Diabetic retinopathy: Prevention and treatment

AUTHORS: Donald J D'Amico, MD, Anjali R Shah, MD
SECTION EDITORS: David M Nathan, MD, Jonathan Trobe, MD
DEPUTY EDITOR: Katya Rubinow, MD

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INTRODUCTION

Diabetic retinopathy is one of the most important causes of vision loss worldwide and is the principal cause of impaired vision in patients between 25 and 74 years of age [1-3]. Several preventive and therapeutic interventions have been evaluated in an attempt to minimize the morbidity associated with diabetic retinopathy and diabetic macular edema (DME), which can occur at any stage or severity of diabetic retinopathy [4].

Prevention and treatment of diabetic retinopathy will be reviewed here. The screening, pathogenesis, and clinical features of diabetic retinopathy are discussed elsewhere. (See "Diabetic retinopathy: Screening" and "Diabetic retinopathy: Classification and clinical features" and "Diabetic retinopathy: Pathogenesis".)

RISK FACTORS

The primary risk factors for development and progression of diabetic retinopathy are (figure 1) [5]:

- Duration of diabetes.
- Level of glycemic management.

Additional risk factors include [6-8]:

- Hypertension.

- The presence of other microvascular complications, such as diabetes-related nephropathy and neuropathy.
- Dyslipidemia.
- Pregnancy, which transiently increases risk and progression. (See "Diabetic retinopathy: Classification and clinical features", section on 'Worsening during pregnancy'.)

Although these risk factors, in particular duration of disease and level of glycemic management, are strongly predictive of the development and severity of retinopathy in populations and controlling these risk factors is important for the prevention of retinopathy, it is difficult to predict the development or rate of progression of retinopathy in a particular individual. As an example, while lower glycated hemoglobin (A1C) levels are associated with a decreased risk of retinopathy development and progression, good glycemic management does not guarantee that retinopathy will not develop. Regular screening remains important, although the frequency of screening may be adjusted based on levels of glycemia (table 1) [9]. (See "Diabetic retinopathy: Screening".)

PREVENTION

Optimizing treatment of systemic conditions in patients with diabetes is essential to prevent vision loss. In patients with diabetes, this includes maintaining both good glycemic and blood pressure management. Statins to control hyperlipidemia are recommended for most patients with type 2 diabetes; however, we do not specifically prescribe lipid-lowering therapy for the treatment or prevention of retinopathy.

Good glycemic management — Good glycemic management is the primary preventive measure in the management of diabetic retinopathy. Diabetic retinopathy occurs exclusively in the setting of hyperglycemia. Multiple studies have demonstrated that lowering A1C reduces the rate and progression of diabetic retinopathy; the better the glycemic control, the greater the benefits (figure 1 and figure 2) [5,10-14]. Even a small decrease in A1C can be beneficial; a 1 percent decrease in A1C reduces the incidence and progression of diabetic retinopathy by approximately 35 and 15 to 25 percent, respectively [11,12,15].

Rapid improvement in longstanding poorly managed diabetes may be associated with a transient worsening of retinopathy and macular edema; however, long-term benefits of reduction in A1C are evident [16-18]. The Diabetes Control and Complications Trial (DCCT) did not find evidence that a slower reduction of glycemia was beneficial [18]. The optimal rate at which A1C should be improved is not clear.

Glycemic goals and microvascular complications are discussed in detail elsewhere. (See "Glycemic management and vascular complications in type 1 diabetes mellitus", section on 'Microvascular disease' and "Glycemic management and vascular complications in type 2 diabetes mellitus", section on 'Microvascular disease'.)

Good blood pressure management — Good blood pressure control decreases the incidence of diabetic retinopathy [13,19] and, in some trials, also slows the rate of progression of diabetic retinopathy and reduces the risk of vitreous hemorrhage [13,20]. For most patients with hypertension, the American Diabetes Association recommends treating to systolic and diastolic blood pressures of <130 and <80 mmHg, respectively, if they can be achieved safely and without significant side effects [21]. There are insufficient data to recommend a specific antihypertensive agent based upon retinopathy endpoints. (See "Treatment of hypertension in patients with diabetes mellitus" and "Overview of general medical care in nonpregnant adults with diabetes mellitus", section on 'Blood pressure control'.)

Lipid-lowering therapy — Although lipid-lowering therapy is not used specifically for the treatment or prevention of retinopathy, most patients with type 2 diabetes will require treatment with statins to control hyperlipidemia and prevent atherosclerotic CVD. The benefit of cholesterol-lowering therapy for the prevention of diabetic retinopathy has not been well established [7,22,23]. In a retrospective study, statins reduced the risk of diabetic macular edema (DME) [7]. Lowering triglyceride levels with fenofibrates may have a beneficial effect [10,13,22,24-26]. As an example, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study, there was a reduction in progression of retinopathy in patients taking fenofibrate group (6.5 versus 10.2 percent with placebo, odds ratio [OR] 0.60, 95% CI 0.42-0.87) [27].

Lipid abnormalities are common in patients with diabetes mellitus, and the optimal therapy of dyslipidemia to reduce the risk of cardiovascular disease is discussed in detail separately. (See "Low-density lipoprotein cholesterol-lowering therapy in the primary prevention of cardiovascular disease" and "Management of low density lipoprotein cholesterol (LDL-C) in the secondary prevention of cardiovascular disease" and "Hypertriglyceridemia in adults: Management".)

Other

- There are several lifestyle modifications that may decrease the incidence and rate of progression of diabetic retinopathy. Regular exercise and increased physical activity may lead to a reduction in retinopathy [28,29]. Although activities resulting in a Valsalva maneuver may precipitate a vitreous hemorrhage in patients with unstable proliferative

retinopathy [30,31]; the benefits of exercise are likely to outweigh the low potential risk. (Temporary activity restrictions are recommended in cases of acute vitreous hemorrhage to achieve a more rapid short-term improvement in visual acuity). (See 'Vitreous hemorrhage' below.)

- Sleep apnea is associated with increased retinopathy, and treatment of obstructive sleep apnea may reduce risk of development and progression [32,33].

- Reduction of systemic fluid volume and systemic uremia achieved by initiation of hemodialysis and peritoneal dialysis in cases of kidney insufficiency has been associated with reduction in DME [34-36]. Though similar effects have been reported with the use of diuretics such as furosemide [37], good data are lacking.

- Because ischemia contributes to the ocular complications of diabetes, the use of antiplatelet agents has been studied as a possible treatment strategy, as well as for safety issues. However, a systematic review found that aspirin had no beneficial or harmful effect on the development or progression of proliferative retinopathy, vitreous bleeding, or visual loss [38]. Thus, there are no ophthalmic contraindications to aspirin therapy in diabetic patients, in whom aspirin is an important drug for cardiovascular risk reduction. The use of antiplatelet or anticoagulant medication in patients undergoing elective ophthalmic surgery or intravitreal injections is reviewed below. (See 'Patients taking antiplatelet or anticoagulant medication' below and "Overview of general medical care in nonpregnant adults with diabetes mellitus", section on 'Aspirin'.)

TREATMENT

The goals of treatment of diabetic retinopathy include improvement in vision, preservation of vision, and reduction in the rate of progression and frequency of retinopathy, vitreous hemorrhage, and macular edema.

With proper screening, good glucose and blood pressure management, and early intervention with both surgical and pharmacologic therapies, severe visual loss can be avoided in many patients. For the ophthalmologist, a management strategy must be tailored for each patient to maximize vision preservation and minimize side effects, based upon each patient's unique manifestations and progression of diabetic retinopathy.

Diabetic macular edema — Diabetic macular edema (DME) is defined as the presence of intraretinal fluid (edema) and thickening involving the macula, the part of the retina responsible for central vision (table 2). It is a vision-threatening complication of diabetes and can occur at

any stage or severity of diabetic retinopathy. Edema that is centrally located within the macula can be associated with more substantial decreases in visual acuity.

DME is diagnosed using clinical examination and optical coherence tomography (OCT) (image 1), which has greatly improved the detection and quantification of DME. In many studies, the term center-involving DME (CI-DME) is used to define edema that is located in the center of the macula on OCT. The term clinically significant macular edema (CSME) is an older terminology that was used when the diagnosis of DME was based on specific criteria on fundus examination alone (table 2). However, the term has little relevance today with the use of OCT for detection of DME.

