REVIEW ARTICLE

Julie R. Ingelfinger, M.D., *Editor*

Evaluation and Care of Patients with Diabetic Retinopathy

Lee M. Jampol, M.D., Adam R. Glassman, M.S., and Jennifer Sun, M.D., M.P.H.

Vascular complications of diabetes mellitus, including the evolution of the retinal damage known as diabetic retinopathy, have been recognized for centuries. Over the past decade, advances in technology such as retinal imaging and the development of new therapies have dramatically improved the evaluation, treatment, and visual outcomes of patients with diabetic retinopathy. Nonetheless, diabetic macular edema and proliferative diabetic retinopathy remain the leading causes of both moderate and severe vision loss in most developed countries. This article reviews the worldwide effect of diabetic retinopathy and recent changes in the evaluation and treatment of affected patients.

From the Feinberg School of Medicine, Northwestern University, Chicago (L.M.J.); the Jaeb Center for Health Research, Tampa, FL (A.R.G.); and the Department of Ophthalmology, Harvard Medical School, and Beetham Eye Institute at Joslin Diabetes Center — both in Boston (J.S.). Address reprint requests to Mr. Glassman at the Jaeb Center for Health Research, 15310 Amberly Dr., Suite 350, Tampa, FL 33647, or at drcrstat2@jaeb.org.

N Engl J Med 2020;382:1629-37.
DOI: 10.1056/NEJMra1909637

Global Scope of Diabetes and Diabetic Retinopathy

In most patients, retinopathy develops 10 to 15 years after diabetes has been diagnosed. With the increasing prevalence of diabetes, more people are at risk for retinopathy, and greater resources are required to identify and treat this condition. Globally, 629 million persons are expected to have diabetes by 2045.[1] The prevalence of diabetes has been increasing in both developing and developed countries.[2] In China, the prevalence of diabetes rose from less than 1% in 1980 to 11.6%, with 114 million persons affected, in 2013.[1] In 2018, the estimated prevalence of diabetes among adults in the United States was 10.2% (26.8 million cases).[3] In 2019, the disease was responsible for 4.2 million deaths worldwide, as well as $760 billion in health care expenditures.[1]

Efficient and accurate diagnosis of diabetic retinopathy, risk assessment, and treatment are critical, given the disease burden. Globally, from 1990 to 2010, visual impairment due to diabetic retinopathy increased by 64% and blindness by 27%.[4] By 2010, diabetic retinopathy was responsible for 3.7 million cases of visual impairment and more than 833,000 cases of blindness, and diabetes-related eye disease was the fifth most common cause of moderate-to-severe vision loss and blindness worldwide.[4,5] Fortunately, recent improvements in the identification, assessment, and treatment of diabetes-related eye disease are helping to reduce the overall burden of vision loss in some countries, particularly those with nationwide screening programs for diabetic retinopathy.

Pathogenesis of Diabetic Retinopathy

The duration of diabetes and the level of glycemic control have a major effect on the development of complications of diabetes (Fig. 1).[6] However, known risk factors are relatively poor predictors of retinopathy development or progression, and genetic association studies have proved disappointing.

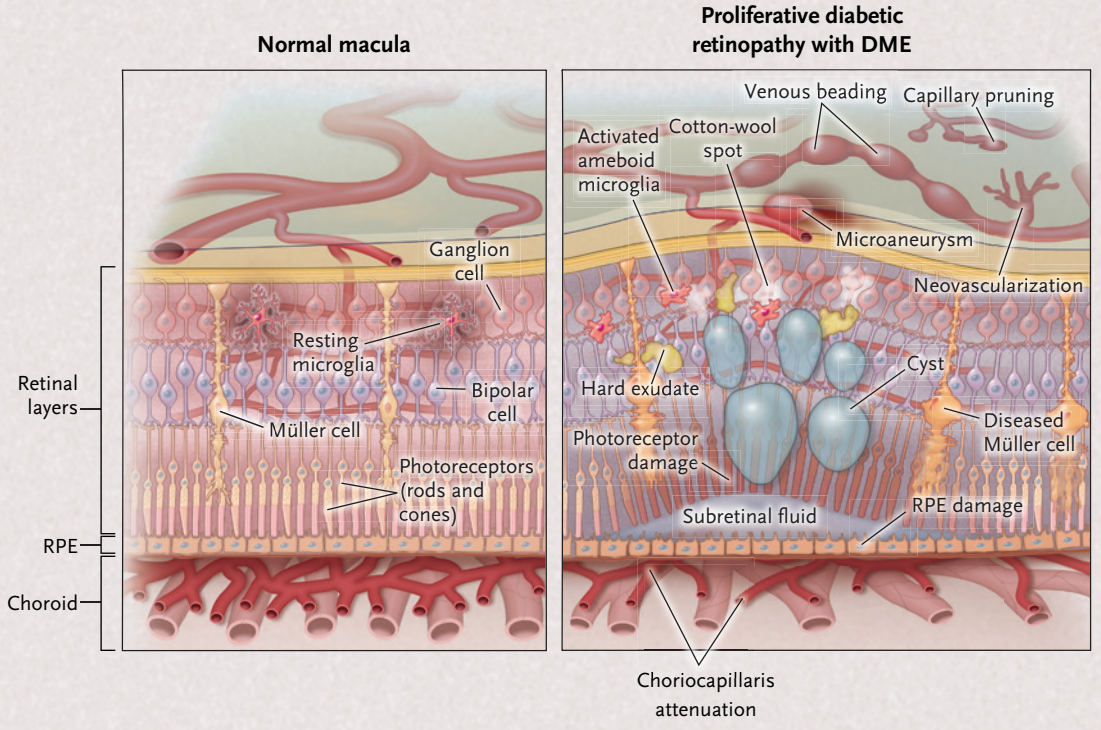

Figure 1. Normal Macula as Compared with Macula with Diabetic Macular Edema (DME).

