

Managed Care Implications of Diabetic Macular Edema

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Diabetic retinopathy (DR) is the leading cause of blindness among adults aged 20 to 74 in the United States, as well as the leading ocular complication associated with diabetes mellitus (DM).¹ Between 2000 and 2010, cases of DR increased 89% from 4.1 million to 7.7 million, a figure that is expected to nearly double by 2050.²

Diabetic macular edema (DME) is a form of diabetic retinopathy that, left untreated, leads to significant vision loss. From 2005 to 2008, 4.4% of adults with DM who were 40 years or older had advanced DR, either DME or proliferative diabetic retinopathy (PDR), that threatened their vision.³

Healthcare Communications, LLC Economic Costs of Diabetic Macular Edema

Visual impairment across a wide range of causes and severity leads to direct medical costs nearly twice those of non-blind individuals, primarily because of hospitalization and the use of healthcare services around the time of diagnosis and treatment. Long-term care, home-based nursing, assistive devices, and home modifications contribute to levels of non-medical services more than 10-fold higher than for those with normal vision.⁴

In a Medicare population, researchers identified that annual eye- and non-eye-related costs for those with moderate visual loss, severe loss, or blindness from any eye-related condition were \$2193, \$3301, and \$4443 higher (2003 dollars), respectively, than for those with normal vision. Overall, blindness and vision loss cost Medicare an estimated \$2.14 billion in excess costs that year (2003).⁵

Approximately 90% of these increased costs were related to treatment of depression, treatment for injury, skilled-nursing facility utilization, and long-term care admission, all of which are borne by the Medicare system. Preventing vision loss, the authors concluded, “is not only a medical imperative, but also an economic one.”⁵

An analysis of Medicare claims from 2000 to 2004 of patients with DME found a 3-fold increase in ophthal-

Abstract

Diabetic retinopathy (DR) is both the leading cause of blindness among adults aged 20 to 74 in the United States, and the leading ocular complication associated with diabetes mellitus (DM). An estimated 4.4% of adults with DM over 40 years of age have the more advanced form of DR: diabetic macular edema (DME), which significantly increases the risk of blindness. Medical costs for Medicare patients with DME are a third higher than for patients without DME. The majority of these costs stem from other DM-related complications, as DME is a marker for poorly controlled DM overall. Commercially insured patients with DME incur direct and indirect costs up to 75% higher than for those with DR without DME. Early detection, treatment, and improved glycemic control can limit the onset or progression of microvascular complications of DR, including DME, resulting in significant savings for payers. However, there are significant gaps in adherence to national guidelines regarding DM control and early identification of DR. In addition, patients face several barriers to screening. Improving screening for and management of early DR could decrease progression to DME, which would provide significant savings for payers, as well as improve the quality of care and outcomes for patients with DM. Managed care organizations and employers should also consider the cost-effectiveness of currently available treatments for DME: focal laser photocoagulation, vascular endothelial growth factor inhibitors, and intravitreal corticosteroid injections and implants, in their formulary design; they should also identify opportunities to improve patient adherence to treatment.

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mologist visits in the year after diagnosis, with nearly 60% receiving 1 or more fluorescein angiographies; 38%, laser photocoagulation; 18%, evaluation with optical coherence tomography (OCT); and 6%, at least 1 intravitreal injection (vascular endothelial growth factors [VEGF] inhibitors were just coming into use). There was a significant shift during the study time in treatment patterns from laser photocoagulation to intravitreal injections (use of laser photocoagulation shifted from 43% to 30%, and use of intravitreal injections shifted from <1% to 13%).⁶

Medicare costs for beneficiaries with DME were 31% higher at 1 year and 29% higher at 3 years than for controls, with inpatient costs responsible for about half the costs. However, it was the patients with diabetic complications in the control group that made the costs between the two groups more comparable, suggesting that diabetic complications drove the higher costs.⁶ Another retrospective study, which focused on approximately 147,000 insured working-age adults in the United States with DM, found higher rates of myocardial infarction, stroke, congestive heart failure, peripheral vascular disease, cerebrovascular disease, lower limb amputation, and renal disease in patients with DME, as well as significantly higher healthcare resource utilization.⁷ These findings suggest DME may be a marker for patients with poor glycemic control, with patients who have DME representing a subset of patients with DM who would benefit from more individualized, intensive management.

