ARTICLE REVIEW

International Journal of Retina (*IJRETINA*) 2024, Volume 7, Number 2
P-ISSN. 2614-8684, E-ISSN.2614-8536

IJRETINA
International Journal of Retina

GUIDELINES FOR THE DIAGNOSIS AND MANAGEMENT OF DIABETIC RETINOPATHY AND DIABETIC MACULAR EDEMA IN INDONESIA

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ABSTRACT

Diabetic retinopathy (DR) and diabetic macular edema (DME) are among the microvascular complications in individuals with diabetes mellitus (DM) that can lead to blindness if not diagnosed early and managed appropriately. Both disorders can be diagnosed and treated using a variety of techniques. Treatment modalities include laser photocoagulation therapy, vitrectomy surgery, intraocular steroid injections, and anti-vascular endothelial growth factor (anti-VEGF) injections. These methods can help avoid blindness when used in conjunction with metabolic control. These recommendations were created with the use of evidence-based medicine principles to help medical professionals—particularly ophthalmologists—identify and treat cases of DR and DME. The primary objective is to provide consensus recommendations and hopefully reduce the incidence of blindness caused by DR and DME in Indonesia.

Keywords: Diabetes, diabetic macular edema, diabetic retinopathy, laser, intravitreal injections, vitrectomy
Cite This Article: HARLEY, Ohisa et al. GUIDELINES FOR THE DIAGNOSIS AND MANAGEMENT OF DIABETIC RETINOPATHY AND DIABETIC MACULAR EDEMA IN INDONESIA. International Journal of Retina, [S.l.], v. 7, n. 2, sep. 2024. ISSN 2614-8536. Available at: <https://www.ijretina.com/index.php/ijretina/article/view/300>. Date accessed: 22 sep. 2024. doi: https://doi.org/10.35479/ijretina.2024.vol007.iss002.300.

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INTRODUCTION

Statistics indicate that 1 in 3 DM patients will develop DR, and about one-tenth of them will face vision-threatening conditions such as DME.[1] In Indonesia, the prevalence of DR is 43.1%, the second most prevalent complications of DM after nephropathy.[2] DR is a complication of microangiopathy in DM, characterized by microvascular alterations in the retinal blood vessels due to chronic hyperglycemia.[3]

This condition is chronic, progressive, and poses a threat to vision without appropriate management.[4] Meanwhile, DME is a condition resulting from vascular hyperpermeability in the retina, leading to the accumulation of fluid in the extracellular space in the macular region, especially in the inner nuclear layer, outer plexiform layer, Henle's fiber layer, and subretinal area.[3] The combination of various available therapeutic modalities for DR and DME with early detection and systemic DM management has reduced the blindness rate due to DR and DME worldwide.[1] Therefore, these recommendations are developed to assist healthcare practitioners, particularly ophthalmologists, in diagnosing and managing DR and DME cases, also serve as a guide for policymakers and healthcare services in developing local protocols.

DIAGNOSIS AND EXAMINATION

The initial history-taking should consider the following factors: duration of DM, blood sugar control (HbA1c, fasting blood sugar levels, and 2-hour postprandial blood sugar levels), identifying DR risk factors in patients (puberty, genetics, smoking), and comorbidities (DM, obesity, systemic hypertension, dyslipidemia, pregnancy), treatment history, DM complications (DM nephropathy, DM neuropathy, diabetic foot), eye disease history (e.g., trauma, eye injections, surgeries, including laser therapy and refractive surgery). Symptoms may include asymptomatic/no symptoms (if abnormalities in DR have not caused disturbances in the macula or visual media), blurred vision, floaters, sudden obstruction of vision, pain in/around the eye (due to increased intraocular pressure in cases of neovascular glaucoma).[5-7]

INITIAL EXAMINATIONS

Initial examinations include: 1) visual acuity (VA), which typically determined using the Snellen chart with results expressed in metric figures such as 6/6, 6/50, etc. Alternatively, logarithm of the Minimum Angle of Resolution (log MAR) or Early Treatment Diabetic Retinopathy Study (ETDRS) charts may be used, as they are considered to provide a more accurate assessment; 2) slit lamp biomicroscope, a tool to assess the anterior segment of the eye, and neovascularization of the iris needs evaluation before pupil dilation; 3) intraocular pressure (IOP); 4) gonioscopy, if there are indications such as suspicion of iris neovascularization and/or increased IOP; and 5) funduscopic, to evaluate the optic disc, retina, vasculature, vitreous, and macula. Maximum pupil dilation is necessary for optimal imaging. It is recommended to use slit lamp biomicroscopes with condensing lens or indirect ophthalmoscopy. Important observations include signs of severe non-proliferative diabetic retinopathy (NPDR) (such as intraretinal hemorrhages/microaneurysms, venous beading, and intraretinal microvascular abnormality/IRMA), signs of neovascularization of the optic disc/NVD or neovascularization elsewhere/NVE, vitreous or preretinal hemorrhage, retinal traction, and the presence of macular edema.[5-7]

