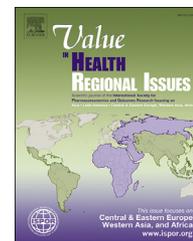




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Policy Perspective

The Burden of Macular Diseases in Central and Eastern Europe—Implications for Healthcare Systems

Polona Jaki Mekjavić, MD, PhD ^{1,2,*}, Vilma Jūratė Balčiūnienė, MD, PhD ³, Lala Čeklić, MD, PhD ⁴, Jan Ernest, MD, PhD ⁵, Zuzana Jamrichova, MD ⁶, Zoltán Zsolt Nagy, MD, Med.Habil, DSc, FEBO ^{7,8}, Iva Petkova, MD ⁹, Sławomir Teper, MD, PhD ¹⁰, Ivana Gardašević Topčić, MD, PhD ¹¹, Miroslav Veith, MD ¹²

¹Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia; ²Eye Hospital, University Medical Centre Ljubljana, Ljubljana, Slovenia; ³Eye Clinic, Lithuanian University of Health Sciences, Kaunas, Lithuania; ⁴Ministry of Health of Republic of Srpska, Barja Luka, Bosnia and Herzegovina; ⁵Central Military Hospital, Prague, Czech Republic; ⁶Faculty Hospital Bratislava, Bratislava, Slovakia; ⁷Department of Ophthalmology, Semmelweis University, Budapest, Hungary; ⁸Department of Clinical Ophthalmology, Faculty of Health Sciences, Semmelweis University, Budapest, Hungary; ⁹University Eye Hospital Sofia, Sofia, Bulgaria; ¹⁰Medical University of Silesia, Katowice, Poland; ¹¹General Hospital Novo mesto, Novo mesto, Slovenia; ¹²Faculty Hospital Kralovske Vinohrady, Prague, Czech Republic



ABSTRACT

Background: Despite the significant impact of retinal diseases such as wet age-related macular degeneration (wAMD) and diabetic macular edema (DME), there is a limited understanding of how these conditions are managed in Central and Eastern Europe (CEE). **Objectives:** To provide a comprehensive overview of the clinical and economic burden of wAMD and DME in CEE and the status quo associated with their management. **Methods:** A narrative literature review was undertaken to identify existing data on wAMD and DME, including epidemiology, economic burden, clinical guidelines, and available and reimbursed treatments. Data were collected from relevant sources such as PubMed, ophthalmology associations, national statistical offices, and government agency websites; practical viewpoints were provided by local ophthalmologists and healthcare economics experts in CEE. **Results:** Epidemiological data on wAMD and DME are limited in CEE, and intercountry comparison is difficult because of differences in data collection methodologies. There are effective treatment options for wAMD and DME, and international guidelines advocate the

use of intravitreal anti-vascular endothelial growth factor injections as first-line therapy. Local expert organizations broadly support these recommendations; nevertheless, no clinical practice guidelines exist on the treatment of wAMD and DME in CEE. Access to and reimbursement of anti-vascular endothelial growth factor agents vary significantly in the region and, as a result, many patients remain untreated or inadequately treated. **Conclusions:** There is an urgent need for the creation of a wAMD/DME treatment program in CEE to ensure that patients have timely access to the most appropriate treatments.

Keywords: age-related macular degeneration, anti-VEGF, diabetic retinopathy, health policy, indirect costs, macular edema, retinal diseases

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Introduction

Retinal diseases are the main cause of visual impairment and blindness in patients aged 50 years and older in Europe, predominantly age-related macular degeneration (AMD) and diabetic macular edema (DME).^{1,2} AMD is a chronic and degenerative eye disease caused by multiple genetic factors and aging. It can lead to

severe vision loss and legal blindness among the elderly, especially in developed countries.^{3,4} Neovascular or wet AMD (wAMD) is an advanced form of AMD. Although wAMD contributes to only 10% to 15% of the overall prevalence of AMD, it represents approximately 90% of severe vision loss caused by macular degeneration because of its rapid progression.^{3,5} If left untreated, wAMD may lead to blindness.⁶ Diabetes, one of the most prevalent

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* Address correspondence to: Polona Jaki Mekjavić, MD, PhD, Faculty of Medicine, University of Ljubljana, Vrazov trg 2, Ljubljana 1000, Slovenia.