On the employer side, Lee and colleagues conducted a retrospective claims analysis of a commercially insured population, estimating that employees with DME had mean annual direct and indirect costs 75% higher than employees with DR who did not have DME (US dollars, \$28,606 vs \$16,363, $P < .0001$). Indirect costs included employer-provided disability payments and absenteeism; direct medical costs accounted for 80% of the higher expenditures in the DME population.⁸

Beyond the significant effect on quality of life, vision loss also interferes with patients' ability to manage their DM, including insulin administration, glucose monitoring, and exercise.⁹ This, in turn, may contribute to poorer glycemic control and a greater risk of additional DM-related complications and costs.

Mitigating Costs and Consequences of DME Through Screening and Early Treatment

Early detection, treatment, and improved glycemic control can limit the onset or progression of microvascular complications of DR, including DME.¹⁰⁻²⁰ Thus,

the American Diabetes Association (ADA) recommends that patients with type 1 diabetes mellitus have an initial dilated and comprehensive examination by an ophthalmologist or optometrist within 5 years of onset, and that those with type 2 diabetes mellitus (T2DM) have an initial exam at diagnosis. If any evidence of retinopathy is found, patients should be screened at least annually, more frequently if retinopathy is progressing or sight threatening. Otherwise, patients may be screened every 2 years.²¹

The American Academy of Ophthalmology (AAO) has similar guidelines; however, it recommends annual screenings for patients with T2DM.²²

These recommendations are particularly important given that 1 in 5 patients with T2DM has retinopathy on initial screening.²³ At this point, patients may already require treatment.

Early treatment can not only prevent blindness, but also result in significant savings. In 1994, Javitt and colleagues estimated that screening for and treating eye disease in patients with T2DM would generate annual savings of \$247.9 million for Medicare, even considering suboptimal levels of care prevalent at that time. If all patients with DM would have received recommended care, the predicted net savings could have exceeded \$472.1 million, for a net savings of \$975 per person (all 1994 dollars). Nearly all the savings were associated with the detection and treatment of DME.²⁴

Health plans, accountable care organizations, and other providers have a vested interest in ensuring their patients with DM receive recommended vision screenings. Quality indicators from the Centers for Medicare and Medicaid Services require that physicians document the presence or absence of macular edema and the level of severity of retinopathy, at least annually.²⁵ In 2014, just 56.2% of commercial HMOs, 48.7% of commercial PPOs, 54.4% of Medicaid HMOs, and 68.5% of Medicare HMOs documented that members with DM had at least 1 retinal exam.²⁶

Poor Adherence to Screening Recommendations

Despite evidence that screening can prevent or reduce the effects of DR, patient and provider adherence to ADA- and AAO-recommended screening intervals is poor, even when patients receive annual reminders.²⁷⁻³² One study, which was published in 2008 and consisted of 5000 patients with DM in a large managed care organization, found that about half of the patients received an eye examination during the enrollment period. Of those, just one-third had another examination within a year, while another third did not see an eye professional for 2 years, even though most had already been diagnosed with retinopathy.²⁸

Report

A study of Medicare claims from the 1990s found that just 50% to 60% of beneficiaries with DM had eye exams in a 15-month period, with significant gaps in the time to next exam being up to 75 months.²⁹ It appears that little progress has been made when comparing 1990s data with 2008 and 2014 data.

Receiving information from a healthcare provider about the importance of eye screening, however, is independently associated with the likelihood of undergoing regular eye exams.³³

Sundling and colleagues found that just half of 1352 surveyed patients had received information about the need for regular eye exams from their general practitioner. Those who had received such information, however, were more than twice as likely to have their eyes examined based on current guidelines.^{31,33}

In the Victorian Population Health Survey, a large population-based health survey conducted in Australia, researchers found that participants with DM were more likely to have received an eye exam in the previous 2 years if they had also seen another healthcare practitioner, even if the visit was unrelated to DM (skin examination and dental check, for instance).³⁴

