Integrated Care for the Diabetic Patient:
How to Diagnose and Manage the At-Risk Patient
Part 2

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LEARNING METHOD
This educational activity consists of a supplement and 20 study questions. To obtain credit, the participant should read the learning objectives, read the material, answer all questions in the post test, and complete the activity evaluation form. This educational activity should take a maximum of 2.0 hours to complete.

CONTENT SOURCE
This continuing education (CE) activity captures content from a roundtable discussion held in September 2016.

ACTIVITY DESCRIPTION
It remains clear that although diabetes is a systemic disorder, the manifestations of diabetic complications will occur without optimal glycemic and blood pressure control. Optometrists can help continually reinforce that message by educating patients about the necessity for ongoing and yearly dilated eye examinations, and discussing the potential treatments should vision loss become obvious.

TARGET AUDIENCE
The target audience for this CE Activity is optometrists.

LEARNING OBJECTIVES
After successfully completing this activity, optometrists will have improved their ability to:
• Determine who is a high-risk patient for the onset of diabetic eye disease
• Discuss the importance of conducting yearly dilated exams on diabetic patients
• Develop plans to initiate comanagement of the diabetic patient with both ophthalmologists and primary care physicians/endocrinologists
• Implement strategies to educate patients on the ocular manifestations of diabetes

ACCREDITATION DESIGNATION STATEMENT
This course is COPE approved for 2.0 hours of CE credit for optometrists.

DISCLOSURES
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Integrated Care for the Diabetic Patient: How to Diagnose and Manage the At-Risk Patient

New cases of diabetes are being diagnosed at epidemic proportions. Several factors, including poor dietary habits, declining exercise, and an increase in sedentary activities are contributing to an accelerating rate of new cases. As this public health crisis emerges, it is becoming clear that early diagnosis and treatment can set patients up for more favorable outcomes. This sentiment is true for systemic complications as well as those that affect vision.

A look at the numbers suggests that many patients may be slipping through the cracks. Of the approximately 8 million individuals living with diabetic retinopathy, only about 5.8 million are diagnosed.1–3 Perhaps even more surprising, of the 2.3 million with diabetic macular edema, only about 1.5 million receive a diagnosis,1 and only about 400,000 make it into the retina specialist to receive treatment.3,4 About one in four patients 40 years of age and older with diabetes does not comply with the recommended yearly eye examination, and the number one reason stated is that they “do not see a need” for this step.5 The American Academy of Ophthalmology suggests this number may be as high as 40%.6

These figures confirm that optometrists are more important than ever in helping to manage the volume of patients, because the implications for undiagnosed disease are dire: left unmonitored, patients can quickly lose vision that even the most aggressive treatment will not restore. Moreover, if a patient is losing vision as a consequence of uncontrolled disease, he or she is also at greater risk for systemic complications as a result of uncontrolled disease: every percentage reduction in glycosylated hemoglobin (A1C) reduces the risk of microvascular complications by almost 40%, and for every 10 mm Hg decrease in systolic blood pressure, the risk of diabetes complications drops 12%.7,8

In the pages that follow, the expert panel and I review the emerging evidence regarding early diagnosis and treatment, as well as the criteria for when patients should be referred for treatment. We also discuss the important role optometrists can play in educating patients about their disease.

Mark Dunbar, OD: From a historical perspective, what was the importance of the Early Treatment of Diabetic Retinopathy Study (ETDRS), and how did that shape practice patterns and referral guidelines?

Leo Semes, OD: At the time the ETDRS was conducted, it was widely speculated that laser was beneficial for treating diabetic retinopathy (DR), but there were very little published data. The ETDRS investigators sought to evaluate argon laser photocoagulation in the management of patients with nonproliferative DR (NPDR) or early proliferative DR (PDR). The study actually followed the Diabetic Retinopathy Study effort, which concluded that laser helped slow severe vision loss.9–13 The ETDRS had three objectives: (1) to determine when in the course of DR it was most effective to initiate photocoagulation therapy to slow the progression of DR; (2) to determine if focal laser photocoagulation was effective in the treatment of macular edema (ME); and (3) to study if aspirin was effective in altering the course of DR. Although the aspirin question never became significant, there were several important findings from the ETDRS, with implications for both the retinal physician community and for optometrists.

As for treatment, it was shown that early panretinal photocoagulation (PRP) reduced the risk of severe vision loss by about 23%, and early PRP resulted in a significant reduction in the rate of developing high-risk PDR compared with deferral of photocoagulation.14 Using focal laser treatment for ME (specifically, clinically significant ME [CSME]), which was predefined in the ETDRS, reduced the risk of moderate vision loss by at least 50%. The ETDRS established that laser treatment reduces vision loss but also that laser was not good for restoring lost vision: Fewer than 3% of those treated with laser had a greater than 15-letter increase in vision.

