DIABETIC RETINOPATHY (DR) PREFERRED PRACTICE PATTERNS (PPP) Philippines 2016

The Diabetic Retinopathy (DR) Preferred Practice Patterns (PPP) Philippines: 2016 was prepared by the VitreoRetina Society of the Philippines (VRSP) for the Philippine Academy of Ophthalmology (PAO) Preferred Practice Patterns (PPP) of selected eye diseases.

The DR PPP Philippines 2016 was adapted from the American Academy of Ophthalmology (AAO) PPP for diabetic retinopathy. [1]

The 2016 DR PPP Philippines was reviewed and edited through correspondence by a panel of experts with interest in this condition. The panel then convened to draft the current manuscript.

This PPP is designed to be a working document and will be updated on an ongoing basis.

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DIABETIC RETINOPATHY (DR) PREFERRED PRACTICE PATTERNS (PPP) Philippines: Updated 2016

Preferred Practice Patterns (PPP)

The Preferred Practice Patterns (PPP) for Diabetic Retinopathy (DR) were adapted from the American Academy of Ophthalmology (AAO). Each was determined by a panel of experts composed of VitreoRetina Society of the Philippines (VRSP) members to be clinically relevant and specific enough to provide useful information to practitioners.

Preferred Practice Patterns (PPP) aim to provide guidance to practitioners for patient care. They do not aim to provide standards for the care of a particular individual. PPP cannot meet the needs of all patients. Adherence to these PPP will not ensure a successful outcome in every situation. It may be necessary to approach each patient's needs in different ways. The physician must make the ultimate decisions about the propriety of the care of every patient weighing all the circumstances presented.

The PPP are not medical standards to be adhered to in all individual situations. The Philippine Academy of Ophthalmology (PAO) and VitreoRetina Society of the Philippines (VRSP) specifically disclaim any and all liability for injury or other damages of any kind from negligence or otherwise for any and all claims that may arise out of the use of any recommendations or other information contained herein.

It is essential to recognize that true medical excellence is achieved only when skills are applied in such a manner that patients' needs are the foremost consideration.

This PPP will be updated on an ongoing basis.

HIGHLIGHTED FINDINGS AND RECOMMENDATIONS FOR CARE[1]

The prevalence of DR and vision-threatening DR are expected to increase as the prevalence of diabetes increases worldwide.

Patients with Type 1 diabetes should have annual retinal examinations for DR 3-5 years after the onset of their disease, whereas patients with Type 2 diabetes should have a prompt retinal examination at the time of diagnosis and follow-up examinations at least yearly.

Patients should be advised to maintain their blood glucose levels, serum lipids and their blood pressure near-normal to decrease the risk of developing retinopathy and retard its progression. Ophthalmologists should communicate the need to adhere to the primary care physician's guidance to maximize metabolic control.

Patients may continue to use aspirin for other medical indications without any adverse effects on their risk for DR.

Patients who develop diabetes during pregnancy (gestational diabetics) do not require retinal evaluations and will most likely not develop diabetic retinopathy.

However, for patients with diabetes planning to become pregnant, retinal examination is recommended prior to conception and every trimester or more frequent at the discretion of the ophthalmologist based on the severity of the retinal disease.

Consultation with an ophthalmologist experienced in the management of diabetic retinal disease is recommended once a patient is diagnosed with diabetes.

It is essential that the severity level of DR and DME be accurately determined. Each severity level has inherent risks for progression. This risk can be increased or decreased based on adherence to overall control of blood glucose levels and other co-existing medical conditions.

The ophthalmologic findings and level of DR and DME should be communicated to the primary care physician. Ophthalmologists should encourage the patient to achieve good metabolic control.

Intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents have been shown to be an effective treatment for central-involving DME (ci-DME).

The preferred treatment for non-central-involving DME (nci-DME) remains to be laser photocoagulation at this time.

Those whose conditions fail to respond to surgery and those for whom further treatment is unavailable should be provided with proper professional support and offered referral for counseling, vision rehabilitation, or social services as appropriate. Patients with functionally limiting post-operative visual impairment should be referred for vision rehabilitation and social services.

DIABETIC RETINOPATHY CARE PROCESS

Patients with DR require lifelong care. This means that the ophthalmologist should obtain and update medical histories, perform regular follow-up ophthalmologic examinations. Alternatively, evaluation of high-quality retinal photographs for DR may be used. Patients, family and friends should be made to understand the importance of regular examinations even if the patient has no complaints related to the eye. Patients should be informed that even if they have good vision they may still have "diabetes of the eye" which may need treatment. They should be educated that early treatment has been shown to significantly reduce the risk of vision loss, emphasizing the need for regular follow-up examinations. (see Table 1)

Patients with Type 2 diabetes mellitus without any sign of DR should have their retina examined with a dilated eye exam at least every year.[2-19]

Patients with Type 1 diabetes mellitus should have dilated eye examinations beginning 3-5 years after the onset of diabetes.[2,20]

The following summarizes the timing of the first and follow-up ophthalmic examinations.

TABLE 1. Recommended Eye Examination for Patients with Diabetes Mellitus and No Diabetic Retinopathy

Diabetes Type	Recommended Initial Evaluation	Recommended Follow-up*
Type 1	5 years after diagnosis[2]	Yearly[2]
Type 2	At time of diagnosis[1,21]	Yearly[1,21]
Pregnancy ^ Type 1 or Type 2	Prior to or soon after conception and early in the first trimester[2]	• No retinopathy to mild or moderate NPDR: every 3-12 months[22] • Severe NPDR or worse: every 1-3 months[1-2]

NPDR = nonproliferative diabetic retinopathy

Abnormal findings may dictate frequent follow-up examinations
^ Women who develop gestational diabetes do not require an eye examination during pregnancy and do not appear to be at increased risk for diabetic retinopathy during pregnancy.

The risk of developing retinopathy and/or the risk of progressing retinopathy is decreased if glucose, blood pressure and serum lipid levels are maintained near-normal levels.[23-26] Aspirin may be taken for other medical conditions. Studies show that there is no indication that aspirin intake will worsen diabetic retinopathy or increase the risk of developing a vitreous hemorrhage.[27]

DISEASE DEFINITION

Diabetic retinopathy (DR) is a leading cause of visual impairment in the working age group. The earliest fundus findings of DR include microaneurysms and intraretinal hemorrhages. Further microvascular damage leads to increasing number of hemorrhages, capillary non-perfusion, venous changes, cotton wool spots and intraretinal microvascular abnormalities (IRMA). During this stage, increased permeability from the capillaries can result in retinal thickening (edema) and/or exudates which may result into a decrease in central visual acuity. The proliferative stage of DR is manifested as proliferation of new vessels on the disc, retina, iris and filtration angle due to the closure of arterioles and venules. This new vessel growth results in traction retinal detachments, vitreous hemorrhage and neovascular glaucoma. Macular edema (ME) and/or ischemia, vitreous hemorrhage and traction retinal detachments involving the macula will result in decreased visual acuity.

All patients with diabetes mellitus should have routine life-long retinal examinations to identify worsening of diabetic retinal disease allowing prompt treatment to preserve vision and prevent visual loss.

RISK FACTORS

The major risk factor for the development of diabetic retinopathy (DR) is the duration of diabetes mellitus. After 5 years, approximately 25% of Type 1 patients will have retinopathy. After 10 years, almost 60% of patients will have some form of retinopathy. After 15 years, 80% will have some form of retinopathy.[5] proliferative diabetic retinopathy (PDR), the most vision-threatening stage of the disease is present in approximately 50-60% of Type 1 patients who have the disease for more than 20 years.[3,5]

The duration of diabetes and severity of hyperglycemia are the major risk factors for developing retinopathy. The key modifiable risk factor is glycemic control. [25,28-35]

Once retinopathy is present, glycemic control becomes a more significant factor in the progress of the retinopathy from its early to the more vision-threatening stages.[36] It is recommended that HbA1c of 7% or lower is the target for glycemic control in most patients, whereas 6.5% is recommended for selected patients.[36] Intensive management of hypertension and serum lipids may reduce and slow retinopathy progression.[23-25]

NATURAL COURSE

Asymptomatic DR commonly progresses to vision threatening disease without timely and appropriate intervention. The accurate determination of the severity is critical to recognize the stages when treatment would be most effective. Studies show that current treatment strategies are 90% effective in preventing moderate and severe vision loss.[37] Landmark clinical studies have been conducted whose results support the current management of diabetic retinopathy.

The major studies are listed below.

1) Diabetes Control and Complications Trial (DCCT)[24,38,39]

2) Follow-up study to the DCCT title Epidemiology of Diabetes Interventions and Complications (EDIC)[24,29,40-42]
3) Diabetic Retinopathy Study (DRS)[43,44]
4) Early Treatment Diabetic Retinopathy Study (ETDRS)[45-47]
5) Diabetic Retinopathy Vitrectomy Study (DRVS)[48]
6) Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR)[49]
7) Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study[50]
8) Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial[51]
9) Diabetic Retinopathy Clinical Research network (DRCR net) Protocol I Study[52]
10) United Kingdom Prospective Diabetes Study (UKPDS)[25,26,53]

The early stage is called Nonproliferative DR (NPDR). This is characterized by microaneurysms, intraretinal hemorrhages, venous dilation and cotton wool spots. Retinal thickening (edema) at the macula and lipid deposits (hard exudates) occur as vascular permeability increases. Diabetic Macular Edema (DME) is a term used to describe retinal thickening and/or adjacent hard exudates that involve the center of the macula or threaten to involve it. It is divided into central-involving (ci-DME) and non-central-involving (nci-DME) diabetic macular edema.

As the retinopathy progresses, the retinal vessels gradually close which results in impaired perfusion and retinal ischemia. Retina findings which indicate that retinal ischemia is increasing include: venous abnormalities (dilation, beading and loops), intraretinal microvascular abnormalities (IRMA), more extensive hemorrhages and exudates. When retinopathy approaches high risk PDR, patients should be considered for pan-retinal photocoagulation (PRP). In patients with type 2 diabetes, there is evidence to suggest earlier treatment when eye findings reach severe NPDR.

Proliferative Diabetic Retinopathy (PDR) is an advanced stage of retinopathy wherein there is retinal new vessel growth (neovascularization) due to widespread ischemia. Neovascularization (NV) grow on or near the optic disc (NVD) or elsewhere on the retina (NVE). These new vessels increase the risk for vitreous hemorrhage. Moreover, the new vessels form fibrous scaffolds which may contract causing traction and retinal detachment. Other fibrous forms of fibrous proliferation may result such as epiretinal macular membranes.

When the new vessels at the disc (NVD) occupy greater than or equal to about one-fourth to one-third disc area, even in the absence of vitreous hemorrhage, PDR is considered high risk for severe visual loss; defined by the DRS as VA <5/200 on two consecutive visits 4 months apart or decrease in VA by 6 lines or 30 letters on the ETDRS chart.

Other high risk PDR characteristics are : any one of the ff: NVD $\geq$ 1/3 disc area (DA), any NVD with vitreous hemorrhage or NVE $\geq$ ½ DA with VH. Or any three or more of the following: presence of VH or pre-retinal hemorrhage, active NV, location of NV on or within one disc diameter of the optic disc or NVD >1/2 DA or NVE > ½ DA.

The Diabetic Retinopathy Study (DRS) was a randomized prospective multicenter clinical trial which evaluated the effect of PRP argon or xenon arc to prevent severe vision loss in eyes with DR. The results showed that PRP reduced the risk of severe vision loss by at least 50% in treated eyes. The greatest benefit was seen in eyes with high risk PDR. Eyes with high risk PDR demonstrated the greatest benefit from PRP and had significantly greater risk of severe visual loss. The conclusion was that PRP reduces the risk of severe vision loss compared with no treatment in eyes with high risk PDR and that eyes with HR PDR should receive prompt treatment with PRP.[43,44]

New vessels may also grow at the iris and at the angle structures of the eye causing neovascular glaucoma (NVG). Patients who approach high-risk PDR and/or NVG should receive prompt PRP.

