Residual Risk Reduction initiative

Diabetic Retinopathy as a Residual Microvascular Condition

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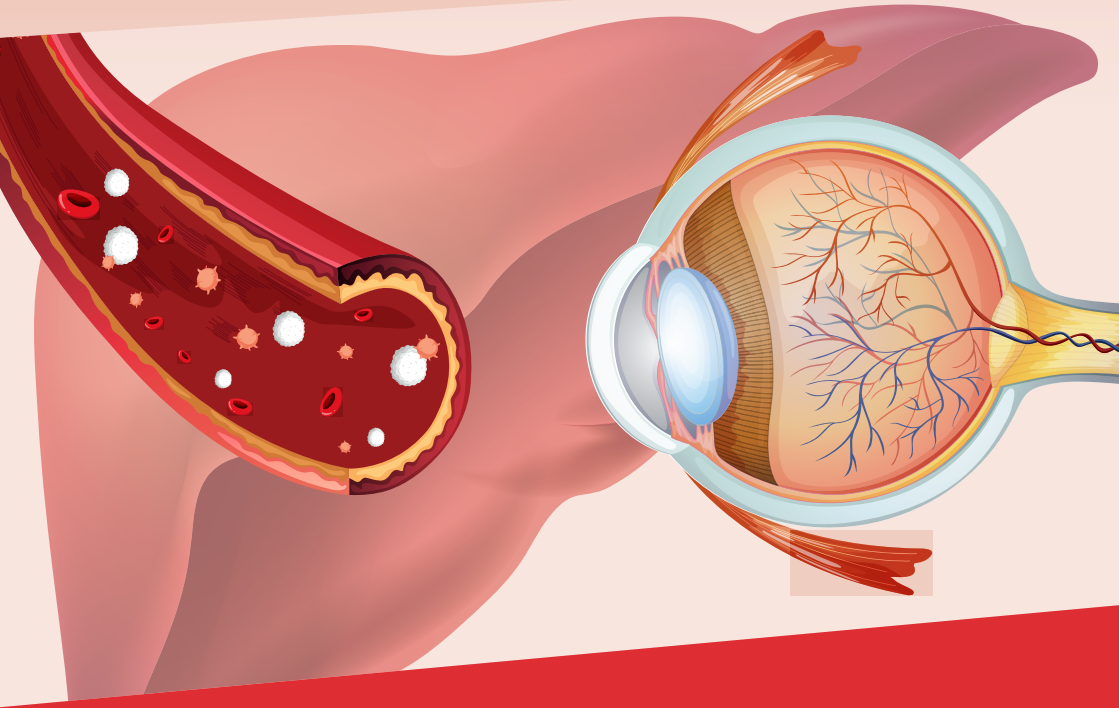

DEFINING TOMORROW'S VASCULAR STRATEGIES

Preface

This booklet, a project of the Residual Risk Reduction Initiative (R3i), is designed to significantly increase awareness and understanding of diabetic retinopathy (DR) as a persistent and often overlooked residual microvascular condition. DR remains a leading cause of preventable vision loss, and our initiative is dedicated to equipping healthcare professionals with the knowledge necessary to not only identify and effectively manage this complex disease, but to ultimately reduce its devastating impact on patients' lives. We firmly believe that a proactive, multi-faceted approach to risk reduction is absolutely essential in preserving vision and dramatically improving outcomes for individuals living with diabetes.

The content presented within this resource provides a comprehensive overview of key aspects of DR, systematically covering everything from its underlying pathophysiology and classification based on severity, to the critical risk factors that contribute to its progression. The booklet also offers a detailed exploration of current best practices in diagnostic methodologies and highlights both established and innovative treatment strategies for managing DR at various stages. It aims to offer a current perspective on the disease, showcasing both firmly rooted established knowledge, alongside emerging trends and promising breakthroughs in the field. While substantial progress has been made in the realm of DR treatment, it's imperative to acknowledge that the condition remains a complex and challenging one, requiring ongoing vigilance and a commitment to continuous learning and improvement in patient care.

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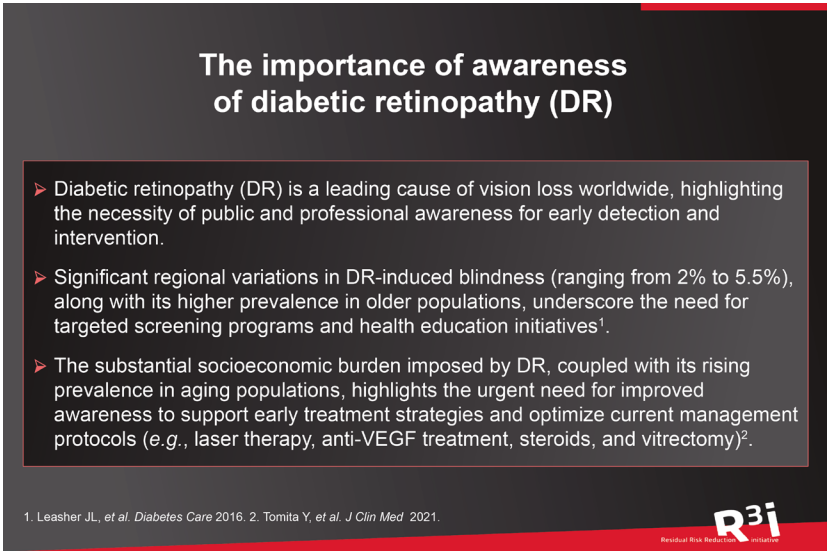


The importance of awareness of diabetic retinopathy (DR)

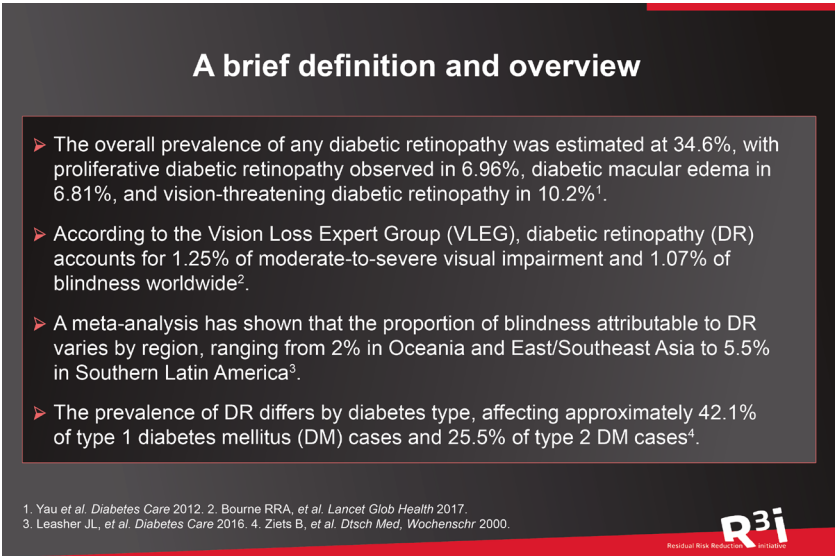
The importance of awareness regarding diabetic retinopathy (DR) as a major cause of vision loss worldwide. It highlights the need for public and professional awareness for early detection and intervention.

The prevalence of DR-related blindness varies regionally (2%–5.5%) and is higher in older populations, underscoring the necessity of targeted screening programs and health education.

Additionally, the socioeconomic burden of DR and its increasing prevalence in aging populations stress the urgency for improved awareness to support early treatment strategies and optimize management, including laser therapy, anti-VEGF treatment, steroids, and vitrectomy.

References:

1. Leasher JL, *et al. Diabetes Care* 2016.
2. Tomita Y, *et al. J Clin Med* 2021.



A brief definition and overview

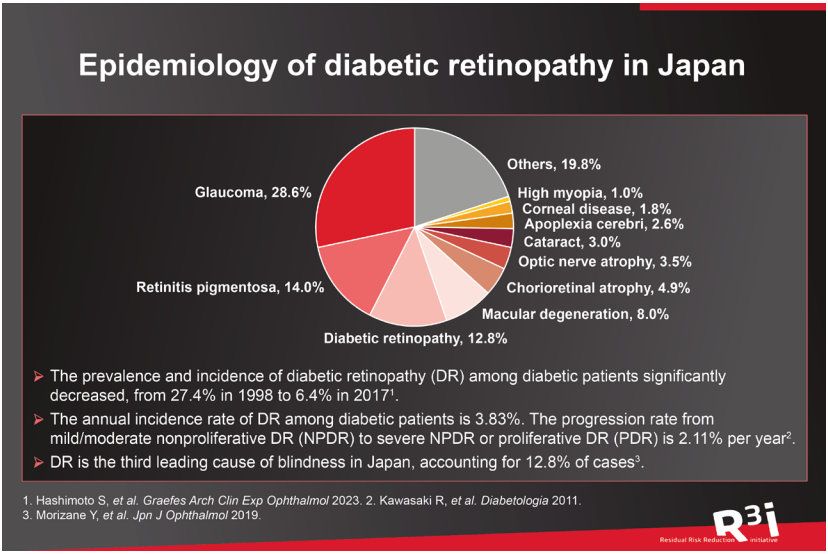
Among 35 studies conducted between 1980 and 2008, data were obtained from 22,896 individuals with diabetes. The overall prevalence of any diabetic retinopathy was estimated at 34.6% (95% CI, 34.5–34.8), with proliferative diabetic retinopathy observed in 6.96% (95% CI, 6.87–7.04), diabetic macular edema in 6.81% (95% CI, 6.74–6.89), and vision-threatening diabetic retinopathy in 10.2% (95% CI, 10.1–10.3).

According to the Vision Loss Expert Group (VLEG), DR contributes to 1.25% of moderate-to-severe visual impairment and 1.07% of global blindness.

A meta-analysis indicates regional variability in the proportion of blindness due to DR, ranging from 2% in Oceania and East/Southeast Asia to 5.5% in Southern Latin America. Additionally, the prevalence of DR differs by diabetes type, affecting approximately 42.1% of type 1 diabetes mellitus (DM) cases and 25.5% of type 2 DM cases.

References:

1. Yau *et al. Diabetes Care* 2012.
2. Bourne RRA, *et al. Lancet Glob Health* 2017.
3. Leasher JL, *et al. Diabetes Care* 2016.
4. Ziets B, *et al. Dtsch Med, Wochenschr* 2000.