Participants who did not receive an eye screening were nearly 3 times less likely to have seen a general practitioner, and significantly less likely to have had DM-related health checks, including blood pressure (odds ratio [OR], 11.29; 95% confidence interval [CI], 2.69-47.46; $P < .001$), cholesterol (OR, 5.23; 95% CI, 2.77-9.86; $P < .001$), and blood sugar levels [OR, 3.19; 95% CI, 1.25-8.14; $P < .021$].³⁴

Furthermore, delaying screening increases the risk of vision-threatening DR. An analysis of a cohort of 6556 individuals with DM who received their first screening in 2008 found that those with mild retinopathy on the baseline screening who did not attend 2 consecutive years of screening were nearly 4 times as likely (OR, 3.76; 95% CI, 2.14-6.61; $P < .001$) to develop sight-threatening DR.³⁵

The results of these and other studies suggest that hundreds of thousands of people with DM in the United States are not getting the necessary information, support, or treatment to prevent DME.³¹ This provides an important opportunity for managed care organizations to educate patients and healthcare providers about the importance of regular eye exams, the impact of DM on vision, and the risk of vision-related disease resulting from poor glycemic control.

Barriers to Screening

Barriers to regular screening include cost, lack of insurance, lack of symptoms, time, acute health-related con-

ditions, availability of ophthalmologists, having to see yet another provider, and family crises.³⁶⁻³⁸ Conversely, having eye problems or having a doctor stress the importance of an eye exam can provide powerful incentives to undergo screening.³⁹

There is also evidence that patients are unaware of the importance of early diagnosis of retinopathy or the availability of treatments. In a random cross-sectional sample of 64 telephone conversations with African Americans with DM, just 21% thought there were effective treatments for retinopathy, and 87% thought they would have symptoms if they had DM-related eye disease. While 36% had heard of retinopathy, just 8% accurately described it.³⁹

Bressler and colleagues conducted a cross-sectional analysis of data from participants aged 40 or older with DM in the 2005 to 2008 National Health and Nutrition Examination survey. Of the nearly 800 people in the sample, 238 had DR and 48 had DME. Just 44.7% of those with DME had been told of a link between DM and eye disease or had been told they had retinopathy by their doctor, compared with 26.1% of those with DR and no DME and 15.3% of those without either retinopathy or DME.³¹

Patients with DME were significantly less likely to have seen a DM nurse educator, nutritionist, or dietician in the previous year than those with DM and DR (48.8% vs 66.5% [95% CI, 23.8%-43.3%]) or with DM only (69.5% [95% CI, 26.1%-34.9%]). About 60% of those with DME had a dilated eye exam in the past year compared with 67.5% and 61.8% of those with DR or DM only (95% CI, 59.6%-75.4% and 54.7%-68.9%, respectively).³¹

Opportunities to Reduce Screening Barriers

Given that an estimated 73% of individuals with DR are not aware that they have the disease, thus preventing them from receiving early care that could slow the progression to DME, it is important that patients receive education on DR and the need for regular examinations.⁴⁰

One intervention in an African American population used a low-literacy 9-page color booklet, a motivational videotape, and semi-structured telephone education and counseling to increase screening frequency. After 6 months of intervention, 55% of the intervention group ($n = 137$) versus 37% of the control group ($n = 143$) had received eye examinations (OR, 4.3; 95% CI, 2.4-7.8).³⁶

A patient- and provider-targeted reminder intervention in a large, networked managed care organization provided patients with educational materials and a report on their most recent eye exam; providers received copies

of the ADA guidelines, a list of patients due for eye exams, and labels and form letters to send to patients. In the year following the intervention, claims for dilated eye exams increased by 27% over the previous year (OR, 1.4).⁴¹

Brooks and colleagues reported on a program in an independent practice managed care organization in which physicians received patient-specific clinical information, current guidelines for care, and assistance mailing letters to their patients. The physicians personally signed the letters, highlighting the importance of the retinal exam. The intervention led to a 25% increase in receipt of screenings compared with the previous 2 years.⁴²

Multiple patient reminders are typically needed. A study of 19,523 patients with DM randomized to receive a single reminder or multiple reminders found a significant improvement in DRE after a second reminder; little benefit was found for patients who received a third or fourth reminder.⁴³