Normal retinal architecture is shown in the left panel. The right panel shows many of the hallmark lesions of diabetic retinopathy, including microaneurysms, venous beading, retinal neovascularization, and cotton-wool spots. Cysts, subretinal fluid, hard exudates, and thickening adjacent to the center of the fovea are evidence of DME. RPE denotes retinal pigment epithelium.

Vision-threatening complications generally arise from increased retinal vascular permeability, complications of retinal or anterior-chamber neovascularization, or extensive vascular loss in the central retina. A variety of mechanisms underlying diabetic retinopathy have been postulated. In humans, antiinflammatory agents such as glucocorticoids can ameliorate diabetic macular edema and decrease rates of complications from proliferative diabetic retinopathy, suggesting that inflammation may be an important component.[7] Whether diabetic retinopathy begins as a vasculopathy or a neuropathy is not known.[8] Thinning of the inner retinal layers precedes clinical evidence of diabetes-related vascular lesions. In addition, psychometric testing has suggested that abnormal neural function occurs before the development of visible vasculopathy, although neuropathy has not yet reliably been shown to predict the development of vasculopathy.[9]

Retinal ischemia results in tissue hypoxia and is manifested as capillary nonperfusion. Hypoxia is a powerful inducer of vascular endothelial growth factor (VEGF) expression, resulting in elevated VEGF concentrations in the vitreous and retina. VEGF is a potent mediator of angiogenesis and vascular permeability. In animal models, either retinal ischemia or the administration of VEGF into the vitreous can induce vascular changes that are similar to diabetic retinopathy, and VEGF inhibitors can block the process.[10]

Several aberrant processes occur individually or together as diabetic retinopathy develops. Increased retinal vascular permeability can cause central retinal thickening (diabetic macular edema) due to the presence of intraretinal and subretinal fluid (Fig. 2). Diabetic macular edema is a major cause of moderate vision loss (frequently defined as a loss of three or more lines of vision on an eye chart, on which one line equals five letters). When retinal ischemia becomes widespread, it can cause vision loss due to dysfunc-

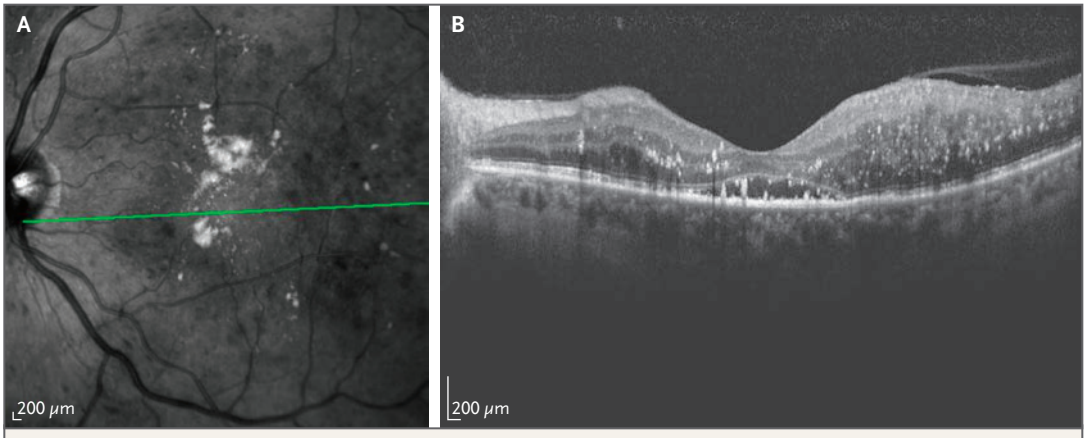

Figure 2. Images of a Retina with Central Diabetic Macular Edema.

In the en face image in Panel A, multiple hard exudates (light spots) and intraretinal hemorrhages (dark spots) can be seen in the central macula, findings suggestive of diabetic macular edema. The green line indicates the location of the cross-sectional image in Panel B, which shows marked retinal swelling, scattered hard exudates (white spots), and central subretinal fluid.

tion or death of neural retinal cells, including the light-sensing retinal photoreceptors. Proliferative diabetic retinopathy may develop with neovascularization in the optic disk, iris, or elsewhere throughout the retina; this disorder and its associated complications, such as vitreous hemorrhage, central retinal ischemia, and tractional retinal detachment, are major causes of marked vision loss in patients with diabetes.