SUPPORTING EXAMINATIONS

1) Color fundus photography

The standard for DR screening recommended by the ETDRS is color fundus photography in 7 standard fields (30°),[8] and alternatively, ultra-widefield (UWF) imaging and confocal scanning laser ophthalmoscope (SLO) can be used (**Figure 1**). UWF imaging provides a wide view of the retina, enabling more optimal detection of peripheral DR lesions, and it can be quickly obtained with SLO technology.[9,10]

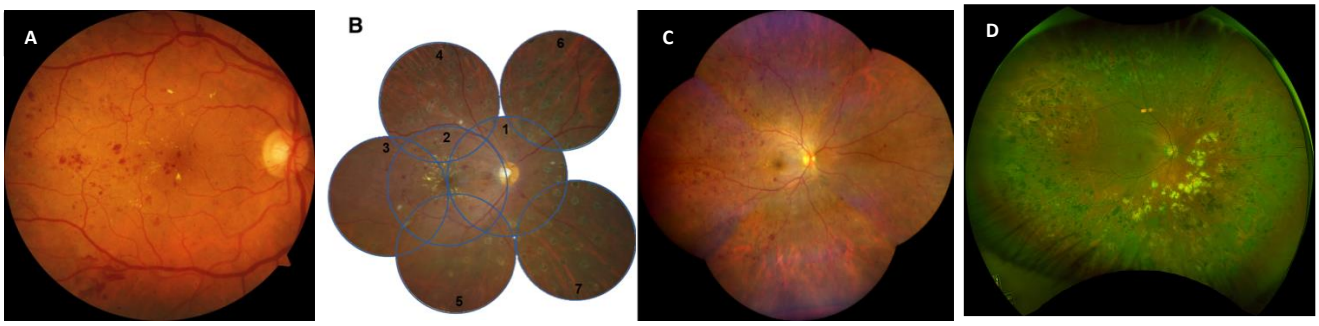

Figure 1. a) Conventional fundus photo displaying the posterior pole area. Source of the image: dr.Sardjito hospital, b) ETDRS-7 field montage. Adapted from: Hirano T, et al,[11] c) UWF Imaging. Source of the image: Jakarta Eye Center, d) Optos UWF retinal imaging.

2) Optical Coherence Tomography (OCT)

OCT is a practical, non-invasive, and accurate modality for evaluating macular conditions as it can generate high-resolution images of retinal layers in cross-sections. OCT is the first-line examination for confirming the diagnosis of DME. OCT findings may include the loss of foveal depression, central retinal thickening, the presence of intraretinal fluid that can manifest as diffuse/cystic/mixed patterns, the presence of hyperreflective retinal foci (HRF), the presence of disorganization of the retinal inner layer (DRIL), and the presence of subretinal fluid.[12,13] Considerations for the use of OCT in DR can be seen in **Table 1**, and OCT images in DME can be observed in **Figure 2.**

Table 1. The Use of OCT in DR. (Adapted from Flaxel CJ, et al.[5])

Situation	Commonly performed	Sometimes
Evaluation of unexplained vision loss	x	
Detection, quantification, and monitoring of DME	x	
Identification of areas with vitreomacular traction	x	
Evaluation of patients with challenging/doubtful DME examinations	x	
Investigation of other causes of macular edema		x
Screening of patients without DR or with minimal DR		x

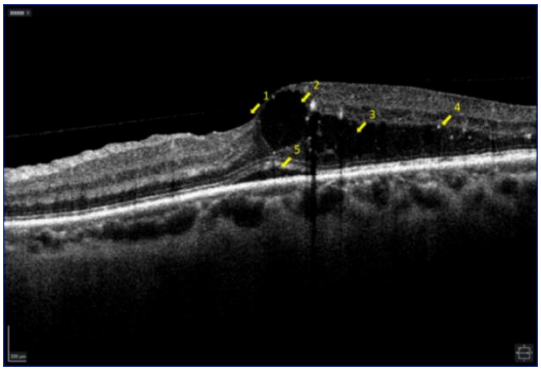

Figure 2. OCT findings in DME. 1) Loss of foveal depression, 2) large cystic cavities due to fluid accumulation, 3) presence of fluid in the intraretinal layers, 4) HRF, 5) presence of subretinal fluid. Source of the image: Cicendo hospital.