To reduce patient burden, health plans may consider communicating the possibility of biannual screenings for patients with no evidence of retinopathy on a baseline screening. This could cut the number of screenings by 25% with no additional delay in treatment; it could also relieve patient burden.⁴⁴ A survey of 600 patients with DM attending a DR clinic found that 65% would accept screening every 2 to 3 years if it were safe and effective.⁴⁵

Access to ophthalmologists also affects screening frequency. One study of 1098 individuals with DM, 345 with DR and 498 with age-related macular degeneration (ARMD), found that local availability to ophthalmologists, but not optometrists, predicted frequency of eye examinations. Managed care organizations should be aware of the availability of ophthalmologists and optometrists, including waiting times for appointments; they could also encourage greater use of telemedicine in the care continuum.⁴⁶ Several studies found the use of telemedicine to be clinically beneficial and cost-effective.⁴⁷⁻⁵¹

Nearly all patients with DM should see a primary care physician or endocrinologist at least once a year, so payers should also consider encouraging vision screening in those settings. Clinicians require training; studies found that after receiving training, clinicians can accurately assess patients' vision and refer them accordingly to ophthalmologists.⁵²

Furthermore, Hatef and colleagues found diabetic eye exam compliance in a Medicaid population increased from 46% to 64% between 2010 and 2012. Factors that increased the likelihood of patients with DM getting eye exams included access to a nonmydriatic fundus camera in the primary care clinic, compliance with glycated hemoglobin testing, and pay-for-performance incentives for providers.⁵³

Managed Care Implications of Treatment for DME

Focal laser photocoagulation was the standard of care for DME for many years until the introduction of the VEGF inhibitors bevacizumab (used off label for DR and DME), ranibizumab, and aflibercept. The safety and efficacy of the 3 drugs were assessed in the Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol T study. One-year results demonstrated vision improvement with any of the 3 drugs, with the relative effect dependent on the initial visual acuity. With worse baseline visual acuity, aflibercept demonstrated a greater benefit; some evidence showed that aflibercept or ranibizumab might provide greater efficacy in patients with thick baseline Ocular Coherence Tomography Central Subfield Thickness (OCT CST) (ie, ≥ 400 μm) than would bevacizumab.⁵⁴

Two-year results showed clinical equivalence in most study parameters between aflibercept and ranibizumab, regardless of initial visual acuity. Patients with good visual acuity demonstrated better "drying" of the retina as measured by OCT compared to bevacizumab. This suggests that while all the drugs are effective for DME, there may be slight differences in subgroup populations of patients with DR and DME.⁵⁵

Numerous other studies have evaluated the cost-effectiveness of the 2 FDA-approved anti-VEGF agents aflibercept and ranibizumab, as well as bevacizumab. A cost-effectiveness model based on 1-year results found a nearly \$8000 higher cost for aflibercept compared with ranibizumab (\$24,460 vs \$16,624), with the majority of costs due to the drug acquisition cost rather than administration, adjunctive laser therapy, or management of associated complications. Quality-of-life years were similar between the 2 FDA-approved anti-VEGF agents for the overall cohort of patients.⁵⁶ The majority of studies found significant cost advantages to bevacizumab in patients with good baseline visual acuity.^{57,58} In 2015, Medicare-allowable charges were \$1961 for aflibercept (2.0 mg per 0.05 mL) and \$1181 (or 60% of the cost of aflibercept) for ranibizumab (0.3 mg per 0.05 mL), with reimbursement for bevacizumab (10 mg used for repackaging a 1.25-mg injection per 0.05) typically ranging from \$45 to \$67 (or 3.4% of the cost of aflibercept).⁵⁸

A cost-effectiveness analyses of the VEGF inhibitors bevacizumab and ranibizumab, focal laser, and intravitreal triamcinolone acetonide (IVTA) concluded that IVTA treatment for 1 year is most efficacious and cost-effective in patients with poor vision (visual acuity 20/200 to 20/320). It also concluded that patients with visual acuity of 20/32 or better should receive focal laser versus VEGF agents and that IVTA therapy appears to

provide greater benefit and cost-effectiveness than VEGF agents for patients with pseudophakic eyes.⁵⁹