ADVANCES IN IMAGING

Unlike the structures of many other organs or portions of organs, the morphologic features of the retina can be viewed directly through noninvasive in-office imaging (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Historically, assessment of diabetic retinopathy relied on standard retinal color photography, which can be used to visualize approximately one third of the retinal surface (posterior retina), and fluorescein angiography, in which an intravenously injected fluorescent dye is used to assess vascular structure and permeability. A newer technique, ultrawide-field photography of the fundus, allows evaluation of more than 80% of the retinal surface from a single image (Fig. 3A and 3B).[11] Findings in the retinal periphery, which is not visible on standard photographs of the fundus, may be associated with an increased risk of the progression of retinopathy.[12] In addition, with the development of increasingly sophisticated optical coherence tomographic (OCT) approaches, we can now noninvasively evaluate retinal structures en face (Fig. 2A) and in cross section (Fig. 2B), including the extent and location of retinal thickening and morphologic changes in the neural retina that may affect visual function.[13,14]

An even more recent advance, termed OCT angiography, permits noninvasive visualization and morphologic evaluation of perfused retinal vessels (Fig. 4). OCT angiography detects blood-cell movement, which it uses to produce a map of perfusion in the three layers of retinal vessels. Given the microvascular damage that occurs early in diabetic retinopathy, quantification of abnormalities of the retinal vasculature may provide information regarding the progression of diabetic retinopathy. However, this technique cannot easily be used to quantitate vascular leakage or the magnitude of blood flow. Thus, fluorescein angiography remains an important diagnostic technique for detecting leakage (i.e., increased vascular permeability). Another sophisticated imaging approach involves adaptive optics technology. This method can be used with either scanning laser ophthalmoscopy or flood illumination. Through the measurement of optical imperfections in the eye and the use of deformable mirrors to correct the resulting aberrations in the wave front reflected from the eye, adaptive optics noninvasively leads to spatial resolution of the retina (down to capillaries of

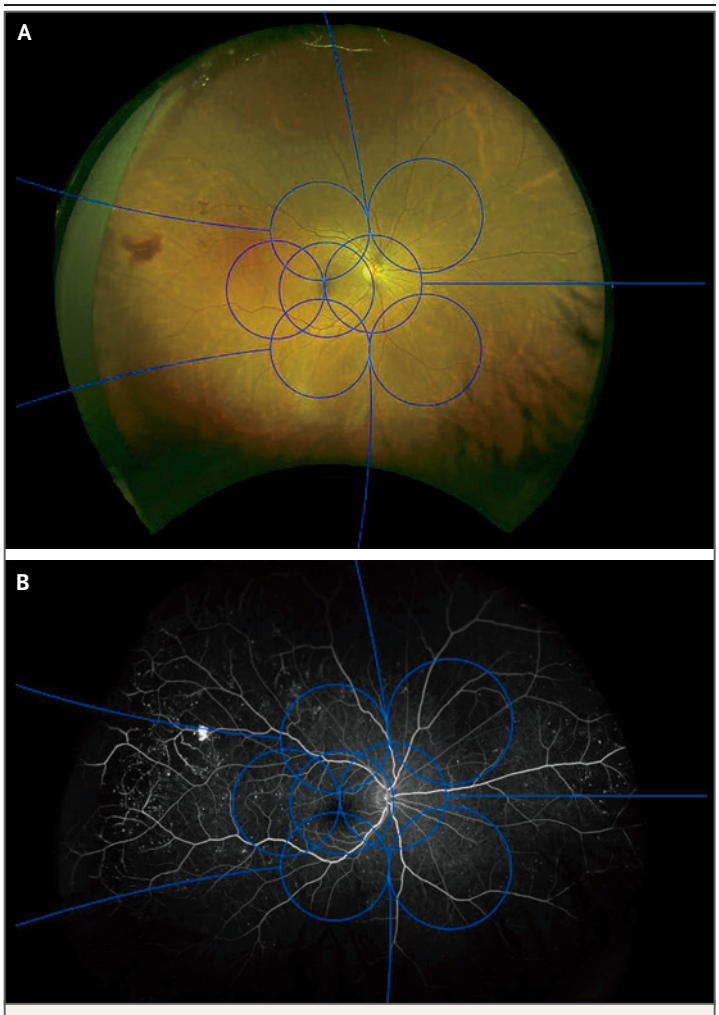

Figure 3. Ultrawide-Field Images of an Eye with Diabetic Retinopathy.

In Panel A, ETDRS (Early Treatment of Diabetic Retinopathy Study) standard fields (blue circles) are superimposed on the full ultrawide-field retinal image. An area of vitreous hemorrhage (reddish splotch) is present at the left, in the area outside the ETDRS fields. Panel B shows an ultrawide-field fluorescein angiogram of the same eye. The fluorescent intravenous dye delineates the perfused retinal vasculature and vascular outpouchings (microaneurysms [small, bright dots]).