Macular edema without visual acuity impairment — Routine prophylactic treatment of DME that is not associated with impaired visual acuity is not recommended. For such patients, treatment can be individualized (observation versus active therapy) with shared decision-making between clinician and patient. Observation is appropriate for asymptomatic patients with center-involving DME and visual acuity of 20/25 or better. In a trial comparing intravitreal aflibercept, focal/grid laser photocoagulation, or observation in 702 adults with center-involving DME and good visual acuity (20/25 or better), there was no difference in vision loss at two years among the three groups (eyes with a ≥5-letter visual acuity decrease occurred in 16, 17, and 19 percent, respectively) [39].

Macular edema with visual acuity impairment — For most patients with DME and impaired visual acuity, we recommend intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents as initial therapy (see 'Anti-VEGF agents' below). Patients treated with VEGF inhibitors may require multiple injections over a period of months to years and therefore require regular follow-up appointments. Focal laser photocoagulation could be considered as initial therapy in poorly compliant patients with DME, who may not return for follow-up appointments. (See 'Focal photocoagulation' below.)

In a meta-analysis of 18 trials comparing a VEGF inhibitor (pegaptanib, bevacizumab, ranibizumab, aflibercept) with another treatment, sham treatment, or no treatment in patients with DME, VEGF inhibitors both increased the chances of gaining three or more lines of vision and decreased the risk of losing three or more lines [40,41]. Specifically, compared with grid laser photocoagulation, anti-VEGF drugs (bevacizumab, ranibizumab, aflibercept) increased the chance of gaining three or more lines of vision at one year (10 trials, 27.4 versus 7.7 percent, relative risk [RR] 3.6, 95% CI 2.7-4.8) and decreased the risk of losing three or more lines (7 trials, 1 versus 11.5 percent, RR 0.11, 95% CI 0.05-0.24).

Anti-VEGF agents — Intravitreal ranibizumab, aflibercept, and brolucizumab are approved by the US Food and Drug Administration (FDA) and European Medicines Agency for treatment of DME. Bevacizumab is used off-label for the treatment of DME, but it must be repackaged in much smaller aliquots containing a small fraction of the systemic dose used in cancer therapy [42]. Faricimab is a bispecific antibody that inhibits VEGF-A and angiopoietin-2 pathways. It was approved by the FDA for the treatment of DME in early 2022 [43].

- **Choice of agent** – Given the wide disparity in cost between the FDA-approved and off-label anti-VEGF agents, retina specialists must consider cost of care, as well as published treatment efficacy and the specific details of a patient's ophthalmic history and retinal examination in making the choice between drugs for a given patient. It is important to note that, at any level of visual acuity, an individual patient may see an improved response with a second or third drug after failing to respond to initial treatment with any of the three drugs.

  There are few head-to-head trial data to guide selection of an individual VEGF inhibitor [42-47]. As examples:

  - In one comparison trial, all three drugs had similar efficacy when visual acuity was better than 20/50 (approximately +8 letters at one year), but when the baseline visual acuity was 20/50 or worse, aflibercept improved visual acuity more than the other two drugs (+19 versus +12 letters with bevacizumab and +19 versus +14 letters with ranibizumab) [42]. There was no difference in improvement in visual acuity between ranibizumab and bevacizumab.

    The median number of intravitreal injections was similar among the three drugs (9, 10, and 10 in the aflibercept, bevacizumab, and ranibizumab groups, respectively). Laser photocoagulation was performed in fewer aflibercept-treated eyes (37, 56, and 46 percent of aflibercept-, bevacizumab-, and ranibizumab-treated eyes, respectively). Rates of adverse events were generally low and similar among the three groups.

  - In a subsequent trial, patients with moderate vision loss were randomly assigned to aflibercept or a progressive regimen (bevacizumab first, with a switch to the more costly aflibercept if specific ophthalmic criteria [eg, change in retinal thickness, change in visual acuity] for suboptimal response were met) [44]. Over two years, the mean improvement in visual acuity was similar in the two groups. During the trial, 70 percent of eyes in the bevacizumab group were switched to aflibercept.

  - In phase III clinical trials comparing faricimab (injected at intervals of three to four months) with aflibercept (injected every eight weeks), there was similar improvement in

visual acuity [43]. About one-half of patients treated with faricimab for DME achieved dosing schedules of every four months.

- **Adverse effects of VEGF inhibitors** – Potential adverse effects of VEGF inhibitors include transient increases in intraocular pressure and injection-related infectious endophthalmitis. Rare cases of retinal vasculitis with or without occlusion also have been reported. In one trial, elevation in intraocular pressure of 10 mmHg or more from baseline occurred in 9 to 12 percent of patients [42]. Endophthalmitis is uncommon, with reported rates ranging from 0.056 to 0.8 percent of patients. In one early study, endophthalmitis occurred as a complication of treatment in 0.8 percent of patients receiving the study drug [48-51]. Intraocular injections are performed in the clinic with local, topical anesthesia. Although most patients tolerate these procedures well, there can often be mild discomfort (eg, burning, stinging, tearing, and mild pain) in the injected eye for approximately 24 hours after the procedure.

  Initial data from patients treated with ranibizumab and bevacizumab for age-related macular degeneration suggested a higher risk of stroke, possibly associated with a transient increase in blood pressure noted after treatment. Additionally, on-label use of bevacizumab for the treatment of cancer is associated with transient ischemic attack and ischemic stroke [52]; however, this has not been demonstrated in clinical trials. Meta-analyses of trials comparing VEGF inhibitors with either sham or photocoagulation for DME (nine trials) did not show a significant difference for arterial thromboembolic events (RR 0.85, 95% CI 0.56-1.28) or overall mortality (33 events in 1262 patients versus 20 events in 897 patients, RR 0.95, 95% CI 0.52-1.74) [53].

- **Treatment burden** – A primary challenge of VEGF inhibitor therapy is the need for repeated intravitreal injections, which contributes to nonadherence and undertreatment. Alternative dosing regimens may help ease this treatment burden [54,55]. For example, in a 48-week trial in 660 adults (mean age 62.3 years) with type 1 or type 2 diabetes and center involved DME, participants were randomly assigned to one of the following aflibercept regimens: 2 mg every 8 weeks, 8 mg every 12 weeks, or 8 mg every 16 weeks [54]. Each of the regimens followed initial treatment with three, once-monthly aflibercept treatments. Improvement in visual acuity was similar among treatment groups (mean change +9.2, +8.8, and +7.9 letters with aflibercept 2 mg every 8 weeks, 8 mg every 12 weeks, and 8 mg every 16 weeks, respectively). For participants in the extended-interval dosing groups, the study protocol allowed increased dosing frequency as needed; however, 93 percent of these participants continued treatment intervals of at least 12 weeks through study week 48.

Many retina physicians will also employ an individualized "treat and extend" dosing regimen, in which intervals between treatments are increased at each injection visit as indicated based on markers of disease activity. This strategy has been shown to be effective with multiple anti-VEGF agents [56].

Incomplete response to anti-VEGF agents — In our experience, the addition of focal laser photocoagulation to anti-VEGF therapy may be beneficial in eyes that do not respond to or have an incomplete response to anti-VEGF therapy. In one meta-analysis, compared with laser alone, combination ranibizumab plus photocoagulation approximately doubled the chances of gaining three or more lines of vision (RR 2.11, 95% CI 1.67-2.67) and decreased the chance of losing three or more lines (RR 0.29, 95% CI 0.15-0.55) [53]. Combination therapy appears to provide immediate short-term benefit that is maintained in the longer term with the least frequent intravitreal injections. Most data were obtained at one year, and additional longer-term studies are required to determine the optimal regimen for individual patients with varying degrees of DME.

Focal photocoagulation — Focal photocoagulation is an established treatment for DME [57]. It can be used as initial therapy in poorly compliant patients with DME, who may not return for follow-up appointments, worsening DME that threatens to involve the central macula (ie, fovea), or as adjunctive therapy for patients who do not respond or have an incomplete response to anti-VEGF therapy.