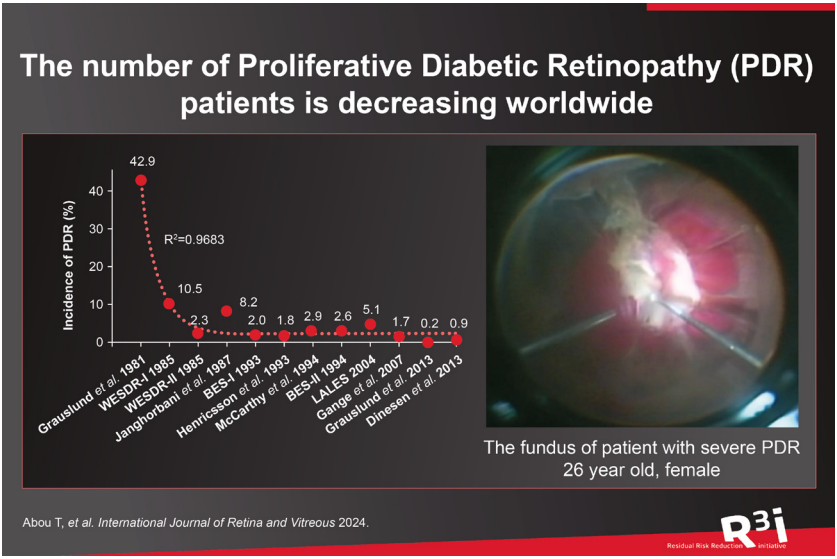
Epidemiology of diabetic retinopathy in Japan

In Japan, the prevalence of diabetic retinopathy (DR) decreased from 27.4% in 1998 to 6.4% in 2017. The annual incidence rate is 3.83%, with a progression rate of 2.11% per year from mild/moderate NPDR to severe NPDR or PDR.

DR is the third leading cause of blindness, accounting for 12.8% of cases.

References:

1. Hashimoto S, *et al. Graefes Arch Clin Exp Ophthalmol* 2023.
2. Kawasaki R, *et al. Diabetologia* 2011.
3. Morizane Y, *et al. Jpn J Ophthalmol* 2019.



The number of Proliferative Diabetic Retinopathy (PDR) patients is decreasing worldwide

This slide illustrates the global decline in proliferative diabetic retinopathy (PDR) incidence, attributed to advancements in diabetes management and ophthalmologic treatments. Improved glycemic and blood pressure control have reduced microvascular complications.

Additionally, systematic screening, laser therapy, and anti-VEGF treatments have enhanced early detection and management. However, severe cases, especially in younger patients, often lead to blindness, making early detection and early intervention essential.

References:

1. Abou T, *et al. International Journal of Retina and Vitreous* 2024.

Physiopathology and Mechanisms of Diabetic Retinopathy

SECTION

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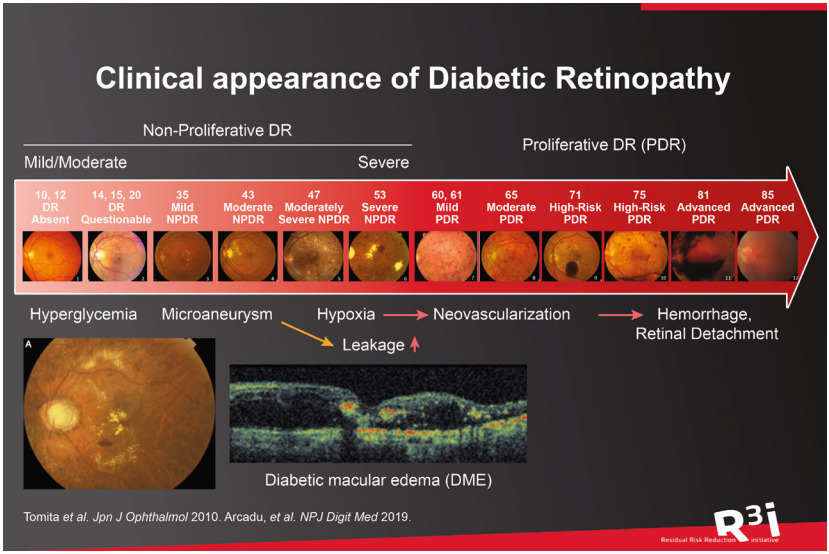


Clinical appearance of Diabetic Retinopathy

Pathophysiology of Diabetic Retinopathy (DR)

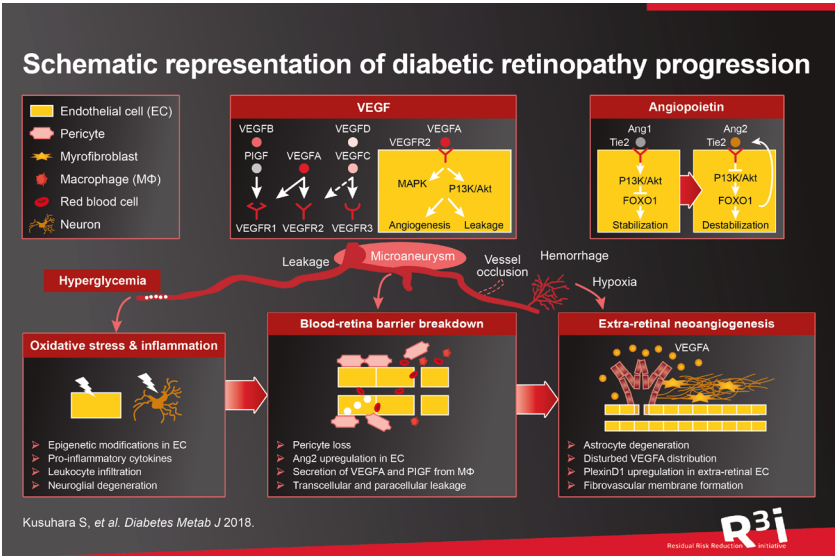
Diabetic retinopathy (DR) is classified into mild, moderate, and severe non-proliferative diabetic retinopathy (NPDR), as well as the advanced stage, proliferative diabetic retinopathy (PDR).

During the mild to moderate stages, hyperglycemia induces endothelial cell damage and pericyte loss, leading to microaneurysm formation and increased vascular permeability. As the disease progresses, vascular occlusion occurs, resulting in widespread retinal ischemia, marking the transition to the severe stage. In response to ischemia, excessive vascular endothelial growth factor (VEGF) production triggers neovascularization, leading to the PDR stage. These newly formed blood vessels are fragile and prone to hemorrhage, which can cause retinal detachment and, if left untreated, lead to blindness.

Additionally, regardless of the disease stage, plasma components can leak into the retina, leading to macular edema. This condition affects the macula, the most crucial part of the retina, and can result in significant visual impairment.

References:

1. Tomita *et al. Jpn J Ophthalmol* 2010.
2. Arcadu, *et al. NPJ Digit Med* 2019.



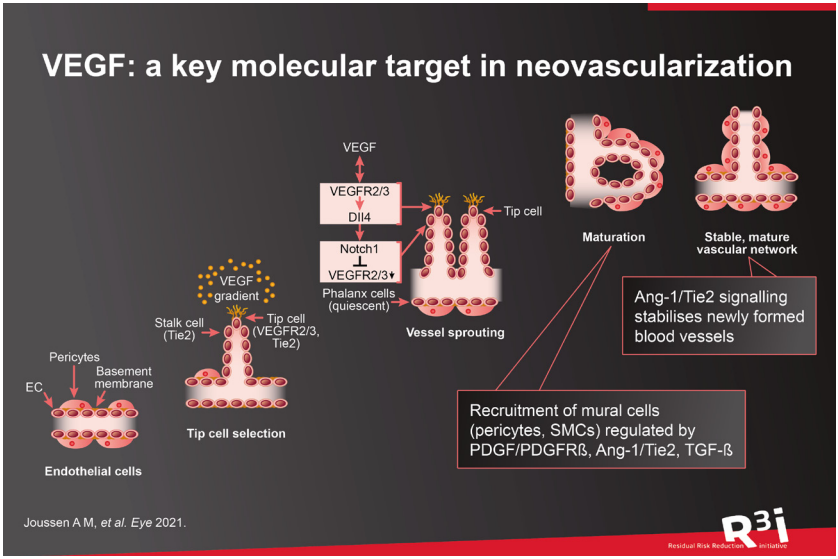
Schematic representation of diabetic retinopathy progression

Hyperglycemia induces oxidative stress, epigenetic modifications, and inflammation in endothelial cells (ECs), leading to neuroglial degeneration. Pericyte loss sensitizes ECs to environmental cues, while macrophages secrete VEGFA and PlGF, exacerbating vascular instability.

Angiopoietin-2 (Ang2) and FOXO1 form a destabilizing loop, contributing to blood-retina barrier breakdown. Hypoxia from vessel occlusion triggers extra-retinal neovascularization and fibrovascular membrane formation. VEGFR2-mediated MAPK and PI3K/Akt signaling drives angiogenesis and vascular leakage.

References:

1. Kusuhara S, *et al. Diabetes Metab J* 2018.



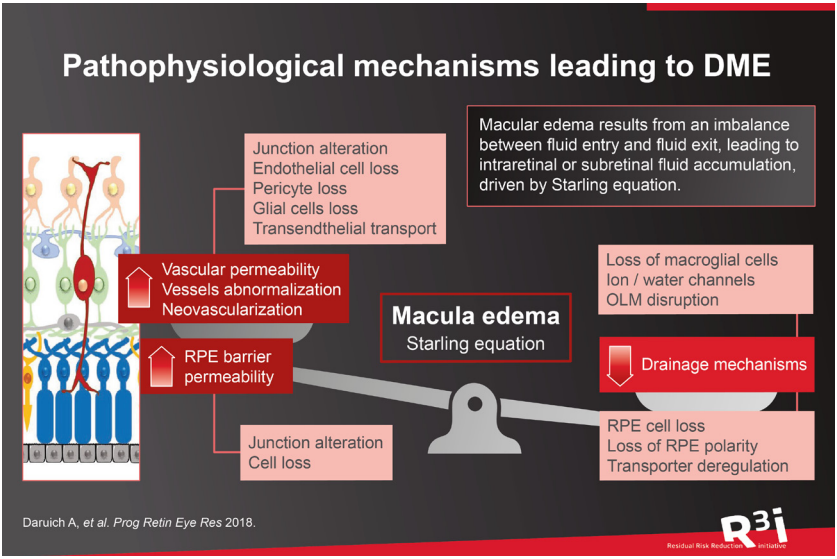
VEGF: a key molecular target in neovascularization

Vascular network formation requires vessel sprouting, maturation, and remodeling. Tip cells (Tie2 low, VEGFR2/3 high) lead stalk cells (Tie2 high) in response to a VEGF gradient. VEGF signaling induces Dll4 expression, which activates Notch1 in stalk cells, suppressing VEGFR2/3 and tip cell fate.

