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GUIDELINES

Diabetic Disease of the Eye in Canada: Consensus Statements from a Retina Specialist Working Group

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ABSTRACT

Despite advances in systemic care, diabetic disease of the eye (DDE) remains the leading cause of blindness worldwide. There is a critical gap of up-to-date, evidence-based guidance for ophthalmologists in Canada that includes evidence from recent randomized controlled trials. Previous guidance has not always given special consideration to applying treatments and managing DDE in the context of the healthcare system. This consensus statement aims to assist practitioners in the field by providing a spectrum of acceptable opinions on DDE treatment and management from recognized experts in the field. In compiling evidence and generating consensus, a working group of retinal specialists in Canada addressed clinical questions surrounding the four themes of disease, patient, management, and collaboration. The working group reviewed literature representing the highest level of evidence on DDE and shared their opinions on topics surrounding the epidemiology and pathophysiology of diabetic retinopathy and diabetic macular edema; diagnosis and monitoring; considerations around diabetes medication use; strategic considerations for management given systemic comorbidities, ocular comorbidities, and pregnancy; treatment goals and modalities for diabetic macular edema, non-proliferative and prolifer-

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ative diabetic retinopathy, and retinal detachment; and interdisciplinary collaboration. Ultimately, this work highlighted that the retinal examination in DDE not only informs the treating ophthalmologist but can serve as a global index for disease progression across many tissues of the body. It highlighted further that DDE can be treated regardless of diabetic control, that a systemic approach to patient care will result in the best health outcomes, and prevention of visual complications requires a multidisciplinary management approach. Ophthalmologists must tailor their clinical approach to the needs and circumstances of individual patients and work within the realities of their healthcare setting.

Keywords: Diabetes complications; Diabetic disease of the eye; Diabetic retinopathy; Macular edema; Therapeutics

Key Summary Points

Despite significant accumulated clinical evidence in diabetic disease of the eye (DDE), treatment decisions continue to require a degree of management personalization based on individual patient parameters and needs; this publication aims to assist practitioners in the field by providing a spectrum of acceptable opinions from recognized experts.

The retinal examination in DDE not only informs the treating ophthalmologist but can serve as a global index for disease progression across many tissues in the body.

Vision loss remains the single most-feared complication by patients with diabetes, and prevention of visual complications requires early screening, timely treatment, and a multidisciplinary management approach.

While DDE can be treated regardless of diabetic control, a systemic approach to patient care will result in the best health outcomes.

Ophthalmologists must tailor their clinical approach to the needs and circumstances of individual patients, and work within the realities of their healthcare setting.

INTRODUCTION

Over four million Canadians (approximately 10%) have been diagnosed with diabetes, and an estimated 30% are believed to be living with diabetes or prediabetes [1]. The prevalence of diagnosed diabetes in Canada is estimated to rise to over five million individuals or 12% of the population by 2033 [1], and complications are likely to follow. Among Canadian adults, diabetes represents the leading cause of blindness, end-stage renal disease, and non-traumatic amputation [1, 2]. However, a global survey of 652 adults with diabetes suggested that visual problems were the complication that patients feared most [3]. Even with the recent advances in systemic diabetic care, diabetic disease of the eye (DDE) remains the leading cause of blindness worldwide [4] and a major visual morbidity for working-age people [5]. In general, the extent of microvascular damage and the incidence of visual impairment depend on the type of diabetes (i.e., 1 or 2) [6]. As of 2004, it was expected that almost all patients with type 1 diabetes and over 60% of patients with type 2 diabetes would develop some form of diabetic retinopathy (DR) in the first two decades after diagnosis [7]. In Canada, prevalence rates may be higher for population subgroups such as Indigenous peoples, whose rates of diabetes are estimated to be 2.5 to 5 times higher than the general population [8].

The management of DDE is complex as ophthalmologists may need to tailor their clinical approach to individual patients and work

Table 1 Definitions for classifying DR, adapted from the ETDRS trial [53]

ETDRS level	Disease severity	Definition
10	No retinopathy	Diabetic retinopathy absent
20	Very mild NPDR	MA only
35	Mild NPDR	MA plus hard exudates, soft exudates (cotton wool spots), and/or mild retinal hemorrhages
43	Moderate NPDR	MA plus mild IRMA or moderate retinal hemorrhages
47	Moderately severe NPDR	More extensive IRMA. Severe retinal hemorrhages or venous beading in 1 quadrant only
53	Severe NPDR	Severe retinal hemorrhages in 4 quadrants, or venous beading in at least 2 quadrants, or moderately severe IRMA in at least 1 quadrant
61	Mild PDR	NVE $<$ 1/2 disc area in 1 or more quadrants
65	Moderate PDR	NVE $\geq$ 1/2 disc area in 1 or more quadrants or NVD $<$ 1/4–1/3 disc area
71–75	High-risk PDR	NVD $\geq$ 1/4–1/3 disc area and/or vitreous hemorrhage
81–85	Advanced PDR	Fundus partially obscured

DR diabetic retinopathy, *ETDRS* Early Treatment of Diabetic Retinopathy Study, *IRMA* intraretinal microvascular abnormalities, *MA* microaneurysms, *NPDR* nonproliferative diabetic retinopathy, *NVD* new vessels of the disc, *NVE* new vessels elsewhere, *PDR* proliferative diabetic retinopathy

within the realities of their healthcare setting. Cross-specialty communication and collaboration may be limited and not standardized; patient awareness of risk factors and compliance may be challenging [9]; and patients with DDE may have several risk factors and comorbidities [10–14]. Furthermore, the existence of multiple sources of information on how to manage DDE [8, 10, 15–22] and wide variation in guidelines [23] add layers of uncertainty.

Although international guidelines, including from the USA and Europe [19, 20], have been published recently, there is a critical gap of evidence-based guidance for ophthalmologists practicing in Canada. The most recent Canadian guideline was published in 2018 [5] with substantial evolution in the ophthalmic literature and interventions for DDE since then. Investigators forming the Diabetic Retinopathy Clinical Research (DRCR) Network published randomized controlled trials (RCTs) on the effectiveness of various treatment types and thresholds for treatment initiation in DDE [24–30]. Furthermore, new intravitreal agents have shown non-inferiority in clinical trials compared with available agents, namely aflibercept 8 mg formulation (PHOTON trial), brolucizumab (KITE/KESTREL trials), and faricimab (YOSEMITE/RHINE trials). Ongoing safety reviews and provincial drug applications have varied the adoption of these newer agents across Canada. As well, most existing guidelines have excluded discussion of the comorbidities that may complicate DDE, such as pregnancy [31], renal failure [32], and blood dyscrasias [33]. With a lack of evidence-based guidance, management remains challenging for ophthalmologists.

Special considerations are required for DDE management in the context of Canada's healthcare system. The Canada Health Act [34] defines national principles governing health coverage for all Canadians. In brief, these principles dictate that Canadian healthcare should be publicly administered, comprehensive, and universal in coverage as well as portable across provincial geographies to ensure accessible care [35]. These tenets create unique care criteria for Canada. Moreover, Canadian provinces have the exclusive jurisdiction to decide on drug and

Table 2 Definitions related to DR/DME, adapted from landmark trials

Condition	Type	Definition
Diabetic retinopathy	High-risk PDR (DRS) [48]	High-risk PDR is defined as any 1 of the following: 1. NVD $\geq$ 1/3 disc area 2. Any NVD with vitreous hemorrhage 3. NVE $\geq$ 1/2 disc area with vitreous hemorrhage High-risk PDR is also defined as 3 or more of the following high-risk characteristics: 1. Presence of vitreous hemorrhage or pre-retinal hemorrhage 2. Presence of any active neovascularization 3. Location of neovascularization on or within 1 disc diameter of the optic disc 4. NVD > 1/3 disc area or NVE > 1/2 disc area
	Severe NPDR (DRS) [48]	Severe NPDR was defined as the presence at least 3 of the following: 1. Cotton wool spots 2. Venous beading 3. IRMA in at least 2 contiguous overlapping photographic fields 4. Moderate to severe retinal hemorrhages and/or MAs
Macular edema	Diabetic macular edema (DRCRnet) [54]	1. Center-involved DME: Retinal thickening in the macula that involves the central subfield zone (1 mm in diameter) 2. Non-center-involved DME: Retinal thickening in the macula that does not involve the central subfield zone (1 mm in diameter)
	Clinically significant macular edema (ETDRS) [55]	CSME is defined as 1 or more of the following: 1. Retinal thickening at or within 500 µm of the center of the macula 2. Hard exudates at or within 500 µm of the center of the macula, if associated with adjacent retinal thickening 3. A zone or zones of retinal thickening 1 disc area in size, at least part of which is within 1 disc diameter of the center of the macula

CSME clinically significant macular edema, *DME* diabetic macular edema, *DR* diabetic retinopathy, *DRCRnet* Diabetic Retinopathy Clinical Research net, *DRS* Diabetic Retinopathy Study, *ETDRS* Early Treatment of Diabetic Retinopathy Study, *IRMA* intraretinal microvascular abnormalities, *MA* microaneurysms, *NPDR* non-proliferative diabetic retinopathy, *NVD* new vessels on or within 1 disc diameter of the optic disc, *NVE* new vessels "elsewhere", *PDR* proliferative diabetic retinopathy

investigational coverage. Amid emerging treatment technologies and disparate provincial coverage decisions, the vast Canadian geographic landscape poses additional challenges in administering universal care for diabetes across all jurisdictions. For example,

people living in remote regions of Canada may not have access to annual eye examination by an eye-care professional [1, 36]. Furthermore, whereas the majority of diabetic disease eye care in the USA or the UK is delivered by fellowship trained retina specialists, in Canada, the population is served for these needs by mostly fellowship untrained practitioners. This places a responsibility on retinal specialists within the community to support these practitioners who may not be privy to the latest evolutions within the retina fields.