For practicing optometrists, the most important point learned from the ETDRS was the criteria for CSME. (See ETDRS Criteria for CSME.) At the time, these definitions were crucial for understanding what was going on in a patient’s eye. Of course, they are also inherently limited, because the clinical examination is not always conducted under ideal conditions. For instance, poor dilation or a cloudy media may obscure the surgeon’s view. And this is why we are fortunate to now have optical coherence tomography (OCT) at our disposal for identifying CSME, which, of course, we call center-involving ME (Figure 1).

Dr. Dunbar: In the era of OCT, what is the potential role of establishing a diagnosis of CSME?

Jay M. Haynie, OD: CSME is still relevant because it is a helpful data point for building a risk profile. We know from studies what happens to untreated patients who have CSME. For those who do not use OCT, CSME is even more important.

**ETDRS Criteria for CSME**

The Early Treatment of Diabetic Retinopathy Study (ETDRS) investigators developed three criteria for diagnosing clinically significant macular edema:

1. Retinal thickening within 500 µm of the center of the foveal avascular zone
2. Hard exudates associated with retinal thickening within 500 µm from the center of the foveal avascular zone
3. Zones of retinal thickening at least a disc area in size, any part of which is one disc diameter from the center of the fovea
Steven G. Ferrucci, OD: I still teach residents about CSME and how to identify it based on the three definitions. However, the advent of OCT really drove appreciation for whether the edema was affecting the macula. I think it becomes easier with experience to recognize ME, but very mild edema is still extremely difficult to recognize. For that reason, I still think that CSME is important to teach to residents and that it is useful for understanding the complete picture.

A. Paul Chous, OD: How do you define “center involved”? Does it have to be in the foveal center?

Dr. Ferrucci: I interpret “center involved” to mean that the ME is actually in the fovea.

Dr. Chous: I agree, and I use those criteria in my clinic as well.

Dr. Haynie: OCT thickness maps are divided into subfields. Any edema that involves the very central subfield would be, by definition, center involved, and if it does not involve the central subfield, but involves the four parafoveal subfields, then it is not center involved (Figure 2).

Dr. Dunbar: OCT has certainly changed the paradigm, but there are some estimates that fewer than half of practicing optometrists have the technology in their clinics, which may mean that the classic definition of CSME is still relevant. However, discovering retinal thickening on clinical examination can be technically challenging. Do you have any perspective on what retinal thickening may look like clinically or how to identify it without the benefit of OCT?

Dr. Semes: Use of a very fine beam at the slit lamp in conjunction with a +78.00 D or +60.00 D lens and moving that beam from the disc across to the macula may help in appreciating retinal thickening. Look for distortion or thickening within that beam to see where any portion of the retina might be farther away from the retinal pigment epithelium than the surrounding normal retina.

Dr. Chous: An additional step that may be helpful is to offset the illumination, which essentially creates an optic section through the retinal tissue. An interesting article published in *Optometry and Vision Science* also showed that any hard exudate within 1,000 µm of the foveal center is highly predictive of CSME diagnosed by seven-field stereo photography. 

Dr. Haynie: Noting the color of the retinal tissue may be helpful. The retina is transparent, and in the absence of thickening, edema, or cystic changes, the retinal vasculature, retinal pigment epithelium, and, sometimes, the choroid are apparent. When there is thickening in the retina, however, whether due to fluid or cystoid edema, the posterior details become less obvious, if they are seen at all.

**REFERRAL CRITERIA**

Dr. Dunbar: In my view, both center-involved and noncenter-involved ME are clinically significant, although perhaps for different reasons. Center-involved is typically treated more aggressively with pharmacotherapeutics, while there is more of a risk-benefit analysis for patients with noncenter-involved ME in terms of treatment. Those with noncenter-involved ME have to be watched closely for signs of progression, but do they need to be referred promptly or can they be observed by the optometrist?

Dr. Haynie: For providers not using OCT, if they have a patient with ME that meets one of the three criteria for CSME, I think there is an obligation to refer that patient. For those using OCT, if they have a patient with noncenter-involved ME, other factors become important. For example, the compliance of the patient: Is the patient going to come back in 2 months for follow-up? Also, the A1C level and general control of the diabetes, which can be viewed as risk factors—those with a higher risk profile warrant a more prompt referral. For the optometrist in the
community, I do not see a problem with following noncenter-involved ME as long as it is watched closely. Once an increase in ME has been documented, whether it is noncenter-involved ME or not, referral is most likely needed, given that the barrier for initiating treatment is much lower today than compared to historical precedent.

**Dr. Chous:** I tell patients that the retina is essentially like a sponge, and if it swells up with fluid, the quality of what you can see gets degraded. If a patient needs treatment, I emphasize that we are trying to prevent vision loss. However, vision is not the only guide for initiating treatment—in fact, some in the retina community are more aggressive in treating mild ME in the presence of good vision. My preference is to err on the side of caution and refer early when any risk factors are present, and there are several important ones to be aware of. Obviously, the higher the A1C level, the higher the risk for the disease process to initiate and progress. Other risk factors include whether the patient has type 1 or type 2 diabetes, as the prevalence of diabetic macular edema (DME) is higher in patients with type 1 disease, although the major burden of disease is among those with type 2 based on sheer numbers of patients. The epidemiological evidence suggests that patients with type 1 diabetes have a higher risk for progression to center-involved DME. Ethnicity is important, as people of color have a higher risk, and a body mass index higher than 30 can confer a significantly greater likelihood of developing proliferative disease in patients with type 2 diabetes, according to some reports. Dyslipidemia, hypertension, and presence of obstructive sleep apnea are other important risk factors.

