In a study of 50,254 eyes, baseline features and level of NPDR were associated with 5-year progression to PDR.[113] Eyes with IRMA had an increased HR of developing PDR (HR = 1.77; P = 0.0013) compared with eyes with venous beading, and eyes with 4-quadrants of dot-blot hemorrhages had higher risk for developing vitreous hemorrhage (HR = 3.84; P = 0.0095).[113, 114] For eyes with PDR, the Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol S study found that worse baseline levels of PDR were associated with an increased risk of PDR progressing, regardless of treatment with intravitreal anti-VEGF agents (including those that may or may not treat other targets such as placental growth factor or angiopoietin-2, which will be referred to hereafter as anti-VEGF agents) or panretinal photocoagulation surgery (PRP, also known as scatter laser surgery) (64% [high-risk PDR or worse] vs. 23% [moderate PDR or better]; HR = 3.97; $P < 0.001$). In the PRP group, eyes receiving pattern scan versus conventional single-spot PRP were at higher risk for worsening PDR (60% vs. 39%; HR = 2.04; P = 0.008), regardless of the number of spots placed.[114] Ocular imaging risk factors have been identified. Optical coherence tomography and optical coherence tomography angiography (OCTA) imaging have revealed biomarkers for the progression of DR.

NATURAL HISTORY

Diabetic retinopathy progresses in an orderly fashion from mild to more severe stages when there is not appropriate intervention. It is important to recognize the stages when treatment may be most beneficial. Several decades of clinical research have provided excellent data on the natural course of the disease and on treatment strategies that are 90% effective in preventing the occurrence of severe vision loss (visual acuity < 5/200).[115] The outcomes of key clinical trials form a solid foundation in support of treating DR. The results of these studies are summarized in Appendices 3 and 4. Major studies include the following (see Glossary):

- Diabetes Control and Complications Trial (DCCT)[69, 116, 117]
- Follow-up study to the DCCT titled Epidemiology of Diabetes Interventions and Complications (EDIC)[68, 70, 90, 118, 119]
- Diabetic Retinopathy Study (DRS)[120, 121]
- Early Treatment Diabetic Retinopathy Study (ETDRS)[122-124]
- Diabetic Retinopathy Vitrectomy Study (DRVS)[125]
- Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR)[126]
- Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study[127]
- Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial[128]
- Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocols [129-133]
- United Kingdom Prospective Diabetes Study (UKPDS)[71, 86, 134]

The nonproliferative stages of DR are characterized by retinal vascular related abnormalities such as microaneurysms, intraretinal hemorrhages, venous dilation, and cotton wool spots. Increased retinal vascular permeability that occurs at these or later stages of retinopathy may result in retinal thickening (edema) and lipid deposits (hard exudates). Clinically significant macular edema is a term commonly used to describe retinal thickening and/or adjacent hard exudates that either involve the center of the macula or threaten to involve it. Patients with CSME should be considered for timely treatment when the center of the macula is involved, if retinal thickening and/or hard exudates are close to the center (see Care Process), and if there is associated vision loss or potential for vision loss. Clinically significant macular edema can be divided into center-involved and non-center-involved macular edema. (See Glossary.)

As DR progresses, gradual closure of retinal vessels results in impaired perfusion and retinal ischemia. Signs of increasing ischemia include venous abnormalities (e.g., dilation, beading, loops), IRMA, and more severe and extensive vascular leakage characterized by increasing retinal hemorrhages and exudation. When these signs progress beyond certain defined thresholds, severe NPDR is diagnosed (see Table 1). Such patients should be considered candidates for treatment with PRP or anti-VEGF agents (see Care Process).