Email: polona.jaki@guest.arnes.si

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global diseases, can lead to diabetic retinopathy (DR) and/or DME.⁷ About one-third of people with diabetes will develop DR,⁸ a third of whom will have vision-threatening DR, including DME.⁹ DME is characterized by a progression of retinal thickening from accumulated fluid in the macula, causing gradual deterioration of visual acuity and blindness.¹⁰

Treatments for wAMD and DME include laser photocoagulation, intravitreal steroids, and/or intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents. Anti-VEGF therapy has been shown to be more effective than the standard of care in preventing and reversing vision loss due to DME,¹¹ and it is fast becoming the preferred treatment in managing wAMD and DME. Despite the requirement of frequent injections and the need for continued treatment for an extended period of time in most cases, anti-VEGF therapy has improved visual outcomes in many patients.^{12,13} In Western Europe, the introduction of anti-VEGF therapy has led to a decline in the incidence of blindness due to AMD/DME.¹⁴ In Denmark, the incidence of legal blindness due to AMD in people aged 50 years and older decreased almost 2-fold (52.2 vs 25.7 cases/y/100 000 patients in 2000 and 2010, respectively), with most of these reductions taking place after the introduction of intravitreal anti-VEGF agents in 2006.¹⁴ Despite comprehensive licensing and reimbursement at a national or regional level, not all patients in Europe have equal access to anti-VEGF therapy because of large intercountry variations in approval and reimbursement policies.¹⁵ Nevertheless, compared with the economic burden of nontreatment, loss of vision and blindness may have a more significant impact on current and future costs and quality of life (QOL).

This article reviews existing literature on the availability of treatments for macular diseases; wAMD and DME management, particularly in the Central and Eastern European (CEE) region including Bosnia and Herzegovina, Bulgaria, Czech Republic, Hungary, Lithuania, Poland, Romania, Slovakia, and Slovenia; and the collaboration required between specialist clinicians, manufacturers, and payers to improve the care of this patient population.

Overview of Available Global and CEE Data

To identify existing global and CEE data on wAMD and DME, including epidemiology, economic burden, clinical guidelines, and available and reimbursed treatments, a narrative literature review was undertaken using data and evidence published in relevant medical databases such as PubMed, the Cost-Effectiveness Analysis Registry, the International Society for Pharmacoeconomics and Outcomes Research website, ophthalmology associations, national statistical offices, and government and health technology assessment agency websites of the CEE countries. Consultations with local ophthalmology, retinal disease, and healthcare economics experts provided robust and practical viewpoints.

The present study is a review article and, as such, no experimental procedures were performed. All original research articles cited in this review were published in reputable peer-reviewed international scientific journals. The authors therefore assume that the original research articles cited received approval from an ethics review board, as requested by the publishing journal.

The Clinical Burden of Macular Diseases

Epidemiological data suggest that AMD and DME prevalence is increasing because of aging populations and the increase in the number of people with diabetes.¹⁶ In 2014, 170 million people worldwide had AMD and this number is expected to rise to 196 million in 2020 and to 288 million in 2040.¹⁷ Europe is expected to

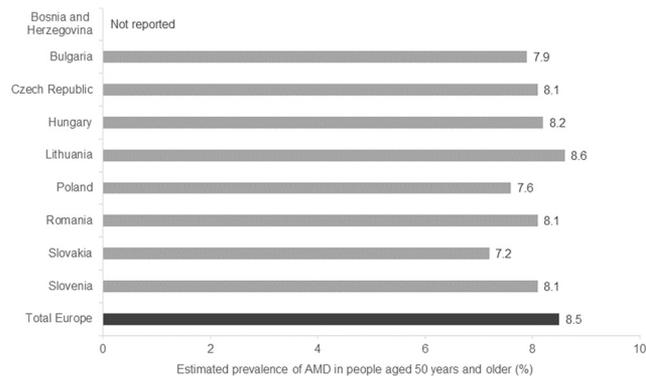


Fig. 1 – Estimated prevalence of AMD among adults aged ≥ 50 y in Central and Eastern Europe in 2016 (Shanahan¹⁸). AMD indicates age-related macular degeneration.

be the continent, behind Asia, with the highest number of estimated AMD cases.¹⁷ In the CEE region, the estimated prevalence of AMD in 2016 ranged from 7.2% in Slovakia to 8.6% in Lithuania among individuals aged 50 years and older (Fig. 1).¹⁸ Global prevalence of diabetes and DME burden are also expected to increase significantly. The International Diabetes Federation estimated that in 2015, 415 million people worldwide (aged 20–79 years) had type 1 or type 2 diabetes.¹⁹ If current trends continue, the global prevalence of diabetes will increase to 642 million by 2040.¹⁹ In Europe, 60 million people had diabetes in 2015, which is expected to rise to 71 million by 2040.¹⁹ The International Diabetes Federation has estimated that national diabetes prevalence rates vary widely among CEE countries, ranging from 5.5% in Lithuania to 12.3% in Bosnia and Herzegovina (Fig. 2).⁸