Focal laser photocoagulation can be performed directly on microaneurysms, at least 500 microns from the fovea, or may be performed in the area of retinal edema without treating specific retinal vascular lesions. The mechanism of edema reduction after laser treatment is unknown. Many studies suggest that improvement in edema is most probably dependent on creating a grid pattern of light burns of the retinal pigment epithelium, which underlies the retina (figure 3).

The treatment is painless and takes less than 10 minutes to perform under topical anesthesia. Reduction of edema occurs over several weeks to several months. The treatment is highly efficacious compared with the expected progression of untreated DME with the great majority of patients achieving stabilization and, with longer follow-up, a modest improvement in acuity after therapy [57].

Laser treatment may be repeated. The retreatment decision is based on the persistence of retinal thickening and of leakage recorded by OCT (image 1) and perhaps fluorescein angiography. Anti-VEGF agents can also be used in patients with DME who already had focal laser therapy but have persistent DME on OCT.

Complications of focal laser photocoagulation for DME include accidental foveal photocoagulation as well as the subsequent development of laser scars that tend to increase in size with time, causing paracentral scotomas. Subthreshold laser technology offers the potential to reduce these complications. However, clinical trials to address noninferiority or superiority to conventional focal laser photocoagulation are needed.

Less effective therapies

Intravitreal glucocorticoids — Monotherapy with intravitreal triamcinolone may have some benefit in patients with refractory DME. However, as with other intravitreal injections, these benefits are transient and are counterbalanced by an increased risk of side effects, including glaucoma and cataract [58,59]. Intravitreal implants have been designed to deliver glucocorticoids over an extended time frame. The use of these implants is also associated with high rates of cataract formation and glaucoma [60].

Glucocorticoids in combination with photocoagulation or anti-VEGF agents do not appear to improve visual acuity [61,62] or reduce the number of anti-VEGF injections in all cases [63], though combination therapy that includes glucocorticoids may be beneficial in refractory cases of DME. A study evaluating the sustained delivery intravitreal fluocinolone acetonide 0.19 mg implant in patients who had undergone at least one prior macular laser treatment showed that a greater percentage of patients with chronic DME gained 15 letters or more, compared with patients with nonchronic DME (34 versus 22 percent), highlighting the potential utility of this implant for patients that have had insufficient response to other treatment [64].

Larger clinical trials are required to clarify whether there is a role for intravitreal triamcinolone injection or intravitreal steroid implants in patients with refractory DME.

Vitrectomy — In patients with clinically significant DME refractory to intravitreal anti-VEGF pharmacotherapy and photocoagulation and with evidence of vitreomacular traction, we suggest vitrectomy rather than continued medical therapy.

Vitrectomy may be beneficial in selective cases of DME. However, the results of vitrectomy are somewhat variable, ranging from no benefit to visual acuity gains of several lines or more [65-69]. Some authors advocate simple removal of the central vitreous gel, others recommend additional removal of the posterior hyaloid (ie, portion of vitreous adjacent to the retina), and still others perform both of these and also remove the internal limiting membrane ("ILM peeling") of the retina itself. A systematic review of trials assessing a combination of these techniques versus observation or focal photocoagulation reported that vitrectomy may be beneficial in some patients with DME, particularly in those with evidence of vitreomacular

traction, although the evidence was weak [13]. In addition, many patients may have limited response to anti-VEGF medications after undergoing vitrectomy [70].

Given that the risks versus benefits are not clearly established, vitrectomy has generally been reserved for patients who have not had sufficient response to intravitreal pharmacotherapy and one or perhaps two or more laser treatments. The expectation in these cases is a modest improvement in visual acuity.

Postoperative complications are similar to those described for vitrectomy for proliferative diabetic retinopathy. (See 'Vitreous hemorrhage' below.)

Nonproliferative diabetic retinopathy — In patients with severe nonproliferative diabetic retinopathy (table 2)and significant areas of retinal nonperfusion on fluorescein angiography, panretinal laser photocoagulation may reduce the risk of progression to proliferative diabetic retinopathy [71-73] (see 'Panretinal photocoagulation' below). Generally, however, most patients with nonproliferative diabetic retinopathy are not treated, unless accompanied by DME (table 2). In this setting, the treatment of DME takes precedence. (See 'Diabetic macular edema' above.)

The treatment of DME with anti-VEGF agents has been shown to improve the severity of background retinopathy and prevent its progression [74-77]. However, the use of anti-VEGF agents in the earliest phases of diabetic retinopathy without DME remains unsettled and requires additional study [78,79]. The decision to offer early, preventive therapy should be informed by costs, inconvenience, complications, and the high likelihood of treatment interruptions [80]. (See 'Proliferative diabetic retinopathy' below and 'Macular edema with visual acuity impairment' above.)

Proliferative diabetic retinopathy

Our approach: Combination therapy — We use a combination of panretinal photocoagulation and anti-VEGF agents for the treatment of proliferative diabetic retinopathy (table 2). Although anti-VEGF agents are more effective in the short term, delays in treatment (missed appointments) can lead to significant progression of disease [80], whereas panretinal photocoagulation is a more durable treatment than anti-VEGF inhibitors to prevent severe vision loss. Anti-VEGF agents can be used to stabilize disease and allow time to perform panretinal photocoagulation. In addition, anti-VEGF agents have the potential to both bolster standard treatments and reduce the need for additional photocoagulation [81]. There is not a uniform approach to combining the modalities, and the treatment plan depends upon individual patient characteristics, including severity of the proliferative diabetic retinopathy, presence or absence of DME, presence or absence of vitreous hemorrhage, and ability to attend scheduled visits.

Both modalities have been shown to be effective in preventing progression of proliferative diabetic retinopathy and subsequent visual loss [13,82-85]. Five-year data comparing initial treatment of proliferative diabetic retinopathy with ranibizumab versus panretinal photocoagulation show equivalent visual acuity outcomes (+3 letters), with an increased rate of development of DME in the panretinal photocoagulation group and an increased number of injections needed in the ranibizumab group [86]. With regular anti-VEGF treatment, proliferative changes may improve and minimize the necessity of panretinal photocoagulation. However, there is a significant risk of proliferative diabetic retinopathy recurrence and/or progression with cessation of anti-VEGF monotherapy or loss to follow-up [80]. Long-term efficacy and safety of anti-VEGF therapy have not been established. (See 'Anti-VEGF agents' below.)

In a systematic review of 23 trials that evaluated the efficacy of anti-VEGF agents in proliferative diabetic retinopathy, anti-VEGF therapy alone or in combination with panretinal photocoagulation increased visual acuity compared with panretinal photocoagulation alone over a median of 12 months follow-up (10 trials; mean difference -0.08 logMAR, 95% CI -0.12 to -0.04; corresponds to a mean difference in four letters) [87]. Anti-VEGF therapy with or without panretinal photocoagulation also led to lower risk of vitreous hemorrhage (six trials; RR 0.72, 95% CI 0.57-0.9) and greater likelihood of complete regression of new vessels. There are limited data comparing anti-VEGF agents plus panretinal photocoagulation with anti-VEGF agents alone.

Panretinal photocoagulation — Laser photocoagulation makes use of wavelengths that pass through the ocular media but are absorbed by pigment in the retinal pigment epithelium, which underlies the transparent retina, and creates focal burns that involve the retinal tissue (picture 1).

In the Diabetic Retinopathy Study, where 1758 diabetic patients with advanced retinopathy were assigned to panretinal photocoagulation in one eye (with the other eye being the control), the cumulative risk of developing severe visual loss at six years was reduced by more than 50 percent in the treated eyes (figure 4) [82]. In addition, regression of neovascularization occurred in 21 to 62 percent of eyes at one year after panretinal photocoagulation, compared with 5 to 24 percent of untreated controls [82,83].

Regression of proliferative retinopathy following panretinal photocoagulation is affected by the level of glycemic control during the pre-treatment, treatment, and post-treatment periods. In an observational study of 76 type 2 diabetic patients undergoing photocoagulation (115 eyes treated), 57 percent had a successful response at 12 weeks [88]. The probability of having a satisfactory response to panretinal photocoagulation was greater in those with lower A1C

values (odds ratio [OR] of response to panretinal photocoagulation among subjects with A1C >8.0 percent compared with A1C <8.0 percent was 0.28, 95% CI 0.13-0.62).