In order to improve worldwide communication between ophthalmologists and primary care physicians, an international clinical disease severity scale has been developed for diabetic retinopathy and macular edema.[54] (see Tables 2 and 3)

TABLE 2 Diabetic Retinopathy Disease Severity Scale and International Clinical Diabetic Retinopathy Disease Severity Scale[54]

Disease Severity Scale	Findings Observable upon Dilated Ophthalmoscopy
No apparent retinopathy	No abnormalities
Mild NPDR *	Microaneurysms only
Moderate NPDR*	More than just microaneurysms but less than severe NPDR
Severe NPDR	Any of the following (4-2-1 rule) and no signs of proliferative retinopathy: • Severe intraretinal hemorrhages and microaneurysms in each of **four** quadrants • Definite venous beading in **two** or more quadrants • Moderate IRMA^ in **one** or more quadrants
PDR**	One or more of the following: • Neovascularization • Vitreous/preretinal hemorrhage

*NPDR = Nonproliferative Diabetic Retinopathy
**PDR = Proliferative Diabetic Retinopathy
^ IRMA = intraretinal microvascular abnormalities

Note
- Any patient with two or more of the characteristics of severe NPDR is considered to have very severe NPDR
- PDR may be classified as high-risk and non-high risk. (see Table 6 Management Recommendations for Diabetic Retinopathy)

TABLE 3. International Clinical Diabetic Macular Edema Disease Severity Scale[54]

Proposed Disease Severity Level	Findings Observable upon Dilated Ophthalmoscopy
Diabetic macular edema apparently absent	No apparent retinal thickening or hard exudates in posterior pole
Diabetic macular edema apparently present	Some apparent retinal thickening or hard exudates in posterior pole
If diabetic macular edema is present, it can be categorized as follows:	
Proposed Disease Severity Level	**Findings Observable upon Dilated Ophthalmoscopy ***
Diabetic macular edema present	• Mild diabetic macular edema: some retinal thickening or hard exudates in posterior pole but distant from the center of the macula • Moderate diabetic macular edema: retinal thickening or hard exudates approaching the center of the macula but not involving the center

	• Severe diabetic macular edema: retinal thickening or hard exudates involving the center of the macula

- Hard exudates are a sign of current or previous macular edema. Diabetic macular edema is defined as retinal thickening; this requires a three-dimensional assessment that is best performed by dilated examination using slit-lamp biomicroscopy and/or stereoscopic fundus photography. Optical coherence tomography may supplement and confirm the fundus evaluation for determining the presence of macular edema.

CLINICAL OBJECTIVES

Identify patients at risk of developing diabetic retinopathy.

Collaborate with primary care physician, endocrinologists, subspecialists in the management of each patient; with particular attention to control of blood sugar (glycosylated hemoglobin levels), blood pressure, serum lipids, body weight, renal disease, coronary artery disease and neuropathy.

The initial examination for a patient with diabetes mellitus includes all features of the comprehensive adult medical eye evaluation, with particular attention to those aspects relevant to diabetic retinopathy. Educate patients regarding need to monitor the progress of retinopathy on a lifelong basis and to be compliant with the medications for their systemic problems.

Refer for visual rehabilitation if a patient develops visual impairment.

PATIENT OUTCOME CRITERIA

Patient outcome criteria are the following:

- Stabilization or improvement of visual function
- Stabilization or improvement of vision-related quality of life
- Optimal control of glucose, blood pressure and other risk factors through close communication with the patient's primary care physician regarding the status of the diabetic retinopathy and the need for optimal metabolic control

DIAGNOSIS

The initial examination to screen for diabetic retinopathy includes all aspects of the comprehensive adult medical eye examination[55] with particular attention to the features relevant to diabetic retinopathy.

Initial Exam and History Key elements

1) Duration of diabetes[3,35,56]
2) Past glycemic control (hemoglobin A1c)[35,39,56]
3) Medications
4) Systemic history e.g. obesity, renal disease,[3,57] systemic hypertension,[3,57] serum lipid levels[58] pregnancy[59,60]neuropathy
5) Ocular history

DOCUMENTATION

Eye Exam Key elements

1) Visual Acuity[61]
2) Measurement of IOP
3) Slit lamp biomicroscopy
4) Gonioscopy before dilation when indicated for neovascularization of the iris (NVI) or increased IOP. Iris neovascularization is best recognized prior to dilation. Undilated gonioscopy can detect neovascularization in the anterior chamber angle (NVA).
5) Pupillary assessment for optic nerve dysfunction
6) Dilated funduscopy including stereoscopic exam of the posterior pole [47]
7) Examination of the peripheral retina and vitreous
   A dilated pupil is recommended to ensure optimal examination of the retina. This is because only 50% of eyes are classified accurately for the presence and severity of diabetic retinopathy if the pupils are not dilated.[62] Examination of the peripheral retina is best performed with indirect ophthalmoscopy or slit lamp biomicroscopy combined with a wide field contact lens.

   The following features of diabetic retinopathy should receive particular attention because they often lead to visual impairment and because treatment is effective in reducing the risk of visual loss if these features are detected early. These include:
   - Macular edema
   - Signs of severe NPDR (extensive retinal hemorrhages/microaneurysms, venous beading and IRMA)
   - NVD and/or NVE (Disc neovascularization and/or neovascularization elsewhere)
   - Vitreous or preretinal hemorrhage

Diagnostic / Ancillary Tests

The following tests may enhance patient care. They are used ancillary to the eye examination and requested based on the clinical findings. The most common tests include the following:

1) Color and red-free fundus photography
2) Macular optical coherence tomography (OCT)
3) Fluorescein Angiography (FA)
4) Ultrasonography (B Scan Ultrasound: UTS)

1) **Color Fundus Photography** is a technique which is increasingly used for systematic screening or for early detection, monitoring and follow-up of diabetic retinopathy. Fundus photos are useful for documenting the fundus changes as the retinopathy becomes more severe, such as documenting the presence of NVD and NVE, the response to treatment and the need for additional treatment at future visits.
2) **Optical Coherence Tomography** (OCT) of the macula can be used to quantify and monitor retinal thickness, identify vitreomacular traction and detect other forms of macular disease.[63-68] (see Table 4) Large population clinical trials to assess anti-VEGF treatment for macular edema have used OCT instead of stereoscopic photographs or clinical examination to evaluate follow up macular edema status. The OCT offers an objective and accurate assessment of the amount and location of retinal thickening. [52,69-71] In clinical practice, the OCT is used to assess the need for repeat anti-VEGF injections, a change in therapeutic agent, the start of laser treatment or to perform intraocular surgery: pars plans vitrectomy

(PPV). However, it should be noted that macular thickness as measured by OCT only moderately correlates with visual acuity.[72,73]

TABLE 4 Use of Optical Coherence Tomography (OCT) for Diabetic Retinopathy

Situation	Usually	Occasionally	Never
To evaluate unexplained visual acuity loss	•		
To identify areas of vitreomacular traction	•		
To evaluate patients with difficult and/or questionable examinations for diabetic macular edema (DME)	•		
To document and/or confirm the presence of macular edema	•		
To monitor response to treatment	•		
To investigate other causes of macular swelling		•	
To screen a patient with no or minimal diabetic retinopathy			•

3) **Fluorescein Angiography** (FA) is used as a guide for laser treatment of DME and as a means of evaluating the cause of unexplained decreased vision. FA can identify macular capillary non-perfusion or sources of capillary leakage resulting in macular edema as possible explanations of visual loss. Together with the clinical examination, FA may be used to verify the diagnosis of DME or PDR, both of which are diagnosed by means of the clinical exam or fundus photography.

   FA is useful to identify the differential etiologies of macular swelling aside from diabetic retinopathy or for a patient with unexplained vision loss (see Table 5). FA can identify the locations of capillary non-perfusion[74] in the fovea or entire macula. FA may help detect areas of peripheral untreated retinal capillary nonperfusion which could explain retinal or disc neovascularization which fail to regress after previous scatter laser surgery.

   FA remains a valuable tool to help the ophthalmologist to diagnose and treat patients with diabetic retinopathy, however, should not be used to screen for the presence of diabetic retinopathy.

TABLE 5 Use of Fluorescein Angiography for Diabetic Retinopathy

Situation	Usually	Occasionally	Never
To guide laser treatment of CSME	•		
To evaluate unexplained visual loss	•		
To identify suspected but clinically obscure retinal neovascularization	•		
To identify areas of vitreomacular traction		•	
To rule out other causes of macular swelling		•	
To identify large areas of capillary nonperfusion		•	
To evaluate patients with difficult and/or questionable examinations for DME		•	
To screen a patient with no diabetic retinopathy			•

The patient should be made aware of the potential risks associated with the FA. There can be severe medical complications in 1:1900 patients, including death in about 1/220,000 patients.[75] Each angiography facility should have emergency care plans and a protocol to minimize the risks and manage the potential complications. The fluorescein dye crosses the placenta[76] into the fetal circulation although no FA related detrimental effects have been documented

4) **Ultrasonography /B Scan Ultrasonography (UTS)** is used to assess the status of the retina in the presence of a vitreous hemorrhage or other media opacity. UTS may be helpful to define the extent and severity of vitreous retina traction especially on the macula of diabetic eyes.

THERAPEUTICS/ MEDICAL AND SURGICAL MANAGEMENT

Patient education

1) Discuss results of exam and implications
2) Encourage patient with diabetes but without diabetic retinopathy to have annual dilated eye exams
3) Inform patients that effective treatment for diabetic retinopathy depends on timely intervention, despite good vision and no ocular surgery
4) Educate patients about the importance of maintaining near normal glucose levels and near normal blood pressure and lowering serum lipid levels
5) Communicate with the attending physician e.g. family physician internist or endocrinologist. regarding the eye findings
6) Provide patients whose conditions fail to respond to surgery and for whom treatment is unavailable with proper professional support and offer referral for counseling, rehabilitation or social service as appropriate
7) Refer patients with reduced visual function for vision rehabilitation and social services

Diabetic Retinopathy Management Guidelines

Diabetic retinopathy is an important cause of avoidable blindness worldwide. Seventy percent of diabetes occur in low and low middle income countries.

Management recommendations for patients with diabetes are presented in Table 6. They are arranged according to the severity of the retinopathy. Because of the recent evidence showing the efficacy of anti-VEGF therapies in patients with center-involved diabetic macular edema, the population may be differentiated as having center-involving or non-center-involving diabetic macular edema. The table provides guidance for a preferred practice pattern for the general population of patients with diabetes. However, specific needs will vary from patient to patient. Table 7 lists the possible side effects and complications of treatment.

TABLE 6: Management Recommendations for Patients with Diabetes

Severity of retinopathy	Presence of Macular Edema	Follow up in months	Panretinal Photocoagulation (Scatter) laser	Focal and or grid laser*	Intravitreal anti VEGF treatment
Normal or minimal NPDR	No	12	No	No	No
Mild NPDR	No ME CSME^	12 4-6 1*	No No No	No No Recommended	No No Recommended if central-involving
Moderate NPDR	No ME CSME^	6-12 3-6 1*	No No No	No No Recommended	No No Recommended if central-involving
Severe NPDR	No ME CSME^	4 2-4 1*	Sometimes Sometimes Sometimes	No No Recommended	No No Recommended if central-involving
Non-high risk PDR	No ME CSME^	4 4 1*	Recommended Recommended Recommended	No No Recommended	No No Recommended if central-involving
High risk PDR	No ME CSME^	4 4 1*	Recommended Recommended Recommended	No Sometimes Recommended	Sometimes[116,117] Sometimes** Recommended if central-involving

Anti-VEGF = anti-vascular endothelial growth factor, CSME = clinically significant macular edema

ME = Non-clinically significant macular edema, NPDR = Non proliferative diabetic retinopathy PDR = Proliferative Diabetic retinopathy

*Adjunctive treatments that may be considered include intravitreal corticosteroids or anti-VEGF agents (off-label use except aflibercept and ranibizumab). Data from the Diabetic Retinopathy clinical research Network in 2011 demonstrated that, at two years of follow up intravitreal ranibizumab with prompt or deferred laser resulted in greater visual acuity gain. The study also showed that intravitreal triamcinolone acetonide plus laser also resulted in greater visual gain in pseudophakic eyes compared with laser alone. Individuals receiving the intravitreal injections of anti-VEGF agents may be re-examined as early as one month following injection.