3) Optical Coherence Tomography Angiography (OCTA)

OCTA is a non-invasive angiography for evaluating retinal blood vessels without the need for contrast agents. Its utility in DR includes providing detailed information about retinal blood vessels, demarcating the foveal avascular zone (FAZ) to help assess foveal ischemia, accurately detecting IRMA, and assisting in depicting areas of capillary dropout. Unfortunately, OCTA is unable to identify neovascular leakage.[14,15] OCTA images of DR can be seen in **Figure 3.**

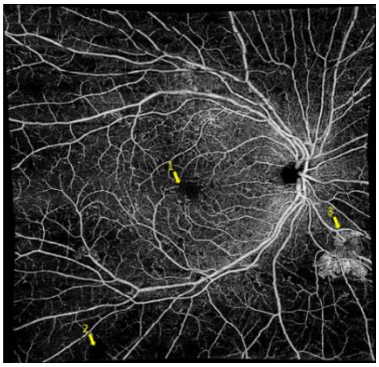

Figure 3. DR observed with OCTA. 1) Demarcation of FAZ to aid in assessing foveal ischemia, 2) non-perfused area, 3) IRMA. Source of the image: Carl Zeiss Meditec.

4) Fundus Fluorescein Angiography (FFA)

This examination is an invasive procedure that can identify the location of leakage and ischemia in the retina,[16] as illustrated in **Figure 4**. FFA is commonly performed in the following situations: as guidelines for performing laser therapy in clinically significant macular edema, to evaluate unexplained vision loss, and to identify suspected cases of retinal neovascularization with unclear clinical indications.[5]

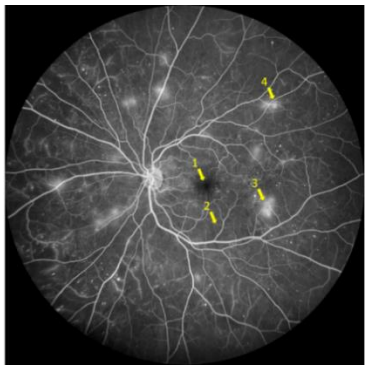

Figure 4. Standard widefield FFA shows: (1) widening of FAZ, (2) scattered microaneurysms throughout the macula, (3) there is leakage from the neovascularization area, and (4) IRMA. Source of the image: Carl Zeiss Meditec.

5) Ultrasonography (USG)

USG can be used to assess the amount of vitreous hemorrhage, determine the extent and severity of vitreoretinal traction, and diagnose tractional retinal detachment.[17] Illustrations can be seen in **Figure 5**.

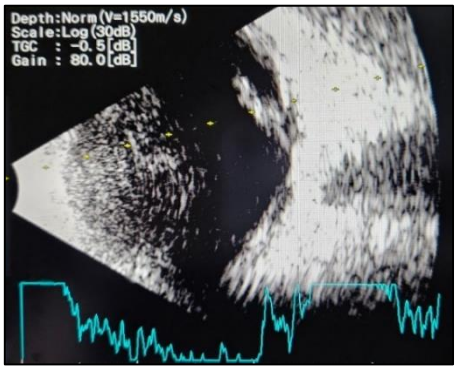

Figure 5. USG of a type 1 DM with vitreous hemorrhage, tractional retinal detachment, and proliferative diabetic retinopathy (PDR). Source of the image: Kirana dr. Cipto Mangunkusumo hospital.

MANAGEMENT OF DR

General Management

Systemic intervention is required to control the underlying disease, manage systemic risk factors beyond diabetes, reduce the progression of retinopathy, and support the treatment process in the eye field.

Recommendations:

1. Control systemic risk factors in patients with diabetic maculopathy by managing blood pressure and maintaining optimal glycemic control
2. Good glycemic control is defined as HbA1c less than 7%, fasting blood sugar between 80-130 mg/dL, or 2-hour postprandial blood sugar between 140-180 mg/dL. (*level of evidence* b)
3. Other metabolic controls include: hypertension (diastolic ≤ 90 mmHg and systolic ≤ 140 mmHg), dyslipidemia (LDL ≤ 100 mg/dL, triglycerides ≤ 150 mg/dL, HDL ≥ 40 mg/dL for men and ≥ 50 mg/dL for women). (*level of evidence* b dan c)
4. Control dyslipidemia through lifestyle improvements and pharmacological therapy in patients with type 2 DM.
5. Perform DR screening at the time of initial diagnosis in type 2 DM patients, after 5 years of diagnosis in type 1 DM patients, and promptly after conception or in the early first trimester in pregnant patients with type 1 and type 2 DM. Screening for early detection is conducted by ophthalmologists and general practitioners with competence in posterior segment examination using fundoscopy.

Level of evidence IV, Recommendation C

Management in Ophthalmic Field

1) Severe NPDR

As retinopathy approaches the proliferative stage, scatter laser therapy should be considered to prevent its progression to high-risk PDR. Pan-retinal photocoagulation (PRP) laser therapy should be considered for severe to very severe NPDR in elderly patients with type 2 DM, difficulty in retinal examination, a history of cataract surgery (potential for inflammation), one eye affected by PDR, routine clinical visits are not feasible, or it is difficult to perform examinations on patients due to certain reasons.