In 2021–2022, a working group of Canadian retina specialists with expertise in the management of patients with DR and diabetic macular edema (DME) convened to develop clinical care recommendations and provide evidence-based guidance. Their goals were to assist in care decisions and improve overall DDE-associated visual morbidity. The group's main objectives were to:

- Review the scientific evidence and clinical data for guiding optimal DDE management.
- Discuss DDE specificities and identify main challenges to optimal patient care.
- Produce key recommendations related to DDE management.
- Share these recommendations with ophthalmologists in Canada and worldwide.

In achieving these objectives, four main themes were identified by the working group: the disease, the patient, management, and care collaboration. These selected themes represented an attempt to classify the significant diversity of clinical presentation in DDE into distinct entities that would be amenable to independent evaluation. In each discussion, working group members focused on answering the following overarching questions and respective themes:

1. The disease: What features of DDE should be considered when managing patients (e.g., control, systemic complications, medication management, etc.)?
2. The patient: Which patient characteristics—such as pregnancy, sleep apnea, obesity, and renal failure, etc.—should be considered during DDE management?
3. The management: Is there a clear path for management of patients with DDE regarding screening and diagnosis, treatment of DDE in the context of systemic and ocular comorbidities, and surgical and non-surgical approaches to treatment?
4. Care collaboration: What are the key aspects that should be integrated into the collaborative framework for patient management?

This manuscript provides a summary of reviews on the pathogenesis of DME and DR alongside a Canadian working group's clinical insights and suggestions regarding the four identified themes. The resulting consensus statement is based on the best available scientific evidence and clinical information accessible at the time of manuscript production and reflects the consensus of experts in the field. Of note, this article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

EVIDENCE REVIEW

Working Group Members

The working group comprised seven ophthalmologists, together representing different provinces of Canada, who specialized in the treatment and management of retinal diseases. Their roles were working group chair (A.O.) or working group member (R.G.W., J.W., J.N., M.B., M.G., S.O.). In October 2021, all group members attended a 2-h virtual kickoff meeting at which time the chair and a discussion facilitator (M.L.) delivered a slide presentation to introduce the rationale for the working group and discuss the potential to address the four themes outlined above. The facilitator, employed with Bayer Inc. Canada in the Department of Medical & Scientific Affairs, played the role of group supporter and initiator as opposed to a working group member.

Table 3 Summary of working group consensus recommendations for follow-up, by DR classification and presence of DME

International classification of diabetic retinopathy	Disease severity	Recommended follow-up
Diabetic retinopathy	No apparent DR	1–2 years
	Mild NPDR	1–2 years
	Moderate NPDR	4–12 months
	Severe NPDR	2–4 months
	PDR	Based on clinical stability
DME classification by center of macula involvement using optical coherence tomography	Non-center-involved DME	1–12 months
	Center-involved DME	1–6 months

DME diabetic macular edema, *DR* diabetic retinopathy, *NPDR* non-proliferative diabetic retinopathy, *PDR* proliferative diabetic retinopathy

Targeted Literature Review

A targeted literature search using PubMed® was conducted in December 2021 by the group facilitator (M.L.) and the working group chair (A.O.). The aim of the search was to identify the highest level of evidence addressing the four themes outlined above (disease, patient, management, and care collaboration). For article inclusion, the study design must have been rigorous and widely accepted within the community and/or endorsed by learning societies (e.g., landmark diabetes trials, DRCR network published results, or RCTs that validated treatment effects), the article must have been published in a peer-reviewed journal, and the publication must have been written in English language. This database search was supplemented with articles put forth by the chair (A.O.). Full-text articles identified through the literature search (Supplementary Material 1) were emailed by Meducom (an independent medical communications agency) to all working group members as pre-reads. Each member was requested to review these articles in preparation for the virtual workshop described below.

Virtual Workshop

In January 2022, all working group members attended a live 2.5-h virtual workshop to share their reflections, insights, and feedback on the four main themes. The format of the meeting included both round table and smaller breakout group discussions. As in the kickoff meeting, one working group member acted as chair (A.O.) and a group facilitator (M.L.) observed and supported the discussions as needed. Three employees of an independent medical communications agency recorded the meeting notes.

Survey

Following the workshop, 41 survey questions addressing the four main themes (the disease, the patient, the management, and care collaboration) were developed by the chair (A.O.) with assistance from Meducom, an independent medical communications agency. The survey items were a combination of checklists ("check all that apply, if any"), two-choice questions ("agree/disagree"), and semi-open questions (e.g., "disagree [please elaborate]") (Supplementary Material 2).

The survey was conducted using SurveyMonkey®. Working group members completed their surveys independently and anonymously. Six of the seven working group members submitted responses; one did not respond. Responses were anonymous except to the medical communications agency, Meducom, and were analyzed in aggregate in Microsoft Excel® by the Meducom staff and the facilitator. In the current report regarding the survey, "most" refers to more than 50% of respondents; "some" refers to 50%; "few" refers to less than 50%; "all" and "none" are self-explanatory.

Consensus Statement Development

The working group chair, with assistance from Meducom, compiled information from the individual survey responses, workshop meeting notes from group discussions, and the targeted literature review described above to develop the current report. The findings below represent clinical consensus statements on DDE by a panel of retina specialists. These statements by definition [37] represent the panel's collective analysis, evaluation, and opinions of DDE based partly on the workshop proceedings and partly on the up-to-date evidence available at the time. The statements do not imply unanimity.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

FINDINGS

The sections below highlight evidence considered by the working group members, their survey responses (also in Supplementary Material 3), and general guidance from the working group.

Epidemiology and Pathophysiology

DR is the most common cause of incident blindness in people of working age, with an estimated prevalence of 25% for people with diabetes in Canada as of 2022 [1]. Proliferative diabetic retinopathy (PDR) has been shown to affect 23% of patients with type 1 diabetes and 14% of patients with type 2 diabetes on insulin therapy [5]. The primary risk factors for the incidence and progression of DR are disease duration, poor glycemic control, and comorbid systemic hypertension [38]. Tight glycemic control in patients with type 1 diabetes can reduce the risk of new retinopathy by 76% and the progression of existing DR by 54% [38, 39]. Maintaining HbA1c levels below 7.6% has also been associated with delayed progression of DR [38, 40]. A Canadian cohort study demonstrated the prevalence of DME amongst patients with type 1 and 2 diabetes to be 15.7% [41]. This prevalence rate is higher in certain ethnic groups, particularly those of Black or Indigenous heritage [5, 10, 36, 41, 42].

DR is characterized as a microangiopathy. It occurs from progressive hyperglycemic injury to the retinal microvasculature leading to pericyte and endothelial cell loss and subsequent disruption to the blood–retina barrier with consequences related to altered tissue permeability. Furthermore, thickening of the vascular basement membrane occludes capillaries and provokes damage to the retinal vascular plexus in addition to neurons and glia [43, 44]. Choroidal vascular changes have also been noted in the context of diabetic disease [45, 46]. To combat this retinal ischemia, the retina and retinal pigment epithelium release vasoproliferative factors, including vascular endothelial growth factor (VEGF), angiopoietin-2 (Ang-2), and placental growth factor (PGF), to promote neovascularization [10, 47].

Non-proliferative DR (NPDR) is characterized by superficial and deep hemorrhages, microaneurysms, venous dilation, and cotton wool spots [43, 44]. As disease progresses, retinal perfusion becomes increasingly impaired and generalized ischemia worsens. PDR occurs with the formation of new fragile blood vessels at the inner surface of the retina, often accompanied by growth into the vitreous cavity [43]. Patients with PDR can experience vitreous hemorrhaging or tractional retinal detachment [44]. As the severity of DR increases, so does the risk of developing DME [44].

The Diabetic Retinopathy Study (DRS) [48] showed that severe vision loss can be reduced over a 5-year follow-up period by 50% through application of pan-retinal photocoagulation (PRP) to patients with severe NPDR or worse. Patients with the most benefit were those displaying high risk of PDR criteria. The criteria for grading of DR in the DRS continue to inform clinical grading and were originally developed from the Airlie House Classification, using seven standard photographic fields and color stereoscopic fundus photographs. The DRS classification was further refined in the Early Treatment of Diabetic Retinopathy Study (ETDRS), specifically the NPDR categories (Table 1). Recently the utility of ultrawide field (UWF) imaging in DR severity grading was compared to standard seven-photo ETDRS images with moderate to substantial agreement [30].