(See Diabetes: By the Numbers.)

**Dr. Dunbar:** Do you have a preferred time frame for when a patient should follow-up with a retina specialist? A couple weeks? Four weeks? Six weeks?

**Dr. Ferrucci:** I do not think there is a right or wrong answer. Edema from diabetes tends to develop relatively slowly. But there is also no sense in waiting, especially if compliance may be an issue.

**Diabetes: By the Numbers**

- Diabetes mellitus affects 9.3% of the US population (29.1 million people) and is the seventh leading cause of death in the United States.
- Thirty-eight percent of US adults have prediabetes, and 83% of adults over the age of 65 have diabetes or prediabetes.
- Worldwide, more than 422,000,000 individuals have type 2 diabetes.
- Patients with diabetes have rates of stroke and death due to cardiovascular disease that are approximately 1.5 and 1.7 times higher than those without diabetes. Diabetes also puts one at higher risk for lower limb amputation, neuropathy, and nephropathy.
- About 21% of those with diabetes will also develop diabetic retinopathy, and roughly 5% of those will suffer severe vision loss.


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**Dr. Semes:** I try to explain the urgency to the patient using an analogy: Having fluid in the eye is like having a flood in your basement. The longer it is there, the more damage it is going to do. In terms of urgency, if there is an inversion of foveal contour, observed at clinical evaluation or demonstrated on OCT, then I would like to see that patient have the appointment within a 2-week period. This recommendation is consistent with clinical guidelines.

**Dr. Dunbar:** Obviously, the patient with PDR should be referred, but are there scenarios for referring those with NPDR as well?

**Dr. Ferrucci:** Yes. One situation I can think of immediately is the patient with NPDR in whom a fluorescein angiogram or a widefield fluorescein angiography shows signs of ischemia. Some retina specialists want to start treatment in that case, and so earlier referral is indicated.

**Dr. Haynie:** My sense is that retina surgeons are more aggressive with the severe and very severe NPDR cases because they will eventually evolve into proliferative, sight-threatening DR. So why wait until the patient has neovascularization or a vitreous hemorrhage?

**Dr. Semes:** We also need to acknowledge cost. We are in an age of medicine where there is increasing pressure to protect our health care resources, which in practical terms means finding patients earlier in the disease course so that intervention can be started and evolution of the disease process can be slowed or halted. For the patient with diabetic eye disease, it is incumbent on us to find patients earlier so that evolution to proliferative disease that can lead to sight-threatening complications is averted. Referring a patient with advancing or advanced NPDR for potential treatment may be in the patient’s best interest, but it may also be prudent in terms of preventing an outcome that will be more burdensome to the system. This is a lower threat level than center-involving ME, which as we have noted earlier, is a significant vision-threatening finding.

**Dr. Dunbar:** Who makes the actual appointment for the patient? Do you have your staff do that, or do you hand the patient a card with a name on it and rely on him or her to follow up?

**Dr. Semes:** We have a staff person make the appointment so that the patient has an appointment time when they leave the clinic.

**Dr. Chous:** I have my front desk call, and if I am not busy, I will make the call myself. I also like to follow-up with the patient personally to make sure they were seen. I have had many patients with a number of different conditions who did not keep their appointments, so it is good optometric management to follow-up with patients to make sure they kept an appointment, especially if they have a sight-threatening condition.

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**THE EVOLUTION OF THERAPY FOR CENTER-INVOLVED DME**

**Dr. Dunbar:** To the great benefit of our patients, the treatment paradigm for those with center-involved DME has evolved tremendously. Without question, the gold standard for managing patients with center-involved DME is antivascular endothelial growth factor (anti-VEGF) therapy, of which there are a few options. Having several
### OVERVIEW OF MEDICATIONS FOR TREATMENT OF DIABETES