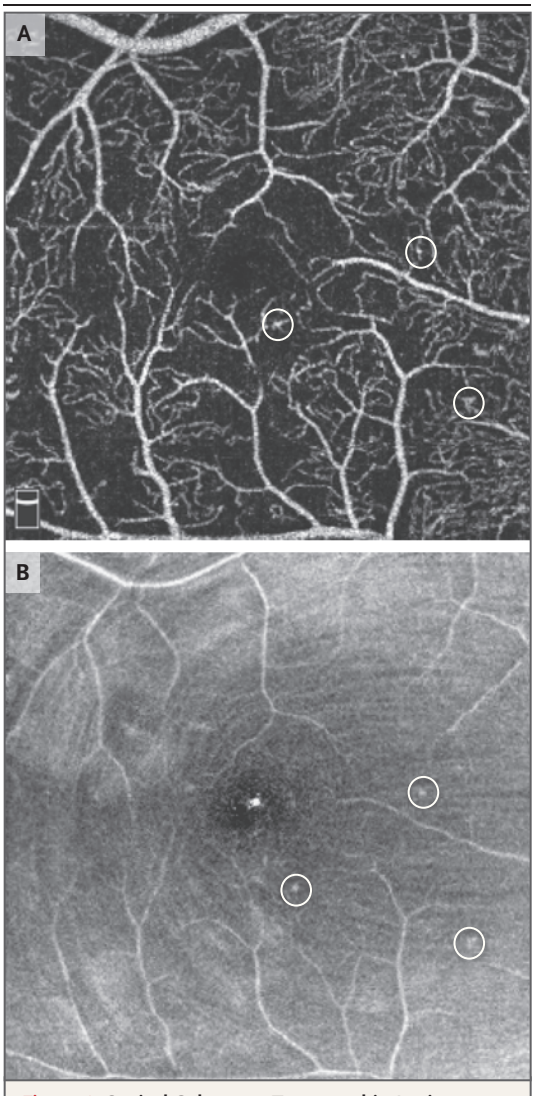

Figure 4. Optical Coherence Tomographic Angiogram of the Macula in a 32-Year-Old Woman with Nonproliferative Diabetic Retinopathy.

The central foveal area is characterized by irregular vessels (Panel A). Abnormal nonperfusion in surrounding areas (larger black zones) is widespread. The circles surround three microaneurysms. An en face image of the area shows the circled microaneurysms (Panel B).

approximately 2 μm in diameter),[15] allowing visualization of individual photoreceptors and red cells.

Together, these new tools permit unprecedented noninvasive, longitudinal evaluation of retinal structure and disease. However, the use of such imaging technologies may be hampered by uneven reliability and the difficulty of obtaining high-quality images, as well as high cost and lack of reimbursement.

With the copious data generated from imaging techniques, artificial intelligence (AI) with deep learning is now being applied to retinal images to identify factors that are related to retinopathy outcomes.[16] Specifically, AI approaches have been shown to be effective at identifying eyes at certain thresholds of retinopathy, including eyes requiring referral for retinal examina-

tion.[17,18] Additional efforts are focusing on identifying retinal image features that may predict the risk of worsening retinopathy and treatment response.[16,19] It is clear that as new imaging techniques generate more detailed and more expansive information and computerized approaches analyze this information in new ways, discoveries are likely to emerge that will permit detection of the earliest changes in diabetic retinopathy and prediction of disease progression or regression.

CHANGES IN THE MANAGEMENT OF DIABETIC RETINOPATHY

Before the early 1970s, pituitary ablation was the primary treatment for severe diabetic retinopathy, despite its limited efficacy and frequent, often severe sequelae, including death. With the advent of panretinal laser photocoagulation in the 1970s, the risk of severe vision loss from proliferative diabetic retinopathy was reduced by more than 90%.[20] Focal laser treatment of diabetic macular edema reduced the associated risk of moderate vision loss by 50%.[21] With these treatment successes, the identification, classification, and prompt treatment of patients with diabetes at risk for vision loss became crucial.

As noted above, elevated VEGF concentrations in the posterior segment of the eye are involved in the development of diabetic retinopathy and diabetic macular edema.[22,23] The permeability and angiogenic effects of VEGF provided a rationale for developing a therapy targeting VEGF in patients with diabetic retinopathy. Studies investigating whether injection of antibodies to VEGF into the vitreous could reduce diabetic macular edema, ameliorate proliferative diabetic retinopathy, and improve visual acuity stimulated multiple clinical trials that have changed the standard of care for diabetic retinopathy and diabetic macular edema. These studies are described below.

DIABETIC MACULAR EDEMA

In 2010, the DRCR Retina Network (previously known as the Diabetic Retinopathy Clinical Research Network) showed that intravitreal injections of ranibizumab, an antibody to VEGF, with immediate or deferred laser treatment to the macula, if necessary, were superior to the use of a laser alone for the treatment of vision-impairing edema[24] (Fig. 5). At 1 year after therapy, 88 of 188 eyes (47%) randomly assigned to ranibizumab had improved by two or more lines on a vision chart, as compared with 81 of 293 eyes (28%) assigned to macular laser treatment alone (relative risk of improvement, 1.68 [95% confidence interval, 1.27 to 2.21; P<0.001]). Conversely, only 6 eyes treated with ranibizumab (3%) lost two or more lines of vision, as compared with 39 eyes treated with laser alone (13%). A change of two lines of vision on an eye chart is usually considered to be clinically relevant.