** Potential complications should be considered when contemplating anti-VEGF injection.

^Exceptions include hypertension or fluid retention associated with heart failure, renal failure, pregnancy or any other causes that may aggravate macular edema. Deferral of photocoagulation for a brief period of medical treatment may be considered in these cases. Also deferral of CSME treatment is an option when the center of the macula is not involved, visual acuity is good, close follow-up is possible and the patient understands the risks.

TABLE 7: Side Effects and Complications of Treatment for Diabetic Retinopathy

Treatment	Side Effect/Complication
Focal laser photocoagulation for diabetic macular edema	• Possible transient initial decrease in central vision • Paracentral scotomas if laser burns have been placed close to the fovea, especially large or confluent burns[77] • Permanent central scotoma from inadvertent foveal burns • Expansion of laser scar area (over many years)
Panretinal photocoagulation (scatter) for severe NPDR or PDR	• Transient central vision loss from macular edema[61] • Peripheral visual field constriction with delayed dark adaptation • Vitreous hemorrhage if neovascularization is present • Reduced or compromised accommodation[78] • Pupillary dilation (mydriasis)
Vitrectomy	• Recurrent vitreous hemorrhage[79,80] • Retinal tear or detachment[81] • Vision loss [81,82] • Infectious endophthalmitis[83] • Cataract[84]
Intravitreal injections	• Cataract[85,86] • Elevated intraocular pressure (i.e., corticosteroids)[85,86] • Infectious endophthalmitis • Noninfectious inflammatory reactions • Possible systemic effect from intravitreal medication • Increased retinal traction • Vitreous hemorrhage • Retinal tear and detachment

NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy

Normal or Minimal NPDR

Annual eye examinations are recommended for a patient with a normal retinal examination or with minimal NPDR (with rare microaneurysms).[3] This is because 5% to 10% of patients with diabetes without retinopathy will develop some form of diabetic retinopathy within 1 year. Those patients already with retinopathy will worsen by a similar percentage.[38,87-92] At this time, color fundus photography, fluorescein angiography and laser surgery are not necessarily indicated at this time.

Mild to Moderate NPDR without Macular Edema

Re-evaluation is needed within 6-12 months, if a patient's fundus shows microaneurysms and occasional blot hemorrhages or hard exudates. This is because disease progression is common. Approximately 16% of Type 1 diabetic patients with Mild Diabetic Retinopathy (hard exudates and microaneurysms only) may progress rapidly to Proliferative Diabetic Retinopathy within 4 years.[87]

For patients with Mild to Moderate NPDR without Macular Edema, Fluorescein Angiography (FA) or Laser Surgery is not indicated. Baseline tests with color fundus photography and OCT imaging of the macula may be helpful for future comparison and may be used for patient education.

If macular edema that is not clinically significant is present, repeat examinations are indicated in 3-4 months because these patients may develop CSME.[47]

Mild to Moderate NPDR with Clinically Significant Macular Edema (CSME)

The ETDRS defined CSME as macular changes that include any of the following features:

- Thickening of the retina at or within 500 um of the center of the macula
- Hard exudates at or within 500 um of the center of the macula, when associated with adjacent retinal thickening. (This criteria does not apply to residual hard exudates that remain after successful treatment of prior retinal thickening.)
- A zone or zones of retinal thickening one disc area or larger, where any portion of the thickening is within one disc diameter of the center of the macula

Macular edema is now subdivided into whether or not the center of the macula is involved, because the need for treatment and the risk of visual loss is greater when there is center involvement. An ophthalmologist who treats patients for macular edema should be familiar with relevant studies and techniques as described in the ETDRS.

Patients with mild or moderate NPDR and Non-clinically significant macular edema should be re-examined within 3-4 months. Slit lamp biomicroscopy with a dilated pupil, OCT and/or stereoscopic fundus photography are the recommended ways to evaluate macular edema. Fluorescein Angiography (FA) is helpful in order to identify lesions which may be treated with laser surgery. FA is less needed when there are circinate lipid exudates or when the leaking lesions can be identified within the ring of lipids. Areas of capillary drop out and disruption/enlargement of the foveal avascular zone may be detected with FA. Identifying these features may be useful in planning treatment.[47] Color fundus photography is also helpful to document retinal changes even if laser is not performed. It has the advantage over FA in that color fundus photography has no unwanted side effects. Patients with suspected macular edema that is difficult to detect may be documented with OCT. OCT of the macula may also be used to document and confirm the diagnosis of macular edema as well as to monitor its response to treatment.

Laser surgery has been the traditional treatment for CSME. Currently, the data from multiple, well-designed studies have shown that intravitreal anti-VEGF agents provide more effective treatment for central-involving DME (ci-DME) compared to monotherapy with laser surgery.[47,52,70.74,77,93-99] The gain in visual acuity and reduction in macular thickness after treatment with the combination of intravitreal ranibizumab with prompt or deferred laser surgery showed better results than laser alone after 2 years of follow up.[77]

Recent clinical trials have divided clinically significant diabetic macular edema into central-involving (ci-DME) and non-central-involving (nci-DME). Enrollment in these recent clinical trials included only subjects with ci-DME. When ci-DME is present the anti-VEGF treatments provide better visual acuity and less macular edema when compared to focal/grid laser surgery alone in patients. The gain in visual acuity and the reduction in macular thickness after the administration of combined intravitreal ranibizumab with prompt or “deferred” laser surgery showed better outcomes compared to laser alone.

The ETDRS showed a definite benefit of laser photocoagulation surgery in both ci-CSME and nci-CSME. Thus, both anti-VEGF and laser remain effective treatment options for DME.

Anti-VEGF Therapy

The benefit of anti-VEGF intravitreal injections in cases of central-involving diabetic macular edema has been demonstrated by multiple studies. (Appendix 2) Thus, in ci-DME without evidence of macular traction, the initial treatment of choice is anti-VEGF therapy with subsequent or deferred laser treatment.

The Ranibizumab for Edema of the macula in Diabetes (READ-2) study showed that patients who received anti-VEGF therapy alone or with laser treatment did better than the group treated with laser alone.[100]

The Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol I also showed that anti-VEGF with either prompt or deferred laser treatment was better than either laser alone or laser combined with triamcinolone acetonide.[52]

The Bevacizumab or Laser Treatment (BOLT) study showed that off-label bevacizumab treated eyes with ci-DME had favorable outcomes.[101]

The DME and VEGF Trap-Eye: Investigation of Clinical Impact (DA VINCI) study used another pharmacologic agent called aflibercept. Results of this study showed better outcomes in eyes treated with aflibercept when compared to eyes treated with laser treatment for ci-DME.[102]

The DRCR.net protocol T demonstrated that treatment with the anti-VEGF agents: bevacizumab, ranibizumab or aflibercept are effective for ci-DME. When initial visual acuity loss is mild (20/40 or better) there's little difference in visual acuity outcomes among the 3 agents. Aflibercept, however, was more effective in improving visual acuity when compared to bevacizumab and ranibizumab when the initial visual acuity was 20/50 or worse at 1 year.[103] At 2 years, all three anti-VEGFs showed gains in vision with half of the number of anti-VEGF injections used in the first year, regardless of which anti-VEGF drug was used. However, aflibercept and ranibizumab showed superior results compared to bevacizumab. There was also a decrease in the frequency of visits and decreased amounts of focal/grid laser photocoagulation treatment with all three drugs.[104]

Ophthalmologists who treat patients with macular edema using anti-VEGF agents should note that the use of betadine antiseptic drops and a bladed lid speculum is recommended during intravitreal injections. The use of antibiotic eye drops before or following intravitreal injections is at the discretion of the injecting ophthalmologist.[105]

Follow-up examinations after anti-VEGF injection are performed typically within 1 month or at the discretion of the treating ophthalmologist.. (See Table 6.) Although, severe side effects and adverse events have been associated with the procedure or anti-VEGF agents, these are rare. They include infectious endophthalmitis, cataract formation, retinal detachment and elevated IOP, particularly for corticosteroids such as triamcinolone (See Table 7).

Intraocular Steroids

Studies demonstrated the role of intravitreal administration of short and long term corticosteroids for the treatment of diabetic macular edema.

Dexamethasone implant that is injected into the vitreous is an option to treat adults with diabetic macular edema. The most common adverse events included the development of cataracts and elevated intraocular pressure (IOP).[123]

Focal or Grid Laser Photocoagulation

Pre-operatively, the ophthalmologist should discuss the risks, benefits and side effects of laser treatment. A follow-up examination within 3-4 months should be performed for patients with DME who have been treated with laser photocoagulation.[47]

Other Treatments

When vitreomacular traction is present, pars plana vitrectomy (PPV) may improve visual acuity in selected patients with diffuse DME that is unresponsive to previous macular laser photocoagulation and/or anti-VEGF treatments.[109-110] However, the value of PPV in DME remains controversial, and is difficult to study in a randomized clinical trial because of the many variables.[111]

Treatment Deferral

It is recommended that the patient be observed every 3-4 months for signs of progression, when treatment for macular edema is deferred.

Severe NPDR and Non-High Risk PDR

The ETDRS data showed that Severe NPDR and Non-High Risk PDR have a similar clinical course. Subsequently, the recommendations for their treatment are similar.

PDR will develop within 1 year in half of patients with severe NPDR and 15% will have developed high risk PDR.[63] In patients with very severe NPDR, 75% of them are at risk of developing high-risk PDR within 1 year. Moreover, 45% will deteriorate to high-risk PDR also within 1 year. Thus, these patients should be examined more closely every 2 to 4 months.[62,112]

The ETDRS did not provide definitive guidelines for mild to moderate NPDR. The study suggested that pan-retinal photocoagulation should not be recommended for eyes with mild or moderate NPDR, as long as follow-up examinations were regularly performed. However, when retinopathy is more severe, pan-retinal photocoagulation should no longer be delayed when the eye reaches the high-risk proliferative stage.[62] If a patient cannot be followed up at every 3-4 months or when access to eye care is difficult early pan retinal laser photocoagulation may be warranted.[62,112] Partial or limited pan-retinal photocoagulation treatment is not recommended.[43]

For Type 2 diabetic patients with severe NPDR or non-high-risk PDR, the ETDRS results suggest that pan-retinal photocoagulation should be considered before high-risk PDR develops. The risk of severe vision loss or PPV can be reduced by 50% in patients with Type 2 diabetes when treated early compared with deferral of pan-retinal photocoagulation until high-risk PDR develops.[112]

For Type 1 and Type 2 diabetic patients, the decision to perform pan-retinal photocoagulation will be influenced by cataract surgery or pregnancy, both of which may increase the risk of progression of diabetic retinopathy.