DME develops from disturbances in the inner retinal blood barrier and has also been linked to macular ischemia. Accumulation of extracellular fluid causes progressive macular thickening and disruption of the cellular retinal architecture with functional vision loss [44]. DME severity is associated with the location and extent of thickening, with central changes corresponding to a nearly tenfold greater risk of developing moderate vision loss [44]. Vision impairment due to DME is estimated to occur in approximately 2.6% of Canadian patients with diabetes [41].

The ETDRS trial showed that the rate of moderate vision loss was reduced by 50% in eyes with clinically significant macular edema (CSME) treated with macular laser compared to those not treated. This clinical grading criteria informed the application of laser for macular edema until the advent of optical coherence tomography (OCT) imaging (Table 2).

Several molecular pathways are involved in the development and progression of DR and DME, presenting key targets for current and emerging therapies. DR is primarily a VEGF-mediated condition commonly treated with laser and anti-VEGF therapies [49]. DME has complex immunopathological mechanisms involving multiple cytokines (e.g., IL-8, MCP-1, IP-10, PlGF). VEGF-A is the predominant cytokine involved in DR and the primary target for DME treatments [50, 51] although the pathogenesis of DME is complex. Sustained hyperglycemia leads to oxidative stress and tissue hypoxia, which initiates several interrelated pathway processes centered around VEGF-A. This results in the breakdown of the blood–retina barrier with subsequent macular swelling and retinal thickening [51, 52]. Moreover, the underlying pathophysiology involves inflammation, increased vascular permeability, and abnormal growth of blood vessels.

Clinical trials that have studied the effects of anti-VEGF agents for DME have used the involvement of the foveal center as the basis for treatment initiation based on OCT structural definitions.

Diagnosis and Monitoring

In their survey responses, working group members indicated that the following disease criteria should be assessed and documented for optimal ophthalmic care and clinical decision-making.

Consensus Statements–1

- Most respondents noted that the following clinical criteria were important determinants of DDE care and required inquiry and documentation: diabetes type, duration of diabetes, nephropathy status, systemic hypertension status, dyslipidemia status, diabetic control status, insulin use, systemic medication usage, smoking status, and the presence/coordinates of primary care physician.
- Few respondents noted that the presence of a sleep apnea diagnosis should also be evaluated.

Regarding specific diagnostic tests, the working group noted that all patients with DDE should receive a dilated ocular examination in a frequency determined by their baseline disease status unless clinically contraindicated. As the presence and extent of peripheral capillary ischemia is associated with increased risk of DR progression, UWF imaging can provide important diagnostic and prognostic information

[56]. Documenting retinal status with digital fundus photography is also helpful to provide comparisons throughout the patient's journey [57].

Angiography, whether dye-based or non-dye based, should be considered in the investigation of all patients with diabetes. A fundus fluorescence angiogram (FFA) provides valuable information regarding vascular leakage, areas of capillary non-perfusion, and enlargement of the foveal avascular zone [10]. An optical coherence tomography angiogram (OCTA), despite providing valuable information regarding retinal perfusion status, is unable to identify dynamic vascular leakage. Studies have shown that OCTA can reliably capture capillary networks in different slabs and areas obscured by fluorescein leakage, capillary dropout, intraretinal microvascular abnormalities, and the growth and branching complexity of neovascularization [10, 58]. Angiography should at least be considered for patients with vision loss at presentation, sub-responders to therapy, or those being assessed for PRP laser. Angiography may be deferred for patients with diabetes and early NPDR clinically or patients complicated by renal failure not currently on dialysis.

Consensus Statements–2

- Most respondents stated an assessment of retinal perfusion status through dye-based or non-dye-based angiography is an essential component in the evaluation of disease progression and severity.
- Few respondents noted that angiography is only required in cases with clinically evident retinopathy.

When clinicians are diagnosing DME, patients require OCT. This may be conducted on each visit or sporadically throughout care. Clinicians may also wish to conduct an OCTA or FFA to better elucidate macular perfusion status.

Consensus Statement–3

- All respondents agreed that patients with diabetes with vision worse than 20/30 require an OCT scan of their macula to assess for DME and evaluate its centricity. In addition, subclinical central DME can present with vision better than 20/30; in that case, an OCT scan is also recommended at screening to determine intervals of follow-up and subsequent treatment planning or functional worsening.

Consensus Statements–4

- Most respondents agreed that patients on anti-VEGF therapy require OCT scans with each visit to evaluate disease progression or regression.
- Few respondents recommended less frequent OCT scans, such as after every 2–3 anti-VEGF treatments and at the end of treatment.

Working group members indicated that patient monitoring should occur monthly for patients undergoing treatment initiation. Working group members provided the recommendation to monitor untreated patients without DME on the basis of their DR status, with no to mild retinopathy being monitored every 1–2 years, moderate retinopathy every 4–6 months, and severe retinopathy every 2–-4 months (Table 3). Follow-up for DME should be per treatment protocol as these patients would be receiving therapy. Importantly, patients with DME treated with anti-VEGF agents may have regression in their retinopathy; however, when injections are stopped, DR may worsen. Usage of anti-VEGF therapy without serial OCT scans was considered outside of the available evidence, especially for treat-and-extend regimens.

Canadian general ophthalmologists and optometrists are often involved in the monitoring of patients with untreated DR, in addition to screening for DDE in patients with diabetes. Furthermore, various teleophthalmology programs are available in Canada to facilitate DR screening and identification. These programs vary in their usage of monoscope or stereoscopic pictures in single or multiple field montages [5]. OCT scans have also been utilized as an adjunct imaging tool for DME screening. Teleophthalmology systems also provide a recommended frequency of follow-up. A standardized national approach to DR telescreening has been proposed, based on DR/DME grading

using two 45° image fields or a single widefield or UWF image, preferable use of OCT imaging, and a focus on local quality control measures [59]. However, there continues to be no recognized national Canadian screening program for diabetic disease at the time of writing.

In the setting of DME, OCT-derived retinal thickness measures (central retinal thickness or CRT/central macular thickness or CMT/central subfield thickness or CST) are not sufficient to predict visual outcomes (visual acuity [VA] or change in VA) [60, 61]. Several structural OCT biomarkers are emerging for the prognosis of DDE visible through spectral-domain OCT. Disorganization of retinal inner layers (DRIL) has been shown to act as a prognostic imaging biomarker. Patients with DRIL have reduced retinal function, with defective retinal lamination presenting as an early cellular consequence of diabetes. The presence of DRIL has been associated with NPDR and PDR with or without DME, and recent studies suggest it may serve as a structural biomarker [62, 63].

In addition to DRIL, inner retinal vitreomacular interface abnormalities have also been associated with poorer VA outcomes with DME treatment. Outer retinal biomarkers, notably ellipsoid zone and external limiting membrane integrity, especially in the sub-foveal region, correlates strongly with central VA. DME with outer retinal changes usually presents with worse visual acuities. Restoration of the ellipsoid zone with successful DME management also correlates with VA improvement [64, 65]. Macular ischemia evident on OCTA or FFA may also limit VA gains with DME management [66].

Considerations Around Diabetes Medication Use

Meta-analyses have suggested a significant positive association between insulin use and risk of developing DR [67]. Although the working group considered insulin use to be an indicator of more severe diabetes, insulin-treated patients are not managed differently with respect to DDE. If a patient is in the process of initiating insulin, working group members recommended monitoring for early worsening of DDE due to potential rapid improved glycemic control.

Semaglutide, a glucagon-like peptide 1 (GLP-1) analogue, has been shown to be effective in reducing weight, HbA1c, and cardiovascular events in a type 2 diabetic cohort over a 2-year study period in the SUSTAIN 1–6 trials [68]. GLP-1 analogue effects are mediated through improved insulin secretion, inhibition of glycogenolysis and gluconeogenesis with reduced appetite, and delayed gastric motility. A higher risk for retinopathy-related complications (vitreous hemorrhage, blindness, or conditions requiring treatment with an intravitreal agent or photocoagulation) has been observed with semaglutide in the SUSTAIN 6 trial [69], which included patients with proliferative diabetic disease. Although the overall number of these complications was low, there was an unexpected higher rate in the semaglutide group (3%) versus the placebo group (1.8%) (hazard ratio 1.76; 95% CI 1.11–2.78; $P = 0.02$). It is unclear whether this worsening of DR is related to a direct drug effect or is the result of significant and rapid changes in the metabolic control of diabetes, as previously seen with other interventions such as insulin or bariatric therapy. Results from the FOCUS trial (NCT03811561), with a primary outcome (at 5 years) of DR progression in 1500 patients with type 2 diabetes randomized to receive semaglutide (once weekly) or placebo, are expected in 2026 [70]. Working group members recommended closer follow-up of patients initiating semaglutide for both DR and DME progression. The long-term cardiovascular and metabolic benefits of this drug seem to outweigh the potential for transient DR worsening, which may be managed by multiple currently available interventions within the ophthalmologists' armamentarium.