Conclusion:

1. Monitor closely the potential progression from NPDR to PDR.
2. Consider early panretinal photocoagulation laser therapy in patients with severe to very severe NPDR, especially in elderly patients with type 2 diabetes and those with other high-risk factors.

Recommendations:

1. It is advised to routinely perform slit-lamp biomicroscopic examinations to observe neovascularization of the iris due to retinal ischemia.
2. Conduct wide-field retinal examinations in addition to standard screening photos.

Level of evidence IV, Recommendation C

2) PDR

a. PRP Laser Therapy

PRP is the standard therapy for PDR cases indicated to regress new blood vessels on the retina. PRP therapy is preferably performed on the same day or within a 2-week period after confirming the diagnosis. To minimize macular edema effects, conventional single-shot scatter laser therapy can be divided into several sessions. PRP therapy can be administered in multiple laser sessions but generally fewer than 6 sessions. PRP can be performed with a shorter duration, ranging from 20 to 30 ms, with a therapy quantity of 2000 to 4000 burns depending on the severity of PDR.[18] Limitations of PRP therapy include the need for a sufficiently clear media and optimal dilated pupils to allow the laser to reach the target retina. After the therapy, there may be temporary vision reduction, peripheral vision loss, and permanent nyctalopia (night blindness) due to peripheral retina destruction by the laser. Additionally, damage to Bruch's membrane, uveal effusion, closed-angle glaucoma, serous retinal detachment, and vitreous hemorrhage may occur. The illustration of NVE are needs to be avoided during PRP and after PRP therapy in a PDR case is shown in **Figure 6.**

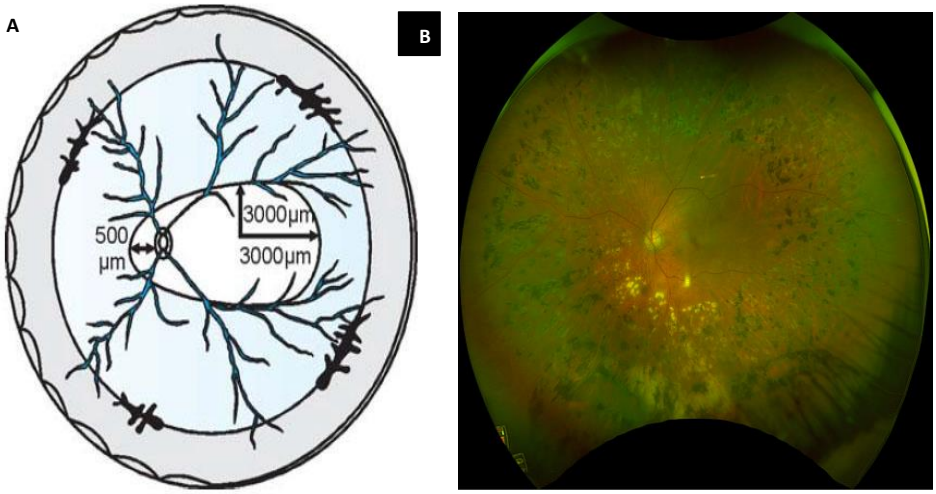

Figure 6. a) Area for PRP in DR patients. Source of the image: adapted from Bhattacharyya B.[19] b) After PRP therapy in PDR case.

b. Anti-VEGF Injection Therapy

Anti-VEGF is often used as adjuvant therapy with PRP in PDR. Administration of anti-VEGF can be done before or after PRP. In eyes showing persistent and active neovascularization, in addition to additional PRP, anti-VEGF has demonstrated a reduction in leakage and improvement in VA. Common side effects of this therapy include temporary increase IOP, occurrence of floaters, traumatic complications to intraocular structures, endophthalmitis, tractional retinal detachment, and uveitis

Conclusion:

1. PRP therapy is indicated for regressing new blood vessels on the retina.
2. Clinical studies indicate that anti-VEGF injection therapy (ranibizumab, aflibercept) has proven to be safe and effective for treating PDR for at least 2 years.

Recommendations:

1. Standard therapy with PRP laser.
2. Anti-VEGF therapy can be used as adjuvant therapy.

Level of evidence IB, Recommendation A

3) Vitreous Hemorrhage and Tractional Retinal Detachment

In advanced stages of retinopathy, PRP therapy has minimal effect on the development of new blood vessels, tractional retinal detachment, as well as bleeding and the development of neovascularization in the anterior segment. Vitrectomy may be considered in cases where there is a delay in administering PRP therapy due to vitreous hemorrhage or other factors causing difficulty in visualizing the retina. Anti-VEGF can be administered to treat PDR but does not reduce the need for vitrectomy as indicated.