Another analysis used a Markov model with a 25-year time horizon to determine the cost-effectiveness of IVTA in a hypothetical cohort of 57-year-old patients with newly diagnosed DME. It found that intravitreal ranibizumab is cost-effective at a willingness-to-pay (WTP) threshold of \$71,271 per quality-adjusted life-year (QALY), while bevacizumab is cost-effective at a WTP threshold of \$11,138/QALY. Intravitreal corticosteroids were significantly more costly and less effective, given the prevalence of side effects and the cost of managing them.⁵⁷ Those adverse effects include development of cataract and glaucoma. The associated costs can be mitigated by careful patient selection by the physician.

Most managed care organizations cover all 3 VEGF inhibitors, as well as long-acting corticosteroid implants and focal laser therapy. It is necessary to realize DME is a different disease in different patients, and physician access to all the treatment modalities is necessary to successfully manage this sight-threatening disease.

Patient Adherence to Therapy

Studies of ranibizumab find a correlation between visual improvement and injection frequency: the more injections a patient with DME receives, the better the visual outcome.⁶⁰⁻⁶⁴ For example, patients with DME in the RESTORE, Protocol 1, and RISE/RIDE trials received a mean annual number of 7 to 11 annual injections.^{60,61,63} Mean visual acuity improvement was significant, an outcome not possible in the era of laser treatment. Nonadherence to recommended injection frequency and follow-up intervals impacts the long-term outcomes of treatment with VEGF inhibitors, leading to wasted resources.⁶⁵

Unfortunately, real-life studies find poor adherence to recommended injection frequency. A recently published study based on the electronic medical records of 110 patients (121 eyes) with a DME diagnosis who received anti-VEGF treatment between January 2007 and May 2012 found that despite a mean of 9.2 ophthalmologist visits over 12 months, only 59% of study eyes had regular (at least quarterly) visits, and fewer than 2% had the monthly visits utilized in large randomized clinical trials. Furthermore, nearly 70% received 3 or fewer anti-VEGF injections over the 12-month study period. Only 3% of eyes in the study received injections at a frequency approaching monthly dosing.⁶⁶ This resulted in less favorable visual outcomes than those seen in clinical trials.^{60,61,63} Fewer ophthalmologist visits led to fewer anti-VEGF injections, which led to a decrease in vision when measured at 1 year.

Similarly, a retrospective analysis of claims of 2733 patients with DME found a mean annual number of bevacizumab injections of less than 4 throughout the 3-year study period.⁶⁷ Research into the “real world” utilization of anti-VEGF agents for DME has revealed under-treatment as a major problem. The consequences are not only less favorable vision outcomes for patients with DME, but also wasted time, money, and other resources on the injections given with suboptimal frequency.

The frequency with which patients require treatment contributes to patient nonadherence. Ideally, ophthalmology visits, which include anesthesia, the injection itself, and recovery, are monthly. Patients are often unable to drive themselves home, requiring someone else accompany them. This is in addition to the numerous visits they make to other providers for their DM and other complications.^{7,66-69}

Conclusion

DR is the leading cause of blindness among adults worldwide, and its incidence increases every year. Given the lack of symptoms in the early stages of the disease, it is important that people with DM receive regular dilated eye screenings in order to stem the progression of DR to DME, the leading cause of vision loss in patients with DM.

However, only about half of patients with DR adhere to national recommendations for annual or biannual screenings, increasing their risk of un-diagnosed and untreated macular edema, as well as severe vision loss.

Because vision loss is costly both in human and economic terms, DR and DME significantly increase direct and indirect medical costs for payers and employers. Thus, it is important to identify and implement opportunities to reduce the incidence of both DR and DME. Using the electronic health record to identify patients who require more intensive glycemic control and eye examinations, employing evidence regarding the cost effectiveness of currently available treatment options, and improving patient adherence to the recommended intense treatment paradigms required to preserve vision offer payers opportunities to reduce the risk of vision loss in their diabetic populations, as well as the economic costs of vision loss to society.

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