Treatment with glitazones has also been observed to be related to an increased risk of DME due to generalized fluid retention which affects approximately 5–15% of users [71]. These drugs are contraindicated in patients with diabetes and heart failure particularly those receiving concurrent insulin. Pioglitazone use is banned in Canada, while rosiglitazone remains on the market albeit with much less popularity

than at its launch more than a decade ago [72]. Working group members noted the importance of documenting glitazone use in patients with diabetes and close monitoring for the development or worsening of DME.

Strategic Considerations for Management

Pregnancy and Lactation

While gestational diabetes is not a major clinical concern for ophthalmologists, preexisting and postpartum diabetes can present management challenges. Preexisting diabetes is of particular concern if the patient has a history of pregnancy-related high blood pressure disorders (pre-eclampsia or eclampsia), which is associated with the development of more severe DR [73].

For patients with diabetes who become pregnant, it is important to assess DR status at the time of a positive pregnancy test and monitor patients more frequently (i.e., every 4–-6 weeks if clinically indicated on the basis of retinopathy status) [74]. If the severity of a patient's DR worsens during pregnancy, working group members recommended seeing the patient every 2 weeks in the third trimester.

Anti-VEGF drugs have been assigned Pregnancy Category C by the US Food and Drug Administration, meaning animal studies revealed evidence of embryo-fetal toxicity, but human studies are lacking. The potential benefits may warrant usage in pregnant women despite this risk [75]. Working group members noted they do not perform a pregnancy test prior to initiating anti-VEGF therapy; however, they do ask patients if they are or could be pregnant and advise them on the potential for harm with usage during this period.

The working group further noted that early application of PRP may be considered in the special circumstance of a pregnant patient with diabetes presenting with proliferative disease [76]. DME during pregnancy that meets functional and structural criteria for treatment initiation may also be alternatively managed with intraocular steroids or macular laser (if indicated) during this period.

Consensus Statement–5

- Most respondents disagreed that anti-VEGF agents were safe for the control of proliferative disease in female patients with diabetes of child-bearing age. Their opinions were largely based on the lack of current data and the potential for DR to worsen during pregnancy.

A multicenter, prospective study in Canada showed ranibizumab and aflibercept were excreted into human breast milk after intravitreal injections (bevacizumab was not evaluated in this study) [77]. It is unclear whether the amounts secreted pose a clinical risk to the feeding child. The expression of anti-VEGF agents in breast milk should be considered in the counselling and management of lactating patients with diabetes.

Systemic Comorbidities

Working group members noted the need to place emphasis on documenting and monitoring a patient's metabolic control and general medical status. Although poor diabetic control does not exclude patients from receiving treatment for DR or DME, the working group members noted that some insurers will not cover a patient's therapy if HbA1c levels are above 11%. These patients have also been excluded from most clinical trials for DDE. The members further highlighted the need for treating ophthalmologists to work collaboratively with other specialties. Although DDE can be treated regardless of diabetic control, members agreed that a systemic approach to patient care will likely result in the best health outcomes.

Consensus Statements–6

- All respondents stated that patients with diabetes require comorbid systemic disease to be assessed and documented to inform ophthalmic decision-making.
- Most respondents also recommended assessments/documentation of possible obstructive sleep apnea (OSA), obesity, and pregnancy.

These and other systemic comorbidities as well as pregnancy are considered in the sections below.

Obstructive Sleep Apnea For patients not yet diagnosed but with symptoms and body habitus consistent with OSA, working group members recommended contacting the patient's primary care physician to request testing or referring the patient to a sleep clinic. OSA is associated with higher blood pressure, increased cardiac events, and floppy eyelid syndrome [78]. Although OSA does not impact treatment decisions, it is important to ensure patients receive appropriate OSA intervention, as it may improve outcomes. Continuous positive airway pressure treatment has been associated with reduction in advanced DR [79], and severe OSA is associated with a ninefold greater risk of developing DME [80]. Knowledge of OSA is also important when considering surgical procedures, as it impacts anesthesia [81].

Obesity Bariatric surgery remains the most effective treatment for obesity and the only therapeutic intervention proven to correct type 2 diabetic disease [82]. Patients receiving bariatric surgery should be graded prior to surgery and monitored more stringently for the first year following surgery, as initial worsening of DR status has been observed from rapid improvements in glycemic control [82].

Systemic Thromboembolic Events DR is associated with an increased risk of stroke and heart attacks. Cerebrovascular disease risk has been observed in patients with DME receiving both anti-VEGF and intraocular steroid therapies, with a similar incidence between different anti-VEGF agents and steroid formulations [83–85]. Like stroke risk, thromboembolic cardiovascular events are also observed more frequently in patients with advanced DR. Working group members noted that both complications do not influence DDE treatment decisions although patients would benefit from further counselling on systemic complications of diabetic disease associated with the development of DME. Regardless of the therapeutic agent used, the working group noted that patients with DME present with a higher risk of systemic thromboembolic events than the non-diabetic population.

Nephropathy Recent studies have shown that DR progression is strongly associated with chronic kidney disease progression [11]. As such, working group members encouraged ophthalmologists to be cognizant of the occasional need to address comorbid renal complications that may impact DDE severity through collaborative care arrangements with primary care, internal medicine, and nephrology care providers. For patients with kidney disease, working group members noted the importance of verifying kidney status through communication with the collaborative care team or evaluation of previously conducted blood work. Patients with severe nephropathy typically have a poor prognosis; however, there is a lack of evidence surrounding the impact of nephropathy on early diabetic disease.

Although a strong clinical correlation exists between DR and diabetic nephropathy, patients with chronic renal failure were excluded from all RCTs investigating anti-VEGF agents for DME. The impact of fluid retention due to kidney disease on DME and its response to anti-VEGF agents remains to be addressed in studies. Working group members noted anecdotally, through clinical practice observation, that patients on peritoneal dialysis seem to fare a more stable course of DDE compared to those with delayed access to dialysis/transplantation.

Hematologic The oxygenation status of the retina in the setting of adequate retinal perfusion is affected by multiple hematologic conditions that can affect the oxygen-carrying capacity of blood and produce tissue ischemia. Working group members noted that hematologic comorbidities require adequate documentation and management collaboration with the broader diabetes professional care network. Despite this, these comorbidities do not seem to influence management decisions in DDE.

Ocular Considerations

Cataract

Consensus Statements–7

- All respondents noted that an indication for cataract extraction in patients with DDE was

the inability to visualize the posterior segment.
- Most respondents noted that an indication was unexplained vision worse than 20/40 in both eyes.
- Few respondents noted an indication of non-neovascular intraocular pressure elevation due to primary angle closure or open-angle glaucoma.

Patients with diabetes are reported to be up to five times more likely to develop cataract, in particular, at an early age [86]. Eyes from patients with diabetes undergoing cataract surgery, even in the absence of retinopathy, have an increased risk of new macular edema post-surgery, when compared to eyes from patient without diabetes (relative risk, 1.80; 95% CI 1.36–2.36); the risk was higher in the presence of any DR (relative risk, 6.23; 95% CI 5.12–7.58) and increased with DR severity [87]. The current literature recommends that patients undergo a preemptive evaluation of DR prior to cataract surgery [10]. As surgery can lead to an initial worsening of DR and DME, DR should be as well controlled as possible heading into the procedure [10, 88]. For patients treated with anti-VEGF therapy, the working group noted that patients could safely undergo cataract surgery despite DDE not being fully controlled.

Consensus Statements–8

- All respondents noted cataract extraction can be safely performed when proliferative disease is controlled or stable and maculas are dry. Most respondents also felt that it was safe to perform surgery while patients were undergoing active anti-VEGF therapy.
- Some respondents reported only performing surgery in settings of controlled macular edema with tolerance of DR status up to low-risk PDR.
- Few respondents reported they would perform cataract extraction in patients with controlled proliferative disease, regardless of macular status.

The American Academy of Ophthalmology (AAO) advised against using both multifocal intraocular lenses (IOL) and extended depth-of-focus-type lenses in the presence of eye disease [89]. However, a recent literature review on multifocal IOLs and retinal diseases found conflicting evidence regarding the use of multifocal IOLs in the presence of retinal diseases [90].

Consensus Statements–9

- All respondents disagreed with the statement that multifocal IOLs are a safe or convenient long-term option. The reasons for disagreement included decreased contrast sensitivity, increased risk of maculopathy, and the inability to complete PRP. They noted that perhaps an extended depth-of-focus-type lens may be more appropriate in this setting.

Dry Eye Aggravated ocular surface and tear film abnormalities are common comorbidities often attributable to diabetes status [91]. It is important to be sensitive to aggravation of surface issues caused by intravitreal injection procedures.

Maternally Inherited Diabetes and Deafness Mitochondrial mutations are a source of up to 1% of all diabetes cases, including maternally inherited diabetes and deafness (MIDD). Diagnosis of MIDD is generally suspected on the basis of the presence of one or more of (1) maternal heritability of diabetes or impaired glucose tolerance with a normal body mass index (BMI), (2) hearing impairment, and (3) maculopathy [92]. Other features of mitochondrial disease may manifest (e.g., myopathy, gastrointestinal disease, short stature, etc.). MIDD has an ocular phenotype recognizable by parafoveal macular atrophy and an absence of classic DR findings in the context of type 1 diabetes and congenital hearing loss [93, 94].