The end goal of performing pan-retinal photocoagulation laser surgery is to reduce the risk of vision loss. The ophthalmologist should assess for the presence of macular edema before performing laser treatment. The benefits, side effects, risks of vision loss should be discussed with the patient before obtaining informed consent.[113,114]

In a patient with macular edema and severe NPDR or non-high-risk PDR, many experts suggest that performing focal photocoagulation and/or anti-VEGF treatment be performed prior to pan-retinal photocoagulation. It has been reported that macular edema may increase with resultant increase in the risk of moderate visual loss when pan-retinal photocoagulation surgery is performed.[61] However, pan-retinal photocoagulation should be performed as soon as PDR with high-risk characteristics is diagnosed. (ie., if NVD is extensive or vitreous/pre-retinal hemorrhage has occurred recently). In such cases, pan-retinal photocoagulation and anti-VEGF therapy may be performed concomitantly.

The role of anti-VEGF in the management of severe NPDR and non-high-risk PDR is under investigation.

It is helpful to perform fluorescein angiography (FA) to assess the areas with non-perfusion and/or clinically undetected areas of retinal neovascularization as well as to establish the cause for a loss in visual acuity.

High-Risk PDR

High-risk PDR as described by the DRS is characterized by three of the following four features:

- Neovascularization (at any location)
- Neovascularization at the optic disc
- Severe neovascularization
    - New vessels within one disc diameter of the optic nerve head that are larger than one-fourth to one-third disc area in size
    - New vessels elsewhere that are at least one-half disc area in size
- Vitreous or pre-retinal hemorrhage

Panretinal photocoagulation (as described in the DRS and ETDRS) (see Glossary) can reduce the risk of severe visual loss in patients with high-risk PDR.[43,115] Pan-retinal photocoagulation can induce regression of retinal neovascularization.

Additional pan-retinal photocoagulation, anti-VEGF therapy or vitrectomy surgery may be considered to address the following situations:

- Increasing neovascularization of the iris
- Failure of the neovascularization to regress
- Increasing neovascularization of the retina
- New vitreous hemorrhage
- New areas of neovascularization

Combined anti-VEGF therapy and pan-retinal photocoagulation may be performed at the first treatment session for patients with high-risk PDR and DME. Usually, FA does not have to be performed to apply pan-retinal photocoagulation effectively.

It is possible that vitreous hemorrhage recurs after extensive pan-retinal photocoagulation. These hemorrhages may be due to traction on pre-existing or involuted neovascularization and may regress spontaneously without additional pan-retinal laser surgery.

Pars plana vitrectomy should be considered in previously untreated PDR with vitreous opacities and active neovascular or fibrovascular proliferation.[48,118-120] The value of early vitrectomy tends to increase with the increasing severity of neovascularization. The role of anti-VEGFs in these later stages of proliferative retinopathy is under investigation. The use of anti-VEGF injections prior to vitrectomy in selected cases has been reported to be helpful in reducing intraoperative hemorrhage and allowing for easier dissection of fibrovascular membranes.[121] The use of intraoperative anti-VEGF in selected case has been reported to lower the incidence of early post-operative vitreous cavity hemorrhage (POVCH) within the first few days.[122]

High-Risk PDR Not Amenable to Photocoagulation

In some patients, it is not possible to perform laser photocoagulation adequately due to severe vitreous or preretinal hemorrhage. In addition, advanced active PDR may persist despite extensive panretinal photocoagulation. In such cases, vitrectomy surgery may be needed.

Macula-threatening traction retinal detachment (especially of recent onset), traction combined with rhegmatogenous retinal detachment and vitreous hemorrhage which preclude the performance of pan-retinal photocoagulation will need pars plana vitrectomy. Patients with vitreous hemorrhage and neovascularization of the iris should be considered for prompt pars plana vitrectomy with intraoperative panretinal photocoagulation surgery. The role of anti-VEGFs in these cases is under investigation. The use of anti-VEGF agents in selected cases prior to and during pars plana vitrectomy has been reported to have benefits.[121,122]

FOLLOW UP

The follow-up evaluation includes a history and eye examination.

History

A follow-up history should evaluate changes in the following areas:

1) Visual Acuity
2) Symptoms and changes in symptoms
3) Systemic status e.g. pregnancy, blood pressure, serum cholesterol , renal status
4) Glycemic status Hemoglobin A1c[39,56,60,]

Physical Examination

A follow-up examination should include the following elements:

1) Visual Acuity
2) Slit lamp biomicroscopy with iris exam[124]
3) Measurement of IOP
4) Gonioscopy preferably before dilation when iris neovascularization is suspected or present or if intraocular pressure is elevated
5) Stereocoscopic exam of the posterior pole after dilation of the pupils
6) Exam of the peripheral retina and vitreous when indicated
7) OCT imaging when appropriate

Recommended intervals for follow-up are given in Table 6.

PROVIDER AND SETTING

It is the ophthalmologist who will perform majority of the eye examinations and all of the surgery. There are some aspects of patient data collection which may be performed by trained individuals under the ophthalmologist's supervision and review. Caring for patients with diabetic retinopathy is complex . The attending ophthalmologist should be knowledgeable with the specific recommendations of the relevant clinical trials.

The ophthalmologist should refer patients with diabetes to a primary care physician for appropriate management of their systemic condition, and should communicate examination results to the physician managing the patient's ongoing diabetes care.

Those whose conditions fail to respond to surgery and those or whom further treatment is unavailable should be provided with proper professional support and offered referral for counseling, vision rehabilitation, or social services as appropriate.

Patients with functionally limiting post-operative visual impairment should be referred for vision rehabilitation and social services.

The Philippine Academy of Ophthalmology and VitreoRetina Society of the Philippines have made a consensus statement regarding the role of the ophthalmologist in the delivery of intravitreal agents. (See Appendix 3)

APPENDIX 1. PREFERRED PRACTICE PATTERN RECOMMENDATION GRADING

The grades reported here have been adapted from the AAO PPP on Diabetic Retinopathy 2016.

Details of these grading systems are reported in the Methods and Key to Ratings presented below.

Methods and Key to Ratings

Preferred Practice patterns® should be clinically relevant and specific enough to provide useful information to practitioners. Where evidence exists to support a recommendation for care, the recommendation should be given an explicit rating that shows the strength of evidence. To accomplish these aims, methods from the Scottish Intercollegiate Guideline Network.[125] (SIGN) (I++; I+;I-;II++,II+; II-; III) and the Grading of Recommendations Assessment, Development and Evaluation.[126] GRADE) . GRADE is a systematic approach to grading the strength of the total body of evidence (Good, Moderate, Insufficient) that is available to support recommendations on a specific clinical management issue (Strong, Discretionary). Organizations that have adopted GRADE include SIGN, the World Health Organization, the Agency or Healthcare Research and Policy, and the American College of Physicians.[127]

- All studies used to form a recommendation for care are graded for strength of evidence individually, and that grade is listed with the study citation.
- To rate individual studies, a scale based on SIGN[1] is used. The definitions and levels of evidence to rate individual studies are as follows:

I++	High quality meta-analyses, systematic reviews of randomized controlled trials (RCTs) or, RCTs with a very low risk of bias
I+	Well conducted meta-analyses, systematic reviews of RCTs or RCTs with a low risk of bias
I-	Meta-analyses, systematic reviews of RCTs or RCTs with a high risk of bias
II++	High quality systematic reviews of case-control or cohort studies High quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
II+	Well conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
II-	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
III	Nonanalytic studies (e.g. case reports, case series)

- Recommendations for care are formed based on the body of evidence. The body of evidence quality ratings are defined by GRADE[126] as follows:

Good quality	Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Insufficient quality	Further research is very unlikely to have an important impact on our confidence in the estimate of effect is likely to change the estimate Any estimate of effect is very uncertain

- Key recommendations for care are defined by GRADE[126] as follows:

Strong recommendation	Used when the desirable effects of an intervention clearly outweigh the undesirable effects or clearly do not
Discretionary recommendation	Used when the trade-offs are less certain-either because of low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced

- The Highlighted Findings and Recommendations for Care section lists points determined

HIGHLIGHTED FINDINGS AND RECOMMENDATIONS FOR CARE

The prevalence of diabetes worldwide is increasing: as such the prevalence of diabetic retinopathy and vision threatening diabetic retinopathy is also expected to increase.

People with Type 1 diabetes should have annual screenings for diabetic retinopathy beginning 5 years after the onset of their disease, whereas those with Type 2 diabetes should have prompt examination at the time of diagnosis and at least yearly examinations thereafter. II+; Good; Strong

Maintaining near-normal glucose levels and near-normal blood pressure lowers the risk of retinopathy developing and/or progressing, so patients should be informed of the importance of maintaining good glycosylated hemoglobin levels, serum lipids and blood pressure.

Patients with diabetes may use aspirin for other medical indications without an adverse effect on their risk of diabetic retinopathy. I++; Good; Discretionary

Women who develop gestational diabetes do not require an eye examination during pregnancy and do not appear to be at increased risk of developing diabetic retinopathy during pregnancy. However, patients with diabetes who become pregnant should be examined early in the course of the pregnancy. II+; Good; Strong

Referral to an ophthalmologist is required when there is any nonproliferative diabetic retinopathy, proliferative retinopathy or macular edema. III; Good; Strong

Ophthalmologists should communicate both ophthalmologic findings and level of retinopathy to the primary care physician. They should emphasize to the patient the need to adhere to the primary care physician's guidance to optimize metabolic control. III; Good; Strong

Intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents have been shown to be an effective treatment for center-involving diabetic macular edema and also as an alternative therapy for proliferative diabetic retinopathy. I++, Good; Strong

At this time, laser photocoagulation remains the preferred treatment for non-center-involving diabetic macular edema. I++, Good; Strong

The grades report the SIGN grade associated with the included studies supporting each recommendation (I++; I+; II-; II++; II+; II-; III), the GRADE evaluation of the body of evidence (Good Moderate, Insufficient) and the GRADE assessment of the strength of the recommendation (Strong, Discretionary).

Care Process

- Page 4: The care process for diabetic retinopathy includes a medical history, a regular ophthalmologic examination or screening of high quality retinal photographs of patients who

have not had previous treatment for diabetic retinopathy or other eye disease and regular follow-up: III; Good; Strong

- Page 4: Patients must be informed that they have good vision and no ocular symptoms, yet may still have significant disease that needs treatment. They should be educated that early treatment works best and is why they need to return for an annual eye examination, even when their vision is good: III; Good; Strong
- Page 4: Patients with Type 2 diabetes mellitus without diabetic retinopathy should be encouraged to have an annual dilated eye exam or screenings using fundus photography to detect the onset of diabetic retinopathy: II++; Good; Strong
- Page 4: Those with Type 1 diabetes mellitus without retinopathy should have annual dilated eye examinations or screenings beginning 3-5 years after the onset of diabetes: II++; Good; Strong
- Page 4: Table 1: Recommended initial evaluation for Type 1 diabetes; 5 years after diagnosis: II++; Good; Strong
- Page 4: Table 1: Recommended follow-up evaluation for Type 1 diabetes: yearly: III; Good; Strong
- Page 4: Table 1: Recommended initial evaluation for Type 2 diabetes: At time of diagnosis: II+; Good; Strong
- Page 4: Table 1: Recommended follow-up evaluation for Type 2 diabetes: Yearly: III; Good; Strong
- Page 4: Table 1: Recommended initial evaluation for pregnant women with diabetes (Type 1 or Type 2): soon after conception and early in first trimester: III; Good; Strong
- Page 4: Table 1: Recommended follow-up evaluation for pregnant women with diabetes (type 1 or Type 2), no retinopathy to mild or moderate NPDR: Every 3-12 months: III; Good; Strong
- Page 4: Table 1: Recommended follow-up evaluation for pregnant women with diabetes (Type 1 or Type 2), severe NPDR or worse: Every 1-3 months: III; Good; Strong

Risk Factors

- Page 5: it is recommended that an HbA1c of 7.0% or lower is the target for glycemic control in most patients while in selected patients, there may be some benefit to setting a target of 6.5%: I++; good; Strong
- Page 5: Intensive management of hypertension may slow retinopathy progress, but the data are inconclusive: II++; Moderate; Discretionary
- Page 5: Management of serum lipids may reduce retinopathy progression and the need for treatment: II+; Moderate; Discretionary
- Page 5: it is reasonable to encourage patients with diabetes to be as compliant as possible with therapy of all medical aspects of their disease: II++; Good; Strong