With advancements in surgical techniques, instruments, and operating machines, vitrectomy can be performed safely, comfortably for patients, and with more efficient timing. Vitrectomy procedures can be conducted with varying anesthesia techniques, ranging from local anesthesia to general anesthesia. The determination of the appropriate anesthesia technique is tailored to the patient's needs based on an evaluation of intraocular and systemic conditions, as well as the patient's psychological state. Most patients undergoing vitrectomy still require observation, so inpatient care is not uncommon. In more stable patient conditions and with local anesthesia, vitrectomy procedures can be performed on an outpatient setting.[20]

Indications for vitrectomy include vitreous hemorrhage, thick sub-hyaloid pre-macular hemorrhage, tractional retinal detachment involving/threatening the macula, combined tractional and rhegmatogenous retinal detachment, tightly adherent posterior hyaloid causing vitreo-papillary traction, progressive fibrovascular proliferation, refractory macular edema associated with vitreomacular traction (VMT) and epiretinal membrane (ERM), and chronic non-tractional macular edema.[20-22] The administration of intravitreal anti-VEGF injections, ideally performed within 14 days before vitrectomy in complicated PDR cases, shows better surgical outcomes, shorter vitrectomy duration, and reduced rates of post-vitrectomy recurrent bleeding and intraoperative bleeding.[23]

Complications of vitrectomy in DR and DME include cataracts, iatrogenic breaks, recurrent bleeding, retinal detachment, progressive fibrovascular anterior hyaloid proliferation, neovascular glaucoma, and endophthalmitis.

Conclusion:

1. Vitrectomy is indicated for patients with PDR who are not responsive to non-surgical therapy.
2. The development of fibrovascular proliferation in PDR patients can lead to TRD.
3. Surgical vitrectomy can be performed to restore vision by removing bleeding and relieving traction.

Recommendations:

1. In cases of PDR, laser therapy is the primary treatment. In more advanced conditions, surgical intervention (vitrectomy) may be performed.
2. Anti-VEGF can be considered as an initial therapy if vitrectomy cannot be performed promptly.

Level of evidence IB, Recommendation A

Follow up and therapy based on the severity of DR can be seen in **Table 2**.

Table 2. Management Based on the Severity of DR. (Adapted from Wong TY, et al.[1])

Level of DR	Management by Ophthalmologists
No-DR	Follow up every 1-2 years
Mild NPDR	Follow up every 6-12 months
Moderate NPDR	Follow up every 3-6 months
Severe NPDR	Follow-up less than 3 months, consider PRP and/or consider anti-VEGF treatment
PDR	Follow-up less than 1 month, PRP can be performed as the gold standard, anti-VEGF treatment can be considered as an adjuvant and monotherapy with close monitoring, vitrectomy as indicated
Stable / managed PDR	Follow up every 6-12 months

MANAGEMENT OF DME

The therapy for DME has evolved significantly, starting from PRP therapy, intravitreal steroid therapy, to the latest being anti-VEGF therapy. According to the International Council of Ophthalmology (ICO) Guidelines,[1,24] the management of DME is described in accordance with **Diagram 1**. Non-central DME should be observed for its progression to central DME or consider focal laser to puncture microaneurysms if thickening poses a threat to the fovea. For central DME and good VA (better than 6/9 or 20/30), three treatment options have been evaluated through clinical trials, including: (1) careful monitoring with anti-VEGF for worsening DME; (2) intravitreal anti-VEGF injections; or (3) PRP therapy with anti-VEGF if necessary.