Other Ocular Comorbidities The working group further considered corneal guttata, neurotrophic corneal ulcers, diabetic papillitis, and nerve palsies as other possible diabetes-related ocular complications and noted the importance of investigating these possible complications following suggestive symptoms and signs.

While rare, diabetic neurotrophic keratopathy leading to corneal ulcers has been described and is hypothesized to be a manifestation of peripheral neuropathy [95]. Recent developments with drugs such as cenegermin offer a new therapeutic pathway for this potentially devastating ocular complication [96]. Diabetic papillopathy occurs among patients with type 1 or type 2 diabetes. The condition is characterized by optic disc swelling caused by vascular leakage and axonal edema near the optic nerve head [97]. Trochlear, abducens, and oculomotor palsy are frequent neuro-ophthalmologic complications among patients with diabetes [98, 99].

Treatment Goals

Working group members identified the prevention of blindness and optimization of eye health as primary goals for DDE management. There was no clear consensus achieved on defining generalized objectives for care of patients with DDE.

Consensus Statements–10

- Few respondents defined long-term, lifetime success of vision care as the maintenance of vision stability; few defined it as best attainable binocular central vision and perimetry at all stages of life; and few defined it as maintenance of at least one eye with better-than-reading vision throughout life.
- Few respondents added that the attainment of long-term vision goals in patients with diabetes is not the exclusive responsibility of the ophthalmologist; it also requires a compliant patient and a dedicated care team.

The working group highlighted clinical data, physician experience, access and reimbursement, and patient preference as the key factors influencing their choice of treatment. They also noted the value of international learning opportunities, as every country has slightly different guidelines and practice habits, which may offer new perspectives. For example, European ophthalmologists were early adopters of intravitreal steroids and multimodal imaging techniques [20].

NPDR Management

The RCT known as Protocol W was conducted in multiple sites in the USA and Canada [26]. Adult patients with moderate to severe NPDR without center-involved DME were included. The trial aims were to examine whether aflibercept treatment of moderate to severe NPDR prevented vision-threatening complications and benefitted VA versus a sham treatment. Ultimately, the trial showed the 2-year rate of developing center-involved DME with vision loss or PDR was lower with aflibercept than with the sham (16.3% versus 43.5%). The difference in the 2-year mean VA change (aflibercept versus sham) was 0.5 letters. Similarly, the PANORAMA trial demonstrated that significantly more eyes with moderately severe to severe NPDR, treated with aflibercept, showed a two-step or greater improvement in the diabetic retinopathy severity scale (DRSS) level at 24, 52, and 100 weeks, and significantly fewer eyes treated with aflibercept versus sham developed vision-threatening complications and center-involved DME [100]. On the basis of these findings, which showed a lack of VA improvement with anti-VEGF therapy in the non-proliferative stage of the disease, monitoring patients for the development of vision-threatening complications and timely implementation of necessary treatment remains the current standard of care. Anti-VEGF therapy is not approved as a treatment option for NPDR in Canada.

Consensus Statement–11

- Most respondents stated they did not feel there was currently any individual or collective value to the widespread adoption of anti-VEGF intervention to limit progression to proliferative disease.

Diabetic Macular Edema and Clinically Significant Diabetic Macular Edema

DME Without PDR

Pharmacologic treatment for DME is initiated in patients with center-involved disease who experience worsening VA (i.e., 20/32 or worse)

[101]. Treatment should also be considered for subcentral DME with a central retinal thickness > 305 to 320 μm, depending on sex and the OCT machine used [102]. The following values have been proposed as the minimum thickness criteria for defining the presence of DME [102]: 320 μm for men, 305 μm for women (Heidelberg Spectralis OCT); 305 μm for men, 290 μm for women (Zeiss Cirrus OCT); and 250 μm for men and women (Zeiss Stratus OCT) [103].

DME is primarily treated with approved anti-VEGF therapies, such as aflibercept, ranibizumab, brolucizumab, and the bispecific Ang-2 and VEGF inhibitor faricimab in alignment with clinical trial protocols [84, 85, 104, 105]. Off-label use with bevacizumab has also been an accepted treatment option and is currently under application for approval in the USA [84, 85]. Implementation of brolucizumab therapy has been hampered by emerging safety signals with development of intraocular inflammation, retinal vascular inflammation, and occlusive vasculitis limiting its uptake [106, 107]. At the time of writing, the clinical exposure of the working group to faricimab in clinical practice was limited as a result of its very recent Canadian market introduction. Anti-VEGF therapy for DME is associated with improved VA outcomes and a lower risk of ocular side effects such as cataract and glaucoma when compared to intraocular steroid therapy. Anti-VEGF VA improvements have been observed equally in pseudophakic eyes [108].

Consensus Statements–12

- Most respondents agreed that the presence or absence of macular ischemia has no impact on their threshold to initiate anti-VEGF therapy for DME.
- In the presence of macular ischemia, few respondents noted they would initiate three injections and then reassess, stopping if there was no improvement.
- Few respondents noted that the absence of macular ischemia would only have an impact on their threshold for anti-VEGF therapy implementation in cases of unexplained vision loss or decline.

Consensus Statements–13

- Most respondents stated that in the context of 20/30 vision or worse, an anti-VEGF should be initiated in patients with DME/NPDR when OCT findings are at the physician-determined structural threshold based on the OCT technology being used.
- Few respondents noted initiating anti-VEGF when OCT findings indicate qualitative foveal-involving edema on B-scan cut.
- Few respondents noted leveraging a quantitative predetermined CMT (or foveal minimum thickness) cutoff on OCT topography.

Consensus Statement–14

- All respondents agreed that in treatment-naïve patients with OCT structural changes consistent with center-involved DME and with non-proliferative retinopathy findings, anti-VEGF should *only* be started if there is an associated functional decline.

Consensus Statement–15

- All respondents agreed that intravitreal anti-VEGF therapy is the primary treatment intervention for center-involved DME without PDR.

Working group members also identified steroids as a consideration for second-line therapy for refractory disease. Several trials have assessed the efficacy of dexamethasone (DEX) in the context of DME [109]. The MEAD trial was a 3-year RCT comparing low-dose DEX, high-dose DEX, and sham intravitreal therapies for the management of DME [83]. This trial showed improved VA in the treatment groups versus sham. The BEVORDEX study was an RCT assessing the efficacy of bevacizumab versus a slow-release intravitreal DEX implant [110, 111]. Both year 1 and year 2 results showed no significant difference in VA between the two treatment groups. Another 12-month RCT, described by Callanan et al., compared a DEX intravitreal implant to ranibizumab in patients with DME [112]. This trial showed that both DEX implant and ranibizumab were well tolerated and resulted in improved VA and anatomic outcomes. Protocol I was an RCT comparing long-term vision and the anatomic

effects of four treatment groups: sham plus prompt focal/grid laser; ranibizumab plus prompt laser; ranibizumab plus deferred ($\geq$ 24 weeks) laser; and triamcinolone plus prompt laser in DME [108]. The eyes receiving initial ranibizumab therapy for center-involved DME were more likely to have better long-term vision than triamcinolone plus prompt laser. The worst VA group in the pseudophakic subset received triamcinolone, prompt laser, and deferred ranibizumab [108].

The simultaneous use of an intravitreal DEX implant combined with continued ranibizumab intravitreal administration did not improve VA versus ranibizumab alone [29]. However, intravitreal DEX implants have been shown to be beneficial for pseudophakic eyes without comorbid glaucomatous neuropathy, with improvements noted in best-corrected VA and central macular thickness [113]. Working group members recommended against the addition of intraocular steroids to anti-VEGF therapy given the lack of further functional improvement and an increased risk of side effects.

Consensus Statements–16

- Most respondents stated they would use steroids for the management of DME if disease was refractory to the loading phase of anti-VEGF.
- Few respondents stated they would use them in patient cases with resistant or recurrent or refractory or chronic DME.

Consensus Statements–17

- Few respondents stated that the steroid formulation dexamethasone implant (Ozurdex®) was available under their provincial coverage plan, and few noted that triamcinolone acetonide injectable suspension (Triesence®) was available under their plan.
- All respondents stated that off-label Kenalog® was available under their plan.

While clinical experience suggests that vitrectomy may be an important adjunctive therapy in the setting of epiretinal membrane proliferation complicating DME, VA outcomes have been limited with concurrent surgical management of the vitreo-retinal interface [114].

Consensus Statement–18

- Most respondents agreed that pars plana vitrectomy was a valuable tool in the management of resistant or recurrent or refractory or chronic DME.

ETDRS criteria regarding the application of macular laser to CSME remain the evidence-based standard for the management of clinically significant non-center-involving DME. A DRCR Network trial (Protocol A) assessed the effect of focal/grid photocoagulation on VA and retinal thickening in eyes with non-center-involved CSME. Results showed that use of focal/grid laser in the non-center-involved eyes was associated with relatively stable VA and retinal thickness measurements and a decreased fluorescein leakage area at 1 year [115].