Subsequently, several large, randomized trials extended the initial DRCR Retina Network findings, showing that other anti-VEGF agents (beva-

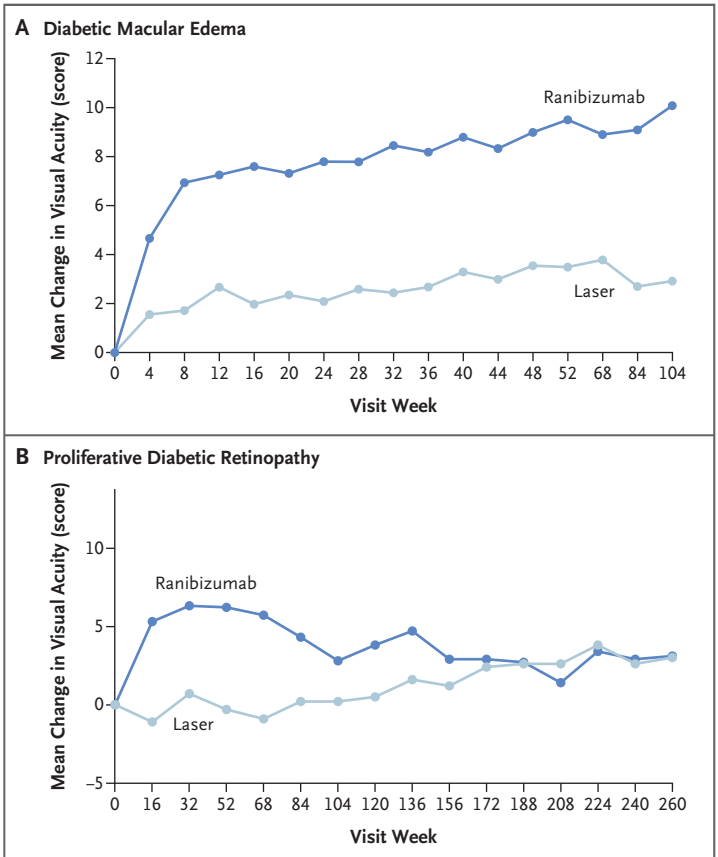

Figure 5. Laser as Compared with Vascular Endothelial Growth Factor (VEGF) Inhibitor for the Treatment of Diabetic Retinopathy.

Shown is the mean change from baseline in the letter score (five letters equals one line) for visual acuity in patients who received laser therapy or the VEGF inhibitor ranibizumab for the treatment of diabetic macular edema (central retinal thickening) (Panel A) or proliferative diabetic retinopathy (Panel B).

cizumab and aflibercept) were also superior to laser treatment.[25-28] Both aflibercept and ranibizumab have been approved by the Food and Drug Administration for the treatment of diabetic macular edema, and bevacizumab is often used off label for this indication. Because of its greater efficacy in reducing diabetic macular edema and improving vision, treatment with intravitreal anti-VEGF injection has generally replaced macular laser therapy worldwide as the initial standard treatment for eyes with visual-acuity loss from diabetic macular edema.

Before the use of anti-VEGF agents, intravitreal glucocorticoid therapy gained popularity among treating physicians. However, in 2008, the DRCR Retina Network showed that laser photocoagulation was superior to intravitreal triamcinolone injections for diabetic macular edema.[29] Glucocorticoids such as sustained-release fluocinolone acetonide and dexamethasone implants also were shown to reduce retinal thickening and to improve vision[30,31]; however, intravitreal treatment with glucocorticoids results in an increased risk of cataracts requiring surgery and can induce increased intraocular pressure and glaucoma. Given the variable efficacy of glucocorticoids and concern about ocular safety, anti-VEGF therapy has become the principal treatment for diabetic macular edema.

With the rapid shift to the use of anti-VEGF injections for diabetic macular edema, important questions have arisen. Anti-VEGF agents are generally cleared from the eye within a month after injection, yet the duration of the treatment benefit varies. The frequency of injections and overall duration of treatment for adequate results are currently unknown. Nonetheless, in the DRCR Retina Network trial assessing ranibizumab for diabetic macular edema, a treatment algorithm was developed that allowed for a reduction in the number of injections over time if therapeutic success or stability was achieved in an eye.[24] In that study, treatment was administered monthly for 6 months (unless diabetic macular edema had resolved and vision was 20/20 at month 4 or 5). After 6 months, according to the algorithm, treatment could be deferred if vision and macular thickness in the eye were stable after two consecutive injections. There are no direct comparisons of this approach with monthly treatment or treatment every other month. However, with the use of this algorithm, a median of 8, 2, 1, and 0 injections were administered in years 1, 2, 3, and 4, respectively, with maintenance of the visual benefit over the entire 5 years. The resulting benefits were similar to those achieved in studies using more frequent, even monthly, treatments.[27,28] This approach appears to have decreased the burden of treatment on patients and physicians and has saved money (e.g., for patients, insurance providers, and Medicare) while preserving visual function.

A clinician's decision regarding which anti-VEGF agent to use is multifaceted and depends on efficacy, availability, and cost. In 2020, the Medicare-allowable reimbursement for each injection was $1,876 for aflibercept (2.0 mg per 0.05 ml), $1,030 for ranibizumab (0.3 mg per 0.05 ml), and approximately $65 for bevacizumab (1.25 mg per 0.05 ml). A direct comparison of these VEGF inhibitors in a DRCR Retina Network trial involving 660 eyes with diabetic macular edema showed that all three agents resulted in improved visual acuity and reduced retinal thickening.[32,33] When visual acuity was relatively good at the start of treatment (Snellen equivalent, 20/32 to 20/40), average visual acuity at 2 years was similar for all three anti-VEGF agents.[33] However, when initial visual acuity was 20/50 or worse, treatment with aflibercept resulted in better visual acuity at 2 years than treatment with bevacizumab.