There are limited epidemiological data on wAMD and DME prevalence in the CEE region, and intercountry comparison is difficult because of differences in data-gathering methodologies. Some countries lack domestic, real-life data on wAMD and/or DME prevalence and incidence (eg, Bulgaria, Hungary, and Slovenia). The Czech Republic's nationwide registry monitors patients with AMD and DME who are treated with anti-VEGF agents. By December 2016, 8665 patients with wAMD and 388 patients with DME were registered.^{20,21} In Slovakia, an epidemiological survey involving 3278 patients found that the prevalence of wAMD in the study population was 1.0% (prevalence of AMD was 9.0%).²² In Poland, on the basis of the statistical reports for years 2009 to 2015 published by the Polish National Health Fund, DME

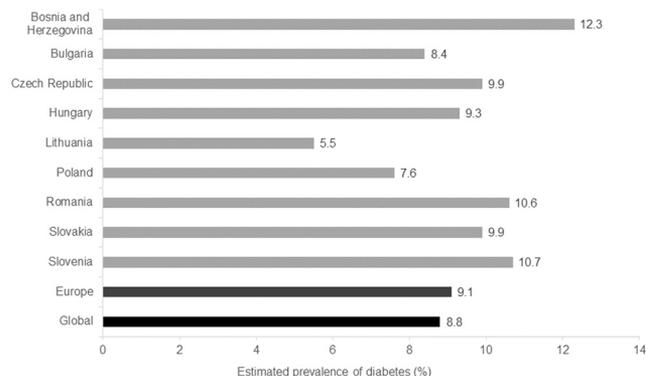
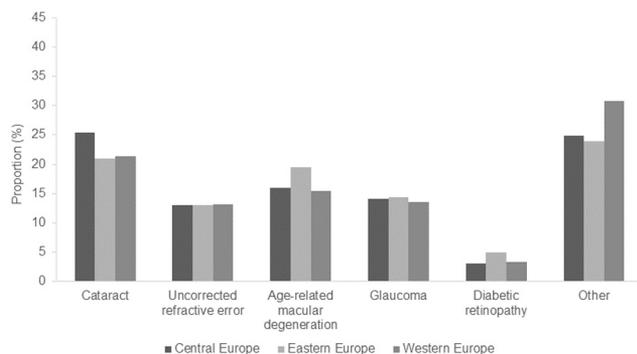


Fig. 2 – Estimated prevalence of diabetes in Central and Eastern Europe in 2015 (International Diabetes Federation¹⁹).



Countries considered part of Central Europe include Czech Republic, Hungary, Poland, Slovakia and Slovenia; countries considered part of Eastern Europe include Bosnia and Herzegovina, Bulgaria, Lithuania and Romania.

Fig. 3 – Main causes of blindness in Europe in 2015 (Flaxman et al²⁴).

prevalence was estimated to be 7.5% of the overall diabetes population.²³

Both AMD and DR are among the leading causes of vision impairment.²⁴ Blindness due to AMD is slightly higher in Eastern Europe (19.5%) than in Central and Western Europe (15.9% and 15.4%, respectively); blindness due to DR ranged from 3.1% in Central Europe and 4.9% in Eastern Europe (Fig. 3).²⁴ The impact of vision loss on patients' everyday life is also apparent. A UK survey revealed that healthy adults were more afraid of vision loss than of Alzheimer's disease, Parkinson's disease, heart disease, or using a wheelchair.²⁵ A US poll on severe vision loss/blindness in 2007 reported a more negative impact of sight loss on patient QOL than of other conditions, such as HIV, AIDS, cancer, or stroke.²⁶ Retinal diseases lead to progressive visual impairment, affecting functionality, independence, and overall QOL.²⁷ AMD causes a severity-dependent decrease in QOL, which manifests as increased social dependence, difficulty with daily living, higher rates of depression, and a greater risk of falls, premature nursing home admissions, and suicide.²⁸ A Lithuanian study showed that general vision impairment by AMD was significantly associated with mental health ($P=.020$) and role difficulties ($P=.010$), and anxiety and depression symptoms were significantly worse in those with AMD than in those without (hospital anxiety scores: 6.44 vs 3.30, respectively [$P<.0001$]; depression scores: 6.84 vs 2.50, respectively [$P<.0001$]).²⁹ Investigators observed that the negative effect of AMD on QOL was comparable with that of systemic diseases, such as cancer, ischemic heart disease, and severe stroke.²⁸

