights a range of costs for these conditions, though it is limited in evaluating expenditure trends, as a detailed predictive analysis requires a mathematical model beyond a literature review. In the future, it will be essential for patients to have access to structured diagnostic-therapeutic pathways, ensuring early diagnosis for optimal disease management, preventing complications, disease progression to advanced stages, and the need for high-cost (surgical) treatments and visual disability.

Riassunto

I costi sanitari diretti e indiretti delle malattie oculari in Italia: una revisione della letteratura su glaucoma, retinopatia diabetica e degenerazione maculare

Background. Il glaucoma, la retinopatia diabetica e la degenerazione maculare legata all'età impongono sostanziali oneri economici ai sistemi sanitari a causa della loro elevata prevalenza e natura cronica. Tuttavia, dati italiani complessivi sono attualmente limitati. Questo studio si propone di analizzare in modo approfondito i dati disponibili sull'impatto economico di queste condizioni, al fine di supportare una pianificazione sanitaria più efficiente ed efficace.

Disegno dello studio. Revisione sistematica.

Metodi. È stata effettuata una ricerca sistematica della letteratura in conformità alle linee guida PRISMA, utilizzando i database PubMed, Scopus, Web of Science ed EMBASE. Sono stati inclusi studi che riportavano valutazioni economiche nella gestione del glaucoma, della retinopatia diabetica e della degenerazione maculare legata all'età in Italia, considerando sia i costi diretti sia quelli indiretti.

Risultati. La revisione ha incluso 23 studi che mostrano una notevole eterogeneità in termini di periodi temporali, aree geografiche e approcci metodologici nelle valutazioni economiche. Per il glaucoma, i costi diretti annuali variavano da €788,70 per i casi in stadio iniziale a €8.368,51 per i casi avanzati che richiedevano interventi chirurgici. I costi annuali associati alla retinopatia diabetica oscillavano tra €4.050 e €5.799 per paziente, in funzione della gravità della malattia e dell'approccio terapeutico adottato. L'onere finanziario della degenerazione maculare legata all'età presentava variazioni significative, con costi che andavano da €1.399,20 per i casi in stadio iniziale a €3.973,30 per gli stadi avanzati. Sebbene i costi indiretti, come la perdita di produttività e le spese di assistenza, siano stati meno frequentemente valutati, essi rappresentano comunque un contributo rilevante al carico economico totale.

Conclusioni. Questo studio evidenzia il considerevole onere economico che le patologie oculari impongono al sistema sanitario italiano. L'implementazione di interventi precoci e strategie preventive potrebbe ridurre i costi a lungo termine nella gestione della retinopatia diabetica e della degenerazione maculare legata all'età. Sono necessarie ulteriori ricerche sui costi indiretti e su interventi costo-efficaci per supportare un'allocazione più efficiente delle risorse sanitarie.

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Supplementary table 1 - Full search strategy developed for each database.

Database	Search strategy	Number of retrieved records
PubMed/MEDLINE	("Glaucoma"[MeSH Terms] OR "Retinal Diseases"[MeSH Terms] OR "Macular Degeneration"[MeSH Terms] OR "Glaucomas"[Title/Abstract] OR "Maculopathy"[Title/Abstract] OR "Maculopathies"[Title/Abstract] OR "Eye Diseases"[MeSH Terms] OR "Blindness"[Mesh] OR "Blindness"[Title/Abstract]) AND ("Cost of Illness"[MeSH Terms] OR "Health Care Costs"[MeSH Terms] OR "Health Expenditures"[MeSH Terms] OR "Direct Service Costs"[MeSH Terms] OR "Costs and Cost Analysis"[MeSH Terms] OR "Costs"[Title/Abstract] OR "Cost"[Title/Abstract]) AND ("Italy"[MeSH Terms] OR "Italy"[Title/Abstract])	77
Scopus	(TITLE-ABS-KEY(Glaucoma OR "Retinal Diseases" OR "Macular Degeneration" OR "Maculopathy" OR "Maculopathies" OR "Eye Diseases" OR "Blindness")) AND (TITLE-ABS-KEY(cost OR costs)) AND (TITLE-ABS-KEY(Italy))	80
EMBASE	'cost'/exp OR cost:ti OR cost:ab OR 'cost benefit analysis'/exp OR 'cost benefit analysis':ti OR 'cost benefit analysis':ab OR 'health care cost'/exp OR 'health care cost':ti OR 'health care cost':ab OR 'health expenditure'/exp OR 'health expenditure':ti OR 'health expenditure':ab OR 'health care cost'/exp OR 'health care cost':ti OR 'health care cost':ab OR 'cost of illness'/exp OR 'cost of illness':ti OR 'cost of illness':ab AND 'blindness'/exp OR blindness:ti OR blindness:ab OR 'eye disease'/exp OR 'eye disease':ti OR 'macular degeneration'/exp OR 'macular degeneration':ti OR'retina disease'/exp OR 'retina disease':ti OR 'retina disease':ab OR 'glaucoma'/exp OR glaucoma:ti OR glaucoma:ab AND 'italy'/exp OR italy:ti OR italy:ab	204

Supplementary table 2 - Eligibility criteria defined according to PEOS framework: Population (P), Exposure (E), Outcome (O), and Study design (S).