Recent findings from the DRCR Retina Network suggest that when baseline visual acuity in an eye with diabetic macular edema is 20/25 or better, initial management with observation is a reasonable strategy rather than immediate anti-VEGF therapy or laser treatment, provided that eyes initially managed with observation or laser treatment are followed closely and anti-VEGF therapy is initiated if vision worsens. In a randomized, controlled trial of initial management approaches, aflibercept therapy, laser therapy, and observation were associated with statistically similar rates of vision loss at 2 years (16% with aflibercept, 17% with laser, and 19% with observation).[34]

Most eyes with diabetic macular edema respond to anti-VEGF therapy with some degree of anatomical improvement, visual improvement, or both, but in nearly 40% of eyes, complete

resolution of diabetic macular edema is not achieved.[35] The addition of intravitreal glucocorticoid therapy to anti-VEGF treatment improves retinal thickening but does not improve visual outcomes for patients.[36] In routine clinical care, an incomplete response to anti-VEGF therapy is frequently due to inadequate dosing frequency or an inadequate number of injections given as a result of various patient- and clinician-related factors, including difficulty adhering to frequent, monthly visits for adequate treatment. A 5-year follow-up visit that occurred 3 years after patients finished participation in a 2-year trial of anti-VEGF therapy for DME suggested that on average, vision at 5 years was better than at baseline but declined during the 3 years of standard care.[37]

PROLIFERATIVE DIABETIC RETINOPATHY

Left untreated, nearly half of eyes in which proliferative diabetic retinopathy develops will have profound vision loss from related complications, including retinal detachment and vitreous hemorrhage.[38] Since the 1970s, proliferative diabetic retinopathy has been treated with panretinal laser photocoagulation, which is effective in preserving central vision but can be associated with an exacerbation of macular edema, loss of visual field, impaired night vision, and loss of contrast sensitivity.

More recently, two randomized trials provided evidence that anti-VEGF therapy can be used successfully as an alternative to panretinal laser photocoagulation for the treatment of proliferative diabetic retinopathy. The CLARITY study showed that at 1 year, eyes randomly assigned to aflibercept had better mean visual acuity than eyes assigned to panretinal laser photocoagulation.[39] A DRCR Retina Network randomized trial showed that visual-acuity results with ranibizumab were noninferior to those obtained with panretinal laser photocoagulation at 2 years and 5 years.[40,41] In both the CLARITY and the DRCR Retina Network studies, eyes assigned to the anti-VEGF agent had less diabetic macular edema and less visual-field loss over the course of the study.

However, there are barriers to large-scale adoption of anti-VEGF treatment for proliferative diabetic retinopathy.[42] Frequent anti-VEGF injections are required, and adherence to frequent follow-up visits and treatments is challenging for some patients. The 5-year retention rate, despite maximal efforts in the DRCR Retina Network protocol, was only 66%, excluding patients who died.[41] In one large, retrospective cohort study, 584 of 2302 patients (25.4%) with proliferative diabetic retinopathy were lost to follow-up over a 4-year period.[43] There is increasing evidence that anti-VEGF treatment is unlikely to improve retinal perfusion and may not prevent gradual progression of nonperfusion or loss of the peripheral visual field associated with worsening diabetes-related eye disease. After cessation of anti-VEGF therapy, substantial vision loss may occur if recurrent neovascularization leads to serious ocular complications such as tractional retinal detachment or neovascular glaucoma. Thus, panretinal laser photocoagulation may be a more appropriate initial therapeutic approach in some patients. Some clinicians use a combination of panretinal laser photocoagulation and anti-VEGF therapy; however, this approach and its outcomes have not been fully evaluated in multicenter, randomized clinical trials.

Frequent injections of anti-VEGF agents, particularly aflibercept or ranibizumab, are more costly than panretinal laser photocoagulation (Medicare reimbursement rate for photocoagulation, $351), even if laser photocoagulation is administered more than once, as it was, on average, in the trials described above.[44] Treatment efficacy, the likelihood of adherence to the regimen, cost, and treatment burden all need to be considered in selecting a therapeutic approach for a patient with proliferative diabetic retinopathy.

FUTURE CONSIDERATIONS

Although the global prevalence of diabetes is increasing, recent advances in care are resulting in reduced rates of vision loss in populations that are screened appropriately and given timely access to medical advances. Rates of proliferative diabetic retinopathy and severe vision loss have declined over the past four decades in the United States and other developed countries.[45-47] For the first time in at least five decades, diabetic retinopathy is no longer the leading cause of blindness among working-age adults in England and Wales, a finding that is believed to be, in

part, the result of aggressive national screening and treatment programs.[48] However, as the prevalence of diabetes continues to increase rapidly worldwide, it will be critical to ensure that medical advances are scalable and to improve access to appropriate care for patient populations across the globe.

There is still a need for improved therapeutic approaches. The burden that frequent intravitreal injections impose on patients and health care providers is substantial and expensive. Furthermore, many eyes with diabetic macular edema do not have a full response to therapy; that is, they do not have complete resolution of edema with visual improvement to 20/20 or better. Studies evaluating VEGF-independent pathways that might be targeted for increased therapeutic effectiveness and alternative delivery mechanisms that are noninvasive or provide a longer duration of action are under way. Approaches to preventing the onset of diabetic retinopathy or slowing the worsening of preexisting diabetic retinopathy are also being investigated. Finally, given limited resources and the dramatic global increase in diabetes, appropriate triage is increasingly important, and there is a substantial need to identify the risk of retinopathy and progression to vision loss in a person with diabetes, as well as the likelihood of a response to a given treatment.