Tip cells anastomose, while stalk cells proliferate to elongate the sprout and form a lumen. Vessel stabilization occurs through mural cell recruitment (SMCs, pericytes) regulated by PDGF/PDGFRβ, Ang-1/Tie2, and TGF-β signaling.

References:

1. Joussen A M, *et al. Eye* 2021.



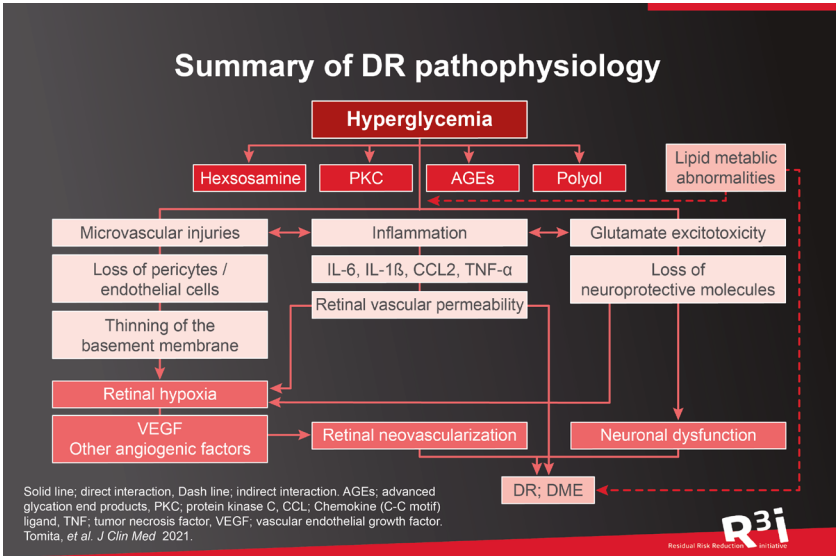
Pathophysiological mechanisms leading to DME

Retinal edema is a consequence of an imbalance between fluid entry, fluid exit and retinal hydraulic conductivity.

In most retinal diseases, macular edema is multifactorial and results from multiple, intricate mechanisms, but in certain specific conditions, one single of these mechanisms predominates, allowing a better analysis of each component.

References:

1. Daruich A, *et al. Prog Retin Eye Res* 2018.



Summary of DR pathophysiology

Hyperglycemia activates metabolic pathways (AGEs, PKC, polyol, hexosamine), leading to microvascular damage, inflammation, and glutamate excitotoxicity. This results in pericyte/endothelial cell loss, basement membrane thinning, increased inflammatory cytokines (IL-6, IL-1, CCL-2, TNF-α), vascular permeability, and VEGF-driven neovascularization.

DR progresses through stages:

- **NPDR (Non-Proliferative DR):** Microaneurysms (mild), hemorrhages (moderate), venous beading and vascular abnormalities (severe).
- **PDR (Proliferative DR):** Neovascularization, vitreous hemorrhage, and retinal detachment.
- **DME (Diabetic Macular Edema):** Retinal thickening causing vision loss at any stage.

Lipid metabolism abnormalities may further worsen retinal damage. DR development involves complex, interrelated mechanisms of metabolic dysfunction, inflammation, and angiogenesis.

References:

1. Tomita, *et al. J Clin Med* 2021.

Classification of Diabetic Retinopathy

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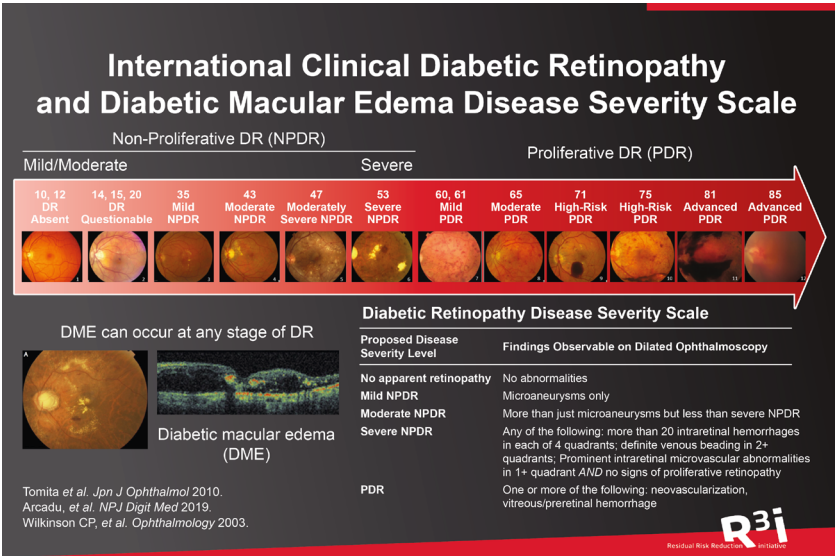
History of classification of DR

The classification of DR has evolved from the Airlie House system to the widely used ETDRS and ICDR classifications, improving the assessment of disease severity and management strategies.

The ICDR classification is currently used worldwide.



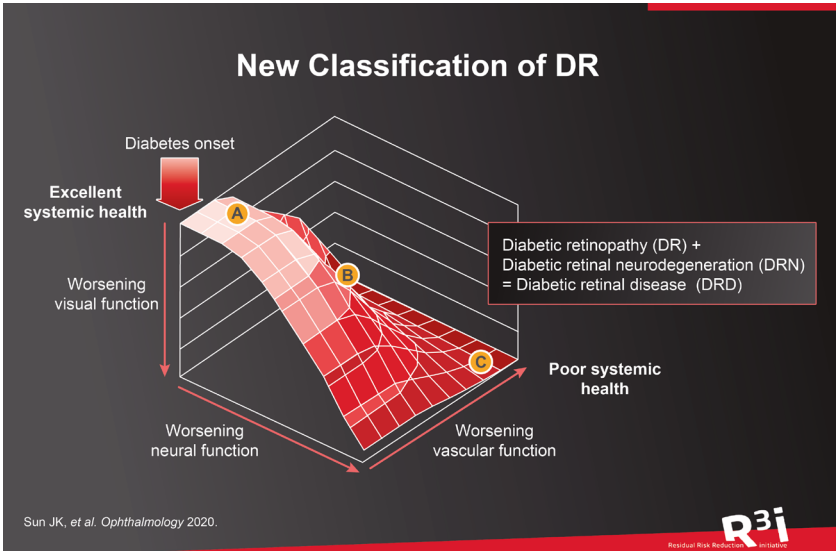
International Clinical Diabetic Retinopathy and Diabetic Macular Edema Disease Severity Scale

The **International Clinical Diabetic Retinopathy** (**ICDR**) **Disease Severity Scale** categorizes DR into **non-proliferative** (**mild, moderate, severe**) **and proliferative** (**PDR**) **stages,** based on fundoscopic findings. Representative retinal images illustrate the progression from **DR absence to advanced PDR,** with increasing severity of hemorrhages, venous beading, and neovascularization.

Diabetic **macular edema** (**DME**)**,** characterized by retinal thickening, can occur at any stage of DR and significantly impacts vision. The **ICDR classification** (**Wilkinson *et al.* 2003**) remains the global standard for assessing DR severity and guiding treatment decisions.

References:

1. Tomita *et al. Jpn J Ophthalmol* 2010.
2. Arcadu, *et al. NPJ Digit Med* 2019.
3. Wilkinson CP, *et al. Ophthalmology* 2003.



New Classification of DR

A new classification of DR has been proposed, emphasizing **both vascular damage and neural dysfunction.** DR should not only be evaluated based on vascular pathology but also on **diabetic retinal neurodegeneration** (**DRN**). This broader perspective introduces the term **diabetic retinal disease** (**DRD**), which encompasses both **diabetic retinopathy** (**DR**) **and DRN.**

The 3D model illustrates the relationship between s**ystemic health, vascular function,** and neural function, showing how worsening systemic conditions contribute to disease progression and visual impairment.

References:

1. Sun JK, *et al. Ophthalmology* 2020.

Risk Factors for Diabetic Retinopathy Progression

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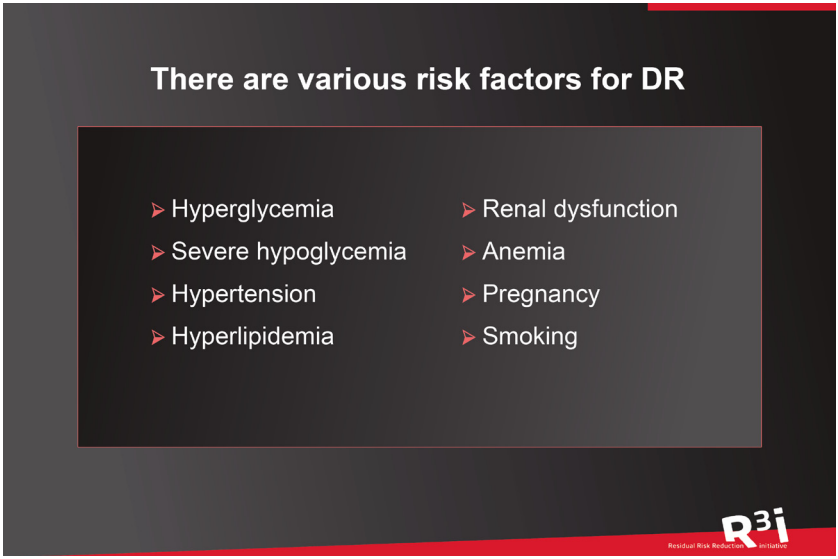
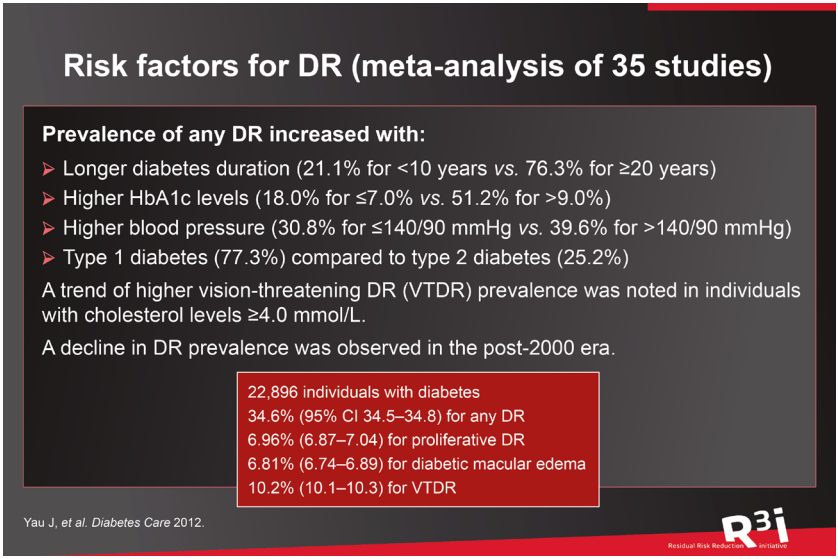


There are various risk factors for DR

These are the major risk factors for the progression of diabetic retinopathy (DR). Poor glycemic control (hyperglycemia) remains the most critical factor, while episodes of severe hypoglycemia may also disrupt stable metabolic regulation, leading to further retinal damage.