Clinical Objectives

- Page 8: Patients should be informed of the importance of good glycosylated hemoglobin levels, serum lipids, and blood pressure: III; Good; Strong
- Page 8: The initial examination for a patient with diabetes mellitus includes all features of the comprehensive adult medical eye evaluation, with particular attention to those aspects relevant to diabetic retinopathy: II++; Good; Strong

Diagnosis: Initial exam and history key elements

- Page 8: An initial history should consider duration of diabetes: II++; Good; Strong
- Page 8: An initial history should consider past glycemic control: II++; Good; Strong
- Page 8: An initial history should consider medications: III; Good; Strong
- Page 8: An initial history should consider ocular history : III; Good; Strong
- Page 9: The initial physical examination should include visual acuity: III; Good; Strong
- Page 9: The initial physical examination should include slit-lamp biomicroscopy: III; Good; Strong
- Page 9: The initial physical examination should include intraocular pressure: III; Good; Strong
- Page 9: The initial physical examination should include gonioscopy before dilation, when indicated: III; Good; Strong

- Page 9: The initial physical examination should include through funduscopy, including stereoscopic examination of the posterior pole: III; Good; Strong
- Page 9: The initial physical examination should include examination of the peripheral retina and vitreous: III; Good; Strong
- Page 9: Slit-lamp biomicroscopy is the recommended method to evaluate retinopathy in the posterior pole and midperipheral retina III; Good; Strong
- Page 9: Slit-lamp biomicroscopy is the recommended method to evaluate retinopathy in the posterior pole and mid peripheral retina: III; Good; Strong
- Page 9: Examination of the peripheral retina is best performed with indirect ophthalmoscopy or with slit lamp biomicroscopy: III; Good; Strong
- Page 9: A detailed examination is indicated to assess for macular edema: III; Good; Strong
- Page 9: A detailed examination is indicated to assess for signs of severe NPDR: III; Good; Strong
- Page 9: A detailed examination is indicated to assess for optic nerve head neovascularization and/or neovascularization elsewhere: III; good; Strong
- Page 9: A detailed examination is indicated to assess for vitreous or preretinal hemorrhage: III; Good; Strong

Diagnosis: Diagnostic/Ancillary Tests

- Page 9: If used appropriately, color and red-free fundus photography ancillary to the clinical examination may enhance patient care: III; Insufficient; Discretionary
- Page 9: If used appropriately, optical coherence tomography ancillary to the clinical examination may enhance patient care: III; Insufficient; Discretionary
- Page 9: If used appropriately, fluorescein angiography ancillary to the clinical examination may enhance patient care: III; Insufficient; Discretionary
- Page 9: If used appropriately, ultrasonography ancillary to the clinical examination may enhance patient care: III; Insufficient; Discretionary
- Page 10: Table 4: OCT is usually used to evaluate unexplained visual acuity loss: III; Insufficient; Discretionary
- Page 10: Table 4: OCT is usually used to identify areas of vitreomacular traction: III; Insufficient; Discretionary
- Page 10: Table 4: OCT is usually used to evaluate patients with difficult and/or questionable examinations for DME: III; Insufficient; Discretionary
- Page 10: Table 4: OCT is occasionally used to investigate other causes of macular swelling: III; Insufficient; Discretionary
- Page 10: Table 4: OCT is never used to screen a patient with no or minimal diabetic retinopathy: III; Good; Strong
- Page 10: Routine fluorescein angiography is not indicated as a part of the regular examination of patients with diabetes: III; Good; Strong
- Page 10: Facilities for fluorescein angiography should be available to physicians who diagnose and treat patients with diabetic retinopathy: II++; Good; Discretionary
- Page 10: Table 5: Fluorescein angiography is usually used to evaluate unexplained visual loss: III; Insufficient; Discretionary
- Page 10: Table 5: Fluorescein angiography is usually used to identify suspected but clinically obscure retinal neovascularization: III; Insufficient; Discretionary
- Page 10: Table 5: Fluorescein angiography is occasionally used to rule out other causes of macular swelling: III; Insufficient; Discretionary
- Page 10: Table 5: Fluorescein angiography is occasionally used to identify large areas of capillary non-perfusion: III; Insufficient; Discretionary
- Page 10: Table 5: Fluorescein angiography is occasionally used to evaluate patients with difficult and/or questionable examinations for DME: III; Insufficient; Discretionary
- Page 10: Table 5: Fluorescein angiography is never used to screen a patient with no or minimal

diabetic retinopathy: III; Good; Strong

- Page 10: Each angiography facility should have in place an emergency care plan and a clear protocol to minimize the risks and to manage complications: III; Good; Strong
- Page 11: Ultrasonography is an extremely valuable diagnostic tool that enables assessment of the status of the retina in the presence of a vitreous hemorrhage or other media opacity: III; Good; Strong
- Page 11: Close partnership with the primary care physician is important to make sure that the care of the patient is optimized: III; Good; Strong
- Page 11: It is important to educate patients with diabetes, in conjunction with their primary care physician, on the importance of optimizing control of blood glucose to as near normal as is safely possible: III; Good; Strong
- Page 12: Table 6: Follow-up for patients with normal or minimal NPDR and no ME: 12 months: III; Good; Strong
- Page 12: Table 6: Follow-up for patients with mild NPDR and no ME: 12 months: III; Good; Strong
- Page 12: Table 6: Follow-up for patients with mild NPDR and ME: 4-6 months: III; Good; Strong
- Page 12: Table 6: Follow up for patients with mild NPDR and CSME: 1 month: III; Good; Strong
- Page 12: Table 6: Panretinal photocoagulation laser treatment not recommended for patients with normal or minimal NPDR: III; Good; Strong
- Page 12: Table 6: Panretinal photocoagulation laser treatment not recommended for patients with mild NPDR and no ME: III; Good; Strong
- Page 12: Table 6: Panretinal photocoagulation laser treatment not recommended for patients with with mild NPDR and CSME: III; Good; Strong
- Page 12: Table 6: Focal and/or grid laser treatment not recommended for patients with normal or minimal NPDR: III; Good; Strong
- Page 12: Table 6: Focal and/or grid laser treatment not recommended for patients with mild NPDR and no ME: III; Good; Strong
- Page 12: Table 6: Focal and/or grid laser treatment sometimes recommended for patients with mild NPDR and ME: I++; Good; Strong
- Page 12: Intravitreal anti-VEGF treatment sometimes recommended for patients with mild NPDR and CSME: I++; Good; Strong
- Page 12: Table 6: Follow up for patients with moderate NPDR and no ME: 6-12 months: III; Good; Strong
- Page 12: Table 6: Follow up for patients with moderate NPDR and ME: 3-6 months: III; Good; Strong
- Page 12: Table 6: Follow up for patients with moderate NPDR and CSME: 1 month: III; Good; Strong
- Page 12: Table 6: Panretinal photocoagulation laser treatment not recommended for patients with moderate NPDR and no DME: III; Good: Strong
- Page 12: Table 6: Panretinal photocoagulation laser treatment not recommended for patients with moderate NPDR and ME: III; Good: Strong
- Page 12: Table 6: Panretinal photocoagulation laser treatment not recommended for patients with moderate NPDR and CSME: III; Good: Strong
- Page 12: Table 6: Focal and/or grid laser treatment not recommended for patients with moderate NPDR and no ME: III; Good; Strong
- Page 12: Table 6: Focal and/or grid laser treatment not recommended for patients with moderate NPDR and ME: III; Good; Strong
- Page 12: Table 6: Focal and/or grid laser treatment sometimes recommended for patients with moderate NPDR and CSME: I++; Good; Strong
- Page 12: Table 6: Intravitreal anti-VEGF treatment sometimes recommended for patients with moderate NPDR and CSME: I++; Good; Strong
- Page 12: Table 6: Follow up for patients with severe NPDR and no ME: 4 months: III; Good; Strong
- Page 12: Table 6: Follow up for patients with severe NPDR and ME: 2-4 months: III; Good; Strong

- Page 12: Table 6: Follow up for patients with severe NPDR and CSME: 1 month: III; Good; Strong
- Page 12: Table 6: Panretinal photocoagulation laser treatment sometimes recommended for patients with severe NPDR and no ME: I++; Good; Strong
- Page 12: Table 6: Panretinal photocoagulation laser treatment sometimes recommended for patients with severe NPDR and ME: I++; Good; Strong
- Page 12: Table 6: Panretinal photocoagulation laser treatment sometimes recommended for patients with severe NPDR and CSME: I++; Good; Strong
- Page 12: Table 6: Focal and/or grid laser treatment not recommended for patients with severe NPDR and no ME: I++; Good; Strong
- Page 12: Table 6: Focal and/or grid laser treatment not recommended for patients with severe NPDR and ME: I++; Good; Strong
- Page 12: Table 6: Focal and/or grid laser treatment sometimes recommended for patients with severe NPDR and CSME: III; Good; Strong
- Page 12: Table 6: Intravitreal anti-VEGF treatment not recommended for patients with severe NPDR and no ME: III; Good; Strong
- Page 12: Table 6: Intravitreal anti-VEGF treatment not recommended for patients with severe NPDR and nci-CSME: III; Good; Strong
- Page 12: Table 6: Intravitreal anti-VEGF treatment recommended for patients with severe NPDR and ci-CSME: III; Good; Strong
- Page 12: Table 6: Follow-up for patients with non-high-risk PDR with no DME: 4 months: III; Good; Strong
- Page 12: Table 6: Follow-up for patients with non-high-risk PDR with ME: 4 months: III; Good; Strong
- Page 12: Table 6: Follow-up for patients with non-high-risk PDR with CSME: 1 months: III; Good; Strong
- Page 12: Table 6: Panretinal photocoagulation laser treatment sometimes recommended for patients with non-high-risk PDR and no DME: I++; Good; Strong
- Page 12: Table 6: Panretinal photocoagulation laser treatment sometimes recommended for patients with non-high-risk PDR and ME: I++; Good; Strong
- Page 12: Table 6: Panretinal photocoagulation laser treatment sometimes recommended for patients with non-high-risk PDR and CSME: I++; Good; Strong
- Page 12: Table 6: Focal and/or grid laser treatment not recommended for patients with non-high-risk PDR and no DME: I++; Good; Strong
- Page 12: Table 6: Focal and/or grid laser treatment not recommended for patients with non-high-risk PDR and ME: III; Good; Strong
- Page 12: Table 6: Focal and/or grid laser treatment sometimes recommended for patients with non-high-risk PDR and CSME: III; Good; Strong
- Page 12: Table 6: Intravitreal anti-VEGF treatment not recommended for patients with non-high-risk PDR and no DME: III; Good; Strong
- Page 12: Table 6: Intravitreal anti-VEGF treatment not recommended for patients with non-high-risk PDR and ME: III; Good; Strong
- Page 12: Table 6: Intravitreal anti-VEGF treatment sometimes recommended for patients with non-high-risk PDR and CSME: III; Insufficient; Discretionary
- Page 12: Table 6: Intravitreal anti-VEGF treatment not recommended for patients with non-high-risk PDR and ME: III; Good; Strong
- Page 12 : Table 6: Follow-up for patients with high-risk PDR with no DME: 4 months: III; Good; Strong
- Page 12: Table 6: Follow-up for patients with high-risk PDR with ME: 4 months: III; Good; Strong
- Page 12: Table 6: Follow-up for patients with high-risk PDR CSME: 1: III; Good; Strong
- Page 12: Table 6: Panretinal photocoagulation laser treatment recommended for patients with high-risk PDR and no DME: I++; Good; Strong