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<tr>
<th>CLASS</th>
<th>MECHANISM OF ACTION</th>
<th>EXAMPLES</th>
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<tr>
<td><strong>Oral Agents</strong></td>
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<tr>
<td>Biguanides</td>
<td>Decrease hepatic glucose production, decrease intestinal glucose absorption, and</td>
<td>Metformin</td>
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<td></td>
<td>improve insulin sensitivity.</td>
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<tr>
<td>α-glucosidase inhibitors</td>
<td>Impair the digestion and utilization of dietary carbohydrates, but usually only</td>
<td>Acarbose, miglitol</td>
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<td>offer modest efficacy, require frequent administration (with every meal), and have</td>
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<td></td>
<td>GI side effects.</td>
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<td>Sulfonylureas</td>
<td>Boost secretion of insulin from the pancreas, but have GI side effects, are</td>
<td>Glipizide, glyburide, glimepiride</td>
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<td></td>
<td>associated with weight gain, and increase the risk of hypoglycemia.</td>
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<tr>
<td>Meglitinides</td>
<td>Result in enhanced insulin production, but have similar side effects to those seen</td>
<td>Repaglinide, nateglinide</td>
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<td></td>
<td>with sulfonylureas.</td>
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<tr>
<td>Thiazolidinediones</td>
<td>Improve glucose utilization and insulin sensitivity in the muscle and fat cells;</td>
<td>Pioglitazone, rosiglitazone</td>
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<td>class is generally well-tolerated, but has been linked to fluid retention,</td>
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<td></td>
<td>hepatotoxicity, and heart failure.</td>
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<td>DPP-4 inhibitors</td>
<td>Delay breakdown of incretins—gut hormones that normally stimulate insulin release</td>
<td><em>Staglinit</em>,  <em>saxagliptin</em>, <em>linagliptin</em>, <em>alagliflozin</em></td>
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<td>(dipeptidyl peptidase-4</td>
<td>from the pancreas. They are generally well-tolerated, although some GI issues have</td>
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<td>inhibitors)</td>
<td>been reported.</td>
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<td>SGLT2 inhibitors</td>
<td>Reduce the ability of kidneys to reabsorb glucose from the urine, and are associated</td>
<td>Canagliflozin, dapagliflozin, empagliflozin</td>
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<td>(sodium-glucose</td>
<td>with weight loss; has been linked to increased urinary tract infections and carries a</td>
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<td>cotransporter 2 inhibitors)</td>
<td>a low risk of diabetic ketoacidosis.</td>
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<td><strong>Injectable Noninsulin Agents</strong></td>
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<tr>
<td>GLP-1 agonists (incretin mimetics)</td>
<td>Mimic the action of the GLP-1 incretin to stimulate the release of insulin. GLP-1 agonists have robust blood glucose–lowering properties, promote weight loss, and are generally well-tolerated, with transient nausea being reported as the most frequent side effect.</td>
<td><em>Liraglutide</em>, <em>exenatide</em>, <em>exenatide ER</em>, <em>dulaglutide</em>, <em>albiglutide</em></td>
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<td>Amylin analogs</td>
<td>Promote glucose absorption of cells and reduce breakdown of glucose reservoirs by</td>
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<td>slowing the process of gastric emptying. The most frequent side effects that have</td>
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<td>been reported are nausea and vomiting.</td>
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<td><strong>Insulin therapy</strong></td>
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<td>Basal insulin</td>
<td>Glargine, detemir, glargine U-300</td>
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<td>Rapid-acting insulin analogs</td>
<td>Aspart, lispro, glulisine, lispro U-200</td>
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<td>Premixed insulin</td>
<td>70:30, 75:25, 50:50</td>
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<td>Regular insulin</td>
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<td>Inhaled insulin</td>
<td>Afrezza</td>
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*According to the American Association of Clinical Endocrinologists comprehensive diabetes management algorithm 2013 consensus statement:

- Patients with hemoglobin A1C > 8%, patients on two or more oral antidiabetic drugs or on GLP-1 therapy, and patients with long-standing type 2 diabetes who are unlikely to achieve their A1C goal may have a single daily dose of basal insulin added to their regimen.
- Rapid-acting insulin analogs begin working about 15 minutes after injection and peak in about 1 hour. They are superior to regular insulin because they are more predictable.
- A popular insulin regimen is to use a premixed insulin formulation in which rapid- and long-acting components are included in the same vial or pen.
- Regular or short-acting insulin usually reaches the bloodstream within 30 minutes after injection and peaks anywhere from 2 to 3 hours after injection.
- In 2015, an inhaled insulin, Afrezza, became available in the United States. Afrezza is a rapid-acting insulin that begins working within 12 to 15 minutes and peaks by 30 minutes.

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options within this category is a good problem to have, as patients may experience individualized responses to therapy. In addition, new steroid formulations and delivery mechanisms further expand the treatment possibilities. When it comes time to educate patients, what information do we need to know to communicate effectively?

**Dr. Chous:** First, we should communicate to our patient the tremendous benefit they can achieve for their visual outcomes by gaining control of their systemic disease. The ACCORD Study showed that patients who gain intensive glycemic and dyslipidemia control have slower progression of DR. The American Diabetes Association recommends that patients optimize glycemic and blood pressure to slow progression of retinopathy and that they should know their “ABCs”—meaning, A1C level, blood pressure, and cholesterol levels. I recommend anyone managing patients with diabetic eye disease become familiar with the American Diabetes Association’s guidance on screening and treatment. Doctors may also wish to have a general understanding of the types of medications used for diabetes treatment so they can have informed conversations with patients (see *Overview of Medications for Treatment of Diabetes*).

There is an ever-expanding array of research in diabetic eye disease, which, as you noted, is a good problem. It behooves the optometrist who manages these patients to stay up to date on the published literature, and the recent Protocol T study is a good example. The most important take-away point from this study is that it showed each of the anti-VEGF agents—bevacizumab, aflibercept, and ranibizumab—helped restore vision in the trial participants. However, the finer points of the study changed from year 1 to 2. Overall, after 1 year, patients gained about 13 more letters in the aflibercept group, about 11 letters in the ranibizumab group, and about 10 letters in the bevacizumab group.