Additional systemic contributors—such as hypertension, hyperlipidemia, and renal dysfunction—worsen vascular compromise in the retina. Anemia can exacerbate retinal ischemia by reducing oxygen delivery, and pregnancy is known to accelerate DR progression, particularly when glycemic control is suboptimal.

Finally, smoking increases oxidative and vascular stress, further driving DR pathology. Effective management of these risk factors is crucial to slow DR progression and preserve visual function.



Risk factors for DR (meta-analysis of 35 studies)

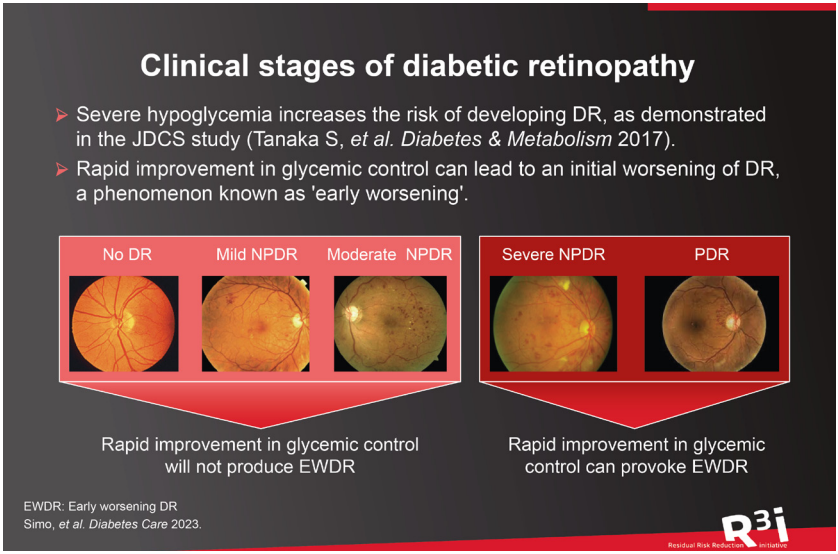
The age-standardized prevalence of diabetic retinopathy (DR) across various risk factors and subgroups. The prevalence of DR varies by ethnicity, with the highest rates observed among African Americans and the lowest among Asians. The prevalence also increases with diabetes duration, rising from 21.1% in those with less than 10 years of diabetes to 76.3% in those with 20 or more years.

Similarly, higher HbA1c levels are associated with increased prevalence, with 18.0% in individuals with HbA1c ≤7.0% compared to 51.2% in those with levels >9.0%. Blood pressure is another significant factor, as individuals with hypertension (>140/90 mmHg) exhibit a higher prevalence (39.6%) compared to those with normal blood pressure (30.8%). Furthermore, the prevalence is markedly higher in individuals with type 1 diabetes (77.3%) compared to type 2 diabetes (25.2%).

A similar pattern is observed for more advanced stages of DR, including proliferative diabetic retinopathy (PDR), diabetic macular edema (DME), and vision-threatening DR (VTDR). Notably, VTDR prevalence is higher among individuals with cholesterol levels ≥4.0 mmol/L. Additionally, an analysis by year and period of fundus photography suggests a decline in DR prevalence in the post-2000 era, likely reflecting improvements in diabetes management and screening strategies.

References:

1. Yau J, *et al. Diabetes Care* 2012.



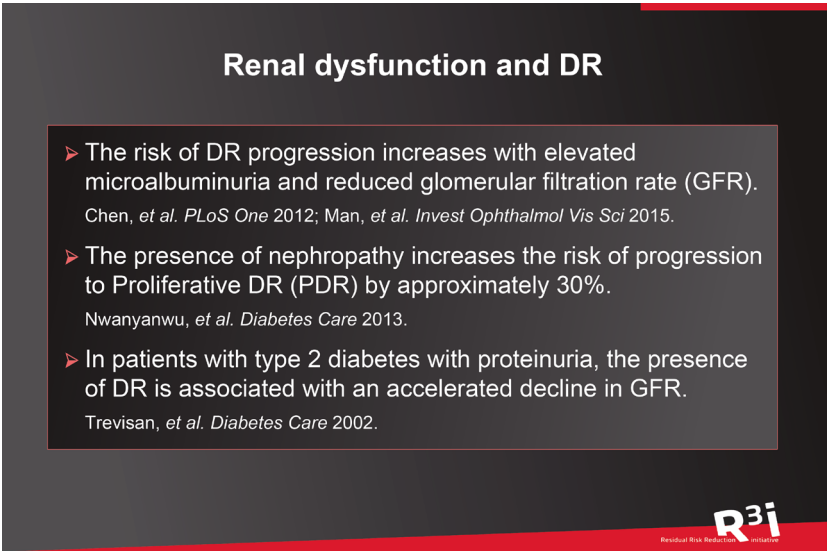
Clinical stages of diabetic retinopathy

Although tight glycemic control remains essential for preventing the progression of DR, lowering blood glucose too rapidly can be problematic. Severe hypoglycemia has been reported to increase the risk of DR onset by 4.35-fold, and abrupt glycemic reductions may trigger "early worsening," an initial exacerbation of DR before subsequent stabilization.

While maintaining a low HbA1c over the long term is generally beneficial, recent evidence suggests that if patients are classified as having moderate NPDR or less, rapid glycemic control does not significantly raise the risk of early worsening. These findings highlight the importance of detailed fundus examinations and accurate DR grading, which guide appropriate timing and intensity of glycemic management in collaboration with internal medicine specialists.

References:

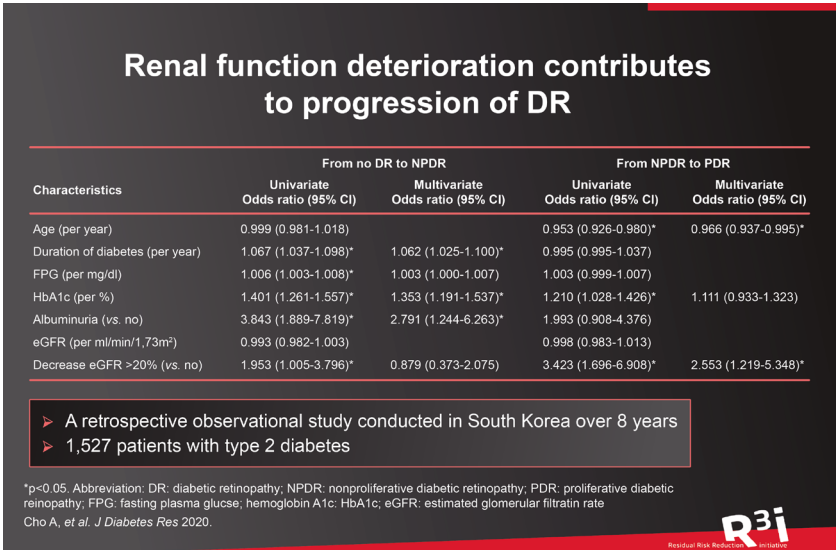
1. Simo, *et al. Diabetes Care* 2023.



Renal dysfunction and DR

Microalbuminuria and reduced glomerular filtration rate (GFR) significantly increase the risk of DR. The presence of nephropathy elevates the likelihood of advancing to proliferative DR (PDR) by approximately 30%.

Furthermore, in patients with type 2 diabetes who exhibit proteinuria, concurrent DR accelerates the decline in GFR . These findings underscore the importance of monitoring and managing renal function to mitigate the progression of DR.



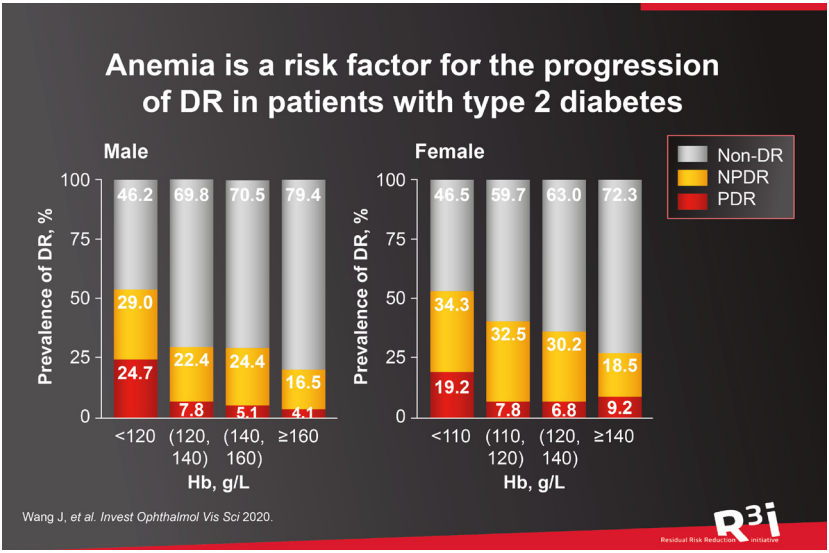
Renal function deterioration contributes to progression of DR

A retrospective observational study in South Korea followed 1,527 patients with type 2 diabetes over eight years. The findings indicate that renal function deterioration—reflected by albuminuria and a more than 20% decline in eGFR—significantly increases the risk of progressing from DR.