- Page 12: Table 6: Panretinal photocoagulation laser treatment recommended for patients with high-risk PDR and ME: I++; Good; Strong
- Page 12: Table 6: Panretinal photocoagulation laser treatment usually recommended for patients with high-risk PDR and CSME: I++; Good; Strong
- Page 12: Table 6: Focal and/or grid laser treatment not recommended for patients with high-risk PDR and no DME: III; Good; Strong
- Page 12: Table 6: Focal and/or grid laser treatment sometimes recommended for patients with high-risk PDR and ME: III; Good; Strong
- Page 12: Table 6: Focal and/or grid laser treatment sometimes recommended for patients with high-risk PDR and CSME: III; Good; Strong
- Page 12: Table 6: Intravitreal anti-VEGF treatment considered for patients with high-risk PDR and no DME: III; Good; Strong
- Page 12: Table 6: Intravitreal anti-VEGF treatment usually recommended for patients with high-risk PDR and ME: III; Good; Strong
- Page 12: Table 6: Intravitreal anti-VEGF treatment usually recommended for patients with high-risk PDR and CSME: III; Good; Strong
- Page 13: The patient with a normal retinal exam or minimal NPDR should be re-examined annually: III; Good; Strong
- Page 13: Laser surgery, color fundus photography, and fluorescein angiography are not indicated for patients with normal retinal examinations or minimal NPDR: III; Good; Strong
- Page 13: Patients with retinal microaneurysms and occasional blot hemorrhages or hard exudates should be re-examined within 6-12 months: III; Good; Strong
- Page 13: Laser surgery and fluorescein angiography are not indicated for mild to moderate NPDR without macular edema: III; Good; Strong
- Page 13: Color fundus photography and OCT imaging of the macula may occasionally be helpful to establish a baseline for future comparison: III; Insufficient; Discretionary
- Page 14: Patients with mild or moderate NPDR and non-clinically significant macular edema should be re-examined within 3-4 months: III; Good; Strong
- Page 14: Macular Edema is best evaluated by dilated examination using slit-lamp biomicroscopy, optical coherence tomography, and/or stereoscopic fundus photography; III; Good; Strong
- Page 14: An ophthalmologist who treats patients for macular edema should be familiar with relevant studies and techniques as described in the ETDRS: III; Good; Strong
- Page 14: Fluorescein angiography prior to laser surgery for CSME is often helpful for identifying treatable lesions: III; Good; Discretionary
- Page 14: Fluorescein angiography is useful for identifying capillary dropout and pathologic enlargement of the foveal avascular zone, a feature that may be useful when planning treatment: III; Good; Discretionary
- Page 14: Color fundus photography is often helpful to document the status of the retina even if laser surgery is not performed: III: Good; Discretionary
- Page 14: Optical coherence tomography is a helpful screening tool to detect subtle edema and to follow the course of edema after treatment: III; good; Discretionary
- Page 14: The treatment of CSME has traditionally been laser surgery; however, current data demonstrates that intravitreal anti-VEGF agents are effective treatments for center-involving CSME : I++; Good; Strong
- Page 14: The ETDRS demonstrated a benefit of laser photocoagulation in both ci-CSME and nci-CSME: I++; Good; Strong
- Page 14: Anti-VEGF therapy is the treatment of choice for macular edema with or without focal laser treatment: I++; Good; Strong
- Page 15: Treating physicians should note that the use of betadine antiseptic drops is recommended during intravitreal injections: III; Good; Strong
- Page 15: The use of routine antibiotic eye drops before or following intravitreal injection

procedures is optional: III; Insufficient; Discretionary

- Page 15: Preoperatively, the ophthalmologist should discuss with the patient the side effects and risks of treatment: III; Good; Strong
- Page 15: A follow-up examination for individuals with CSME should be scheduled within 3-4 months of laser surgery: III; Good; Strong
- Page 15:When treatment for macular edema is deferred, the patient should be observed closely (at least 3 to4 months) for signs of progression: III; Good; Strong
- Page 16: Patients with very severe NPDR should be re-examined within 2 to 4 months: III; Good; Strong
- Page 16: Panretinal photocoagulation should not be recommended for eyes with mild or moderate NPDR, provided that follow-up [can] be maintained: I++; Good; Strong
- Page 16: When retinopathy is more severe, panretinal photocoagulation should be considered and should not be delayed when the eye reaches the high-risk proliferative stage: I++; Good; Strong
- Page 16: If laser surgery is elected, full panretinal photocoagulation is a proven surgical technique: I++; Good; Strong
- Page 16: Partial panretinal photocoagulation treatment is not recommended: III; Good; Strong
- Page 16: The recommendation to consider panretinal photocoagulation before the development of high-risk PDR is particularly appropriate for patients with Type 2 diabetes and severe to non-high risk NPDR: II++; Moderate; Strong
- Page 16: Preoperatively [to laser surgery], the ophthalmologist should assess macular edema, discuss side effects of treatment and risks of visual loss with the patient, and obtain informed consent: III; Good; Strong
- Page 16: When panretinal photocoagulation for severe NPDR or non-high risk PDR is to be performed on eyes with macular edema, many experts think that it is preferable to perform focal photocoagulation and/or anti-VEGF therapy prior to panretinal photocoagulation: III; Good; Strong
- Page 16: Panretinal photocoagulation should not be delayed when PDR is at the high-risk stage: III; Good; Strong
- Page 16: When PDR is at the high-risk stage, anti-VEGF therapy and panretinal photocoagulation may be performed concomitantly: III; Good; Strong
- Page 16: Fluorescein angiography may be helpful to determine the presence or absence of areas of nonperfusion and/or clinically undetected areas of retinal neovascularization and to establish the cause for a loss in visual acuity: III; Moderate; Discretionary
- Page 17: The risk of severe visual loss among patients with high-risk PDR is reduced substantially by treatment using panretinal photocoagulation as described in the DRS and ETDRS: I++; Good; Strong
- Page 17: Panretinal photocoagulation surgery should be expedited in most patients with high-risk PDR: II++; Good; Strong
- Page 17: Additional panretinal photocoagulation or vitrectomy may be required for increasing neovascularization of the iris and may be considered for the following indications: failure of the neovascularization to regress; increasing neovascularization of the retina or iris; new vitreous hemorrhage; new areas of neovascularization: III: Insufficient; Discretionary
- Page 17: For patients who have CSME in addition to high-risk PDR, combined anti-VEGF therapy and panretinal photocoagulation at the first treatment session should be considered: III; Insufficient; Discretionary
- Page 17: Fluorescein angiography does not usually need to be performed in order to apply the panretinal photocoagulation effectively. If CSME is present, however, a fluorescein angiogram may be used to guide focal photocoagulation: III; Insufficient; Discretionary
- Page 17: Vitreous hemorrhages following extensive panretinal photocoagulation may clear spontaneously and do not necessarily require additional laser surgery: III; Insufficient; Discretionary
- Page 17: Some patients with previously untreated PDR who have vitreous opacities and active

neovascular or fibrovascular proliferation should be considered candidates for pars plana vitrectomy: I++; Good; Strong

- Page 17: In some patients with severe vitreous or preretinal hemorrhage, in which advanced, active PDR persists despite extensive panretinal photocoagulation, vitrectomy surgery may be indicated: III; Insufficient; Discretionary
- Page 17: Vitreous surgery is frequently indicated in patients with traction macular detachment (particularly of recent onset), combined traction-rhegmatogenous retinal detachment and vitreous hemorrhage precluding panretinal photocoagulation: III; Insufficient; Discretionary
- Page 17: Patients with vitreous hemorrhage and rubeosis iridis also should be considered for prompt vitrectomy and intraoperative panretinal photocoagulation surgery: III; Insufficient: Discretionary
- Page 18: A follow-up history should include changes in symptoms: III; Good; Strong
- Page 18: A follow-up history should include changes in systemic status: III; Good; Strong
- Page 18: A follow-up history should include changes in glycemic status: III; Good; Strong
- Page 18: A follow-up examination should include visual acuity: III; Good; Strong
- Page 18: A follow-up examination should include slit-lamp biomicroscopy with iris examination: III; Good; Strong
- Page 18: A follow- up examination should include intraocular pressure: III; Good; Strong
- Page 18: A follow-up examination should include gonioscopy (preferably before dilation when iris neovascularization is suspected or if IOP is elevated): III; Good; Strong
- Page 18: A follow-up examination should include stereoscopic examination of the posterior pole after dilation of the pupils: III; Good; Strong
- Page 18: A follow-up examination should include OCT imaging, when appropriate: III; Good; Strong
- Page 18: A follow-up examination should include peripheral retina and vitreous examination, when indicated: III; Good; Strong
- Page 18: Although the ophthalmologist will perform most of the examination and all surgery, certain aspects of data collection may be performed by trained individuals under the ophthalmologist's supervision and review: III; Good; Strong
- Page 18: Because of the complexities of the diagnosis and treatment for diabetic retinopathy, the ophthalmologist caring for patients with this condition should be familiar with the specific recommendations of relevant clinical trials: III; Good; Strong
- Page 18: The ophthalmologist should refer patients with diabetes to a primary care physician for appropriate management of their systemic condition, and should communicate examination results to the physician managing the patient's ongoing diabetes care: III; Good; Strong
- Page 18: Those whose conditions fail to respond to surgery and those or whom further treatment is unavailable should b provided with proper professional support and offered referral for counseling, vision rehabilitation, or social services as appropriate: III; Good; Strong
- Page 18: Patients with functionally limiting post-operative visual impairment should be referred for vision rehabilitation and social services: III; Good; Strong

APPENDIX 2. MAJOR STUDY RESULTS

DIABETIC RETINOPATHY STUDY (1972-1979)

The Diabetic Retinopathy Study (DRS) was designed to investigate the value of laser photocoagulation surgery for patients with severe NPDR and PDR.[43]

The results are shown below.

Table. A4-1. Visual Outcome for Laser Photocoagulation from the Diabetic Retinopathy Study

Baseline Severity of Retinopathy	Duration of Follow-Up (Years)	Control Patients (% with Severe Visual Loss)	Treated patients (% with Severe Visual Loss)
Severe nonproliferative	2	3	3
	4	13	4
Mild proliferative	2	7	3
	4	21	7
High-risk proliferative	2	26	11
	4	44	20
NOTE: Severe visual loss was defined as worse than 5/200 visual acuity at two or more consecutive completed visits (scheduled at 4 month			

WISCONSIN EPIDEMIOLOGIC STUDY OF DIABETIC RETINOPATHY (1979)

The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) began in 1979. It was initially funded by the National Eye Institute, which is part of the National Institutes of Health. The purpose of the WESDR is to describe the frequency and incidence of complications associated with diabetes (eye complications such as diabetic retinopathy and visual loss, kidney complications such as diabetic nephropathy, and amputations), and to identify risk factors (such as poor glycemic control, smoking, and high blood pressure) that may contribute to the development of these complications.[49]

EARLY TREATMENT DIABETIC RETINOPATHY STUDY (1985-1990)

The Early Treatment Diabetic Retinopathy Study (ETDRS) investigated the value of photocoagulation

surgery for patients with NPDR or PDR without high-risk characterisitcs.[47,61] The results for eyes with macular edema are shown in Table A4-2. Visual loss was defined as at least doubling of the visual angle (e.g. 2020 to 20/40 or 20/50 to 20/100)

Table A4-2. Visual Outcome for Laser Photocoagulation Treatment from the Early Treatment Diabetic Retinopathy Study

Extent of Macular Edema	Duration of Follow-up (Years)	Control Patients (% with Visual Loss)	Treated Patients (% with Visual Loss)
CSME	1	8	1
(center of macula not	2	16	6
involved)	3	22	13
CSME	1	13	8
(center of macula	2	24	9
involved)	3	33	14
CSME = clinically significant macular edema NOTE: Visual loss was defined as at least doubling of the visual angle.			