PECOS framework	Inclusion criteria
Population (P),	Subjects of any age affected by glaucoma, diabetic retinopathy, or macular degeneration
Exposure (E)	Any of the three conditions (glaucoma, diabetic retinopathy, and macular degeneration)
Outcome (O)	Healthcare costs (direct and indirect) of the disease
Study design (S)	Observational studies (cohort, case-control, cross-sectional), trials, and economic evaluations using simulation models or administrative databases
Language	English and Italian
Time filter	Last 20 years
	Exclusion criteria
Population (P),	Subjects not affected by glaucoma, diabetic retinopathy, or macular degeneration
Exposure (E)	Anything other than glaucoma, diabetic retinopathy, or macular degeneration
Outcome (O)	Anything not related to direct and indirect costs
Study design (S)	Not original (reviews with or without meta-analysis), not performed among humans, book, book chapter, thesis, no full-text papers (abstract, conference paper, letter, commentary, note)

Supplementary table 3a - ISPOR Good Research Practices assessment.

Study	ISPOR Domain	Assessment
De Natale et al.	Data Sources and Study Design	Partially Adequate
	Transparency of Data Handling	Partially Adequate
	Confounding and Bias Control	Partially Adequate
	Analytic Methods	Partially Adequate
	Contextual Relevance	Adequate

Supplementary table 3b - CHEERS checklist assessment.

Study	Title and Abstract	Background and Objectives	Target Population and Setting	Perspective of Analysis	Comparators	Time Horizon	Discount Rate	Sensitivity Analysis
Christensen et al.	Adequate	Adequate	Partially Adequate	Adequate	Partially Adequate	Partially Adequate	Partially Adequate	Adequate
Fea et al.	Adequate	Adequate	Partially Adequate	Adequate	Partially Adequate	Partially Adequate	Partially Adequate	Adequate
Ferrario et al.	Adequate	Adequate	Partially Adequate	Adequate	Partially Adequate	Partially Adequate	Partially Adequate	Adequate
Foglia E et al	Adequate	Adequate	Adequate	Adequate	Partially Adequate	Partially Adequate	Adequate	Partially Adequate
Holmstrom S et al	Adequate	Adequate	Partially Adequate	Adequate	Partially Adequate	Partially Adequate	Partially Adequate	Adequate
Hommer A et al	Adequate	Adequate	Partially Adequate	Adequate	Partially Adequate	Partially Adequate	Partially Adequate	Adequate
Lazzaro C et al	Adequate	Adequate	Partially Adequate	Adequate	Partially Adequate	Partially Adequate	Partially Adequate	Adequate
Muscio A et al	Adequate	Adequate	Partially Adequate	Adequate	Adequate	Partially Adequate	Partially Adequate	Adequate

Supplementary table 4 - Approved medications and treatment protocols for Glaucoma, DR and AMD in the European Union.