These results underscore the critical role of kidney function in DR pathogenesis and highlight the need for careful renal monitoring and management in diabetic patients to mitigate the progression of retinopathy.

References:

1. Cho A, *et al. J Diabetes Res* 2020.



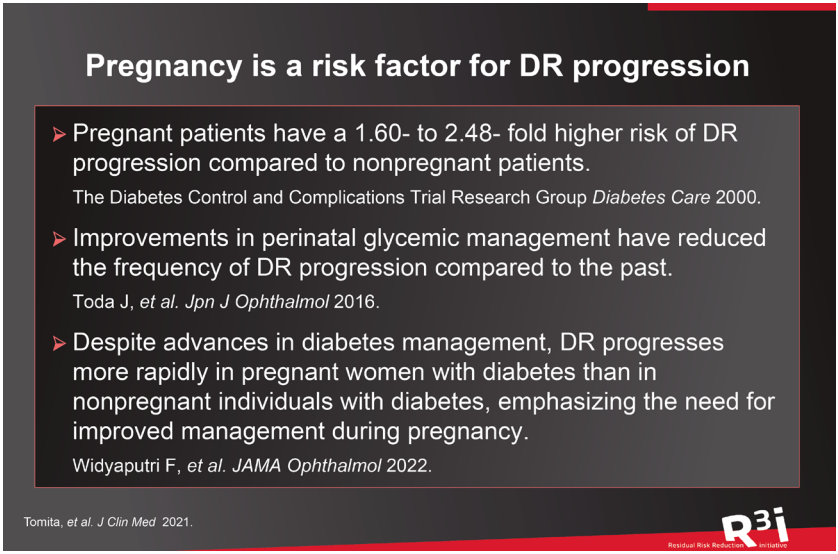
Anemia is a risk factor for the progression of DR in patients with type 2 diabetes

Data from Wang J. et al. indicate that lower hemoglobin levels (i.e., anemia) are associated with a higher prevalence of both non-proliferative and proliferative DR in patients with type 2 diabetes.

These findings underscore the importance of monitoring and managing hemoglobin levels to mitigate DR progression.

References:

1. Wang J, *et al. Invest Ophthalmol Vis Sci* 2020.



Pregnancy is a risk factor for DR progression

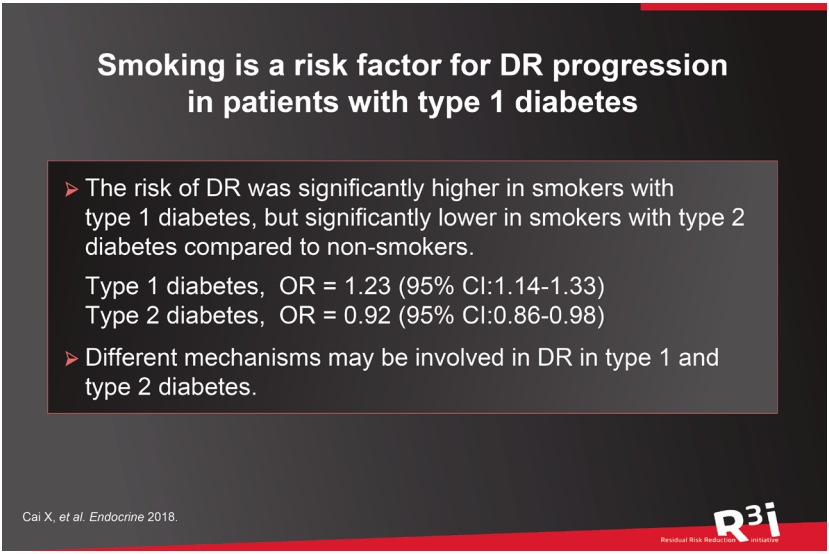
Pregnancy significantly increases the risk of diabetic retinopathy (DR) progression, with pregnant individuals experiencing a 1.60- to 2.48-fold higher likelihood of advancing DR compared to nonpregnant patients.

Advances in perinatal glycemic control have reduced the frequency of DR progression relative to earlier periods; however, DR still tends to worsen more rapidly during pregnancy than in nonpregnant individuals with diabetes.

These findings underscore the need for vigilant screening and meticulous management of glycemic levels throughout pregnancy.

References:

1. Tomita, *et al. J Clin Med* 2021.



Smoking is a risk factor for DR progression in patients with type 1 diabetes

A meta-analysis revealed that smoking significantly increases the risk of DR in patients with type 1 diabetes (OR = 1.23, 95% CI: 1.14–1.33), whereas it appears to modestly decrease the risk in type 2 diabetes (OR = 0.92, 95% CI: 0.86–0.98).

These divergent findings suggest that distinct pathophysiological mechanisms underlie DR in type 1 versus type 2 diabetes, underscoring the need for tailored risk assessments and interventions.

References:

1. Cai X, *et al. Endocrine* 2018.

Diagnosis of Diabetic Retinopathy

SECTION

4

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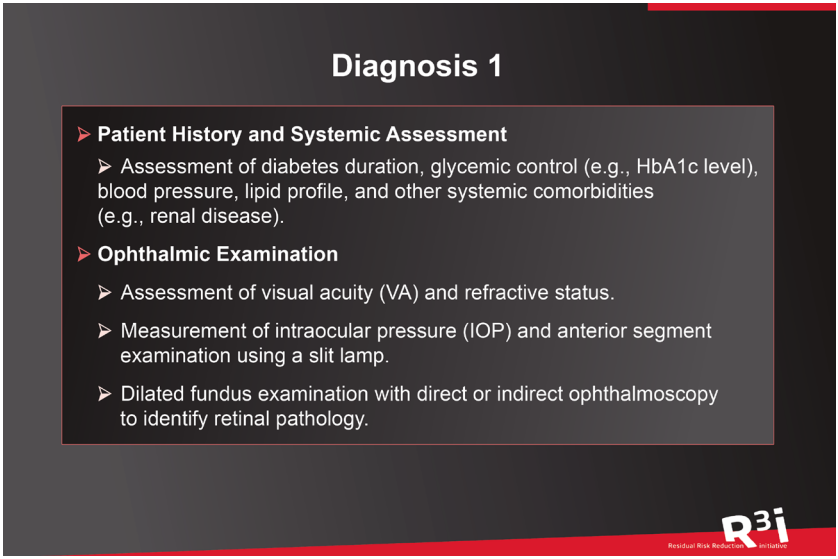
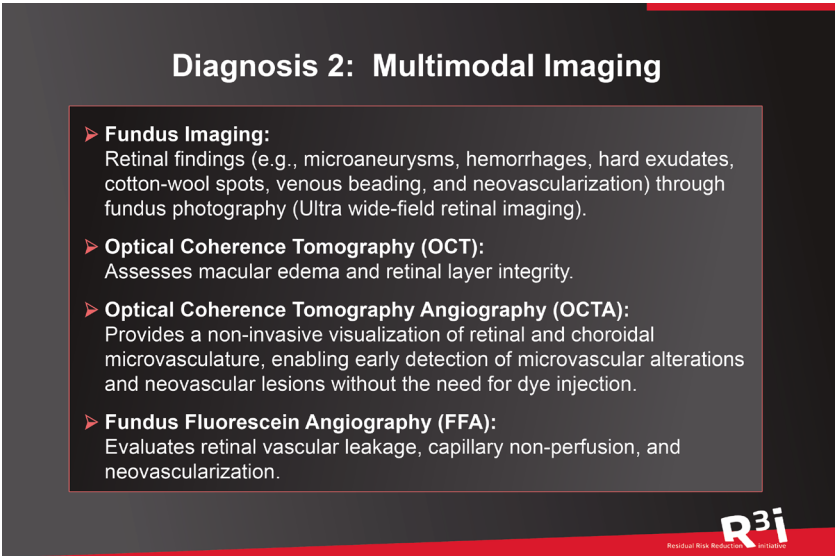


Diagnosis 1

This slide outlines the initial steps in diagnosing diabetic retinopathy. First, a thorough **patient history and systemic assessment** is conducted, focusing on the duration of diabetes, glycemic control (e.g., HbA1c levels), blood pressure, lipid profile, and comorbidities such as renal disease.

Next, an **ophthalmic examination** is performed, which includes measuring visual acuity (VA), assessing refractive status, and checking intraocular pressure (IOP) using a slit lamp to evaluate the anterior segment.

Finally, a **dilated fundus examination**—via direct or indirect ophthalmoscopy—allows detailed visualization of the retina to identify any pathological changes associated with diabetic retinopathy.



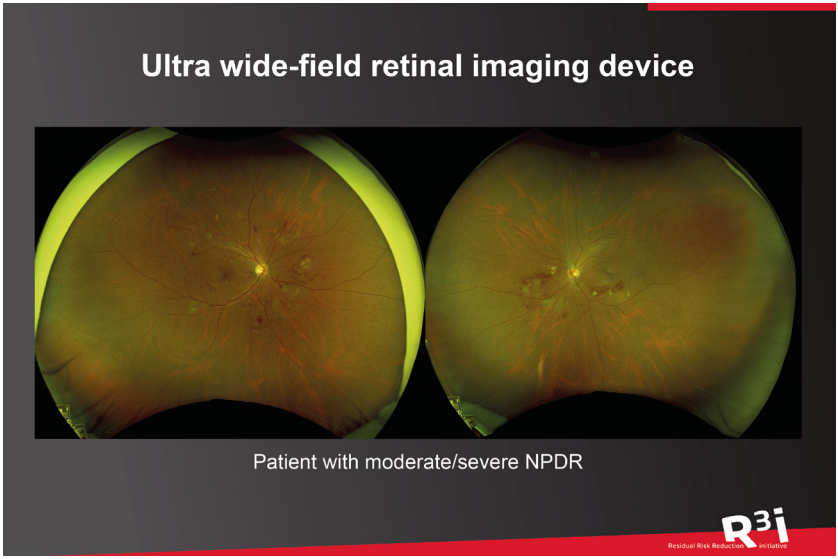
Diagnosis 2: Multimodal Imaging

Fundus photography detects characteristic lesions such as microaneurysms, hemorrhages, exudates, cotton-wool spots, venous beading, and neovascularization.