However, there was diversity of perspectives on the management of this vision-threatening complication amongst the surveyed working group members. Some members recommended treating center-involved DME and monitoring non-center-involved DME. Others felt there was still a role for focal/grid laser for some non-central DME, provided it was far enough from the fovea center. The group noted that focal/-grid laser photocoagulation can be considered for CSME with edema > 1000 to 1500 μm outside the fovea center. They noted further that macular laser could be performed as per ETDRS guidance for CSME, or in combination with anti-VEGF therapy.

Consensus Statements–19

- Some respondents agreed with the ETDRS criteria to inform their decisions for macular laser intervention for non-center-involving CSME.
- Some respondents noted that they rarely used macular laser and followed the DRCR Network Protocol I to monitor non-center CSME.
- Few respondents reported that they used laser similarly to ETDRS and applied it beyond the foveal avascular zone.

Current Anti-VEGF Treatment Landscape

RISE/RIDE was a multicenter, phase III RCT showing 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 non-ocular harm [84]. Another phase III trial, VIVID/VISTA, compared the efficacy and safety of intravitreal aflibercept injections with macular laser photocoagulation for DME [85]. Ultimately, treatments with intravitreal aflibercept injection had positive effects on the DRSS score [85]. In the RISE/RIDE trial, 20–39% of the patients treated in the ranibizumab arm received laser at 2 years; in the VIVID/VISTA trial, 3–11% of participants in the aflibercept arm received laser at 2 years.

In an independent head-to-head study evaluating the 2-year efficacy, safety, and treatment results of three anti-VEGF agents for center-involved DME, the percentage of eyes receiving at least one session of focal/grid laser over 2 years in the aflibercept, bevacizumab, and ranibizumab groups were 41%, 64%, and 52%, respectively [54].

Consensus Statement–20

- Most respondents agreed that macular laser in addition to anti-VEGF therapy (as per the RISE/RIDE [84] and VIVID/VISTA [85] protocols) was an important option for refractory or recurrent DME.

Consensus Statements–21

- Few respondents noted that in the setting of clinically significant non-center-involved DME, their practice preference was to treat with macular laser as per ETDRS.
- Few respondents noted a preference to observe and treat with anti-VEGF only if the disease progresses to center-involved DME.
- Few respondents noted a preference to treat all OCT-based thickening outside of center with macular laser-grid (or focal treatment of leaking microaneurysms).

Working group members noted that there was no sufficient evidence to support the use of micro-pulse laser therapy for treating DME at this time.

Consensus Statements–22

- Regarding anti-VEGF agents, most respondents agreed that options available today had clinically different effects on DME.
- Few respondents referenced Protocol T [54] and the Cochrane review [116] to support their belief that aflibercept is superior.

The RCT Protocol T evaluated the 2-year efficacy, safety, and re-treatment frequency of three anti-VEGF agents (aflibercept, bevacizumab, and ranibizumab) for treating center-involved DME [54]. All three anti-VEGF agents had VA improvement at 2 years with a reduced number of injections in the second year of treatment and comparable ocular and systemic safety profiles. At the 1-year primary endpoint, aflibercept achieved significantly greater mean VA improvements over ranibizumab and bevacizumab. Compared with bevacizumab, aflibercept had superior 2-year VA outcomes. While aflibercept was superior to ranibizumab at year 1, this difference was no longer identified after year 2 [54]. Interestingly, over 2 years, in a post hoc area-under-the-curve analysis, aflibercept vision outcomes were superior to bevacizumab or ranibizumab among eyes with baseline VA of 20/50 to 20/320 [117].

A Cochrane systematic literature review explored the effectiveness and safety as well as the quality of life associated with anti-VEGF agents compared to laser photocoagulation for the treatment of DME [116]. This review reported that at year 1, aflibercept increased the chance of gaining more than three lines of VA by 30% versus ranibizumab and bevacizumab, respectively [116]. There was no evidence of a difference in safety outcomes between anti-VEGF drugs.

Working group members noted that most patients with DME are treated with 5–6 loading doses of anti-VEGF agents before adopting a treat-and-extend approach [118, 119], with dosing intervals gradually extended to every 6–8 weeks as the patient improves. The interval largely depends on the location of fluid, with clinicians monitoring foveal-threatening fluid more closely. If patients experience worsening

status when intervals are extended from loading to every 8 weeks, the working group noted they would consider additive laser therapy to dry the macula. Anti-VEGF therapy would typically be continued until clinical resolution or treatment futility.

Consensus Statement–23

- All respondents agreed that a loading phase of 5–6 doses would improve long-term DME control.

Both the RISE/RIDE trial [84] and the Protocol T trial [54] reported continued improvement in VA through at least six anti-VEGF injections. Further, Protocol T showed an incremental resolution of persistent DME with aflibercept monotherapy. All three anti-VEGF groups had VA improvement at 2 years with a decreased number of injections in year 2 [54].

Consensus Statements–24

- Most respondents noted their algorithm of treatment for anti-VEGFs for DME was a personalized plan with loading followed by a modified treat-and-extend approach.
- Few respondents reported that their algorithm was treat-and-extend, and few reported that their algorithm was fixed treatment interval.

Consensus Statements–25 and 26

- All respondents agreed that monitoring of DR status via clinical examination is necessary while patients receive anti-VEGF therapy for DME.
- Some respondents stated this should be done at every visit; others said that frequency should be based on the patient's retinopathy grading prior to anti-VEGF initiation.

Consensus Statements–27

- Most respondents agreed that assessment of retinal perfusion status is necessary prior to initiating anti-VEGF or focal/grid laser therapy. Perfusion status affects the safety of application of macular laser and the assessment of macular ischemia (which can affect functional gains with anti-VEGF therapy); it also provides baseline DR status to inform future treatment decisions.
- Few respondents disagreed, stating that perfusion status does not prognosticate the anti-VEGF response.

Emerging Anti-VEGF Treatments

At the time of producing this publication, treatment modalities for DME management are being investigated or recently launched in Canada. Faricimab, a bispecific antibody targeting VEGF-A and Ang-2, has been investigated in two phase III trials, YOSEMITE and RHINE, in comparison to standard-of-care aflibercept [105]. Study findings showed that 71–74% of patients with DME could be maintained with 12–16 weeks treatment intervals at the 1-year time point. The clinical trials demonstrated non-inferior anatomical and visual outcomes with faricimab compared to aflibercept dosed every 8 weeks (q8); approximately 20% of patients received faricimab every 12 weeks, and approximately 50% every 16 weeks by using a personalized treatment interval (PTI) protocol with faricimab (but not for aflibercept). All three arms displayed similar mean number of injections at 1 year: 9.4, 8.5, and 9.3 for the faricimab q8, faricimab PTI, and aflibercept q8 arms, respectively.

On the other hand, the PULSAR and PHOTON 96-week studies have been completed and remain officially unreported at the time of this publication. Data presented within conferences demonstrated enhanced durability by quadrupling the aflibercept molar dose [120, 121]. In the PHOTON DME phase II/III trial, treatment arms with aflibercept 8 mg every 12 and 16 weeks, respectively, were compared to aflibercept 2 mg every 8 weeks, with patients in the aflibercept 8 mg arms receiving three initial monthly injections and in the aflibercept 2 mg arm receiving five initial monthly injections. This study demonstrated non-inferior mean changes in best corrected visual acuity (BCVA) at week 48, with 91% of patients in the aflibercept 8 mg 12-week arm and 89% of patients in the 16-week arm maintaining their assigned intervals through week 48. Through week 96, 89% of all patients in the aflibercept 8 mg groups maintained $\geq$ 12-week dosing intervals,

including a considerable number of patients who met the extension criteria for dosing intervals greater than every 16 weeks (indeed, 43% reached ≥ 20-week intervals and 27% reached 24-week intervals by week 96) [122].

In addition, biosimilars have been introduced recently and for the first time into the Canadian ophthalmology landscape after Health Canada approval of the ranibizumab biosimilar (SB11) [123].

Proliferative Diabetic Retinopathy

PRP remains the gold standard for treating and controlling PDR. The DRS trial, an RCT initiated in 1972, determined whether photocoagulation helps to prevent severe visual loss from PDR [124]. The trial suggested, for eyes with high-risk PDR, that PRP reduced the risk of severe vision loss relative to no treatment [124]. Studies have also evaluated the safety and efficacy of PRP in controlling PDR when combined with anti-VEGF agents [125]. Although anti-VEGF agents have shown promising results when administered for PDR, they represent a temporary mode of stabilization of the disease, requiring continuous administration for maintenance of stability of the proliferative disease component.

The DRCR Retina Network's Protocol S, a non-inferiority trial, demonstrated that treatment of PDR with ranibizumab resulted in VA that was non-inferior to PRP treatment at 2 years [28]. In addition, the CLARITY study showed that patients with PDR who were treated with aflibercept had an improved mean BCVA difference compared to those treated with PRP over 1 year of therapy [126]. It is important to note that the CLARITY study was discontinued following the first year of reporting. No long-term studies exist for the management of PDR with anti-VEGF agents beyond 2 years.