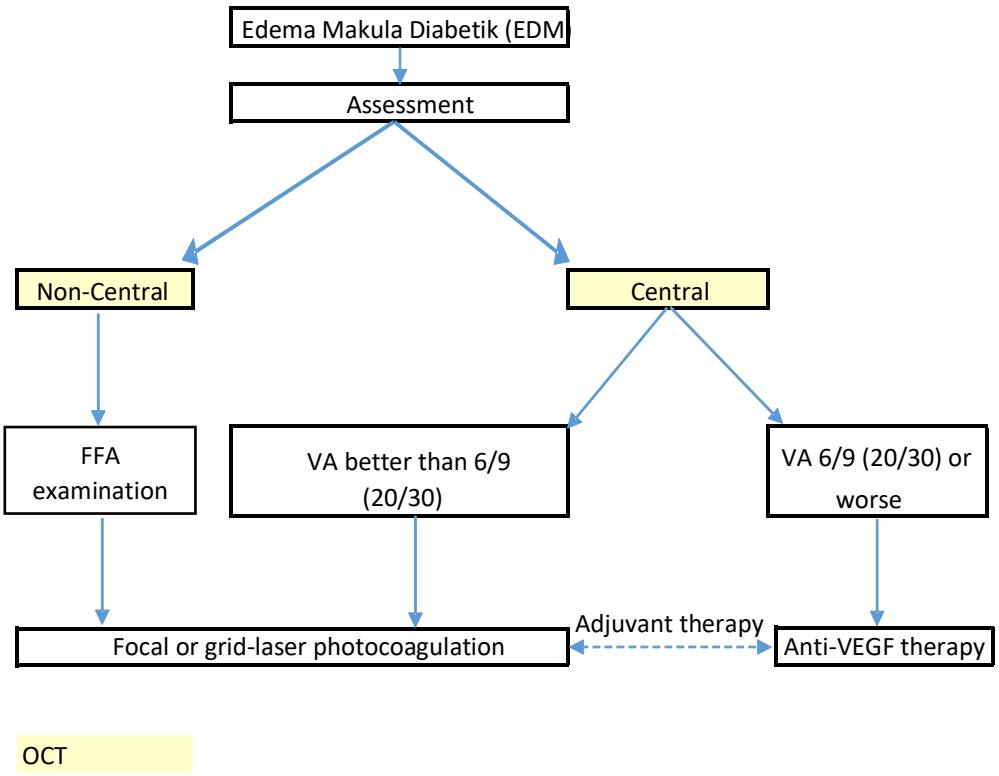

Diagram 1. Treatment for DME based on Central-Involvement and Vision.

The research protocol V DRCR.Net compared the use of anti-VEGF aflibercept, laser photocoagulation, and observation in eyes with center-involved DME (ci-DME) and VA 20/25 (6/7.5) for 2 years. No significant differences were found among the groups, so in cases of ci-DME with initially good VA, therapy may be considered for postponement unless deterioration occurs.[25] The DRCR.Net protocol for DME with good VA can be seen in **Diagram 2**. Several studies about the non-surgical management for DME are shown in **Supplementation 1**.

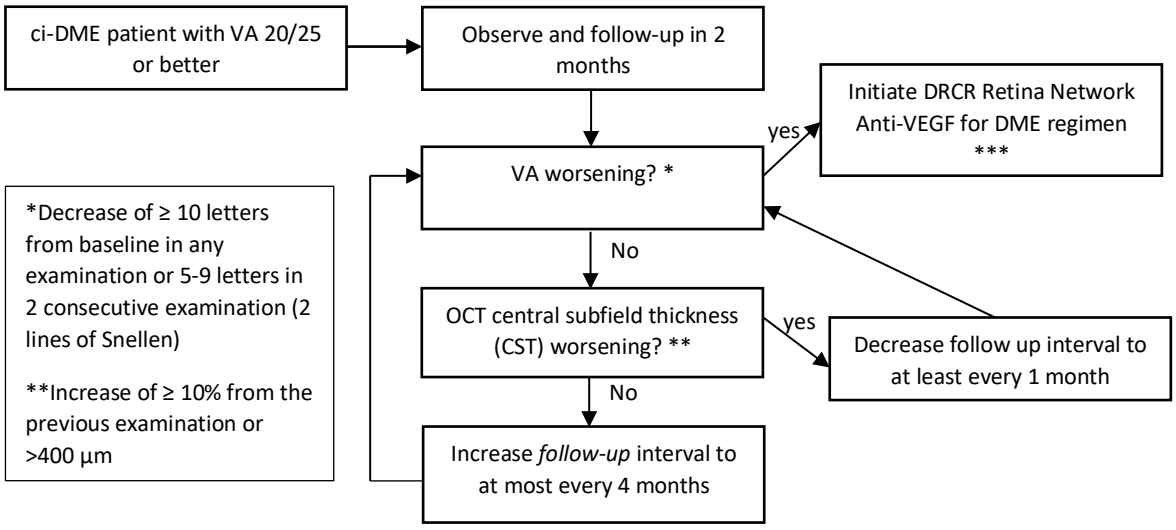

Diagram 2. DRCR Retina Network Follow-up on ci-DME with Good VA Begins with Observation.

1) Anti-VEGF

Anti-VEGF as a first-line therapy is widely applied nowadays. Intravitreal anti-VEGF injections have proven to be superior to macular laser therapy. Types of anti-VEGF include ranibizumab, bevacizumab, aflibercept, brolucizumab, and faricimab. The administration of anti-VEGF is divided into two phases: the loading dose followed by the maintenance dose. During the loading dose, consecutive monthly injections of anti-VEGF are recommended to be given 3-6 times. For the maintenance dose, it is further differentiated into: (1) Pro renata, which involves administering anti-VEGF injections based on the indication or the doctor's discretion; (2) Treat and extend, which entails gradually extending the interval between anti-VEGF injections if there is improvement or stable DME conditions. Typically, interval extensions of 2 or 4 weeks are used; (3) Fixed interval, which involves administering anti-VEGF at a fixed interval, such as every month, every two months (bi-monthly), and so on.

2) Intravitreal Steroid Therapy

There are several types of intravitreal steroids, including triamcinolone acetonide (off-label), dexamethasone implant, and fluocinolone acetonide implant. Steroids can also serve as an alternative to anti-VEGF in certain conditions, such as pregnant or breastfeeding patients, those with specific systemic or vascular conditions (e.g., stroke or myocardial infarction), post-vitrectomy patients, and patients unresponsive to anti-VEGF treatment.