- **Adverse effects** – Adverse effects of panretinal photocoagulation can include pain during treatment, transient increase in intraocular pressure, decrease in vision, visual field and dark adaptation, and development of macular edema. More rarely corneal abrasions, mydriasis due to damage of nerves in the uveal tract, choroidal detachment or hemorrhage, exudative retinal detachment, subretinal neovascularization, vitreous hemorrhage from regression of neovascular tissue, lens opacities, and vascular occlusions may occur. In a systematic review of the adverse visual effects of panretinal photocoagulation in patients with diabetic retinopathy, initial moderate visual loss occurred in a greater proportion of eyes treated with panretinal photocoagulation, particularly in the presence of preexisting DME and less severe retinopathy (at four months, 9.7 versus 3.8 percent of eyes in the deferral group) [89]. In eyes with DME and more severe retinopathy, moderate visual loss (at six weeks) occurred in 7.7 percent of eyes treated with panretinal photocoagulation compared with 1.7 percent in the deferral group. However, panretinal photocoagulation decreased the five-year risk of severe visual loss in patients with severe nonproliferative diabetic retinopathy or early proliferative diabetic retinopathy. In the same review, reduction in visual fields, an anticipated side effect owing to the destruction of peripheral retinal tissue, deteriorated in up to 50 percent of treated patients.

  Pain during laser treatment is highly variable and is thought to depend in part upon the duration of the laser burns, previous laser treatment, and patient anxiety. Similarly, the degree of visual field loss correlates with the percentage of retina ablated, the number of laser burns, the location and intensity of laser burns, and the patient's visual fields prior to laser treatment. Some impairment in dark adaptation is seen in approximately 75 percent of patients [90]. The functional significance and severity of side effects from PRP vary depending on treatment density [91].

Anti-VEGF agents — Ranibizumab, bevacizumab, and aflibercept are anti-vascular endothelial growth factor (VEGF) agents used to treat proliferative diabetic retinopathy. Intravitreal ranibizumab and aflibercept are approved by the FDA and European Medicines Agency for such treatment. Bevacizumab is used off-label for the treatment of retinopathy, but it must be repackaged in aliquots containing just a fraction of the systemic dose used to treat cancers.

Ranibizumab and aflibercept are also used in the treatment of age-related macular degeneration and macular edema due to retinal vein occlusions and diabetes. Intravenous

bevacizumab is used in the treatment of advanced colorectal cancer, and it is commonly used intravitreally off-label in the treatment of age-related macular degeneration, macular edema from diabetes and retinal vein occlusions, and choroidal and retinal neovascularization. (See "Retinal vein occlusion: Treatment", section on 'Vascular endothelial growth factor inhibitors' and "Initial systemic therapy for metastatic colorectal cancer", section on 'Efficacy and toxicity of bevacizumab and biosimilars'.)

- **Choice of agent** – VEGF inhibitors have been shown to shrink neovascularizations of the optic disc, retina, and iris and decrease fluorescein leakage. A large clinical trial showed that ranibizumab is noninferior to panretinal photocoagulation with regard to visual acuity outcomes at five years [86]. Another trial suggested that aflibercept has favorable visual acuity outcomes at one year compared with panretinal photocoagulation [85]. There are no data to suggest that one anti-VEGF agent is superior to another for reducing neovascularization. The selection of a particular anti-VEGF agent to treat proliferative retinopathy is often based upon availability, clinician familiarity with the agent, cost, and selected patient characteristics (eg, concomitant presence or absence of DME, severity of retinopathy, and history of previous intravitreal anti-VEGF treatments).

- **Adverse effects** – Anti-VEGF drugs are generally well tolerated. Adverse effects are reviewed above. (See 'Anti-VEGF agents' above.)

Ongoing clinical trials of other pharmaceutical treatments for proliferative diabetic retinopathy can be found through the DRCR Retina Network.

Progressive disease

Vitreous hemorrhage — The management of acute vitreous hemorrhage is complex and may involve observation, intravitreal anti-VEGF injections, photocoagulation, and vitrectomy; simple elevation of the head of the bed for sleeping will often permit inferior settling of the intraocular blood and enhance vision and subsequent management decisions. Ultrasound examination is also extremely helpful in eyes with intraocular hemorrhage to determine whether a simultaneous retinal detachment is present; if a detachment is detected on ultrasound, prompt surgery is indicated.

New vessel proliferation due to incomplete panretinal photocoagulation or progression despite laser can result in severe visual impairment due to vitreous hemorrhage. In addition to bleeding from fragile new vessels, vitreous hemorrhage can result from contraction of the vitreous or fibrovascular proliferation that leads to avulsion of a retinal vessel (picture 2). Blood behind the detached posterior vitreous face remains red and is absorbed over weeks to months. In contrast, blood in the formed vitreous can turn white over time and is absorbed more slowly.

Removal of the opaque vitreous humor followed by photocoagulation to the retina can restore vision to the level that the retinal integrity permits.

In a trial comparing aflibercept versus vitrectomy with panretinal photocoagulation in 205 patients with vitreous hemorrhage from proliferative diabetic retinopathy, there was no difference in visual acuity over 24 weeks following initial therapy (mean visual acuity letter score 59.3 versus 63.0, adjusted difference -5.0, 95% CI -10.2 to 0.3) [92].

Indications for vitrectomy — In individuals with vitreous hemorrhage and symptomatic visual loss, vitrectomy is indicated if the vitreous does not sufficiently clear spontaneously in three to four weeks. Other indications for vitrectomy include traction retinal detachment involving the macula, tangential traction of the macula resulting in visual loss, combined traction-rhegmatogenous retinal detachment, rubeosis precluding panretinal photocoagulation, visual loss due to an epiretinal membrane or an opacified posterior vitreous face, progressive neovascularization that is unresponsive to photocoagulation, and vitreous hemorrhage that repeatedly recurs [93].

Tractional retinal detachments can also occur as a result of vitreal contraction and fibrovascular proliferation (picture 3). Retinal traction can decrease vision under the following circumstances:

- When it results in a detachment involving the fovea
- When there is distortion or horizontal displacement of the macula (tangential traction)
- When fibrovascular proliferation obscures the fovea

In these cases, the major goals of vitrectomy are to remove media opacities (such as vitreous hemorrhage or cataract), to relieve vitreous traction, and to provide adequate retinal ablation by means of effective endophotocoagulation. Postoperative complications can include corneal defects, cataract formation, hemorrhage, retinal detachment, endophthalmitis, iris and angle neovascularization, and anterior hyaloidal fibrovascular proliferation.

Observational studies have shown that 66 to 78 percent of patients with vitreous hemorrhage alone will have improved vision six months post-vitrectomy, as will 57 to 75 percent of patients with traction retinal detachment involving the fovea [94-100].

Optimizing vitrectomy outcomes

- **Timing** – In patients with severe proliferative diabetic retinopathy and with vitreous hemorrhage and/or traction involving the macula, we recommend early rather than delayed vitrectomy. The timing of vitrectomy is important. The Diabetic Retinopathy

Vitrectomy Study trials have shown that early vitrectomy may benefit those with the most advanced proliferative diabetic retinopathy and severe neovascularization:

- In a randomized trial of early vitrectomy versus conventional management in 370 eyes with advanced retinal changes and visual acuity of 10/200 or better, a greater proportion of eyes in the early vitrectomy group (44 versus 28 percent) had a visual acuity of 10/20 or better after four years [101]. Early vitrectomy was most beneficial in the subgroup of patients with the most severe neovascularization.

- In another trial of 616 eyes with recent severe vitreous hemorrhage and visual acuity of ≤5/200 randomly assigned to early or deferred (for one year) vitrectomy, the proportion of eyes with visual acuity of 10/20 or better was higher in the early vitrectomy group (25 versus 15 percent) over the four-year follow-up [93,102]. Patients with type 1 diabetes and severe proliferative retinopathy had the most benefit from early vitrectomy.