The working group recommended treating PDR without associated macular edema using anti-VEGF therapy, where available, followed by PRP; anti-VEGF therapy can be discontinued post-laser treatment. Importantly, this option is not available in all regions in Canada as some provinces restrict use of anti-VEGF to patients with DME.

Consensus Statements–28

- Few respondents noted that their threshold to intervene in PDR was based on low-risk PDR.
- Few respondents noted a threshold to intervene based on results from the DRS trial (i.e., high-risk PDR).
- Few respondents noted a threshold to intervene based on patient factors independent of the proliferative threshold for retinopathy status.

Consensus Statement–29

- All respondents agreed that PRP represents the *only* permanent therapy for control of PDR.

Consensus Statements–30

- For patients with threshold PDR and threshold center-involved DME, most respondents stated that their preferred treatment would be to start an anti-VEGF therapy for rapid control, then add PRP while continuing anti-VEGF therapy.
- A few respondents stated that they would use a personalized treatment based on the patient's preference and visual goals.

Consensus Statements–31

- In instances where both sub-threshold PDR and sub-threshold center-involved DME are present, some respondents said that they would intervene when either DME or PDR met their threshold.
- Some respondents said they would intervene at the earliest opportunity regardless of risk criteria.

Vitreous Hemorrhage

The DRCR Retina Network's Protocol AB assessed the impact of aflibercept versus vitrectomy with PRP for treating vitreous hemorrhage (VH) from PDR. The initial results showed no statistically significant difference in the mean VA letter score over 24 weeks. However, the eyes

that received vitrectomy with PRP had faster VH clearance and faster recovery of vision when baseline VA was worse than 20/800 [27, 127].

Consensus Statements–32

- In cases of non-resolving diabetic VH with no detachment, all respondents stated that a vitrectomy would be indicated when vision loss from VH persists for more than 1—3 months [128].
- Most respondents stated that early vitrectomy would be indicated for VH in the only seeing eye.
- Some respondents stated it would be indicated with an inability to visualize or assess the posterior segment for presence or absence of retinal detachment.
- Some respondents stated it would be indicated at the onset of VH in a patient with type 1 diabetes.
- Some respondents noted that all four reasons above indicate a need for vitrectomy.

Tractional ± Rhegmatogenous Detachment

Tractional retinal detachment (TRD) and traction/rhegmatogenous retinal detachment (TRD/RRD) can be treated with surgical interventions [129]. Working group members noted that patients presenting with TRD or TRD with macular involvement and RRD should be referred to surgery.

Consensus Statements–33

- Most respondents stated vitrectomy was necessary for macula-involving tractional detachments.
- Few respondents noted it was necessary only for foveal-involving tractional detachments.

Consensus Statement–34

- All respondents agreed that retinal stabilization by means of a pars plana vitrectomy should be conducted in all cases of combined TRD/RRD.

Cystoid Macular Edema (CME)

CME is frequently encountered in patients with diabetes undergoing cataract extraction. Uneventful cataract extraction in patients with diabetes is associated with a 3.2% risk of postoperative CME [130, 131]. There was no consensus reached on the necessary investigation modalities to differentiate DME from CME amongst working group members. All survey responders indicated topical combined steroid and non-steroidal anti-inflammatory drugs (NSAID) as first-line therapy.

Consensus Statement–35

- All respondents stated that their preferred treatment for postoperative CME in patients with diabetes was a combination of topical steroid and topical non-steroid anti-inflammatory drugs.

Consensus Statements–36

- To differentiate postoperative CME from DME, some respondents would use FA.
- Some respondents would use only OCT imaging.
- Some respondents noted differentiation was unnecessary as clinical management was the same.

Special Considerations

There was a lack of consensus amongst working group members regarding whether switching between anti-VEGF agents provides an added clinical benefit, especially if aflibercept is used as first-line therapy. Although case studies and case series have suggested beneficial effects from anti-VEGF switching following a limited initial clinical response, there are no well-controlled clinical trials to support this practice [132]. There was also no consensus regarding the definition of a DME treatment (non) sub-responder.

INTERDISCIPLINARY COLLABORATION

Considering the broader risk of diabetic complications in patients with DR, an interdisciplinary approach to preventative care should be implemented to optimize patient health [74]. Timely screening for DR is critical to help prevent vision loss and may help to identify patients at elevated risk of other diabetes-related complications [133].

Care for patients with DR should include a multidisciplinary team of healthcare providers to support the holistic aspects of diagnosis, monitoring, and treatment. This team may include primary care providers, ophthalmologists, optometrists, nurse practitioners, dietitians, podiatrists, psychologists, pharmacists, specialists, and diabetic education providers. The working group noted that web-based applications accessible to both patients and healthcare providers may facilitate multidisciplinary communication. Engaging and educating multidisciplinary teams may help alleviate the burden on the ophthalmologists treating DR; it may also generate feedback to identify discipline-specific educational gaps.

Consensus Statement–37

- All respondents agreed that timely referral to vision rehabilitation centers was an important management strategy for assistance with adaptation to advanced vision loss.

Consensus Statements–38

- Most respondents believed the working group should seek to establish a minimum communication standard for ophthalmology consultations to inform the multidisciplinary care team.
- The working group specified that the key information to communicate is visual acuity, intraocular pressure, macular status, DR status, interventions performed, the recommended treatment plan, and the current follow-up schedule with periodic updates based on change in the diabetic status.

Consensus Statements–39

- All respondents noted that key responsibilities of the treating ophthalmologist were to educate patients about the importance of diabetes control, DDE, treatment compliance, and potential complications; to provide emotional support to the patient; and to establish a lifelong relationship with the patient.
- All respondents felt responsibility towards the broader multidisciplinary care team.

At the time of this writing, no national standardized Canadian DDE screening program existed. Several regional screening programs with variable adoptions of imaging technologies, telemedicine tools, and artificial intelligence (AI) are operational. Some working group members noted a strong preference for programs that include published, standardized criteria for screening. They noted further that the measured sensitivity and specificity of methods of detection should be included in any formulated list of regional screening programs. Although Canadian provinces have established DR/DDE screening programs, such as the Diabetes Eye Screening Program in Ontario, a national standardized screening approach would connect providers across the country.

Teleophthalmology has been shown to be as effective as in-person appointments for DR detection [134] and may be a beneficial tool to help reach underscreened and rural populations [135]. Telemedicine programs that rely on fundus photography are used widely in Canada and internationally for the identification and triage of DR [5]. Working group members noted, however, that not all provinces provide teleophthalmology funds.

The Canadian Retina Research Network recently established evidence-based guidelines for teleretina screening based on DR/DME grading using two 45° image fields or a single widefield/UWF image, adjunct OCT imaging, and quality control [59]. Interpretation of retinal photography and OCT results may vary depending on the healthcare provider, especially considering engagement of less-ophthalmology-experienced multidisciplinary teams to support screening needs [136]. Machine-based

analysis of retinal photographs for DR detection is a promising technique which could increase the efficiency and reproducibility of screening while alleviating the labor-intensive barrier on providers [36]. In multiple studies, deep-learning systems for automated DR classification were found to be equal to or better than board-certified specialists [137–141].

Consensus Statements–40

- Most working group respondents noted there were currently no active screening programs in their region.
- Few respondents noted that Ontario Community Health Centers have a Diabetes Eye Screening Program [142], or that Edmonton uses the Secure Diagnostic Imaging (SDI) system to help screen remote Northern Alberta communities.

The Diabetes Eye Screening Program (DESP) was established to provide free screening for patients with diabetes aged 18 years or older who have not had an eye exam with dilating drops in the past year [142]; a referral from a doctor or a nurse practitioner is required. The purpose of the program is to reduce the possibility of diabetes-related damage to the eyes (retinopathy), which could result in vision loss, through yearly diabetes eye screening [142].

Consensus Statement–41

- Most respondents named current efforts regarding the establishment of diabetic screening programs.

One such program was the Diabetic Retinopathy Screening program initiated by Diabetes Action Canada. The program's goals are to determine the cost-effectiveness of teleretina screening, identify barriers and enablers to DR screening, and identify at-risk individuals to start preventative screening.

DISCUSSION

The aim of this consensus statement was to develop recommendations that help advance care for patients with DDE, acknowledging that vision loss remains the single most-feared complication among patients with diabetes [3]. This paper, unlike some previous guidelines [19, 20], demonstrates sensitivity to the patient factors that may influence DDE and its management (e.g., obesity, sleep apnea, and comorbid hematologic disease, etc.). It also addresses the current diversity in treatments and need for personalized treatment approaches. The fortunate availability of multiple treatment interventions has led to a degree of choice for the practitioner; this report is intended to support those choices for DDE while acknowledging safety concerns with certain treatments.

Guidelines published previously in Canada focused on only one aspect of DDE (e.g., retinopathy [5, 8]), were published for optometrists [143], or did not discuss the diversity of treatment choices of DDE in detail. For example, the latest guideline from Diabetes Canada published in 2018 [5] reported a less comprehensive analysis of DR and excluded important recent clinical trial information, such as the effect of anti-VEGF therapy on retinopathy regression [5]. The current report addresses diversity in management, different healthcare coverage by province, and the variable prevalence of diabetes in the Canadian population.