3) Macular Laser Therapy

Macular laser therapy has been a standard treatment for DME since the early 1980s, before the era of intravitreal injections. It is important to note that despite photocoagulation, patients may still experience vision loss, albeit at a slower rate. Macular laser therapy is a competency of retina specialists and should be performed by experienced operators to maintain consistent therapeutic outcomes. FFA examination should be performed beforehand.

4) Subthreshold Photothermal Macular Laser Therapy

A relatively new therapy is the use of micro-pulse subthreshold macular laser. This therapy theoretically avoids damage to the neurosensory part of the retina and reduces potential complications such as paracentral scotoma and post-laser therapy scar expansion.

Conclusion:

1. Non-central DME should be observed to monitor its progression to central DME.
2. Intravitreal anti-VEGF injections have proven to be superior to macular laser therapy.

Recommendations:

1. Anti-VEGF is the first-line therapy for DME.
2. Therapy with intravitreal triamcinolone injections can be considered in pseudophakic eyes that do not respond to anti-VEGF and in patients with certain systemic or vascular conditions.
3. Non-central DME is treated using focal or grid laser photocoagulation. Prior FFA examination is recommended.
4. Macular laser (focal/grid) becomes an option when intravitreal anti-VEGF injections are unavailable or when monthly follow-ups are not feasible. Prior FFA examination is recommended.

Level of evidence IB, Recommendation A

Supplementation 1. Several Studies regarding Non-surgical Management of DME.

Study	Year	Drug	Summary
DRCR.Net Protocol T[26]	2017	Bevacizumab, Ranibizumab, Aflibercept	Comparing 3 types of anti-VEGF. - All anti-VEGF treatments demonstrate improvement in VA within a year. - Aflibercept offers superior VA gain (about 1 line compared to the other 2 anti-VEGF) in DME patients with VA 20/50 or worse. - All medications have relatively the same adverse effects. - After two years, it is difficult to discern the differences in VA changes (Aflibercept is marginally superior to Bevacizumab, but comparable to Ranibizumab). - After two years, all medications indicate improvements in VA, and fewer injections are administered in the second year than the first.
PHOTON[27]	2023	Aflibercept 8 mg	Non inferiority trial comparing Aflibercept 8 mg (every 12 weeks and 16 weeks after 3 monthly doses) against Aflibercept 2 mg (every 8 weeks after 5 monthly doses). - Following a 48-week period, there was no significant difference in the groups' best corrected visual acuity (BCVA) (+8.8 and +7.9 vs +9.2 letters). 89% of the 16-week group and 91% of the 12-week group with 8 mg were able to maintain the injection interval. 93% of patients in the combined 8 mg group were able to maintain an interval of >12 weeks between injections. - There was a comparable level of side effects in the groups taking 8 mg and 2 mg.
KESTREL and KITE[28,29]	2023	Brolucizumab, Aflibercept	Comparing Brolucizumab to Aflibercept. - The VA improvement in the second year between Aflibercept and Brolucizumab was fairly comparable. - Fewer eyes with residual intraretinal fluid (IRF) and subretinal fluid (SRF) were observed when treated with Brolucizumab. - In the group receiving Brolucizumab, the incidence of intraocular inflammation was 2.2-4.2%, while in the group receiving aflibercept, it was 1.1-1.7%. Similar trends were observed in the occurrence of retinal vasculitis (0.5% vs 0%) and retinal vascular occlusion (0.6-1.6% vs 0.5-0.6%).
YOSEMITE and RHINE[30,31]	2022	Faricimab, Aflibercept	Comparing Faricimab to Aflibercept. - Faricimab is not inferior to Aflibercept in VA improvement and CST reduction during either a one-year or two-year timeframe.
DRCR.Net Protocol AC[32]	2022	Aflibercept, Bevacizumab	Aflibercept injection compared to Bevacizumab injection, than switch to Aflibercept if there was no good response. - Clinically (VA) and anatomically (macular thickness), the outcomes were relatively comparable between two groups.
APOLLON[33]	2022	Aflibercept	Real life observational study on the use of Aflibercept monotherapy in France. - After 24 months, the group without prior therapy experienced a change in BCVA of +6.5 (+10.7 letters), while the group with prior therapy—such as anti-VEGF, laser, or intraocular steroid—saw a change in BCVA of +1.6 (+17.0 letters). - The outcomes matched those of the VIVID Study, a randomized controlled trial. - After 24 months, the group that had not received any prior therapy had a reduction in central macular thickness of 134 µm, while the group that had received prior therapy had a reduction of 130 µm.
VIOLET Study[34]	2022	Aflibercept	For patients with DME undergoing therapy for longer than a year, treat and extend in comparison to pro-renata (PRN) compared to fixed dose. - After one year and two years of treatment, the VA obtained with the treat and extend and PRN approaches was comparable to that of the fixed dose (every 8 weeks).