The Economic Burden of Macular Diseases

wAMD and DME pose a significant economic burden, incurring direct and indirect costs on patients, their families, healthcare systems, and society. Direct costs cover disease-related expenses and comprise medical (resources to treat a particular disease) and nonmedical costs (caused by the disease, not by the treatment).³⁰ Indirect costs cover productivity loss from absenteeism and/or presenteeism, and informal care (by family or friends).³¹ The costs associated with vision loss can be high, particularly indirect costs.³² In 2010, direct and indirect costs for vision loss worldwide were \$2.3 trillion and \$652 billion, respectively. By 2020, these are expected to rise to \$2.8 trillion and \$760 billion, respectively.^{32,33} In 2010, direct and indirect costs for visual impairment worldwide due to AMD were \$255 billion and \$88 billion, respectively.³⁴ Data from 2016 revealed that the total cost (including direct and indirect costs) of managing the consequences of severe/late-stage AMD (primarily wAMD) in the European Union was estimated to

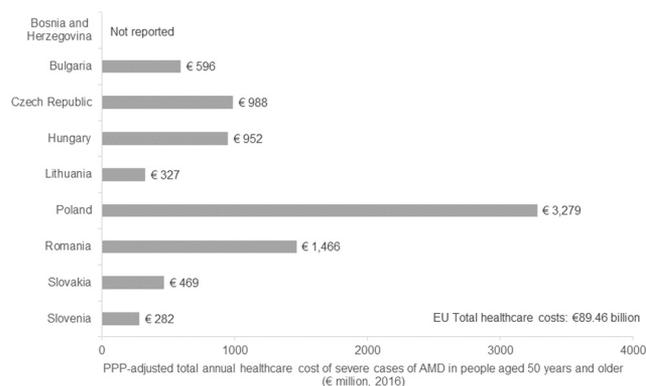


Fig. 4 – PPP-adjusted total annual healthcare cost of severe cases of AMD among adults aged ≥50 y in Central and Eastern Europe in 2016 (Shanahan¹⁸). AMD indicates age-related macular degeneration; PPP, per person per country.

be €89.46 billion per year among adults aged 50 years and older.¹⁸ In the CEE region, this cost ranged from €282 million in Slovenia to €3279 million in Poland (Fig. 4).¹⁸ Unfortunately, comparable DME data are lacking in the CEE region.

It is important to note that indirect costs (eg, absenteeism, loss of salary, part-time employment, working opportunity, and life-years) have a significant impact on patients and their caregivers. An Irish analysis of vision impairment and blindness showed that indirect costs associated with vision impairment and blindness were 70% of the total costs; 40% were due to informal care, 39% deadweight welfare (government expenditure), and 21% productivity.³⁵ A systematic review of 22 studies on the costs associated with visual impairment and blindness showed that loss of productivity and income, premature mortality, and deadweight loss were significant issues.³³ A recent analysis in Europe also revealed the substantial indirect economic burden of vision impairment and blindness, with a combined annual cost of €56.52 billion for lost productivity, on the basis of purchasing power parity-adjusted gross domestic product losses.³⁶ In 2011, the estimated total cost for the Polish National Health Fund to treat retinal diseases (AMD, DME, and retinal vein occlusion) was approximately €25 million. In the same year, indirect costs associated with AMD, DME, and retinal vein occlusion were 4 times higher (~€111 million), and included loss of productivity, informal care, and inability to work (Fig. 5).³⁷ Indirect costs are an important aspect of the total cost associated with retinal diseases and need to be considered in their entirety when assessing treatments.

Vision impairment due to wAMD or DME can be treated using anti-VEGF therapies after a long-term treat-and-extend (TER) or pro re nata (PRN) treatment regimen with frequent injections. In the authors' opinion, TER and PRN are common approaches for wAMD and DME, respectively, in the CEE region. Direct costs can be substantial, especially in the initial years after diagnosis, although it is also worth noting that both nontreatment and undertreatment can lead to blindness, disability, and loss of productivity, resulting in further economic burden to patients, the healthcare system, and society. There is a strong need to provide adequate therapies that are efficacious and cost-effective. Early treatment has the potential to prevent or reverse vision loss, improve and stabilize visual acuity, maintain QOL, and minimize economic burden associated with visual impairment. There are limited data on the cost effectiveness of early treatment in the CEE region, but early intervention with anti-VEGF therapy (or usual