Results of Early Scatter Laser Treatment (ETDRS)

In eyes with NPDR or non-high-risk PDR, early panretinal photocoagulation was compared with deferral of photocoagulation, and although there was a beneficial treatment effect, the outlook for maintaining vision was good in both groups. The 5-year rates of severe visual loss or vitrectomy ranged from 2% to 6% in eyes assigned to early photocoagulation and from 4% to 10% in eyes assigned to deferral. Early panretinal photocoagulation was associated with side effects (small decreases in visual acuity and visual field) in some eyes, and with ETDRS concluded that deferral of photocoagulation was preferable at least until retinopathy was approaching the high-risk stage. Eyes approaching that stage had a 50% risk of reaching it within 12 to 18 months. Eyes in this category had very severe NPDR or non-high-risk PDR characterized by NVD less than one-quarter to one third disc area and/or NVE, without vitreous or preretinal hemorrhage.

Recent additional analyses of visual outcome in ETDRS patients with severe NPDR to non-high-risk PDR suggest that the recommendation to consider panretinal photocoagulation before the development of high-risk PDR is particularly appropriate for patients with Type 2 diabetes.[112] The risk of severe vision loss or vitrectomy was reduced by 50% in patients who were treated early compared with those who deferred treatment until high-risk PDR developed.

For patients with Type 1 diabetes, the timing of panretinal photocoagulation will depend on the compliance with follow-up, status and response to treatment of the fellow eye, impending cataract surgery, and/or pregnancy status.

DIABETIC RETINOPATHY VITRECTOMY STUDY (1983-1987)

The Diabetic Retinopathy Vitrectomy Study (DRVS) investigated the role of vitrectomy in managing eyes with severe PDR. [48,118-120] The benefit of early vitrectomy for severe vitreous hemorrhage (defined as hemorrhage obscuring the macular or major retinal vessels for three disc diameters from the macular center) was seen in Type 1 patients, but no such advantage was found in Type 2 patients, who did not benefit from earlier surgery. Early vitrectomy was beneficial among patients with visual acuity of 5/200 or worse and severe vitreous hemorrhage with reduced vision for at least 1 month and without previous treatment or complications such as retinal detachment or neovascularization of the iris. Overall at 2 years after surgery, 25% of the early vitrectomy group and 15% of the deferral group had visual acuity of 20/40 or better. The advantage was most pronounced in patients with Type 1 diabetes (36% vs. 12% for early vitrectomy versus deferral of vitrectomy, respectively) and was not statistically significant for patients with Type 2 diabetes)

The DRVS showed that early vitrectomy was beneficial or patients with visual acuity of 20/400 or better plus one of the following: (1) severe neovascularization and fibrous proliferation; (2) fibrous proliferation and moderate vitreous hemorrhage; or (3) moderate neovascularization, severe fibrous proliferation, and moderate vitreous hemorrhage. Among such patients, 44% with early vitrectomy and 28% in the observation group had visual acuity of 20/40 or better at 4 years of follow-up.

The results of the DRVS should be interpreted in light of subsequent advances in vitreoretinal surgery, such as the introduction of small-gauge vitectomy technology, endoscopic and indirect ophthalmoscopic laser photocoagulation, and advanced instrumentation. The use of long-acting intraocular gases such as sulfur hexafluoride and perfluoropropane, the use of viscodissection, and the use of heavier-than-water liquids such as perofluoro-octane are advances in vitreoretinal surgery that developed after the DRVS. Thus, the results may actually bet better than those reported in DRVS.[82,128] Early vitrectomy should be considered for selected patients with Type 2 diabetes, particularly those in whom severe vitreous hemorrhage prohibits laser therapy photocoagulation of active neovascularization.

DIABETIC RETINOPATHY CLINICAL RESEARCH NETWORK (DRCR.Net) (2002-Present)
The Diabetic Retinopathy Clinical Research Network (DRCR.net) is a collaborative network dedicated to facilitating multicenter clinical research of diabetic retinopathy, diabetic macular edema, and associated conditions The DRCR.net supports the identification, design, and implementation of multicenter clinical research initiatives focused on diabetes-induced retinal disorders. Principal emphasis is placed on clinical trials, but epidemiologic outcomes and other research may be supported as well.

The DRCR.net has completed multiple clinical trials evaluating the role of anti-VEGF, laser treatment and corticosteroids in diabetic macular edema. One of the most important is Protocol I: Intravitreal Ranibizumab or Diabetic Macular Edema with Prompt vs. Deferred Laser Treatment. Three-year results were reported in 2012. The study utilized ranibizumab monthly until improvement no longer occurred (with resumption if the condition worsened) and random assignment to focal/grid laser treatment promptly or deferred ($\geq$ 24 weeks). The 3-year results suggest that focal/grid laser treatment at the initiatiin of intravitreal ranibizumab is no better, and possibly worse for vision outcomes, than deferring laser treatment for $\geq$ 24 weeks in eyes with DME involving the fovea and with vision impairment.[52]

A previous publication from Protocol I results confirmed the 1 year results that intravitreal ranibizumab with prompt or deferred laser was more effective through 2 years compared with prompt laser alone for the treatment of DME involving the central macula. Laser was not associated with endophthalmitis, the rare but potentially devastating complication of injecting ranibizumab, In pseudophakic eyes, results with intravitreal triamcinolone plus prompt laser appeared similar to results in the ranibizumab arms and were ore effective than laser along, but the triamcinolone plus prompt laser arm had an increased risk of IOP elevation.[77]

STUDY OF RANIBIZUMAB INJECTION IN SUBJECTS WITH CSDME WITH CENTER INVOLVEMENT SECONDARY TO DIABETES MELLITUS (RISE AND RIDE)
The RISE and RIDE trials were parallel phase III multicenter double-masked sham injection-controlled randomized studies conducted at private and university-based retina specialty clinics in the United States and South America.

The phase III results for both studies were published in 2012. The studies utilized monthly intravitreal ranibizumab (0.5 or 0.3) or sham injections, with macular laser available if needed. The study concluded that ranibizumab rapidly and sustainably improved vision, reduced the risk of further vision loss, and improved macular edema in patients with DME with low rates of ocular and nonocular side effects.[97]

RANIBIZUMAB FOR EDEMA OF THE MACULA IN DIABETES (READ-2)
READ-2 was a phase II multicenter randomized controlled trial that compared 0.5 mg injections of ranibizumab versus focal laser treatment over 2 years in patients with Type 1 or Type 2 diabetes mellitus

and DME. Patients randomized to one arm of the trial received ranibizumab at baseline, and at 1,3 and 5 months after baseline; a second arm receive laser treatment at baseline at 3 months. From month 5, all subjects received ranibizumab every 2 months and/or maintenance laser treatment every 3 months.

At 24 months, differences between the groups were not statistically significant, and all groups experienced improved visual acuity. Patients receiving combined ranibizumab and laser treatment required fewer injections than patients receiving ranibizumab alone.[100]

BEVACIZUMAB OR LASER THERAPY (BOLT) STUDY
BOLT was a phase II 2-year randomized controlled trial that compared intravitreal 1.25 mg bevacizumab injections and focal laser treatment inpatients with persistent DME and visual impairment. Bevacizumab patients received an injection every 6 weeks, whereas laser patients were treated every 4 weeks.

At 2 years, visual acuity results were substantially better in the bevacizumab group compared with the laser group, with significant differences in the proportions of patients gaining 10 letters and 15 letters. No patients lost 10 or more letters in the bevacizumab group, compared with 14% of patients treated with laser[101]

DME AND VEGF TRAP-EYE: INVESTIGATION OF CLINICAL IMPACT (DA VINCI) STUDY
DA VINCI was an active-controlled phase II randomized controlled trial that compared various doses of aflibercept and focal laser treatment in patients with CSME. At 1 year, patients receiving aflibercept had greater gains in visual acuity (averaging 9.7-12.0 letters gained) compared with patients receiving laser treatment (averaging -1.3 letters lost). Aflibercept patients were also more likely to gain 10 or more letters and 15 or more letters than patients in the laser treatment arm.[102]

MEAD : MACULAR EDEMA: ASSESSMENT OF IMPLANTABLE DEXAMETHASONE IN DIABETES
Based on the MEAD (Macular Edema: Assessment of Implantable Dexamethasone in Diabetes) study, Dexamethasone implant (dexamethasone biodegradable intravitreal implant) 0.7 mg delivered via intravitreal injection has been approved by the United States Food and Drug Administration (July 2014) for the treatment of diabetic macular edema. The MEAD demonstrated long-term efficacy in the treatment of DME without having to do monthly injections. MEAD consisted of two randomized multi-center 3-year sham-controlled, masked, clinical studies which showed that the percentage of patients with $\geq$ 15 letter improvement in best-corrected visual acuity (BCVA) from baseline was greater with dexamethasone implant (22.2%) than with placebo implant (12%). The most common adverse events included the development of cataracts and elevated intraocular pressure (IOP).[**123**]

APPENDIX 3: Consensus on Intravitreal Injection Technique: VitreoRetina Society of the Philippines

Vascular endothelial growth factor (VEGF) has been shown to play a central role in the pathophysiologic process underlying neovascular eye diseases. As such, anti-VEGF based pharmacologic agents have emerged as a highly effective treatment modality for various visually debilitating retinal and choroidal vascular pathologies. The introduction of these pharmacologic agents directly into the vitreous cavity by means of an injection through the pars plana has become a widely performed ophthalmic procedure both locally and overseas.

As the sole physician organization of vitreoretinal specialists in the country, the VitreoRetina Society of the Philippines (VRSP), in coordination with the Philippine Academy of Ophthalmology (PAO), through a review of current evidence and a consensus among its members has developed guidelines for the performance of intravitreal injections in the Philippine setting to ensure patient safety and to maximize the benefits Filipino patients may obtain from this highly valuable treatment modality.

I. All intravitreal injections should be performed by a Philippine Board of Ophthalmology certified ophthalmologist who is knowledgeable, skilled and comfortable in the diagnosis and comprehensive management of retinal diseases for which anti-VEGF treatment is indicated, and adept at minimizing the risks and managing the potential complications associated with trans pars plana delivery of these medications.

II. Clinical Setting of Care:
- It is suggested that the procedure be performed in an operating theater or in a room/facility specifically dedicated for intravitreal injections.[1,2]

III. Preprocedural Issues
- Informed Consent [3]
    i. An informed consent has to be signed by the patient prior to the procedure.
    ii. The consent form should include the name of the drug to be injected, the indication for injection, the potential risks and benefits of the use of anti-VEGF agents and of the procedure itself.
    iii. Information must be fully explained to the patient.

iv. A consent form specific for an individual drug is recommended.

- Currently, there is no data that indicates anticoagulant use will affect visual outcomes after intravitreal injection. However, there is an increased likelihood of subconjunctival hemorrhage at the site of injection.
- Medical Clearance
    i. The benefits, risks and indications of anti-VEGF injections should be carefully reconsidered in the following situations:
        1. Patients with a history of myocardial infarction, any cardiac event requiring hospitalization, stroke, transient ischemic attack, or treatment for acute congestive heart failure within the past 4 months [4]
        2. Major surgery within 28 days
        3. Uncontrolled hypertension
        4. Pregnancy
    ii. Necessity for medical clearance is at the discretion of the attending ophthalmologist. While arteriothromboembolic events have been reported, the direct causative relation between stroke and intravitreal anti-VEGF injection use has not been established.