When patients were stratified according to their baseline visual acuity, those who started with 20/50 or worse vision had significantly better vision when they were treated with aflibercept compared to either ranibizumab or bevacizumab. If one had stopped right there, there might be a very different impression about the implications of Protocol T for patient management. As we learned when the year 2 data were published, many of those differences disappeared. There were not statistically significant differences between the three drugs, including patients who were 20/50 or worse at baseline. On the other hand, it was apparent that both branded medications outperformed the nonbranded option. In terms of practical application in the clinic, is the extra letter gain on the ETDRS chart with branded versus nonbranded medication enough to justify the additional expense? To me, the answer really is, “it depends.” For the patient with just one eye or for the patient who is just barely legal to drive a car, that extra cost may be entirely justifiable.

**Dr. Ferrucci:** A recent analysis showed that aflibercept and ranibizumab are not cost effective relative to bevacizumab for DME unless prices decrease substantially. The investigators suggested a price drop of about 60% to 80% before the analysis changed. But even with that in mind, every patient is different. It is possible that patients may not respond to bevacizumab, and there may be extenuating circumstances that would push the treatment decision to a branded option.

**Dr. Dunbar:** There may be a temptation to correlate the anti-VEGF therapy treatment effects in diabetes with other diseases, such as wet age-related macular degeneration and retinal vein occlusion, but doing so may not be realistic or even practical, because each of these conditions produce varying amounts of VEGF. For example, the CATT study showed almost no difference between ranibizumab and bevacizumab for treatment of age-related macular degeneration, but that was likely because both drugs are powerful enough to suppress the level of VEGF expression in that disease state. In diabetic eye disease and retinal vascular disease, VEGF expression is comparatively higher, and therefore, the greater potency available with ranibizumab or aflibercept may be needed.

As we talk about bringing study data into the real world, we need to consider that the treatment schemas are going to be different. RISE and RIDE employed a monthly schedule, and VIVID and VISTA showed favorable results with dosing every 6 weeks after a loading regimen. But patients can be unpredictable regarding how they attend their clinical appointments, so I think it is fair to ask whether there are scenarios having to do with compliance in which a more potent branded drug may be preferable. Based on my own observations in the clinic, I sense that patients treated with either of the branded medications recover vision a little faster, and the drugs stay on board a little longer, which allows the option to treat and extend. There are fewer injections over a 2- or 3-year period compared with bevacizumab, which we saw in year 2 of Protocol T.

**Dr. Haynie:** In our practice, a patient newly diagnosed with DME with vision better than 20/50 will receive bevacizumab. If the vision is worse than 20/50, the retina surgeons prefer to use a branded medication—in our clinic, they use aflibercept—for a year or so before switching the patient over to bevacizumab. As Dr. Semes suggested earlier, if the basement is flooded, the sooner you get the water out, the better. For this reason, retina surgeons are very aggressive at the beginning.

**Dr. Dunbar:** What is the role of steroids in the treatment of patients with DME?

**Dr. Haynie:** Steroids are playing a larger role in our practice, and if a patient receives three serial injections, 1 month apart, and still has persistent fluid, my surgeons will use either intravitreal triamcinolone acetonide (the preservative-free single dose injection), or they will go with a steroid implant, such as the dexamethasone implant, as an adjunct to treatment.

**Dr. Chous:** The results of the so-called EARLY Analysis of Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol I study may be worth mentioning here, which found that if we are not achieving visual acuity gains within the first three injections, then continuing anti-VEGF injections with the same drug is unlikely to provide a benefit. Simply put, some patients should be tried on a different anti-VEGF agent earlier, and some just do not respond to anti-VEGF therapy. Another way to look at this is that half of patients with DME do not achieve a good response to anti-VEGF injections, and a significant percentage do not have dramatically elevated levels of vitreous VEGF, and so something else may be
driving their disease process.\textsuperscript{34} We have to be aware that sometimes these treatments do not work, and there may be a need to move on to other therapies.

**Dr. Ferrucci:** What do your surgeons think about using the dexamethasone implant in patients with concurrent glaucoma?

**Dr. Haynie:** They consider glaucoma to be an absolute contraindication to using the implant.

**Dr. Ferrucci:** The surgeons I work with have the same mindset. If there is concurrent glaucoma, they will not inject a steroid in the vitreous cavity, even if the patient is a nonresponder to topical drops. Our surgeons are also less aggressive with steroids in the phakic patients versus those who are pseudophakic, knowing the risk for inducing a posterior subcapsular cataract.

**Dr. Dunbar:** Unfortunately, if you need a steroid because your anti-VEGF drug is not working, it likely means the disease process is pretty well advanced, and there is most likely a poor prognosis in terms of visual outcomes. The good news, however, is that steroids can nevertheless be effective in select patients to achieve at least a modicum of improved vision.