Most other previous guidelines are outdated [144, 145] or published for use outside of Canada [10, 15, 17–20]. Our paper differs from those in several respects. For example, the AAO guidance on DME and the European Society of Retina Specialists (EURETINA) guidelines only focused on DME diagnosis and management [19, 20], whereas the current paper analyzed different forms of DDE and associated comorbidities as well as pregnancy.

Also, the current report addressed the safety of anti-VEGF for use in female patients of childbearing age. On the basis of the lack of relevant data, working group members did not recommend using anti-VEGF in pregnancy (Consensus Statements–6). Similarly, guidelines from the UK recommended against using anti-VEGF in pregnancy, stating that the best treatment option for progressive DME in pregnancy is intravitreal injection of steroids [10].

Regarding DME diagnosis, an important point discussed in the current paper and not

addressed in previous guidelines [19] pertains to angiography and using FA to characterize diabetic perfusion status. Most working group members agreed that an assessment of retinal perfusion status through dye-based or non-dye-based angiography is an essential component in evaluating disease onset, progression, and severity (Consensus Statements–2). Use of FA can inform the degree of systemic severity of diabetes and, also, the status of macular perfusion in the setting of poor functional gains with DME therapy. Peripheral diabetic lesions detected on UWF-FA are a better predictor of diabetes progression than UWF photos alone or ETDRS standard photos [146, 147]. Guidelines from EURETINA identified FA as the only commonly approved modality that can distinguish non-leaking from leaking microaneurysms [20]. UK guidelines on DDE recommend using FA on a case-by-case basis when the source of leakage is not obvious [10].

For long-term DME control, this report identified the utilization of steroids as second-line therapy (Consensus Statements–16) following 5–6 doses or more of anti-VEGF first-line therapy (Consensus Statements–15 and 23). Similarly, 2021 guidelines on the diagnosis and treatment of DME from the AAO [19] recommend a stepwise approach, starting with anti-VEGF and adding corticosteroids (or focal grid laser photocoagulation) if patients do not respond to the initial treatment. The UK [10] and EURETINA guidelines [20] for DME further support anti-VEGF as first-line therapy and use of steroids for management of chronically persistent DME and in pseudophakic eyes (laser photocoagulation was no longer recommended). Most working group members elected for a treat-and-extend approach following a successful loading phase, while a minority continued a fixed dosing regimen (Consensus Statements–24). Working group members also identified aflibercept as the current drug of choice for DME (Consensus Statement–22). The uptake of newer anti-VEGF agents recently evaluated through clinical trials (brolucizumab, faricimab, or aflibercept 8 mg) within the Canadian context remains to be seen. With the expiry of patents for multiple originator drugs, biosimilar products have recently become available for administration within the vitreous cavity. Provinces in Canada such as Quebec have a mandatory switch policy, mandating the switch to an approved biosimilar form the originator drug once regulatory application for the biosimilar drug is approved.

The current paper also discussed macular laser therapy as an important addition and option for managing DME. Most working group members considered macular laser in addition to anti-VEGF therapy (as per the RISE/RIDE [84] and VIVID/VISTA [85] protocols) as an important option for treating refractory or recurrent DME (Consensus Statements–20). In contrast, EURETINA guidelines discourage laser therapy for DME given insufficient evidence showing that laser adds more benefit than pharmacotherapy [20].

Our working group considers PRP to be the gold standard for PDR care (Consensus Statements–29). Most respondents preferred starting treatment with an anti-VEGF therapy for rapid control, then adding PRP while continuing anti-VEGF therapy (Consensus Statements–30). Similarly, AAO recommendations [18] specific to DR include PRP as the standard of care for PDR, plus anti-VEGF treatment given its effectiveness in regressing neovascularization and improving DRSS levels. Guidance from the AAO further recommends anti-VEGF treatment and a wait-and-watch approach or PRP for NPDR without DME [18]. This differs from Canada, where anti-VEGF therapy is not approved as a treatment option for NPDR. Thus, our working group did not provide recommendations for usage of anti-VEGF in NPDR.

Importantly, the current report underscores the value of collaborative care in DDE diagnosis and management. Working group members identified that the retinal examination in DDE not only informs the treating ophthalmologist but can serve as a global index for disease progression across many tissues in the body. This report highlights further that the prevention of visual complications requires a whole-body, multidisciplinary management approach. While DDE can be treated regardless of diabetic control, working group members agreed that a systemic approach to patient care will likely result in the best health outcomes. However,

collaborative care is challenged by peculiarities of the Canadian healthcare system, such as differences in provincial jurisdictions and healthcare implementation across geographies [148]. There may be variation in physician–physician relationships and few opportunities for the multispecialty coordination required for collaborative care. For example, the coordination and communication between an optometrist, general ophthalmologist, and retina specialist may be sub-optimal. There may also be significant difficulty in applying best collaborative care given challenges to the Canadian primary care network across multiple provinces (e.g., British Columbia, Quebec, Ontario). In 2019, Statistics Canada reported 4.9 million Canadians or 14.5% of the population without access to a primary care network. This survey of primary care coverage did not include the northern territories [149].

Resource implications must also be considered when applying these recommendations to practice. In Canada, retinal experts are mostly concentrated in large cities with academic healthcare networks with only occasional expertise being accessible in more remote areas. Physicians in remote areas managing DDE may not have the same comfort level or experience required to implement best care practices. Therefore, it is important to establish effective referral pathways to allow for more standardized care across broader geographic areas. Furthermore, because of regional differences in drug coverage, certain drugs may not be uniformly available across all provinces. An additional challenge to implementation is the lack of a unifying electronic medical record (EMR) system in Canada to facilitate interprovincial communication and collaborative care.

Other barriers to optimal care include late or delayed referrals to ophthalmology, absent (or poor) screening, diabetic comorbidities affecting the ability to implement best management, and a lack of access to UWF imaging tools, OCTA, and dye-based angiography. Patient barriers to implementation also exist and can include linguistic and psychologic barriers limiting administration of best care.

One of the main strengths of this work was the involvement of clinician experts in DDE from across Canada to develop the consensus statements. The scope, purpose, objectives, applicable population, and target users are specified in the report. Also, the use of a working group survey provided clear and unambiguous opinions to inform the consensus. In addition, the use of broad themes (patient, disease, management, and collaboration) to guide working group discussions brought forth facilitators and barriers to implementation.

There are methodological limitations that should be considered when reviewing this paper. It is important to note that these consensus statements are not based on a systematic review of the literature and thus individual research studies did not undergo a quality appraisal process for inclusion. In addition, formal consensus methods were not employed, and the group did not apply any grading based on the strength of the evidence supporting their recommendations. Instead, the working group members sought to use the best available evidence to address the question being considered in this guideline. Other methodological limitations are related to external validity and applicability, such as external peer review of the recommendations, incorporation of patient preferences, and implementation of strategies for clinical practice. Finally, the literature search excluded non-English language publications; therefore, it is possible that some evidence may have been missed, resulting in selection bias.

CONCLUSION

These consensus statements address challenges faced by ophthalmologists who must tailor their clinical approach to the needs and circumstances of individual patients while working in the reality of their healthcare settings. Significant clinical diversity exists amongst patients with diabetes, which is further complicated by disparate drug coverages across the national geography. This spectrum of diversity within the patient and diabetic disease itself poses significant difficulties in developing standardized algorithm protocols of care for DDE that may be applied uniformly. This work illustrates the

importance of personalizing care of DDE within a supportive collaborative care setting.

Even though these recommendations were developed for use in the Canadian context, they are relevant to other geographies with similar prevalence of diabetes, healthcare expenditure, and healthcare infrastructure. Unlike other healthcare systems where DDE may be exclusively managed by retina specialists, the framework for care delivery in Canada is much broader. The current consensus statements would be helpful for jurisdictions where non-retina-trained ophthalmologists are seeking to improve clarity and gain confidence in the DDE management modalities available.

Importantly, these consensus statements do not imply unanimity. They are based on the best available scientific evidence and clinical information at the time of writing and reflect a spectrum of acceptable opinions from recognized retina experts in Canada. These statements should be re-evaluated periodically as new clinical data emerge, and drug and device technologies evolve.

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Declarations

Conflict of Interest. Amer Omar worked as a consultant for Bayer, Roche, and Apellis. R. Geoff Williams served on advisory boards for Novartis, Bayer, Alcon, Valeant, Allergan, and AbbVie; received financial support from MD Collaborate and Arctic Dx; and worked as an investigator for Novartis, Bayer, Allergan, Regeneron, and Abbott Labs. James Whelan received honoraria from Bayer, Novartis, and Roche. Jason Noble served on the advisory board for Roche, Biogen, and Apellis. Michael H. Brent worked as a consultant for Bayer, Roche, Apellis, and Novartis. Michel Giunta worked as a consultant for Bayer, Roche, Apellis, Novartis, and Alcon. Sébastien Olivier had no declarations. Mustapha Lhor is a Bayer employee.

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