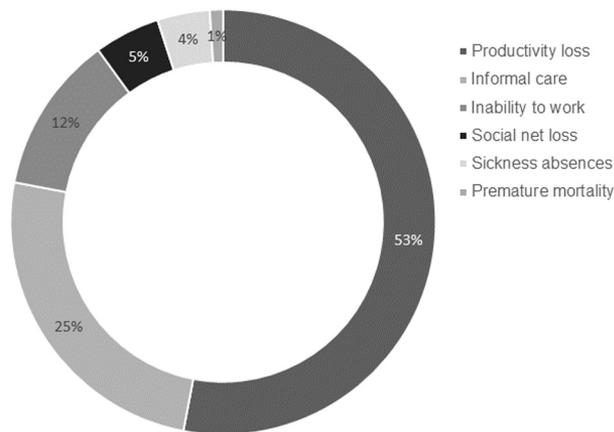


Fig. 5 – Indirect costs of AMD, DME, and retinal vein occlusion in Poland in 2011 (Polish Ophthalmological Society³⁷). AMD indicates age-related macular degeneration; DME, diabetic macular edema.

care) can be cost-effective if the treatment is priced appropriately.^{38,39} Healthcare coverage and costs are at the forefront of public debate and concern. It is important to fully understand the economic burden associated with macular diseases and the implications of undertreatment or nontreatment.

Access to Treatment

International guidelines (by the International Council of Ophthalmology and the European Society of Retina Specialists) advocate the use of intravitreal anti-VEGF injections as first-line therapy in patients with wAMD and DME.^{40–43} Current recommendations issued by local expert organizations in the CEE region (Slovenia, Bosnia and Herzegovina, Hungary, Lithuania, and Poland) broadly support these guidelines, specifically intravitreal injections of aflibercept, ranibizumab, or bevacizumab (bevacizumab: off-label use). The European Society of Retina Specialists guidelines do not recommend the use of pegaptanib, because of its lower efficacy versus other anti-VEGF agents.⁴²

In the CEE region, no clinical practice guidelines exist on the treatment of AMD and DME, despite anti-VEGF agents being increasingly included on national healthcare medicine lists. Access to and reimbursement of anti-VEGF agents vary across Europe. As a result, many patients remain untreated or inadequately treated. In the CEE region, some countries do not currently

reimburse existing or newly emerging treatments (eg, Romania), whereas others reimburse for the treatment of wAMD only (Table 1). In Poland, anti-VEGF agents are reimbursed but are limited to a single indication (wAMD) in a strictly defined target population. There are also restrictions in other countries. For example, in Bosnia and Herzegovina, bevacizumab reimbursement is limited to patients younger than 60 years old with Early Treatment Diabetic Retinopathy Study clinical standard of clinically significant macular edema affecting the fovea, with resistance to laser photocoagulation and resistance to retrolubar or intravitreal corticosteroid therapies. In the authors' opinion, the therapeutic regimen in Bosnia and Herzegovina in most cases is PRN, although some physicians report the use of TER, which is not commonly seen in practice for reimbursed patients. Experts suggest that in clinical practice in Bosnia and Herzegovina, many patients are not diagnosed promptly and remain undertreated because of financial restraints.

In addition to reimbursement, the authors have identified access barriers that include (but are not limited to) the following:

- strict patient inclusion criteria qualifying for reimbursed treatment (reimbursed indication narrowed in relation to the registered indication);
- set patient numbers for whom therapy is restricted, including limitations on therapy duration;
- treatment restricted to selected institutions;
- lack of professional staff and training; and
- lack of technical equipment for diagnosis and early detection.

Guidelines have been designed to support decision making and should be prepared in collaboration with a representative group of specialists. National evidence-based guidelines, or expert consensus statements, ensure a standardized, comprehensive, and integrated healthcare approach. Waiting times for treatment initiation also have a direct impact on therapy outcomes, and early treatment is crucial for maintaining vision. Delays in starting treatment and re-treatment, or inappropriate treatment, are associated with a progressive and irreversible decline in vision.^{44,45} Decisions on treatment access and costs allocation should be made jointly among payers, manufacturers, and specialist clinicians, in a timely manner.

Minimizing the Burden of Macular Diseases in the CEE Region: A Call to Action

Because of the rapid decline in vision, untreated or inadequately treated macular diseases have a significant impact on patients,

Table 1 – Anti-VEGF agents reimbursed in CEE countries for the treatment of wAMD or DME.