- **Perioperative anti-VEGF treatment** – Bevacizumab has been used in conjunction with vitrectomy to reduce postoperative complications such as recurrent hemorrhage [103]. In systematic reviews and meta-analyses of randomized trials examining vitrectomy with or without pretreatment with bevacizumab, administration of bevacizumab (1.25 to 2.5 mg three to seven days prior to surgery) reduced early (≤3 weeks) postoperative recurrent vitreous cavity hemorrhage [104-106]. In addition, preoperative use of bevacizumab reduces intraoperative and postoperative complications in repair of tractional retinal detachment from proliferative diabetic retinopathy [107]. In a systematic review and meta-analysis of 28 trials that evaluated vitrectomy with pre- or intraoperative intravitreal anti-VEGF therapy (most commonly bevacizumab), anti-VEGF treatment both reduced complications of vitrectomy and improved visual acuity compared with vitrectomy alone (13 trials; mean difference in best corrected visual acuity -0.25 logMAR, 95% CI -0.39 to -0.11; lower scores indicate better visual acuity) [108]. Nonetheless, visual acuity outcomes were variable across the included trials, and whether anti-VEGF pretreatment significantly improves visual acuity compared with vitrectomy alone remains uncertain.

SPECIAL POPULATIONS

Pregnancy — Women with diabetes who are planning pregnancy should have a comprehensive ophthalmic examination and receive counseling on the risk of development and/or progression of diabetic retinopathy. Diabetic women who become pregnant should be examined in the first trimester and closely followed until one year postpartum (table 1). Women who develop

gestational diabetes are not at increased risk for the development of diabetic retinopathy and therefore do not need such ophthalmic examination and monitoring.

Progression of retinopathy is seen in 16 to 85 percent of diabetic women who become pregnant [109,110]. The Diabetes in Early Pregnancy study found that an increased risk of progression is associated with the severity of previously existing retinopathy and with poor glycemic control [109]. Despite these short-term risks, however, the long-term risk of retinopathy progression is not altered by pregnancy. In the Diabetes Control and Complications Trial (DCCT), progression over an average of 6.5 years of follow-up was not different among the women who did or did not become pregnant [110]. (See "Diabetic retinopathy: Classification and clinical features", section on 'Worsening during pregnancy'.)

Treatment recommendations for pregnant women are largely the same as for other patients for nonproliferative and proliferative diabetic retinopathy. Both laser therapy and vitreous surgery can be performed safely during pregnancy if needed. Several case studies of anti-vascular endothelial growth factor (VEGF) agents during pregnancy have been reported [111-113]. One case series presented four women who were treated with intravitreal bevacizumab one to six times from gestational week 1 to 36 during five pregnancies [111]. No complications of pregnancy were reported, and all children had normal development at last follow-up (mean 14 months after the most recent injection). A second case series reported two patients with unknown early pregnancies at four and five weeks who received intravitreal bevacizumab and who subsequently suffered early loss of pregnancy at 7 and 10 days following bevacizumab administration [112]. Thus, ophthalmologists need to consider pregnancy when discussing anti-VEGF therapy in premenopausal women and discuss the limited safety evidence during pregnancy and the potential risks and benefits.

Patients taking antiplatelet or anticoagulant medication — Patients undergoing elective ophthalmic surgery or intravitreal injections may be taking antiplatelet or anticoagulant medication. Although use of these agents may increase the risk of bleeding with surgical procedures, interruption of such therapy may increase the risk of stroke or thromboembolism. In general, ocular surgical procedures have a very low risk of bleeding, with retinal surgery probably having the most hemorrhagic complications. Whether the amount of bleeding increases in patients taking an antithrombotic agent who undergo retinal procedures is unclear. (See "Perioperative management of patients receiving anticoagulants" and "Perioperative medication management", section on 'Medications affecting hemostasis'.)

- **Intravitreal injections** – We do not temporarily hold or discontinue anticoagulant and/or antiplatelet medications in patients undergoing treatment with intravitreal injections of anti-VEGF agents. Anticoagulant and antiplatelet agents do not appear to have any

adverse effect on intravitreal injections. In two phase III trials of intravitreal injection of the anti-VEGF agents bevacizumab and ranibizumab, 85 patients receiving warfarin treatment had 18 or more intravitreal injections without hemorrhagic complications [114]. Similar findings were noted in a retrospective case series (2325 injections in patients on warfarin, clopidogrel, or aspirin) [115].

- **Ophthalmic surgery** – The decision to withhold warfarin prior to surgery should be made on an individual basis, depending upon the indication for the anticoagulation. Other factors to consider include whether the patient is monocular or binocular or has risk factors for ocular hemorrhage, such as prior hemorrhage in the fellow eye. Antiplatelet agents (eg, aspirin) can often be continued safely in patients undergoing ocular surgery [38].

  Retrospective studies on the incidence of bleeding following pars plana vitrectomy in patients taking antithrombotic medications are contradictory. As examples:

  - In a report in 139 patients undergoing pars plana vitrectomy for diabetic eye disease, 8 of 29 patients (27.6 percent) who were still taking anticoagulants or antiplatelet agents at the time of surgery had significant persistent vitreous cavity hemorrhage during the postoperative period, with four (13.8 percent) requiring secondary surgery [116]. For the 39 patients who had discontinued such therapy prior to surgery, these percentages were 10.3 and 7.7 percent, respectively, while for the 87 patients not taking these medications, the rates of bleeding and reoperation were 6.9 and 0 percent, respectively.

  - In a second report, in 97 eyes operated on for diabetic vitrectomy, there was no difference in the incidence of postoperative vitreous hemorrhage or surgical reoperation between those who remained on anticoagulation (aspirin, warfarin, or clopidogrel) and those who stopped this medication prior to surgery [117].

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading

level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Diabetic retinopathy (The Basics)" and "Patient education: Detached retina (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Prevention** – Diabetic retinopathy is an important cause of visual loss. With proper screening, good glucose and blood pressure management, and early intervention with both surgical and pharmacologic therapies, severe visual loss can be avoided in many patients. Good glycemic control is the primary preventive measure in the management of diabetic retinopathy (figure 1 and figure 2). Improved glycemic management reduces the risk and progression of retinopathy with a graded benefit across all diabetic glycated hemoglobin (A1C) levels. (See 'Introduction' above and 'Prevention' above.)

- **Treatment**

  - **Macular edema without impaired visual acuity** – For initial therapy in patients with diabetic macular edema (DME) (table 2) without impaired visual acuity, treatment can be individualized (observation versus active therapy) with shared decision-making between clinician and patient. (See 'Macular edema without visual acuity impairment' above.)

  - **Macular edema with impaired visual acuity** – For initial therapy in most patients with DME and impaired visual acuity, we recommend intravitreal vascular endothelial growth factor (VEGF) inhibitors (**Grade 1B**). Focal laser photocoagulation is an option for initial therapy in poorly compliant patients with DME, who may not return for follow-up appointments, or for adjunctive therapy in patients who do not respond to or have an incomplete response to anti-VEGF therapy. (See 'Macular edema with visual acuity impairment' above.)

    - The choice of anti-VEGF agent and frequency of treatment by a retina specialist for an individual patient is based upon several factors, including baseline visual acuity, anatomic characteristics, ophthalmic history, planned future treatments for other

aspects of diabetic retinopathy, and cost of treatment. (See 'Anti-VEGF agents' above.)

- In patients with DME refractory to intravitreal anti-VEGF pharmacotherapy and photocoagulation and with evidence of vitreomacular traction, we suggest vitrectomy rather than continued medical therapy (**Grade 2C**) (see 'Vitrectomy' above). In the absence of vitreomacular traction, some experts will still perform vitrectomy as a therapy of last resort.

- **Nonproliferative diabetic retinopathy** – In patients with severe/very severe nonproliferative diabetic retinopathy (table 2) who are at risk for rapid progression, we suggest panretinal photocoagulation rather than observation (**Grade 2B**). (See 'Nonproliferative diabetic retinopathy' above.)

  Patients with mild and moderate nonproliferative diabetic retinopathy are generally not treated, unless accompanied by center-involving DME. In this setting, the treatment of DME takes precedence. (See 'Diabetic macular edema' above.)

- **Proliferative diabetic retinopathy** – In patients with high-risk and severe proliferative diabetic retinopathy (table 2), we generally suggest a combination of panretinal photocoagulation and anti-VEGF agents, rather than panretinal photocoagulation alone (**Grade 2C**). Although anti-VEGF agents are more effective in the short term, delays in treatment (missed appointments) can lead to significant progression of disease, whereas panretinal photocoagulation is a more durable treatment than anti-VEGF inhibitors to prevent severe vision loss (figure 4). Anti-VEGF agents can be used to stabilize disease and allow time to perform panretinal photocoagulation. In addition, anti-VEGF agents have the potential to both bolster standard treatments and reduce the need for additional photocoagulation.