Disease	Drug Name (Commercial Name)	Mode of Administration and Dosing	Duration of Use	Countries Approved	Usage Limitations (Age, Sex, Comorbidities)
Glaucoma	Bimatoprost (Lumigan)	Topical eye drops, 1 drop in the affected eye(s) once daily in the evening	Long-term	Approved in all EU countries	Not recommended for children under 18 years, caution in patients with a history of macular edema, iritis/uveitis, or aphakia
	Latanoprost (Xalatan)	Topical eye drops, 1 drop in the affected eye(s) once daily in the evening	Long-term	Approved in all EU countries	Not recommended for children under 18 years, caution in patients with severe asthma or in aphakic patients
	Travoprost (Travatan)	Topical eye drops, 1 drop in the affected eye(s) once daily in the evening	Long-term	Approved in all EU countries	Not recommended for children under 18 years, caution in patients with aphakia, pseudophakia with torn posterior lens capsule, or anterior chamber lenses
	Timolol (Timoptic)	Topical eye drops, 1 drop in the affected eye(s) twice daily	Long-term	Approved in all EU countries	Contraindicated in patients with bronchial asthma, severe COPD, sinus bradycardia, AV block, or overt heart failure
	Dorzolamide (Trusopt)	Topical eye drops, 1 drop in the affected eye(s) two to three times daily	Long-term	Approved in al EU countries	Contraindicated in patients with severe renal impairment, hyperchloremic acidosis; not recommended for children under 18 years
	Brinzolamide (Azopt)	Topical eye drops, 1 drop in the affected eye(s) twice daily	Long-term	Approved in all EU countries	Contraindicated in patients with severe renal impairment; not recommended for children under 18 years
	Brimonidine (Alphagan)	Topical eye drops, 1 drop in the affected eye(s) twice daily	Long-term	Approved in all EU countries	Contraindicated in children under 2 years; caution in patients with severe cardiovascular disease or depression
Diabetic etinopathy	Ranibizumab (Lucentis)	Intravitreal injection, 0.5 mg (0.05 mL) into the vitreous cavity once a month for three months, then as needed	Long-term	Approved in all EU countries	Contraindicated in ocular or periocular infections, active intraocular inflammation, known hypersensitivity to ranibizumab
	Aflibercept (Eylea)	Intravitreal injection, 2 mg (0.05 mL) into the vitreous cavity once a month for five months, then every two months	Long-term	Approved in all EU countries	Contraindicated in ocular or periocular infections, active intraocular inflammation, known hypersensitivity to aflibercept
	Bevacizumab (Avastin)	Intravitreal injection, 1.25 mg (0.05 mL) into the vitreous cavity as needed, typically once a month	Long-term	Approved for other indications in all EU countries, used off-label for DR	Contraindicated in ocular or periocular infections, active intraocular inflammation, known hypersensitivity to bevacizumab
	Dexamethasone implant (Ozurdex)	Intravitreal implant, 0.7 mg implant injected into the vitreous cavity, typically every 6 months or as needed	Long-term	Approved in all EU countries	Contraindicated in active ocular infections, advanced glaucoma, aphakia with ruptured posterior lens capsule, or hypersensitivity to dexamethasone
	Brolucizumab (Beovu)	Intravitreal injection, 6 mg (0.05 mL) into the vitreous cavity once a month for three months, then every 8-12 weeks	Long-term	Approved in all EU countries	Contraindicated in ocular or periocular infections, active intraocular inflammation, known hypersensitivity to brolucizumab; caution in patients with a history of intraocular inflammation
	Faricimab (Vabysmo)	Intravitreal injection, 6 mg (0.05 mL) into the vitreous cavity every 4 weeks for the first 4 doses, then every 8-16 weeks depending on disease activity	Long-term	Approved in all EU countries	Contraindicated in ocular or periocular infections, active intraocular inflammation, known hypersensitivity to faricimab

Age-Related Macular Degeneration	Ranibizumab (Lucentis)	Intravitreal injection, 0.5 mg (0.05 mL) into the vitreous cavity once a month, then as needed after three initial monthly doses	Long-term	Approved in all EU countries	Contraindicated in ocular or periocular infections, active intraocular inflammation, known hypersensitivity to ranibizumab
	Aflibercept (Eylea)	Intravitreal injection, 2 mg (0.05 mL) into the vitreous cavity once a month for three months, then every two months	Long-term	Approved in all EU countries	Contraindicated in ocular or periocular infections, active intraocular inflammation, known hypersensitivity to aflibercept
	Bevacizumab (Avastin)	Intravitreal injection, 1.25 mg (0.05 mL) into the vitreous cavity as needed, typically once a month	Long-term	Approved for other indications in all EU countries, used off-label for AMD	Contraindicated in ocular or periocular infections, active intraocular inflammation, known hypersensitivity to bevacizumab
	Verteporfin (Visudyne)	Intravenous injection followed by laser activation, typically one-time treatment, can be repeated if necessary	Short-term/ Long-term	Approved in all EU countries	Not recommended for patients with porphyria or severe hepatic impairment; avoid exposure to sunlight or bright indoor light for 48 hours after treatment
	Brolucizumab (Beovu)	Intravitreal injection, 6 mg (0.05 mL) into the vitreous cavity once a month for three months, then every 8-12 weeks	Long-term	Approved in all EU countries	Contraindicated in ocular or periocular infections, active intraocular inflammation, known hypersensitivity to brolucizumab; caution in patients with a history of intraocular inflammation
	Faricimab (Vabysmo)	Intravitreal injection, 6 mg (0.05 mL) into the vitreous cavity every 4 weeks for the first 4 doses, then every 8-16 weeks depending on disease activity	Long-term	Approved in all EU countries	Contraindicated in ocular or periocular infections, active intraocular inflammation, known hypersensitivity to faricimab