**Dr. Semes:** This discussion reinforces that while we have guidance from clinical trials, there are a number of options for patients, and these individuals have to be managed on a case-by-case basis.

**TREATMENT AND MANAGEMENT DECISIONS FOR PDR**

**Dr. Dunbar:** One of the emerging trends in the treatment of diabetic eye disease is the use of anti-VEGF drugs in patients with DR in the presence of DME.\textsuperscript{15,16} For those with mild or moderate NPDR, we can look to guidelines from the American Optometric Association\textsuperscript{17} and the American Academy of Ophthalmology\textsuperscript{18} for how to manage these patients: annual examination, education about A1C levels, explaining the risk factors, and making sure the endocrinologist or primary care provider is aware of the changes. For severe NPDR, we should be aware of the greater risk for proliferative disease,\textsuperscript{27,19} hence the need to see these patients every 3 to 4 months.

In addition, the DRCR.net Protocol S study showed that ranibizumab was noninferior to laser in visual acuity change at 2 years for treatment of patients with PDR. However, mean peripheral visual field sensitivity loss was worse, and vitrectomy and DME development were more frequent among patients in the laser group.\textsuperscript{40} Given that patients with PDR may respond well to PRP with reductions in neovascularization, but the risk of visual field loss and developing poor night vision is high, do intravitreal injections offer an alternate approach?

**Dr. Semes:** It may depend on the goal of therapy. The goal of PRP is to preserve the macula, but you correctly identified some of the very significant limitations. Number one is going to be reduced visual field, and number two is going to be reduced dark adaptation and vision in limited light settings. There is naturally some give-and-take with the use of laser for PRP that is not necessarily part of the treatment decisions when using anti-VEGF agents.

**Dr. Dunbar:** And yet the burden of treatment may be an important consideration. In Protocol S, in the ranibizumab group, eyes without DME received a median 10 injections through 2 years, and those with DME received a median 14 injections. In the PRP group, there were 92 eyes that required an additional laser session after a median 7 months, and 72 eyes required ranibizumab for treatment of DME. Even still, there were far fewer clinical visits for treatment in the laser group compared with the ranibizumab group.

**Dr. Ferrucci:** Patients’ compliance should be an important consideration, as the pharmacotherapy options are only truly effective if patients commit to follow-up. While this is equally true of medical therapy and laser alike, there will likely need to be some criteria that helps to determine which patients will be sufficiently compliant for use of an anti-VEGF agent instead of laser.

**Dr. Dunbar:** Does anyone foresee a time when anti-VEGF drugs would supplant traditional PRP for PDR? Or will the potential for noncompliance dictate a continuing place for laser in treatment?

**Dr. Chous:** I think that use of anti-VEGFs could present challenges among this specific patient population. A lot of patients with PDR are coming into the clinic with A1C levels above 9% or 10%, and unfortunately, poor A1C may be a tip-off to poor compliance. There is an argument for using laser in some cases because it may be more protective against terrible outcomes among noncompliant patients. In addition, poor compliance or adherence to therapy may not be totally the patients’ fault. Think of the patient who opts for anti-VEGF instead of laser, but who after one injection decides that the copay is too burdensome. He or she skips the next appointment and return to the clinic 16 months later with a detached retina. How do we best serve patients like that who may fall through the cracks? I have had a few patients in this exact scenario.

I would like to add that some of the secondary outcomes of Protocol S in terms of avoiding night vision loss and loss of visual field speak to quality of vision and quality-of-life issues. Interestingly, I recently heard a presentation by one of the DRCR.net investigators who was involved in Protocol S about unpublished quality-of-vision surveys conducted as part of the study. The investigators found that those in the ranibizumab group were happy with the quality of their vision, but the outcome was not statistically significant compared with the laser group.\textsuperscript{41} That sort of flies in the face of what we might expect, but then again, what were these patients comparing their vision to if they only received an intravitreal injection and never had laser? As a patient who had multiple rounds of PRP in the mid-1980s and who has experienced significant degradation of scotopic vision, I would certainly opt for anti-VEGF therapy in favor of less laser.

**Dr. Ferrucci:** The idea that you can potentially save retinal function by doing injections instead of laser is obviously appealing. This was a 2-year study, and I think we need to know what is happening at 5 or 10 years before we really know if intravitreal injection of anti-VEGF drugs for patients with PDR is a viable strategy. I also do not think we can forget cost as an important element in this decision as well, especially as we consider what burden may fall on the patient.
Dr. Chous: If there is concurrent DME and PDR, then anti-VEGF injections make a lot more sense. Both ranibizumab and aflibercept are indicated and approved for treatment of DR in the presence of DME, which may be a clue to how they should be used.

Dr. Dunbar: It is interesting that the rate of vitrectomy was higher in the laser versus ranibizumab group. 15% to 4%. Quality of vision may be difficult to gauge or predict, but if we can prevent the need for patients to go back to the OR, maybe that becomes important.