  There is not a uniform approach to combining the modalities, and the treatment plan depends upon individual patient characteristics, including severity of the proliferative diabetic retinopathy, presence or absence of DME, and ability to attend scheduled visits. (See 'Our approach: Combination therapy' above and 'Panretinal photocoagulation' above and 'Anti-VEGF agents' above.)

- **Proliferative diabetic retinopathy with vitreous hemorrhage and/or traction involving the macula** – In patients with severe proliferative diabetic retinopathy with vitreous hemorrhage and/or traction involving the macula, we recommend early rather than delayed vitrectomy (**Grade 1B**). Vitrectomy can also be considered in type 1 and type 2 patients with severe proliferative diabetic retinopathy unresponsive to panretinal

photocoagulation and as an adjunct to remove media opacity and permit adequate retinal laser ablation. (See 'Vitreous hemorrhage' above.)

- **Patients taking antiplatelet/anticoagulant medications** – Antiplatelet agents (eg, aspirin) can often be continued safely in patients undergoing ocular surgery. The decision to withhold warfarin and/or antiplatelet agents prior to surgery should be made on an individual basis, depending upon the indication for the anticoagulation. Other factors to consider include whether the patient is monocular or binocular or has risk factors for ocular hemorrhage, such as prior hemorrhage in the fellow eye. (See 'Patients taking antiplatelet or anticoagulant medication' above.)

  Patients receiving intravitreal injections of anti-VEGF agents may continue anticoagulation or antiplatelet agents safely.

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REFERENCES

1. Willis JR, Doan QV, Gleeson M, et al. Vision-Related Functional Burden of Diabetic Retinopathy Across Severity Levels in the United States. JAMA Ophthalmol 2017; 135:926.
2. Mazhar K, Varma R, Choudhury F, et al. Severity of diabetic retinopathy and health-related quality of life: the Los Angeles Latino Eye Study. Ophthalmology 2011; 118:649.
3. 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.
4. Jampol LM, Glassman AR, Sun J. Evaluation and Care of Patients with Diabetic Retinopathy. N Engl J Med 2020; 382:1629.
5. Zhang L, Krzentowski G, Albert A, Lefebvre PJ. Risk of developing retinopathy in Diabetes Control and Complications Trial type 1 diabetic patients with good or poor metabolic control. Diabetes Care 2001; 24:1275.
6. Estacio RO, McFarling E, Biggerstaff S, et al. Overt albuminuria predicts diabetic retinopathy in Hispanics with NIDDM. Am J Kidney Dis 1998; 31:947.

7. Chung YR, Park SW, Choi SY, et al. Association of statin use and hypertriglyceridemia with diabetic macular edema in patients with type 2 diabetes and diabetic retinopathy. Cardiovasc Diabetol 2017; 16:4.
8. Kohner EM. Diabetic retinopathy and high blood pressure: defining the risk. Am J Hypertens 1997; 10:181S.
9. DCCT/EDIC Research Group, Nathan DM, Bebu I, et al. Frequency of Evidence-Based Screening for Retinopathy in Type 1 Diabetes. N Engl J Med 2017; 376:1507.
10. Chew EY, Davis MD, Danis RP, et al. The effects of medical management on the progression of diabetic retinopathy in persons with type 2 diabetes: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study. Ophthalmology 2014; 121:2443.
11. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; 352:837.
12. Diabetes Control and Complications Trial Research Group, Nathan DM, Genuth S, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329:977.
13. Mohamed Q, Gillies MC, Wong TY. Management of diabetic retinopathy: a systematic review. JAMA 2007; 298:902.
14. Perais J, Agarwal R, Evans JR, et al. Prognostic factors for the development and progression of proliferative diabetic retinopathy in people with diabetic retinopathy. Cochrane Database Syst Rev 2023; 2:CD013775.
15. Progression of retinopathy with intensive versus conventional treatment in the Diabetes Control and Complications Trial. Diabetes Control and Complications Trial Research Group. Ophthalmology 1995; 102:647.
16. Bain SC, Klufas MA, Ho A, Matthews DR. Worsening of diabetic retinopathy with rapid improvement in systemic glucose control: A review. Diabetes Obes Metab 2019; 21:454.
17. Feldman-Billard S, Larger É, Massin P, Standards for screeningand surveillance of ocular complications in people with diabetes SFD study group. Early worsening of diabetic retinopathy after rapid improvement of blood glucose control in patients with diabetes. Diabetes Metab 2018; 44:4.
18. Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial. Arch Ophthalmol 1998; 116:874.
19. Do DV, Han G, Abariga SA, et al. Blood pressure control for diabetic retinopathy. Cochrane Database Syst Rev 2023; 3:CD006127.

20. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. BMJ 1998; 317:703.
21. American Diabetes Association Professional Practice Committee. 10. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes-2024. Diabetes Care 2024; 47:S179.
22. Marcovecchio ML, Chiesa ST, Bond S, et al. ACE Inhibitors and Statins in Adolescents with Type 1 Diabetes. N Engl J Med 2017; 377:1733.
23. Sen K, Misra A, Kumar A, Pandey RM. Simvastatin retards progression of retinopathy in diabetic patients with hypercholesterolemia. Diabetes Res Clin Pract 2002; 56:1.
24. Keech AC, Mitchell P, Summanen PA, et al. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. Lancet 2007; 370:1687.
25. Knickelbein JE, Abbott AB, Chew EY. Fenofibrate and Diabetic Retinopathy. Curr Diab Rep 2016; 16:90.
26. Kataoka SY, Lois N, Kawano S, et al. Fenofibrate for diabetic retinopathy. Cochrane Database Syst Rev 2023; 6:CD013318.
27. ACCORD Study Group, ACCORD Eye Study Group, Chew EY, et al. Effects of medical therapies on retinopathy progression in type 2 diabetes. N Engl J Med 2010; 363:233.
28. Praidou A, Harris M, Niakas D, Labiris G. Physical activity and its correlation to diabetic retinopathy. J Diabetes Complications 2017; 31:456.
29. Loprinzi PD, Edwards MK, Frith E. Review of the literature examining the association between physical activity and retinopathy. Phys Sportsmed 2018; 46:123.
30. Kassoff A, Catalano RA, Mehu M. Vitreous hemorrhage and the Valsalva maneuver in proliferative diabetic retinopathy. Retina 1988; 8:174.
31. Androudi S, Ahmed M, Brazitikos P, Foster CS. Valsalva retinopathy: diagnostic challenges in a patient with pars-planitis. Acta Ophthalmol Scand 2005; 83:256.
32. Tan NYQ, Chew M, Tham YC, et al. Associations between sleep duration, sleep quality and diabetic retinopathy. PLoS One 2018; 13:e0196399.
33. Altaf QA, Dodson P, Ali A, et al. Obstructive Sleep Apnea and Retinopathy in Patients with Type 2 Diabetes. A Longitudinal Study. Am J Respir Crit Care Med 2017; 196:892.
34. Hwang H, Chae JB, Kim JY, et al. CHANGES IN OPTICAL COHERENCE TOMOGRAPHY FINDINGS IN PATIENTS WITH CHRONIC RENAL FAILURE UNDERGOING DIALYSIS FOR THE FIRST TIME. Retina 2019; 39:2360.