Country	Intravitreal aflibercept	Ranibizumab	Pegaptanib	Bevacizumab (off-label)
Bosnia and Herzegovina	wAMD, DME	wAMD, DME	None	wAMD, DME
Bulgaria	None	None	wAMD	None
Czech Republic	wAMD, DME	wAMD, DME	wAMD	None
Hungary	wAMD, DME	wAMD	None	None
Lithuania	wAMD, DME	wAMD, DME	None	None
Poland	wAMD	wAMD	None	wAMD
Romania	None	None	None	None
Slovakia	wAMD, DME	wAMD, DME	AMD	None
Slovenia	wAMD, DME	wAMD, DME	None	None

anti-VEGF indicates anti-vascular endothelial growth factor; CEE, Central and Eastern European; DME, diabetic macular edema; wAMD, wet age-related macular degeneration.

their caregivers, healthcare systems, and society. This influence is expected to increase as the global population ages and the prevalence of diabetes increases.¹⁶

Vision impairment due to wAMD and DME is treated using pharmacological and nonpharmacological interventions, which reduces the burden on patients and caregivers. A lack or a delay in treatment can lead to loss of vision and may have serious implications on patients, including loss of QOL and independence, social isolation, and limited employment possibilities.²⁸ As part of this review, we have shown that a lack or a delay in treatment is associated with a higher long-term cost to healthcare systems and society, which may directly affect future availability and access to new treatments.³² Anti-VEGF agents, evaluated using perspectives including and excluding indirect costs, could prove to be beneficial. Early diagnosis, monitoring, screening, and preventive blindness programs should be considered and introduced when necessary to help minimize patient burden and societal costs. Screening for AMD every 5 years (starting at age 50 years) has been associated with a 41% decrease in the total number of people with blindness.⁴⁶ There remains uncertainty about the cost effectiveness of screening for AMD or DME, but it has been shown that some screening strategies and technology can provide economic viability.^{38,46–48} Options with the potential to improve the status quo include regular screening for AMD in older people (eg, those aged >65 years), decreased screening frequency for DME in low-risk patients, and use of more portable and less expensive equipment to detect DR.^{38,48} Appropriate early diagnosis and detection approaches may also assist current healthcare systems to transition from long-term care to more effective disease prevention and management.⁴⁹

Retinal specialists play a key role in treating patients with macular diseases. They identify the most effective treatment and collaborate in clinical decisions to ensure patients have access to these treatments. It is also important for pharmaceutical manufacturers and payers to develop outcomes-based agreements and closely align price and value.⁵⁰ Healthcare payers, manufacturers, and retinal specialists need to work together to formulate decisions on treatment access and on cost and resource allocation. Education on how to evaluate costs, particularly indirect costs, should be implemented. Registry data^{20,21} and evidence-based clinical practice guidelines should be used to support decision making and to validate cost savings incurred in treating macular diseases.

Despite restricted access to anti-VEGF agents in some CEE countries, the situation is improving. Some countries reimburse anti-VEGF agents, whereas others limit them to a single indication or specific target population. Nevertheless, future reimbursement decisions may evolve to include a wider patient population and/or other indications. Countries that reimburse treatments could be used as case studies for those where some treatments are not reimbursed, encouraging payers to include these treatments on reimbursement lists. Real-life registry data, such as the Amadeus registry in the Czech Republic,^{20,21} could justify the extension to a given reimbursement population.

Overall, there is an urgent need in the CEE region to create a treatment program for wAMD and DME that includes the most effective treatments (eg, anti-VEGF agents) and encourages the best use of medical staff and the purchase of technical equipment and upgrades for screening and early detection. Retinal specialists, manufacturers, and payers should work together to decide on therapeutic access and cost allocation, ensuring patients have access to the most appropriate treatments. Once implemented, these steps may have a significant impact on the future burden of macular diseases on patients, healthcare systems, and society.