SUMMARY

Advances in retinal imaging and new treatments are changing care for patients with diabetic retinopathy. With the current unprecedented ability to noninvasively observe retinal structures, detect retinopathy, and identify patients at greatest risk for vision loss, the ocular care of persons with diabetes can now be performed faster, with greater precision, and in a manner that is easier for both physician and patient. With the concurrent introduction of intraocular VEGF-inhibitor therapy, which can prevent vision loss and induce visual improvement, the treatment of diabetic macular edema and diabetic retinopathy has changed dramatically for the better, and the evolution of effective treatment should continue for years to come.

Dr. Jampol reports receiving consulting fees from Sanofi Pharmaceuticals; Mr. Glassman, receiving grant support, paid to his institution, from Genentech, Regeneron, and Allergan; and Dr. Sun, receiving grant support and provision of equipment from Optovue, provision of equipment from Boston Micromachines and Adaptive Sensory Technologies, grant support and travel support from Kalvista, Novo Nordisk, and Boehringer Ingelheim, consulting fees and travel support from Merck and Novartis, and grant support, medical writing, and travel support from Roche. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Dr. Lloyd Paul Aiello for his thoughtful input and assistance with a previous draft of this review.

REFERENCES

1. International Diabetes Federation. IDF diabetes atlas. 9th ed. Global fact sheet. 2019 (https://www.idf.org/aboutdiabetes/what-is-diabetes/facts-figures.html).
2. American Diabetes Association. The staggering costs of diabetes. 2018 (http://www.diabetes.org/assets/img/advocacy/2018-cost-of-diabetes.jpg).
3. Centers for Disease Control and Prevention. National diabetes statistics report. 2020 (https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf).
4. Leasher JL, Bourne RR, Flaxman SR, et al. Global estimates on the number of people blind or visually impaired by diabetic retinopathy: a meta-analysis from 1990 to 2010. Diabetes Care 2016;39:1643-9.
5. Bourne RRA, Stevens GA, White RA, et al. Causes of vision loss worldwide, 1990-2010: a systematic analysis. Lancet Glob Health 2013;1(6):e339-e349.
6. Lachin JM, White NH, Hainsworth DP, Sun W, Cleary PA, Nathan DM. Effect of intensive diabetes therapy on the progression of diabetic retinopathy in patients with type 1 diabetes: 18 years of follow-up in the DCCT/EDIC. Diabetes 2015;64:631-42.
7. Yang Y, Bailey C, Loewenstein A, Massin P. Intravitreal corticosteroids in diabetic macular edema: pharmacokinetic considerations. Retina 2015;35:2440-9.
8. Joltikov KA, de Castro VM, Davila JR, et al. Multidimensional functional and structural evaluation reveals neuroretinal impairment in early diabetic retinopathy. Invest Ophthalmol Vis Sci 2017;58:BIO277-BIO290.
9. Lynch SK, Abràmoff MD. Diabetic retinopathy is a neurodegenerative disorder. Vision Res 2017;139:101-7.
10. Miller JW. VEGF: from discovery to therapy: the Champalimaud Award Lecture. Transl Vis Sci Technol 2016;5:9.
11. Oishi A, Hidaka J, Yoshimura N. Quantification of the image obtained with a wide-field scanning ophthalmoscope. Invest Ophthalmol Vis Sci 2014;55:2424-31.
12. Aiello LP, Odia I, Glassman AR, et al. Comparison of early treatment diabetic retinopathy study standard 7-field imaging with ultrawide-field imaging for determining severity of diabetic retinopathy. JAMA Ophthalmol 2019;137:65-73.
13. Sun JK, Radwan SH, Soliman AZ, et al. Neural retinal disorganization as a robust marker of visual acuity in current and resolved diabetic macular edema. Diabetes 2015;64:2560-70.
14. Deák GG, Bolz M, Ritter M, Prager S, Benesch T, Schmidt-Erfurth U. A systematic correlation between morphology and functional alterations in diabetic macular edema. Invest Ophthalmol Vis Sci 2010;51:6710-4.
15. Nesper PL, Scarinci F, Fawzi AA. Adaptive optics reveals photoreceptor abnormalities in diabetic macular ischemia. PLoS One 2017;12(1):e0169926.
16. Schmidt-Erfurth U, Sadeghipour A,