35. Ong SS, Thomas AS, Fekrat S. Improvement of Recalcitrant Diabetic Macular Edema After Peritoneal Dialysis. Ophthalmic Surg Lasers Imaging Retina 2017; 48:834.
36. Theodossiadis PG, Theodoropoulou S, Neamonitou G, et al. Hemodialysis-induced alterations in macular thickness measured by optical coherence tomography in diabetic patients with end-stage renal disease. Ophthalmologica 2012; 227:90.
37. Ciardella AP. Partial resolution of diabetic macular oedema after systemic treatment with furosemide. Br J Ophthalmol 2004; 88:1224.
38. Bergerhoff K, Clar C, Richter B. Aspirin in diabetic retinopathy. A systematic review. Endocrinol Metab Clin North Am 2002; 31:779.
39. 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.
40. Virgili G, Parravano M, Menchini F, Evans JR. Anti-vascular endothelial growth factor for diabetic macular oedema. Cochrane Database Syst Rev 2014; :CD007419.
41. Virgili G, Parravano M, Evans JR, et al. Anti-vascular endothelial growth factor for diabetic macular oedema: a network meta-analysis. Cochrane Database Syst Rev 2018; 10:CD007419.
42. Diabetic Retinopathy Clinical Research Network, Wells JA, Glassman AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. N Engl J Med 2015; 372:1193.
43. Wykoff CC, Abreu F, Adamis AP, et al. Efficacy, durability, and safety of intravitreal faricimab with extended dosing up to every 16 weeks in patients with diabetic macular oedema (YOSEMITE and RHINE): two randomised, double-masked, phase 3 trials. Lancet 2022; 399:741.
44. Jhaveri CD, Glassman AR, Ferris FL 3rd, et al. Aflibercept Monotherapy or Bevacizumab First for Diabetic Macular Edema. N Engl J Med 2022; 387:692.
45. Brown DM, Emanuelli A, Bandello F, et al. KESTREL and KITE: 52-Week Results From Two Phase III Pivotal Trials of Brolucizumab for Diabetic Macular Edema. Am J Ophthalmol 2022; 238:157.
46. Virgili G, Curran K, Lucenteforte E, et al. Anti-vascular endothelial growth factor for diabetic macular oedema: a network meta-analysis. Cochrane Database Syst Rev 2023; :CD007419.
47. Singh RP, Barakat MR, Ip MS, et al. Efficacy and Safety of Brolucizumab for Diabetic Macular Edema: The KINGFISHER Randomized Clinical Trial. JAMA Ophthalmol 2023; 141:1152.

48. Cunningham ET Jr, Adamis AP, Altaweel M, et al. A phase II randomized double-masked trial of pegaptanib, an anti-vascular endothelial growth factor aptamer, for diabetic macular edema. Ophthalmology 2005; 112:1747.
49. Fileta JB, Scott IU, Flynn HW Jr. Meta-analysis of infectious endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents. Ophthalmic Surg Lasers Imaging Retina 2014; 45:143.
50. Wu L, Martínez-Castellanos MA, Quiroz-Mercado H, et al. Twelve-month safety of intravitreal injections of bevacizumab (Avastin): results of the Pan-American Collaborative Retina Study Group (PACORES). Graefes Arch Clin Exp Ophthalmol 2008; 246:81.
51. Day S, Acquah K, Mruthyunjaya P, et al. Ocular complications after anti-vascular endothelial growth factor therapy in Medicare patients with age-related macular degeneration. Am J Ophthalmol 2011; 152:266.
52. Dafer RM, Schneck M, Friberg TR, Jay WM. Intravitreal ranibizumab and bevacizumab: a review of risk. Semin Ophthalmol 2007; 22:201.
53. Virgili G, Parravano M, Menchini F, Brunetti M. Antiangiogenic therapy with anti-vascular endothelial growth factor modalities for diabetic macular oedema. Cochrane Database Syst Rev 2012; 12:CD007419.
54. Brown DM, Boyer DS, Do DV, et al. Intravitreal aflibercept 8 mg in diabetic macular oedema (PHOTON): 48-week results from a randomised, double-masked, non-inferiority, phase 2/3 trial. Lancet 2024; 403:1153.
55. Wykoff CC, Garweg JG, Regillo C, et al. KESTREL and KITE Phase 3 Studies: 100-Week Results With Brolucizumab in Patients With Diabetic Macular Edema. Am J Ophthalmol 2024; 260:70.
56. Sarohia GS, Nanji K, Khan M, et al. Treat-and-extend versus alternate dosing strategies with anti-vascular endothelial growth factor agents to treat center involving diabetic macular edema: A systematic review and meta-analysis of 2,346 eyes. Surv Ophthalmol 2022; 67:1346.
57. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. Arch Ophthalmol 1985; 103:1796.
58. Diabetic Retinopathy Clinical Research Network. A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema. Ophthalmology 2008; 115:1447.
59. Diabetic Retinopathy Clinical Research Network (DRCR.net), Beck RW, Edwards AR, et al. Three-year follow-up of a randomized trial comparing focal/grid photocoagulation and

intravitreal triamcinolone for diabetic macular edema. Arch Ophthalmol 2009; 127:245.

60. Kiddee W, Trope GE, Sheng L, et al. Intraocular pressure monitoring post intravitreal steroids: a systematic review. Surv Ophthalmol 2013; 58:291.
61. Diabetic Retinopathy Clinical Research Network, Elman MJ, Aiello LP, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology 2010; 117:1064.
62. Mehta H, Hennings C, Gillies MC, et al. Anti-vascular endothelial growth factor combined with intravitreal steroids for diabetic macular oedema. Cochrane Database Syst Rev 2018; 4:CD011599.
63. 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.
64. Cunha-Vaz J, Ashton P, Iezzi R, et al. Sustained delivery fluocinolone acetonide vitreous implants: long-term benefit in patients with chronic diabetic macular edema. Ophthalmology 2014; 121:1892.
65. Kralinger MT, Pedri M, Kralinger F, et al. Long-term outcome after vitrectomy for diabetic macular edema. Ophthalmologica 2006; 220:147.
66. Dillinger P, Mester U. Vitrectomy with removal of the internal limiting membrane in chronic diabetic macular oedema. Graefes Arch Clin Exp Ophthalmol 2004; 242:630.
67. Stolba U, Binder S, Gruber D, et al. Vitrectomy for persistent diffuse diabetic macular edema. Am J Ophthalmol 2005; 140:295.
68. Yanyali A, Nohutcu AF, Horozoglu F, Celik E. Modified grid laser photocoagulation versus pars plana vitrectomy with internal limiting membrane removal in diabetic macular edema. Am J Ophthalmol 2005; 139:795.
69. Cho M, D'Amico DJ. Transconjunctival 25-gauge pars plana vitrectomy and internal limiting membrane peeling for chronic macular edema. Clin Ophthalmol 2012; 6:981.
70. Moisseiev E, Waisbourd M, Ben-Artsi E, et al. Pharmacokinetics of bevacizumab after topical and intravitreal administration in human eyes. Graefes Arch Clin Exp Ophthalmol 2014; 252:331.
71. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology 1991; 98:766.
72. Lövestam-Adrian M, Agardh CD, Torffvit O, Agardh E. Type 1 diabetes patients with severe non-proliferative retinopathy may benefit from panretinal photocoagulation. Acta Ophthalmol Scand 2003; 81:221.

73. Japanese Society of Ophthalmic Diabetology, Subcommittee on the Study of Diabetic Retinopathy Treatment, Sato Y, Kojimahara N, et al. Multicenter randomized clinical trial of retinal photocoagulation for preproliferative diabetic retinopathy. Jpn J Ophthalmol 2012; 56:52.

74. Ip MS, Domalpally A, Hopkins JJ, et al. Long-term effects of ranibizumab on diabetic retinopathy severity and progression. Arch Ophthalmol 2012; 130:1145.

75. Bressler SB, Liu D, Glassman AR, et al. Change in Diabetic Retinopathy Through 2 Years: Secondary Analysis of a Randomized Clinical Trial Comparing Aflibercept, Bevacizumab, and Ranibizumab. JAMA Ophthalmol 2017; 135:558.

76. Bressler SB, Odia I, Glassman AR, et al. CHANGES IN DIABETIC RETINOPATHY SEVERITY WHEN TREATING DIABETIC MACULAR EDEMA WITH RANIBIZUMAB: DRCR.net Protocol I 5-Year Report. Retina 2018; 38:1896.

77. Ip MS, Domalpally A, Sun JK, Ehrlich JS. Long-term effects of therapy with ranibizumab on diabetic retinopathy severity and baseline risk factors for worsening retinopathy. Ophthalmology 2015; 122:367.

78. Maturi RK, Glassman AR, Josic K, et al. Four-Year Visual Outcomes in the Protocol W Randomized Trial of Intravitreous Aflibercept for Prevention of Vision-Threatening Complications of Diabetic Retinopathy. JAMA 2023; 329:376.