Dr. Haynie: In our clinic, the decision to go with an intravitreal anti-VEGF for PDR versus PRP depends on how the patient appears at baseline. If a patient has marked capillary nonperfusion and/or large fonds of neovascularization, our surgeons use PRP in conjunction with anti-VEGF injections. Intravitreal injections are used more commonly as monotherapy in those who tend to get diagnosed earlier—patients who might have severe NPDR but only mild neovascularization in the arcades. We have found that those patients can be treated with intravitreal agents and can remain stable for years with an intravitreal injection every 4 to 6 months. We will repeat the fluorescein angiogram 6 months after the anti-VEGF injection to see how things are going, but in most cases, a single intravitreal injection can slow the development of PDR.

Dr. Dunbar: My sense is that there is an emerging interest in trying to get patients back down the ladder a bit: catching the patient with PDR early so that treatment has a chance to get him or her back to NPDR, or intervening when the patient is in the severe NPDR category to try and get him or her to the moderate stage. If you can take that patient with severe symptoms and move him or her back to a moderate or possibly even a mild stage with a periodic injection, that seems like an attractive option and makes you wonder if that may be the future of treating DR.

Dr. Chous: That is a crucial point, but I do not think that should be left to the retina specialist alone, and I think this is where optometrists can be a real asset in this situation. If we are talking about preventing the development of sight-threatening retinopathy, then metabolic control becomes fundamental to that goal. We can and should be counseling patients about the importance of getting blood glucose under control. And the same can be said for sleep apnea, which is an underappreciated risk factor for developing progressive disease. There are estimates that fewer than 30% of those prescribed a sleep apnea device actually use it as recommended.42

We need to educate our patients about this because it obviously increases the risk not only of vision loss but also of dying from a stroke or another cardiovascular cause.

There is also emerging evidence regarding the use of off-label fenta- nifiber therapy to reduce progression of DR to either DME or PDR.43 This strategy has been approved as first-line therapy for NPDR in adults with type 2 diabetes in Australia. These are all options for our patients and opportunities for us as optometrists to educate patients and the other members of the care team about how we can help to improve the quantity and quality of our patients’ lives.

CONCLUSION

Dr. Dunbar: In some regards, the lessons learned during the ETDRS in the 1980s are still very relevant today. We learned almost 3 decades ago that early treatment could help patients save vision. Today, the advent of anti-VEGF medications has changed the agents used in treatment, but not the fundamental principle of early diagnosis and early intervention. If anything, the optometrist’s role in the modern care of diabetic eye disease is even more important. As a profession, we have the greatest access to patients, and our duty as the primary care providers of eye health presents a mandate to recognize early signs of diabetic eye disease, follow and monitor patients closely when appropriate, and to refer them for treatment when necessary.
INSTRUCTIONS FOR CE CREDIT

To receive credit, you must complete the post test and activity evaluation and mail or fax to Evolve Medical Education, PO Box 358, Pine Brook, NJ 07058; Fax: (610) 771-4443. To answer these questions online and receive real-time results, please visit evolvemeded.com and click “Online Courses.” If you are experiencing problems with the online test, please email us at support@evolvemeded.com. Certificates are issued electronically, please provide your email address below.

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INTEGRATED CARE FOR THE DIABETIC PATIENT: HOW TO DIAGNOSE AND MANAGE THE AT-RISK PATIENT PART 2

CE QUESTIONS

1. Results of DRCR.net Protocol T at year 2 showed that:
   a. bevacizumab was superior to ranibizumab and aflibercept for patients with DME
   b. aflibercept was significantly better than ranibizumab and bevacizumab for DME patients with visual acuity of 20/50 or worse at baseline
   c. stroke rates were high in all three groups
   d. baseline acuity did still present differences between the drugs at 2 years

2. Important risk factors for sight-threatening diabetic eye disease include:
   a. poor metabolic control
   b. long diabetes duration
   c. untreated obstructive sleep apnea
   d. obesity
   e. all of the above

3. The “Early Analysis” of DRCR.net Protocol I showed that:
   a. bevacizumab, ranibizumab, and aflibercept are equally effective for PDR
   b. patients with suboptimal response to ranibizumab after three monthly injections for DME were unlikely to achieve the same level of visual improvement as patients who had a robust initial response after three injections when compared at 24 months
   c. patients with poor response to ranibizumab after 6 monthly injections were unlikely to achieve a good response with continued injections at 24 months
   d. none of the above

4. Which treatment(s) are FDA-approved for treating DME?
   a. bevacizumab
   b. ranibizumab
   c. aflibercept
   d. grid and/or focal laser photocoagulation
   e. b, c and d

5. The term CSME is?
   a. still adhered to and focal laser treatment is the most likely treatment
   b. no longer applies to DR classification of ME
   c. slowly being replaced by center- and noncenter-involved ME per OCT imaging
   d. cannot be used if the vision is 20/20 or better

6. Which of the following is most true about the label indication of the anti-VEGF compounds aflibercept and ranibizumab?
   a. They have not been studied in eyes with center-involved ME
   b. They may not be used for treating non-center-involved ME
   c. They are only approved for use with patients who have PDR
   d. They are approved for treating DME as well as DR in the setting of DME