Gerendas BS, Waldstein SM, Bogunović H. Artificial intelligence in retina. Prog Retin Eye Res 2018;67:1-29.
17. Ting DSW, Wu W-C, Toth C. Deep learning for retinopathy of prematurity screening. Br J Ophthalmol 2018 November 23 (Epub ahead of print).
18. Ting DSW, Pasquale LR, Peng L, et al. Artificial intelligence and deep learning in ophthalmology. Br J Ophthalmol 2019; 103:167-75.
19. Arcadu F, Benmansour F, Maunz A, Willis J, Haskova Z, Prunotto M. Deep learning algorithm predicts diabetic retinopathy progression in individual patients. NPJ Digit Med 2019;2:92.
20. The Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy: clinical application of Diabetic Retinopathy Study (DRS) findings, DRS report number 8. Ophthalmology 1981;88:583-600.
21. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema: Early Treatment Diabetic Retinopathy Study report number 1. Arch Ophthalmol 1985;103: 1796-806.
22. Funatsu H, Yamashita H, Noma H, Mimura T, Yamashita T, Hori S. Increased levels of vascular endothelial growth factor and interleukin-6 in the aqueous humor of diabetics with macular edema. Am J Ophthalmol 2002;133:70-7.
23. Aiello LP, Avery RL, Arrigg PG, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. N Engl J Med 1994;331:1480-7.
24. Diabetic Retinopathy Clinical Research Network. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology 2010;117(6):1064.e35-1077.e35.
25. Michaelides M, Kaines A, Hamilton RD, et al. A prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT Study) 12-month data: report 2. Ophthalmology 2010;117(6): 1078.e2-1086.e2.
26. Mitchell P, Bandello F, Schmidt-Erfurth U, et al. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmology 2011;118:615-25.
27. Nguyen QD, Brown DM, Marcus DM, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology 2012;119:789-801.
28. Brown DM, Schmidt-Erfurth U, Do DV, et al. Intravitreal aflibercept for diabetic macular edema: 100-week results from the VISTA and VIVID studies. Ophthalmology 2015;122:2044-52.
29. Diabetic Retinopathy Clinical Research Network. A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema. Ophthalmology 2008;115(9):1447.e1-1449.e1.
30. Maturi RK, Pollack A, Uy HS, et al. Intraocular pressure in patients with diabetic macular edema treated with dexamethasone intravitreal implant in the 3-year Mead Study. Retina 2016;36:1143-52.
31. Campochiaro PA, Brown DM, Pearson A, et al. Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. Ophthalmology 2012;119:2125-32.
32. The Diabetic Retinopathy Clinical Research Network. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. N Engl J Med 2015;372:1193-203.
33. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: two-year results from a comparative effectiveness randomized clinical trial. Ophthalmology 2016;123:1351-9.
34. Baker CW, Glassman AR, Beaulieu WT, et al. Effect of initial management with aflibercept vs laser photocoagulation vs observation on vision loss among patients with diabetic macular edema involving the center of the macula and good visual acuity: a randomized clinical trial. JAMA 2019;321:1880-94.
35. Bressler NM, Beaulieu WT, Glassman AR, et al. Persistent macular thickening following intravitreous aflibercept, bevacizumab, or ranibizumab for central-involved diabetic macular edema with vision impairment: a secondary analysis of a randomized clinical trial. JAMA Ophthalmol 2018;136:257-69.
36. Maturi RK, Glassman AR, Liu D, et al. Effect of adding dexamethasone to continued ranibizumab treatment in patients with persistent diabetic macular edema: a DRCR network phase 2 randomized clinical trial. JAMA Ophthalmol 2018; 136:29-38.
37. Glassman AR, Well JA III, Josic K, et al. Five-year outcomes after initial aflibercept, bevacizumab, or ranibizumab treatment for diabetic macular edema (Protocol T Extension Study). Ophthalmology (in press).
38. The Diabetic Retinopathy Study Research Group. Preliminary report on effects of photocoagulation therapy. Am J Ophthalmol 1976;81:383-96.
39. Sivaprasad S, Prevost AT, Vasconcelos JC, et al. Clinical efficacy of intravitreal aflibercept versus panretinal photocoagulation for best corrected visual acuity in patients with proliferative diabetic retinopathy at 52 weeks (CLARITY): a multicentre, single-blinded, randomised, controlled, phase 2b, non-inferiority trial. Lancet 2017;389:2193-203.
40. Gross JG, Glassman AR, Liu D, et al. Five-year outcomes of panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. JAMA Ophthalmol 2018;136:1138-48.
41. Gross JG, Glassman AR, Jampol LM, et al. Panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. JAMA 2015;314:2137-46.
42. Glassman AR. Results of a randomized clinical trial of aflibercept vs panretinal photocoagulation for proliferative diabetic retinopathy: is it time to retire your laser? JAMA Ophthalmol 2017;135: 685-6.
43. Obeid A, Gao X, Ali FS, et al. Loss to follow-up in patients with proliferative diabetic retinopathy after panretinal photocoagulation or intravitreal anti-VEGF injections. Ophthalmology 2018;125:1386-92.
44. Hutton DW, Stein JD, Bressler NM, Jampol LM, Browning D, Glassman AR. Cost-effectiveness of intravitreous ranibizumab compared with panretinal photocoagulation for proliferative diabetic retinopathy: secondary analysis from a Diabetic Retinopathy Clinical Research Network randomized clinical trial. JAMA Ophthalmol 2017;135:576-84.
45. Wong TY, Mwamburi M, Klein R, et al. Rates of progression in diabetic retinopathy during different time periods: a systematic review and meta-analysis. Diabetes Care 2009;32:2307-13.
46. Klein R, Knudtson MD, Lee KE, Gangnon R, Klein BEK. The Wisconsin Epidemiologic Study of Diabetic Retinopathy XXIII: the twenty-five-year incidence of macular edema in persons with type 1 diabetes. Ophthalmology 2009;116:497-503.
47. Klein R, Knudtson MD, Lee KE, Gangnon R, Klein BEK. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XXII the twenty-five-year progression of retinopathy in persons with type 1 diabetes. Ophthalmology 2008;115:1859-68.
48. Liew G, Michaelides M, Bunce C. A comparison of the causes of blindness certifications in England and Wales in working age adults (16-64 years), 1999-2000 with 2009-2010. BMJ Open 2014; 4(2):e004015.