Optical Coherence Tomography (**OCT**) provides cross-sectional images of the retina to evaluate macular edema and overall retinal structure.

Optical Coherence Tomography Angiography (**OCTA**) offers a dye-free visualization of the retinal and choroidal microvasculature, enabling early detection of neovascular lesions.

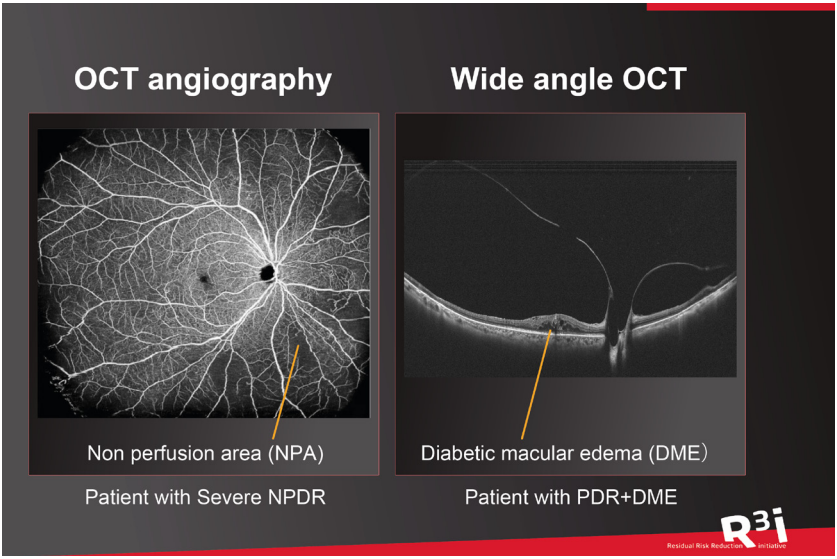
Finally, Fundus Fluorescein Angiography (**FFA**) uses fluorescein dye to identify vascular leakage, areas of non-perfusion, and neovascularization, thereby aiding in disease staging and management (but not necessary).



Ultra wide-field retinal imaging device

Patient with moderate/severe NPDR. There are many hemorrhages and soft exudates.

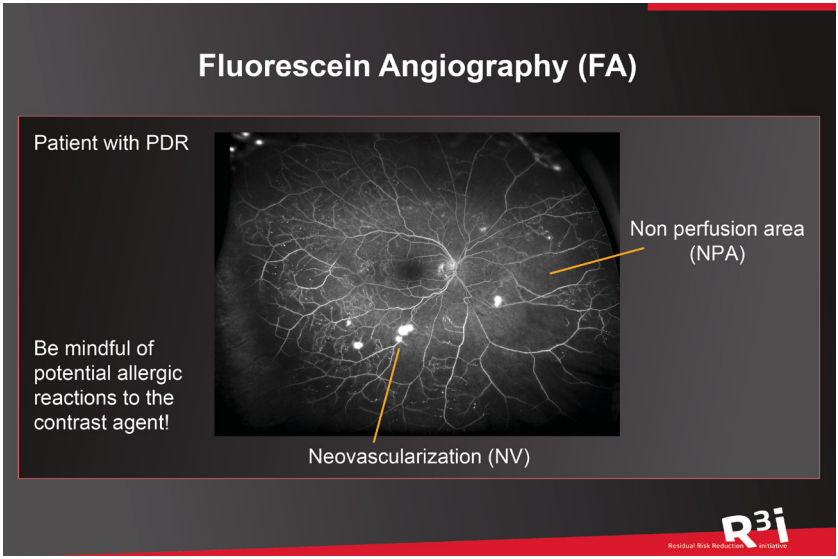
The image was processed using Image Enhancement Software (Soft-MIEr, Logic and Design Inc. Tokyo, Japan).



OCT angiography and wide angle OCT

(Left) Approximately 80° wide-angle OCTA images. In conditions such as diabetic retinopathy, it can detect peripheral vascular abnormalities (including non-perfusion areas and neovascularization).

(Right) Swept source (SS) OCT enables high-resolution imaging from the vitreous to the retina, choroid, and scleral boundary.

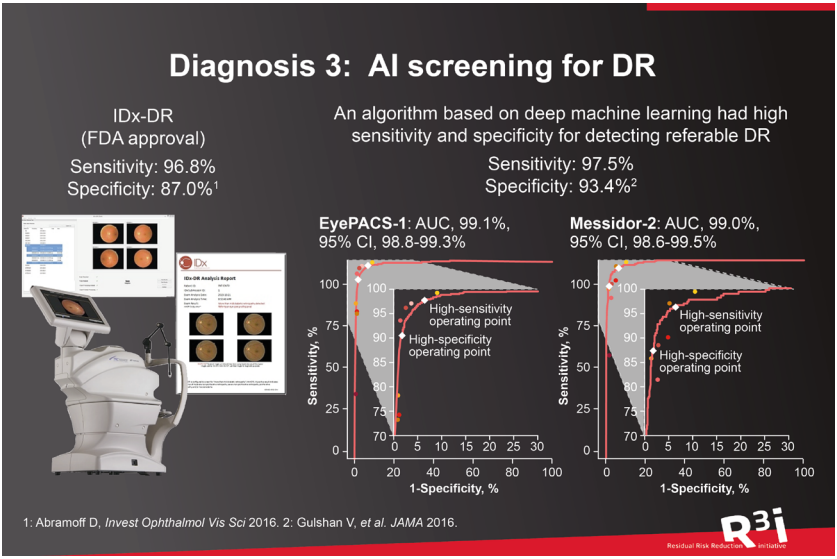


Fluorescein Angiography (FA)

If OCTA cannot be performed, fluorescein angiography (FAG) should be conducted.

This slide shows a fluorescein fundus angiogram of diabetic retinopathy, obtained using a wide-field fundus camera. The dark regions between the retinal vessels represent areas of capillary occlusion, known as non-perfusion areas.

In contrast, the bright white patches indicate substantial fluorescein leakage, suggesting the presence of retinal neovascularization.



Diagnosis 3: AI screening for DR

The IDx-DR system, which has received FDA approval, demonstrated a sensitivity of 96.8% and a specificity of 87.0%.

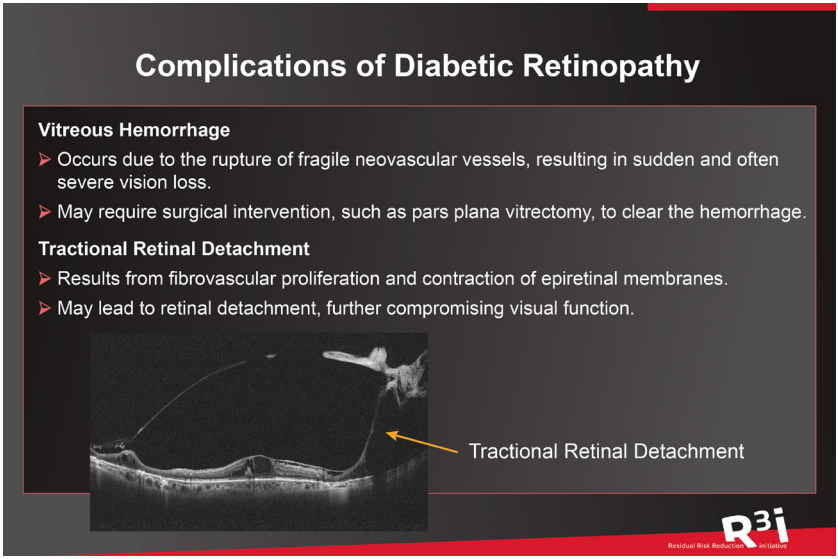
Another deep learning algorithm reported a sensitivity of 97.5% and a specificity of 93.4% for detecting referable DR.

These findings underscore the potential of AI-based methods to improve DR screening efficiency and accuracy, ultimately facilitating earlier intervention and better visual outcomes.

References:

1: Abramoff D, *Invest Ophthalmol Vis Sci* 2016.

2: Gulshan V, *et al. JAMA* 2016.

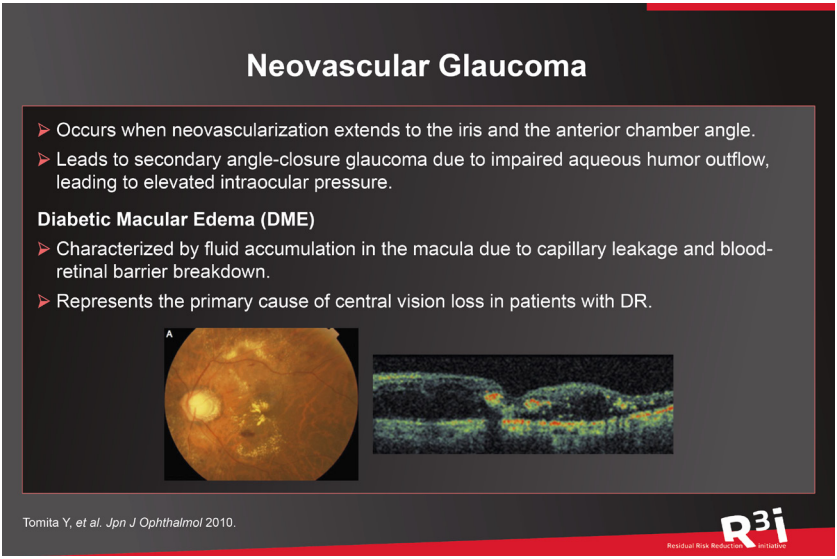


Complications of Diabetic Retinopathy

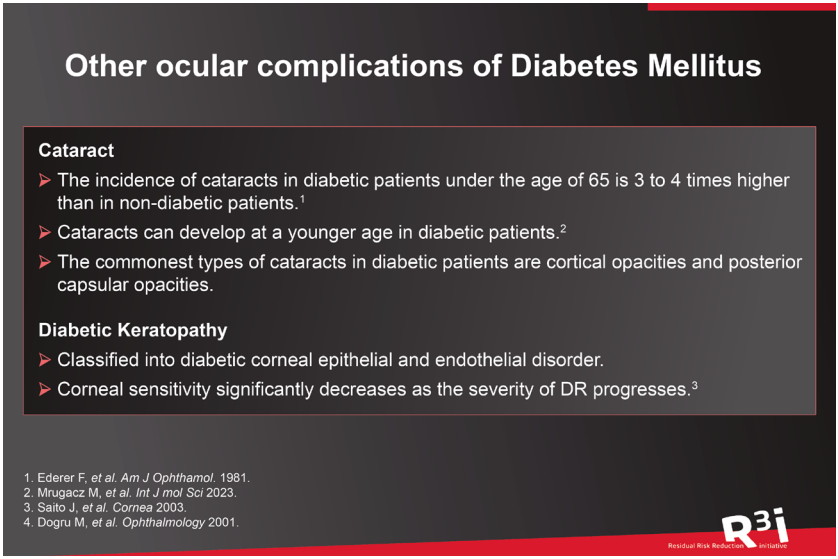
Vitreous hemorrhage arises from the rupture of fragile neovascular vessels, leading to sudden and often severe vision loss. Tractional retinal detachment occurs when fibrovascular proliferation within the preretinal membranes exerts traction on the retina, compromising visual function.