79. Brown DM, Wykoff CC, Boyer D, et al. Evaluation of Intravitreal Aflibercept for the Treatment of Severe Nonproliferative Diabetic Retinopathy: Results From the PANORAMA Randomized Clinical Trial. JAMA Ophthalmol 2021; 139:946.

80. Wubben TJ, Johnson MW, Anti-VEGF Treatment Interruption Study Group. Anti-Vascular Endothelial Growth Factor Therapy for Diabetic Retinopathy: Consequences of Inadvertent Treatment Interruptions. Am J Ophthalmol 2019; 204:13.

81. Simunovic MP, Maberley DA. ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY FOR PROLIFERATIVE DIABETIC RETINOPATHY: A Systematic Review and Meta-Analysis. Retina 2015; 35:1931.

82. Photocoagulation treatment of proliferative diabetic retinopathy. Clinical application of Diabetic Retinopathy Study (DRS) findings, DRS Report Number 8. The Diabetic Retinopathy Study Research Group. Ophthalmology 1981; 88:583.

83. Photocoagulation treatment of proliferative diabetic retinopathy: the second report of diabetic retinopathy study findings. Ophthalmology 1978; 85:82.

84. Writing Committee for the Diabetic Retinopathy Clinical Research Network, Gross JG, Glassman AR, et al. Panretinal Photocoagulation vs Intravitreous Ranibizumab for

Proliferative Diabetic Retinopathy: A Randomized Clinical Trial. JAMA 2015; 314:2137.

85. 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.
86. 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.
87. Martinez-Zapata MJ, Salvador I, Martí-Carvajal AJ, et al. Anti-vascular endothelial growth factor for proliferative diabetic retinopathy. Cochrane Database Syst Rev 2023; 3:CD008721.
88. Kotoula MG, Koukoulis GN, Zintzaras E, et al. Metabolic control of diabetes is associated with an improved response of diabetic retinopathy to panretinal photocoagulation. Diabetes Care 2005; 28:2454.
89. Fong DS, Girach A, Boney A. Visual side effects of successful scatter laser photocoagulation surgery for proliferative diabetic retinopathy: a literature review. Retina 2007; 27:816.
90. Mäntyjärvi M. Colour vision and dark adaptation in diabetic patients after photocoagulation. Acta Ophthalmol (Copenh) 1989; 67:113.
91. Tsilimbaris MK, Kontadakis GA, Tsika C, et al. Effect of panretinal photocoagulation treatment on vision-related quality of life of patients with proliferative diabetic retinopathy. Retina 2013; 33:756.
92. Antoszyk AN, Glassman AR, Beaulieu WT, et al. Effect of Intravitreous Aflibercept vs Vitrectomy With Panretinal Photocoagulation on Visual Acuity in Patients With Vitreous Hemorrhage From Proliferative Diabetic Retinopathy: A Randomized Clinical Trial. JAMA 2020; 324:2383.
93. Early vitrectomy for severe vitreous hemorrhage in diabetic retinopathy. Four-year results of a randomized trial: Diabetic Retinopathy Vitrectomy Study Report 5. Arch Ophthalmol 1990; 108:958.
94. Michels RG, Rice TA, Rice EF. Vitrectomy for diabetic vitreous hemorrhage. Am J Ophthalmol 1983; 95:12.
95. Peyman GA, Raichand M, Huamonte FU, et al. Vitrectomy in 125 eyes with diabetic vitreous haemorrhage. Br J Ophthalmol 1976; 60:752.
96. Mandelcorn MS, Blankenship G, Machemer R. Pars plana vitrectomy for the management of sever diabetic retinopathy. Am J Ophthalmol 1976; 81:561.

97. Barrie T, Feretis E, Leaver P, McLeod D. Closed microsurgery for diabetic traction macular detachment. Br J Ophthalmol 1982; 66:754.

98. Williams DF, Williams GA, Hartz A, et al. Results of vitrectomy for diabetic traction retinal detachments using the en bloc excision technique. Ophthalmology 1989; 96:752.

99. Rice TA, Michels RG, Rice EF. Vitrectomy for diabetic traction retinal detachment involving the macula. Am J Ophthalmol 1983; 95:22.

100. Tolentino FI, Freeman HM, Tolentino FL. Closed vitrectomy in the management of diabetic traction retinal detachment. Ophthalmology 1980; 87:1078.

101. Early vitrectomy for severe proliferative diabetic retinopathy in eyes with useful vision. Results of a randomized trial--Diabetic Retinopathy Vitrectomy Study Report 3. The Diabetic Retinopathy Vitrectomy Study Research Group. Ophthalmology 1988; 95:1307.

102. Early vitrectomy for severe vitreous hemorrhage in diabetic retinopathy. Two-year results of a randomized trial. Diabetic Retinopathy Vitrectomy Study report 2. The Diabetic Retinopathy Vitrectomy Study Research Group. Arch Ophthalmol 1985; 103:1644.

103. Ushida H, Kachi S, Asami T, et al. Influence of preoperative intravitreal bevacizumab on visual function in eyes with proliferative diabetic retinopathy. Ophthalmic Res 2013; 49:30.

104. Smith JM, Steel DH. Anti-vascular endothelial growth factor for prevention of postoperative vitreous cavity haemorrhage after vitrectomy for proliferative diabetic retinopathy. Cochrane Database Syst Rev 2011; :CD008214.

105. Zhao LQ, Zhu H, Zhao PQ, Hu YQ. A systematic review and meta-analysis of clinical outcomes of vitrectomy with or without intravitreal bevacizumab pretreatment for severe diabetic retinopathy. Br J Ophthalmol 2011; 95:1216.

106. Zhang ZH, Liu HY, Hernandez-Da Mota SE, et al. Vitrectomy with or without preoperative intravitreal bevacizumab for proliferative diabetic retinopathy: a meta-analysis of randomized controlled trials. Am J Ophthalmol 2013; 156:106.

107. Arevalo JF, Lasave AF, Kozak I, et al. Preoperative Bevacizumab for Tractional Retinal Detachment in Proliferative Diabetic Retinopathy: A Prospective Randomized Clinical Trial. Am J Ophthalmol 2019; 207:279.

108. Dervenis P, Dervenis N, Smith JM, Steel DH. Anti-vascular endothelial growth factors in combination with vitrectomy for complications of proliferative diabetic retinopathy. Cochrane Database Syst Rev 2023; 5:CD008214.

109. Chew EY, Mills JL, Metzger BE, et al. Metabolic control and progression of retinopathy. The Diabetes in Early Pregnancy Study. National Institute of Child Health and Human Development Diabetes in Early Pregnancy Study. Diabetes Care 1995; 18:631.

110. Diabetes Control and Complications Trial Research Group. Effect of pregnancy on microvascular complications in the diabetes control and complications trial. The Diabetes Control and Complications Trial Research Group. Diabetes Care 2000; 23:1084.
111. Tarantola RM, Folk JC, Boldt HC, Mahajan VB. Intravitreal bevacizumab during pregnancy. Retina 2010; 30:1405.
112. Petrou P, Georgalas I, Giavaras G, et al. Early loss of pregnancy after intravitreal bevacizumab injection. Acta Ophthalmol 2010; 88:e136.
113. Sullivan L, Kelly SP, Glenn A, et al. Intravitreal bevacizumab injection in unrecognised early pregnancy. Eye (Lond) 2014; 28:492.
114. Charles S, Rosenfeld PJ, Gayer S. Medical consequences of stopping anticoagulant therapy before intraocular surgery or intravitreal injections. Retina 2007; 27:813.
115. Mason JO 3rd, Frederick PA, Neimkin MG, et al. Incidence of hemorrhagic complications after intravitreal bevacizumab (avastin) or ranibizumab (lucentis) injections on systemically anticoagulated patients. Retina 2010; 30:1386.
116. Fabinyi DC, O'Neill EC, Connell PP, Clark JB. Vitreous cavity haemorrhage post-vitrectomy for diabetic eye disease: the effect of perioperative anticoagulation and antiplatelet agents. Clin Exp Ophthalmol 2011; 39:878.
117. Brown JS, Mahmoud TH. Anticoagulation and clinically significant postoperative vitreous hemorrhage in diabetic vitrectomy. Retina 2011; 31:1983.

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