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REFERENCES

- Bourne RR, Stevens GA, White RA, et al. Causes of vision loss worldwide, 1990–2010: a systematic analysis. *Lancet Glob Health* 2013;1(6):e339–49.
- Jager RD, Mieler WF, Miller JW. Age-related macular degeneration. *N Engl J Med* 2008;358(24):2606–17.
- Shin O, Kim Y. Age-related macular degeneration (AMD): current concepts in pathogenesis and prospects for treatment. *Tissue Eng Regen Med* 2013;10(4):164–75.
- Michalska-Malécka K, Kabiesz A, Nowak M, Üpiewak D. Age related macular degeneration—challenge for future: pathogenesis and new perspectives for the treatment. *Eur Geriatr Med* 2015;6(1):69–75.
- Nowak JZ. AMD—the retinal disease with an unprecised etiopathogenesis: in search of effective therapeutics. *Acta Pol Pharm* 2014;71(6):900–16.
- Ambati J, Fowler BJ. Mechanisms of age-related macular degeneration. *Neuron* 2012;75(1):26–39.
- Stefanini FR, Badaro E, Falabella P, et al. Anti-VEGF for the management of diabetic macular edema. *J Immunol Res* 2014;2014:632307.
- International Diabetes Federation. International Diabetes Federation diabetes atlas: sixth edition. <https://www.idf.org/e-library/epidemiology-research/diabetes-atlas/19-atlas-6th-edition.html>. Accessed December 21, 2018.
- Klein R, Klein BE, Moss SE, Cruickshanks KJ. The Wisconsin Epidemiologic Study of Diabetic Retinopathy, XV: the long-term incidence of macular edema. *Ophthalmology* 1995;102(1):7–16.
- Merante D, Menchini F, Truitt KE, Bandello FM. Diabetic macular edema: correlations with available diabetes therapies—evidence across a qualitative review of published literature from MEDLINE and EMBASE. *Drug Saf* 2010;33(8):643–52.
- Boyer DS, Hopkins JJ, Sorof J, Ehrlich JS. Anti-vascular endothelial growth factor therapy for diabetic macular edema. *Ther Adv Endocrinol Metab* 2013;4(6):151–69.
- Blinder KJ, Dugel PU, Chen S, et al. Anti-VEGF treatment of diabetic macular edema in clinical practice: effectiveness and patterns of use (ECHO Study Report 1). *Clin Ophthalmol* 2017;11:393–401.
- Fernandez-Robredo P, Sancho A, Johnsen S, et al. Current treatment limitations in age-related macular degeneration and future approaches based on cell therapy and tissue engineering. *J Ophthalmol* 2014;2014:510285.
- Bloch SB, Larsen M, Munch IC. Incidence of legal blindness from age-related macular degeneration in Denmark: year 2000 to 2010. *Am J Ophthalmol* 2012;153(2):209–13.
- Hawlina M. UEMS survey highlights accessibility disparities, inconsistent policies for anti-VEGF treatment across Europe. *Ocular Surgery News Europe Edition*; 2015. p. 5.
- Lee R, Wong T, Sabanayagam C. Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss. *Eye Vis (Lond)* 2015;2:17.
- Wong WL, Su X, Li X, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *Lancet Glob Health* 2014;2(2):e106–16.
- Shanahan C. The economic benefits of using lutein and zeaxanthin food supplements in the European Union. Frost & Sullivan. https://www2.frost.com/files/7015/0772/2735/HCCS_Lutein_AMD.2017.10.12.pdf. Accessed December 21, 2018.
- International Diabetes Federation. International Diabetes Federation diabetes atlas: seventh edition. <https://www.idf.org/e-library/epidemiology-research/diabetes-atlas/13-diabetes-atlas-seventh-edition.html>. Accessed December 21, 2018.
- Amadeus. Amadeus registry—Diabetic macular edema. <http://amadeus.registry.cz/res/file/amadeus-dme-analyza-2016-12.pdf>. Accessed December 21, 2018.