Study	Year	Drug	Summary
DRCR.Net Protocol U[35]	2018	Dexamethasone implant, Ranibizumab	Steroid and anti-VEGF combination therapy. - In patients with persistent DME after receiving six monthly injections of ranibizumab, the first group continued to receive the injection while the second group received both the ranibizumab and dexamethasone implant. VA did not differ significantly, however a greater reduction in macular thickness on OCT was shown in the combination therapy group.
VIVID and VISTA[36,37]	2015-2016	Aflibercept	Injection of Aflibercept every 4 weeks were compared to Aflibercept every 8 weeks after 1x monthly for 5 months compared to macular laser therapy. - VA significantly improved in both of the Aflibercept-treated groups, with a large percentage of eyes showing an improvement of more than three lines. By the conclusion of the third year, the gains noted at the first and second years are still maintained.
REVEAL[38]	2015	Ranibizumab	Injection of Ranibizumab 0.5 mg + sham laser vs Ranibizumab + laser compared with sham injection + laser in the Asian population (China, Hong Kong, Jepang, South Korea, Singapura, Taiwan). - Following a 12-month period, eyes treated with ranibizumab alone or in combination with macular laser demonstrated superior BCVA improvement (+5.9 and +5.7 compared to 1.4 letters), a higher percentage of eyes exhibiting an increase of over 15 letters (18.8% and 17.8% compared to 7.8%), and a more significant decrease in central macular thickness (134.6 µm and 171.8 µm vs 57.2 µm) in comparison to eyes treated with macular laser alone.
RETAIN[39]	2014	Ranibizumab	Non-inferiority between Ranibizumab treat & extend (T&E) +/- laser compared to ranibizumab PRN. - Injections were given to the patient every month until the BCVA stabilized. - Based on the change in BCVA from baseline to month 12 (T&E + laser: +5.9; T&E: +6.1; PRN: +6.2 letters), and the change in BCVA from baseline to month 24 (+8.3; +6.5 dan +8.1 letters), T&E +/- laser is not inferior to PRN. In the T&E group, there are fewer visits.
BOLT Study[40]	2012	Bevacizumab	Intravitreal Bevacizumab injection versus focal laser. - After two years, VA was better in eyes treated with bevacizumab compared to focal laser (both overall and in the percentage of eyes with an increase of two and three lines of VA).
RISE and RIDE[41,42]	2012	Ranibizumab	Ranibizumab injection compared to sham injection. - Ranibizumab is superior in achieving VA improvement, lower the risk of vision loss, and substantially reduce macular thickness.
RESTORE[43]	2011	Ranibizumab	Injection of Ranibizumab 0.5 mg + sham laser vs Ranibizumab + laser vs sham injection + laser. - The results of eyes treated with ranibizumab alone or with ranibizumab plus macular laser after a year were better than those treated with macular laser alone. BCVA improvement was higher (+6.1 and +5.9 compared to 0.8 letters), more eyes had a VA of 6/12 or better (53% and 44.9% compared to 23.6%), and the central macular thickness was reduced more (118.7µm dan 128.3µm vs 61.3µm).
READ-2 Trial[44]	2010	Ranibizumab	The comparison between ranibizumab injection, focal laser +/- ranibizumab, and focal laser + ranibizumab. - After two years, the VA improved in all group. The groups did not differ significantly from one another. - Fewer injections were needed for the group of individuals getting ranibizumab injection and focal laser combination therapy.

Study	Year	Drug	Summary
RESOLVE[45]	2010	Ranibizumab	0.3 mg of ranibizumab in contrast to 0.5 mg Ranibizumab in comparison to sham injection. - Following three injections, all eyes, had PRP laser if needed. - At month 12, Ranibizumab therapy showed a reduction in central retinal thickness (194.2 versus 48.4 μm in the sham injection group) and a notable improvement in VA (10.3 letters compared to a drop of 1.4 letters in the sham group).
DRCR.Net Protocol I[46]	2012	Ranibizumab, Triamcinolone acetonide	Ranibizumab plus immediate or deferred focal/grid laser (≥24 weeks) against focal/grid laser compared to triamcinolone injection + laser. - Eyes in the immediate laser group did not exhibit improved VA after three years. - The administration of triamcinolone injection plus laser was comparable to ranibizumab in pseudophakic eyes, albeit with a larger risk of higher intraocular pressure. Both groups outperformed the group receiving laser therapy alone.
DRCR.Net Protocol B[47]	2008	Triamcinolone acetonide	Comparison between intravitreal triamcinolone injection and focal/grid laser - After two years, laser treatment for DME was more successful and caused fewer side effects than injections of triamcinolone. - Patients with cataracts were still included in protocol B, which could have influenced vision.

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