Neovascular glaucoma develops as newly formed vessels in the iris or angle obstruct aqueous outflow, causing intraocular pressure to rise and vision to deteriorate rapidly. Diabetic macular edema (DME) results from blood–retinal barrier breakdown and increased vascular permeability, leading to fluid accumulation in the macula and subsequent impairment of central vision.

If left untreated, each of these complications can cause irreversible vision loss, underscoring the importance of early detection and timely intervention.



Neovascular Glaucoma



Other ocular complications of Diabetes Mellitus

References:

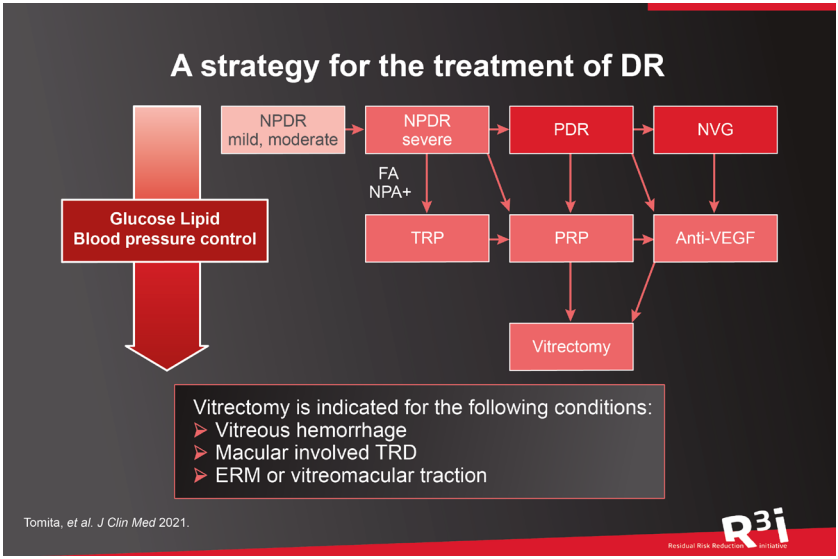
1. Ederer F, *et al. Am J Ophthamol.* 1981.
2. Mrugacz M, *et al. Int J mol Sci* 2023.
3. Saito J, *et al. Cornea* 2003.
4. Dogru M, e*t al. Ophthalmology* 2001.

Treatment and Management of Diabetic Retinopathy

SECTION

5

R3i
Residual Risk Reduction initiative



A strategy for the treatment of DR

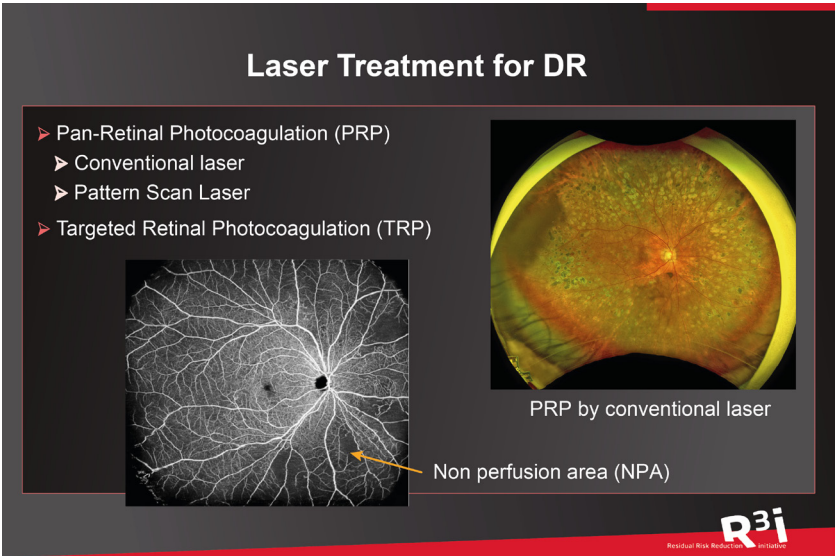
A flowchart illustrating the suggested treatment strategy for diabetic retinopathy (DR) without macular edema.

DR is classified into non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). NPDR is further divided into three subcategories: mild, moderate, and severe.

Maintaining optimal glucose, lipid levels, and blood pressure is crucial at all stages.

Abbreviations:

NPDR: non-proliferative diabetic retinopathy, DME: diabetic macular edema, TRP: targeted retinal photocoagulation, FA: fluorescein angiography, NPA: non-perfusion area, NVG: neovascular glaucoma.



Laser Treatment for DR

Pan-Retinal Photocoagulation (PRP)

- The main treatment for DR, reducing retinal neovascularization and the risk of vision loss.
- Recommended for severe NPDR to early PDR, based on ETDRS guidelines.
- Reduces the risk of severe vison loss by 50%
- Complications include peripheral visual field loss, delayed dark adaptation, atrophic creep.

Pattern Scan Laser

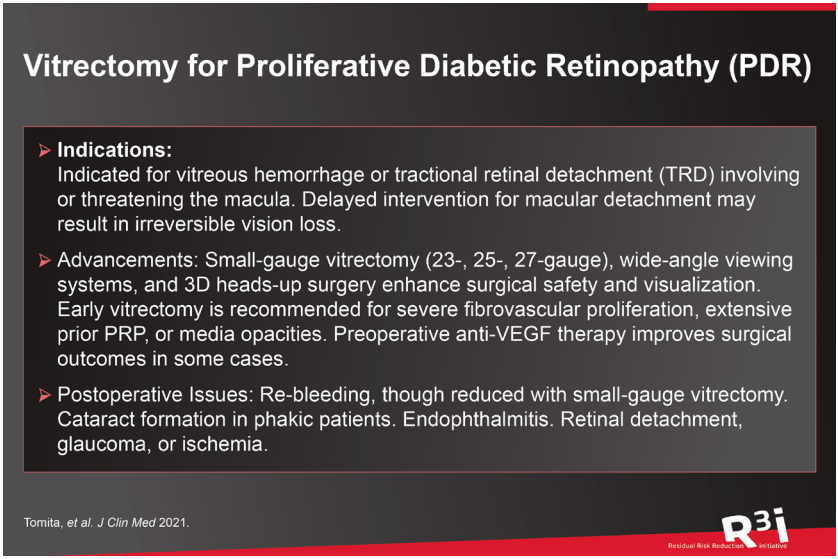
- Designed to minimize the side effects of PRP.
- Benefits include reduced nerve fiber layer damage, less pain, and shorter procedure time.

Targeted Retinal Photocoagulation (TRP) & NAVILAS

- A selective treatment for NPDR that slows the progression to PDR.
- Requires OCTA or fluorescein angiography (FA) to identify non-perfusion areas (NPA).

References:

1. Tomita, *et al. J Clin Med* 2021.



Vitrectomy for Proliferative Diabetic Retinopathy (PDR)

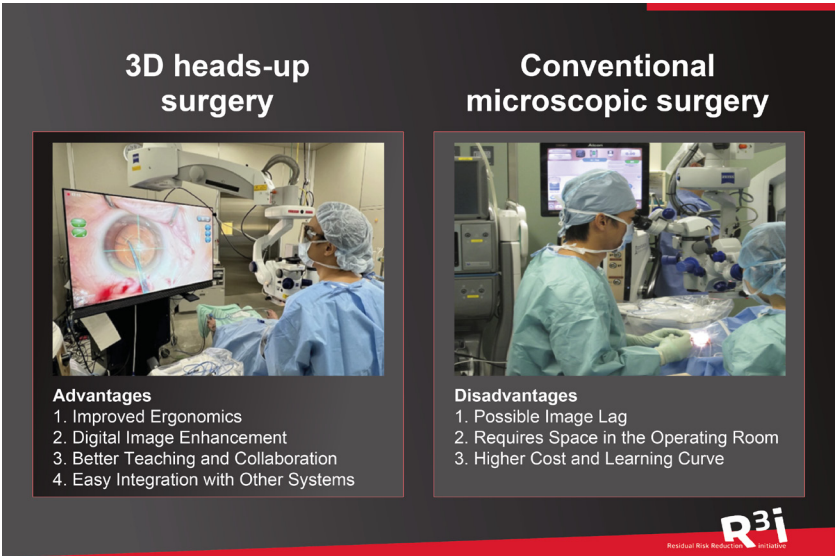
Vitrectomy is indicated for proliferative diabetic retinopathy (PDR) in cases of vitreous hemorrhage or tractional retinal detachment (TRD) involving or threatening the macula. Delayed intervention for macular detachment can result in permanent vision loss.

Recent advances include small-gauge vitrectomy (23-, 25-, or 27-gauge) and wide-angle viewing systems (e.g., Resight®), which enhance surgical safety and visualization. Early vitrectomy is recommended for severe fibrovascular proliferation, extensive prior PRP, or media opacities, and preoperative anti-VEGF therapy may improve surgical outcomes.

Potential complications include retinal detachment, re-bleeding, glaucoma, ischemia, cataract progression, and endophthalmitis. Despite these risks, timely vitrectomy often preserves or improves visual function in patients with advanced PDR.