21. Amadeus. Amadeus registry—Age-related macular degeneration. <http://amadeus.registry.cz/res/file/amadeus-vpmd-analyza-2016-12.pdf>. Accessed December 21, 2018.
22. Krasnik V, Stefanickova J, Popov I, et al. Prevalence of age-related macular degeneration in Slovakia and associated risk factors: a mobile clinic-based cross-sectional epidemiological survey. *Semin Ophthalmol* 2018;33(4):506–11.
23. Pinkas J, Muc R, Radziwilska-Muc A, Grabska-Liberek I. Diabetic macular edema treatment limits in Poland. *J Health Policy Outcomes Res* 2016;1(8):47–52.
24. Flaxman SR, Bourne RRA, Resnikoff S, et al. Global causes of blindness and distance vision impairment 1990-2020: a systematic review and meta-analysis. *Lancet Glob Health* 2017;5(12):e1221–34.
25. Royal National Institute of Blind People. Blindness feared more than Alzheimer's, Parkinson's and heart disease. <http://www.rnib.org.uk/blindness-feared-more-alzheimer%E2%80%99s-parkinson%E2%80%99s-and-heart-disease>. Accessed December 21, 2018.
26. American Foundation for the Blind. Key findings: national poll on severe vision loss/blindness. <http://www.afb.org/info/programs-and-services/public-policy-center/policy-research/national-poll-findings-3376/1235>. Accessed December 21, 2018.
27. Mitchell J, Bradley C. Quality of life in age-related macular degeneration: a review of the literature. *Health Qual Life Outcomes* 2006;4:97.
28. Yuzawa M, Fujita K, Tanaka E, Wang EC. Assessing quality of life in the treatment of patients with age-related macular degeneration: clinical research findings and recommendations for clinical practice. *Clin Ophthalmol* 2013;7:1325–32.
29. Siaudvytyte L, Mitkute D, Balciuniene J. Quality of life in patients with age-related macular degeneration. *Medicina (Kaunas)* 2012;48(2):109–11.
30. Koberlein J, Beifus K, Schaffert C, Finger RP. The economic burden of visual impairment and blindness: a systematic review. *BMJ Open* 2013;3(11):e003471.
31. Ke KM, Montgomery AM, Stevenson M, O'Neill C, Chakravarthy U. Formal and informal care utilisation amongst elderly persons with visual impairment. *Br J Ophthalmol* 2007;91(10):1279–81.
32. International Federation of Ageing. The high cost of low vision—the evidence on ageing and the loss of sight. www.ifa-fiv.org/wp-content/uploads/2013/02/The-High-Cost-of-Low-Vision-The-Evidence-on-Ageing-and-the-Loss-of-Sight.pdf. Accessed December 21, 2018.
33. Gordoïs A, Cutler H, Pezzullo L, et al. An estimation of the worldwide economic and health burden of visual impairment. *Glob Public Health* 2012;7(5):465–81.
34. International Council of Ophthalmology. The global economic cost of visual impairment. www.icoph.org/resources/146/The-Global-Economic-Cost-of-Visual-Impairment.html. Accessed December 21, 2018.
35. National Council for the Blind of Ireland. The cost of sight loss—the economic impact of vision impairment and blindness in the Republic of Ireland. http://www.eyedoctors.ie/documents/Cost_of_Sight_Loss_Full_Rep.pdf. Accessed December 21, 2018.
36. Chakravarthy U, Biundo E, Saka RO, et al. The economic impact of blindness in Europe. *Ophthalmic Epidemiol* 2017;24(4):239–47.
37. Polish Ophthalmological Society. Blindness epidemic report. <http://retina.neo.pl/raport.pdf>. Accessed December 21, 2018.
38. Brown GC, Brown MM, Lieske HB, Lieske PA, Brown KS. A value-based medicine cost-utility analysis of genetic testing for neovascular macular degeneration. *Int J Retina Vitreous* 2015;1:19.
39. Javitt JC, Zlateva GP, Earnshaw SR, et al. Cost-effectiveness model for neovascular age-related macular degeneration: comparing early and late treatment with pegaptanib sodium based on visual acuity. *Value Health* 2008;11(4):563–74.
40. International Council of Ophthalmology. Age-related macular degeneration (management recommendations). http://www.icoph.org/dynamic/attachments/resources/icoarmdma_2.pdf. Accessed December 21, 2018.
41. International Council of Ophthalmology. International Council of Ophthalmology guidelines for diabetic eye care. <http://www.icoph.org/downloads/ICOGuidelinesforDiabeticEyeCare.pdf>. Accessed December 21, 2018.
42. Schmidt-Erfurth U, Garcia-Arumi J, Bandello F, et al. Guidelines for the management of diabetic macular edema by the European Society of Retina Specialists (EURETINA). *Ophthalmologica* 2017;237(4):185–222.
43. Schmidt-Erfurth U, Chong V, Loewenstein A, et al. Guidelines for the management of neovascular age-related macular degeneration by the European Society of Retina Specialists (EURETINA). *Br J Ophthalmol* 2014;98(9):1144–67.
44. Arias L, Armada F, Donate J, et al. Delay in treating age-related macular degeneration in Spain is associated with progressive vision loss. *Eye (Lond)* 2009;23(2):326–33.
45. Lim JH, Wickremasinghe SS, Xie J, et al. Delay to treatment and visual outcomes in patients treated with anti-vascular endothelial growth factor for age-related macular degeneration. *Am J Ophthalmol* 2012;153(4):678–86.
46. Tamura H, Goto R, Akune Y, et al. The clinical effectiveness and cost-effectiveness of screening for age-related macular degeneration in Japan: a Markov modeling study. *PLoS One* 2015;10(7):e0133628.
47. Karnon J, Czoski-Murray C, Smith K, et al. A preliminary model-based assessment of the cost-utility of a screening programme for early age-related macular degeneration. *Health Technol Assess* 2008;12(27):iii–iv, ix–124.
48. Pasquel FJ, Hendrick AM, Ryan M, et al. Cost-effectiveness of different diabetic retinopathy screening modalities. *J Diabetes Sci Technol* 2015;10(2):301–7.
49. Strain WD, Cos X, Prunte C. Considerations for management of patients with diabetic macular edema: optimizing treatment outcomes and minimizing safety concerns through interdisciplinary collaboration. *Diabetes Res Clin Pract* 2017;126:1–9.
50. Brown JD, Sheer R, Pasquale M, et al. Payer and pharmaceutical manufacturer considerations for outcomes-based agreements in the United States. *Value Health* 2018;21(1):33–40.