IV. Surgical Site Preparation

- Intravitreal injections are intraocular procedures that merit equal attention to adherence to principles of asepsis and sterile technique as for conventional intraocular surgeries.
- As part of the World Health Organization Surgical Safety Checklist,[5] "time-out" or surgical site marking is recommended.
- Pre-operative dilation is performed at the discretion of the attending ophthalmologist
- There is no evidence to support that the instillation of a topical antibiotic solution prior to injection reduces the risk of subsequent intraocular infection. Pre-operative antibiotics may be administered at the discretion of the attending ophthalmologist.
- Preoperative disinfection of the *periocular skin* with 10% povidone iodine and a minimum exposure time of 3 minutes is suggested. 10% aqueous chlorhexidine may be used as an alternative in patients with hypersensitivity to povidone iodine. [6]
- The use of a newly opened bottle of topical anesthetic is recommended.
- 5% povidone iodine should be applied onto the *conjunctival cul-de-sac* or *lower fornix* with a minimum contact time of 30 seconds. [6,7,8,9,10,11]
- The use of a sterile solid-blade lid speculum[9, 10] or any type of occlusive dressing is recommended to isolate the lashes from the site of injection.

V. Injection Procedure

- As part of good surgical practice, the use of a sterile eye sheet or equivalent drapes,[11] the donning of sterile surgical gloves and the wearing of a surgical mask [11, 12] are advised. The surgical assist is advised to wear a surgical cap and mask
- The injection site should be 3 to 3.5 mm from the corneoscleral limbus for aphakic and pseudophakic eyes, and 3.5 to 4 mm for phakic eyes.
- The use of a sterile 30-gauge needle is recommended for intravitreal injection of anti-VEGF drugs.
- Once the needle is withdrawn, the ophthalmologist may apply a sterile cotton applicator to prevent reflux of liquid vitreous.
- The ophthalmologist should assess central retinal artery perfusion by checking for gross vision *or* venous pulsation via indirect ophthalmoscopy.

- Anterior chamber paracentesis may be performed in cases with evidence of a sustained rise in intraocular pressure.
- Bilateral Same Day Injections [13]
    i. Each eye should be prepared with povidone-iodine separately.
    ii. A completely new and different surgical set of sterile eye sheet, lid speculum, instruments, 30-gauge needle and syringe should be utilized.
    iii. Whenever feasible, separate vials of medication with different lot numbers should be used for each eye.
- There is no evidence to suggest that the instillation of post-injection antibiotics confers additional benefit in reducing the risk of endophthalmitis following intravitreal injections. Post injection antibiotics may be administered at the discretion of the attending ophthalmologist.

VI. Post-Injection Management

- Post-injection follow-up is recommended within 7 days.
- Patient should be instructed to return sooner if with symptoms of inflammation or infection.

This consensus statement is subject to re-evaluation and revision as new evidence-based studies on intravitreal anti-VEGF injections become published and new practice patterns evolve.

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GLOSSARY

Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial: A large multicenter clinical trial that evaluated intensive control of blood sugar, intensive control of blood pressure, and statin therapy (with or without fibrate treatment) for the prevention of cardiovascular disease events among high-risk patients with Type 2 diabetes.

ACCORD: See Action to Control Cardiovascular Risk in Diabetes trial.

Anti-VEGF: See Anti-vascular endothelial growth factor.

Anti-vascular endothelial growth factor (VEGF):Substances that inhibit the action of vascular endothelial growth factor protein.

Bevacizumab or Laser Treatment (BOLT) study: A randomized trial that evaluated intravitreal bevacizumab or conventional laser treatment for center-involving diabetic macular edema.

BOLT: See Bevacizumab or Laser Treatment study.

Clinically significant macular edema (CSME): Retinal thickening at or within 500 µm of the center of the macula; and/or hard exudates at or within 500 µm of the center of the macula, if associated with thickening of the adjacent retina; and/or a zone or zones of retinal thickening one disc area in size, any part of which is within one disc diameter of the center of the macula.

CSME: See Clinically significant macular edema.

ci-CSME: Center-involving CSME.

DA VINCI: See DME and VEGF Trap-Eye: Investigation of Clinical Impact study.

DCCT: See Diabetes Control and Complications Trial.

Diabetes Control and Complications Trial (DCCT): A multicenter randomized controlled trial designed to study the connection between glycemic control and retinal, renal, and neurologic complications of Type 1 diabetes mellitus. (See Appendix 5.)

Diabetes mellitus: According to the American Diabetes Association Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, the criteria for the diagnosis of diabetes mellitus are as follows.

- Fasting plasma glucose equal to or exceeding 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours. - OR (see next bullet) -
- Symptoms of hyperglycemia and a casual plasma glucose concentration equal to or exceeding 200

mg/dL (11.1 mmol/L). “Casual” is defined as any time of day without regard to time since last meal. The classic symptoms of hyperglycemia include polyuria, polydipsia, and unexplained weight loss. - OR (see next bullet) -

- A plasma glucose measurement at 2 hours postload equal to or exceeding 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water. However, the expert committee has recommended against oral glucose tolerance testing for routine clinical use. (Source: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2008;31 (suppl):55-60.)

Diabetic Retinopathy Clinical Research Network (DRCR.net): A multicenter trial that is evaluating different treatment modalities for diabetic retinopathy.

Diabetic Retinopathy Study (DRS): A study designed to investigate the value of xenon arc and argon photocoagulation surgery for patients with severe NPDR and PDR. (See Appendix 4.)

Diabetic Retinopathy Vitrectomy Study (DRVS): A study that investigated the role of vitrectomy in managing eyes with very severe PDR. (See Appendix 4.)

DME and VEGF Trap-Eye: Investigation of Clinical Impact (DA VINCI) study: A randomized trial of the use of aflibercept for diabetic macular edema.

DRCR.net: See Diabetic Retinopathy Clinical Research Network.

DRS: See Diabetic Retinopathy Study.

DRVS: See Diabetic Retinopathy Vitrectomy Study.

Early Treatment Diabetic Retinopathy Study (ETDRS): A study that investigated the value of photocoagulation surgery for patients with NPDR or PDR who did not have high-risk characteristics. (See Appendix 4.)

Early proliferative diabetic retinopathy (i.e., proliferative retinopathy without DRS high-risk characteristics)**:** New vessels that do not meet the criteria of high-risk proliferative retinopathy.

EDIC: See Epidemiology of Diabetes Interventions and Complications study.

ETDRS: See Early Treatment Diabetic Retinopathy Study.

Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study: A large randomized controlled trial that evaluated long-term fenofibrate therapy for prevention of cardiovascular events in patients with Type 2 diabetes mellitus.

FIELD study: See Fenofibrate Intervention and Event Lowering in Diabetes study.

Focal photocoagulation: A laser technique directed to abnormal blood vessels with specific areas of focal leakage (i.e., microaneurysms) to reduce chronic fluid leakage in patients with macular edema.

Grid photocoagulation: A laser technique in which a grid pattern of scatter burns is applied in areas of diffuse macular edema and nonperfusion. Typically, fluorescein angiograms of these areas show a diffuse pattern rather than focal leakage.

High-risk proliferative diabetic retinopathy (PDR): New vessels on or within one disc diameter of the optic disc equaling or exceeding standard photograph 10A (about one-quarter to one-third disc area), with or without vitreous or preretinal hemorrhage; or vitreous and/or preretinal hemorrhage accompanied by new vessels either on the optic disc less than standard photograph 10A or new vessels elsewhere equaling or exceeding one-quarter disc area. Standard photograph 10A

ICD-9: International Statistical Classification of Diseases and Related Health Problems, Ninth Edition.

ICD-10: International Statistical Classification of Diseases and Related Health Problems, Tenth Edition.

Intraretinal microvascular abnormalities (IRMA): Tortuous intraretinal vascular segments, varying in caliber from barely visible to 31 µm in diameter (one-quarter the width of a major vein at the disc margin); they occasionally can be larger. IRMA may be difficult to distinguish from neovascularization.

IRMA: See Intraretinal microvascular abnormalities.

Macular edema: Thickening of the retina within one or two disc diameters of the center of the macula. (See Clinically significant macular edema.) Any other thickening of the macula not within this area is non-CSME.

Mild nonproliferative diabetic retinopathy (NPDR): At least one microaneurysm and less than moderate nonproliferative diabetic retinopathy.

Moderate nonproliferative diabetic retinopathy (NPDR): Hemorrhages and/or microaneurysms greater

than standard photograph 2A, and/or soft exudates, venous beading, or intraretinal microvascular abnormalities present but less than severe nonproliferative retinopathy.
Moderate visual loss: The loss of 15 or more letters on the ETDRS visual acuity chart, or doubling of the visual angle (e.g., 20/20 to 20/40, or 20/50 to 20/100).
nci-CSME: Non-center-involving CSME.
New vessels at the optic disc (NVD): New vessels at the optic disc; neovascularization on or within one disc diameter of the optic disc.
New vessels elsewhere in the retina (NVE): New vessels elsewhere in the retina; neovascularization elsewhere in the retina and greater than one disc diameter from the optic disc margin.
New vessels on the iris (NVI): New vessels on the iris; neovascularization of the iris.
Nonproliferative diabetic retinopathy (NPDR): The phases of diabetic retinopathy with no evidence of retinal neovascularization.
NPDR: See Nonproliferative diabetic retinopathy.
NVD: See New vessels at the optic disc.
NVE: See New vessels elsewhere in the retina.
NVI: See New vessels on the iris.
OCT: See Optical coherence tomography.
Optical coherence tomography (OCT): A diagnostic test using low energy lasers that takes a cross-section image of the retina, Used mostly to determine if there are membranes on the surface of the macula or fluid within or beneath it.
Panretinal photocoagulation: A type of laser surgery used for patients with proliferative diabetic retinopathy. The surgery is delivered in a scatter pattern throughout the peripheral fundus and is intended to lead to a regression of neovascularization.
PDR: See Proliferative diabetic retinopathy.
Proliferative diabetic retinopathy (PDR): Advanced disease characterized by NVD and/or NVE.
Quality adjusted life year (QALY): A measure of health outcome that assigns to each year of a patient's life a weight (ranging from 0 to 1) corresponding to the health-related quality of life during that year, such that a value of 1 indicates a year of optimal health and a value of 0 indicates a year in a health state judged equivalent to death.
QALY: See Quality adjusted life year.
Ranibizumab for Edema of the mAcula in Diabetes (READ-2) study: A prospective multicenter randomized controlled trial that compared 0.5 mg ranibizumab and laser photocoagulation for the treatment of diabetic macular edema.
READ-2: See Ranibizumab for Edema of the mAcula in Diabetes study.
Retinal hard exudate: Protein and lipid accumulation within the retina.
RIDE: A study of ranibizumab injection in subjects with clinically significant macular edema with center-involvement secondary to diabetes mellitus.
RISE: A study of ranibizumab injection in subjects with clinically significant macular edema with center-involvement secondary to diabetes mellitus.
Scatter photocoagulation: See Panretinal photocoagulation.
Severe nonproliferative diabetic retinopathy (NPDR): Using the 4-2-1 rule, the presence of at least one of the following features: (1) severe intraretinal hemorrhages and microaneurysms, equaling or exceeding standard photograph 2A, present in four quadrants;(2) venous beading in two or more quadrants (standard photograph 6A); or (3) moderate intraretinal microvascular abnormalities equaling or exceeding standard photograph 8A in one or more quadrants. Standard photographs 2A, 6A, and 8A ***Severe visual loss:*** Occurrence of visual acuity worse than 5/200 at any two consecutive visits scheduled at 4-month intervals.
UKPDS: See United Kingdom Prospective Diabetes Study.
United Kingdom Prospective Diabetes Study (UKPDS): A randomized controlled clinical trial of blood glucose control in patients with newly diagnosed Type 2 diabetes.
VTDR: Vision-threatening diabetic retinopathy.
WESDR: See Wisconsin Epidemiologic Study of Diabetic Retinopathy

Wisconsin Epidemiologic Study of Diabetic Retinopathy: A large epidemiologic study of complications associated with diabetes and of risk factors associated with those complications.

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