7. In treating DME, Protocol T discussed the use of aflibercept being more advantageous in the first year for patients with?
   a. Vision worse than 20/50
   b. Vision better than 20/50
   c. Vision worse than 20/70
   d. Vision better than 20/70

8. Traditionally, the preferred treatment for CSME is:
   a. fluorescein angiography
   b. panretinal photocoagulation
   c. vitrectomy
   d. macular laser

9. Which of the following statements concerning CSME is true?
   a. It can be treated using prednisolone acetate four times a day
   b. It can occur at any stage of DR
   c. Fluorescein angiography must be performed in order to diagnose CSME
   d. The preferred treatment of CSME is panretinal photocoagulation

10. Which of the following may be a contraindication to using a dexamethasone implant in a patient with CSME?
    a. uncontrolled glaucoma
    b. good visual acuity
    c. cataracts, if cataract surgery is not intended
    d. aphakia

11. Which of the following was not an objective of the ETDRS?
    a. to determine when in the course of DR it is most effective to initiate photocoagulation therapy to slow the progression of DR
    b. to determine if focal laser photocoagulation was effective in the treatment of ME
    c. to study if aspirin was effective in altering the course of DR
    d. to determine the time course to vision loss secondary to CSME

12. PRP showed a positive effect on vision loss. Which of the following is the approximate amount by which it was reduced?
    a. 10%
    b. 25%
    c. 50%
    d. 100%

13. Focal laser to treat ME, specifically CSME, which was pre-defined in the ETDRS, reduced the risk of moderate vision loss by approximately which of the following?
    a. 25%
    b. 50%
    c. 75%
    d. 100%
14. Inversion of foveal contour observed clinically or demonstrated on OCT indicates a recommendation for treatment of center-involving ME. Within which time period should the patient be evaluated according to contemporary clinical guidelines?
   a. 1 day  
   b. 1 week  
   c. 2 weeks  
   d. 1 month

15. Among the visually significant side effects of correctly applied PRP, which of the following is not one of them?
   a. limited peripheral visual field  
   b. prolonged dark adaptation  
   c. central scotoma  
   d. difficulty with night driving

16. What is not a clinical finding seen with moderate NPDR?
   a. microaneurysms  
   b. blot hemorrhages  
   c. venous beading  
   d. retinal neovascularization

17. Which clinical scenario would warrant referral to a retinal specialist?
   a. few microaneurysms and exudate, but no ME and no neovascularization  
   b. few microaneurysms and exudate associated with center-involved ME, but no neovascularization  
   c. extensive retinal hemorrhages, preretinal hemorrhage, and NVD  
   d. both b and c

18. Which treatment below would not be appropriate for a patient who presented with high-risk PDR?
   a. panretinal photocoagulation  
   b. topical prednisolone acetate  
   c. bevacizumab  
   d. aflibercept

19. According to the American Optometric Association’s guidelines, when should a patient with mild NPDR (without macular edema) be seen again for follow-up?
   a. annually  
   b. every 6 months  
   c. every 4 months  
   d. the patient does not need to be seen unless he or she begins to notice changes in vision

20. What should you expect to find in the retina of a patient with poorly controlled type 1 diabetes who presents with hemorrhage, exudate, and a large preretinal hemorrhage?
   a. could be completely normal  
   b. retinal tear  
   c. retinal neovascularization associated with PDR  
   d. choroidal neovascularization

**ACTIVITY EVALUATION**

Did the program meet the following educational objectives?
Determine who is a high-risk patient for the onset of diabetic eye disease  Agree Neutral Disagree
Discuss the importance of conducting yearly dilated exams on diabetic patients  Agree Neutral Disagree
Develop plans to initiate comanagement of the diabetic patient with both ophthalmologists and primary care physicians/endocrinologists  Agree Neutral Disagree
Implement strategies to educate patients on the ocular manifestations of diabetes  Agree Neutral Disagree

Your responses to the questions below will help us evaluate this CE activity. They will provide us with evidence that improvements were made in patient care as a result of this activity.

Do you feel the program was educationally sound and commercially balanced? ___ Yes ___ No
Comments regarding commercial bias:
_____________________________________________________________________________________________________________________________________________________

Rate your knowledge/skill level prior to participating in this course: 5 = High, 1 = Low
Rate your knowledge/skill level after participating in this course: 5 = High, 1 = Low
Would you recommend this program to a colleague? ___ Yes ___ No
Do you feel the information presented will improve/change your patient care? ___ Yes ___ No
Please identify how you will improve/change:
___ Change the management and/or treatment of patients. Please specify:
_____________________________________________________________________________________________________________________________________________________
___ Create/revise protocols, policies, and/or procedures. Please specify:
_____________________________________________________________________________________________________________________________________________________

Please identify any barriers to change.
___ Cost  ___ Reimbursement/insurance issues
___ Lack of consensus or professional guidelines  ___ Lack of resources (equipment)
___ Lack of administrative support  ___ Patient compliance issues
___ Lack of experience  ___ Other. Please specify _________________________
___ Lack of time to assess/counsel patients  ___ No barriers
___ Lack of opportunity (patients)