References:

1. Tomita, *et al. J Clin Med* 2021.



3D heads-up surgery and conventional microscopic surgery

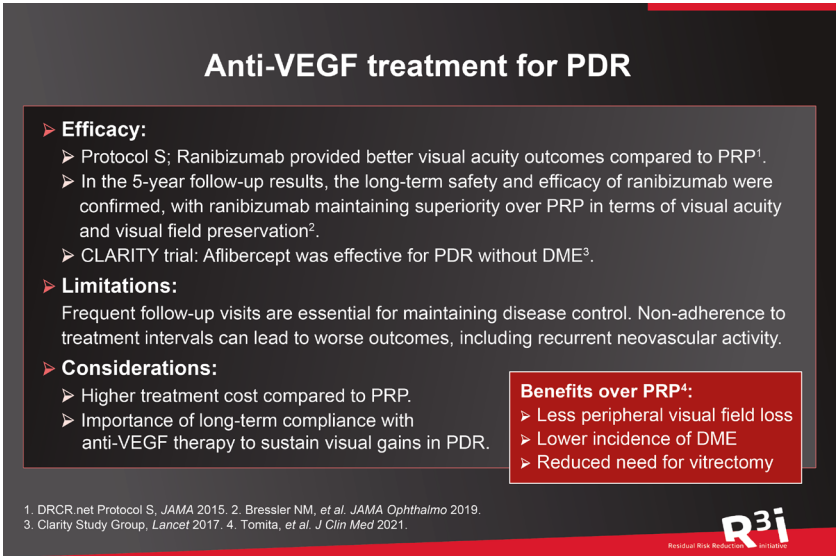
3D heads up surgery

Advantages

1. Improved Ergonomics: Surgeons can operate while viewing a 3D monitor at a comfortable angle, reducing neck and back strain.
2. Digital Image Enhancement: The system can adjust color balance, contrast, and magnification, potentially improving visualization of fine structures.
3. Better Teaching and Collaboration: Everyone in the operating room sees the same high-resolution, stereoscopic image on a large monitor, enhancing training and teamwork.
4. Easy Integration with Other Systems: Digital output facilitates recording, playback, and analysis, useful for documentation and educational purposes.

Disadvantages

1. Possible Image Lag: High-resolution 3D visualization may introduce slight delays, which can affect surgical precision.
2. Requires space in the operation room: The monitor is quite huge.
3. Higher Cost and Learning Curve: The equipment is expensive, and surgeons may require additional training to become proficient.



Anti-VEGF treatment for PDR

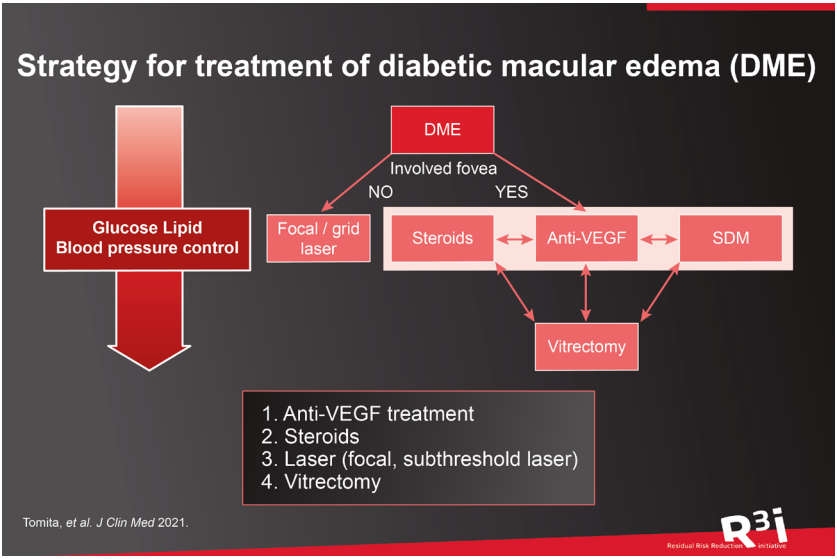
Anti-VEGF therapy for proliferative diabetic retinopathy (PDR) has demonstrated comparable or superior efficacy to panretinal photocoagulation (PRP).

In Protocol S, intravitreal ranibizumab showed improved visual outcomes, reduced peripheral visual field loss, and a lower incidence of diabetic macular edema (DME) compared to PRP.

The CLARITY trial found that aflibercept was also effective for PDR, even in the absence of DME. Although anti-VEGF therapy carries the advantages of fewer visual field defects and a reduced need for vitrectomy, its limitations include higher cost and the need for frequent follow-up. Adherence to treatment intervals is essential for maintaining control of neovascular activity.

References:

1. DRCR.net Protocol S, *JAMA* 2015.
2. Bressler NM, *et al. JAMA Ophthalmo* 2019.
3. Clarity Study Group, *Lancet* 2017.
4. Tomita, *et al. J Clin Med* 2021.



Strategy for treatment of diabetic macular edema (DME)

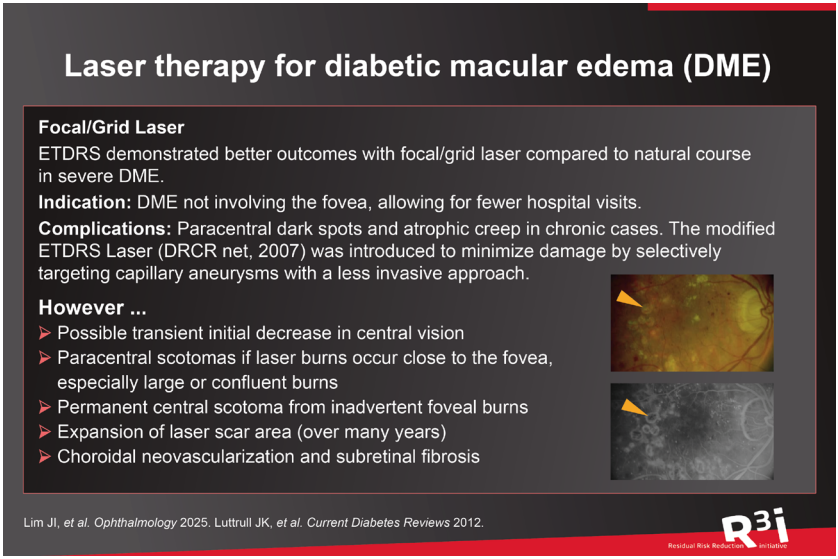
A flowchart illustrating the suggested treatment strategy for diabetic macular edema (DME). The treatment strategy is determined based on whether the edema involves the fovea.

Maintaining optimal glucose, lipid, and blood pressure levels is crucial at all stages.

Abbreviations:
SDM: subthreshold diode laser micropulse photocoagulation;
DME: diabetic macular edema.

References:

1. Tomita, *et al. J Clin Med* 2021.



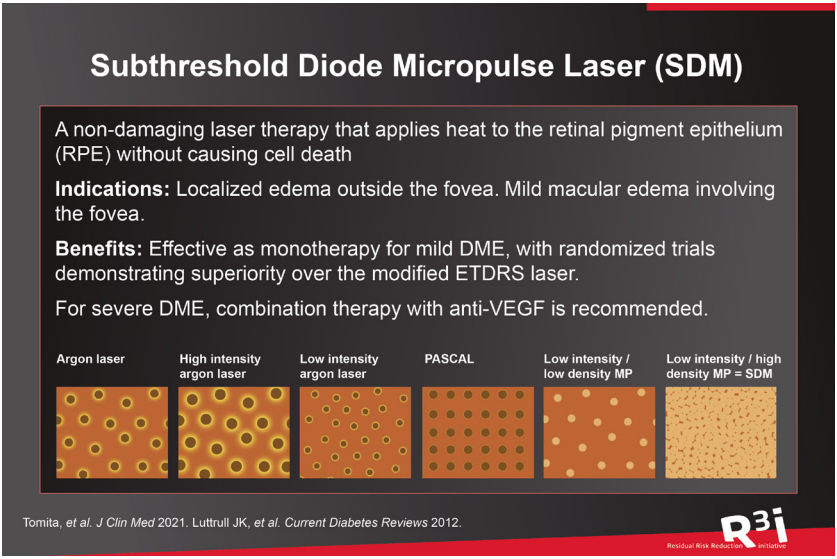
Laser therapy for diabetic macular edema (DME)

Focal or grid laser therapy (ETDRS-based) is effective for DME that does not involve the fovea, stabilizing or improving vision with fewer hospital visits.

Modified protocols reduce laser-induced scotomas and atrophic creep.

References:

1. Lim JI, *et al. Ophthalmology* 2025.
2. Luttrull JK, *et al. Current Diabetes Reviews* 2012.



Subthreshold Diode Micropulse Laser (SDM)

Subthreshold diode micropulse laser (SDM) targets the retinal pigment epithelium without damaging the neural retina, making it suitable for mild DME. For severe DME, combination therapy with anti-VEGF agents is recommended.

A–F. This figure illustrates the 'Effective Surface Area' achieved by various retinal laser treatment modalities for retinal vascular disease.

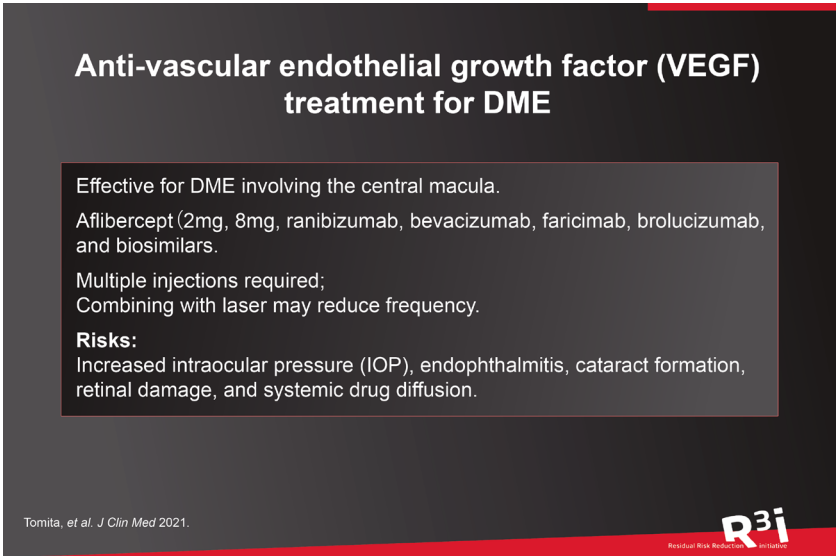
The vermillion (red) regions represent retina untouched by the laser, whereas the brown areas mark retinal tissue ablated by the laser and thus rendered inactive with respect to extracellular cytokine production.

The yellow regions indicate retina that is laser-affected but not destroyed, retaining the potential to support therapeutic outcomes through laser-induced modulation or normalization of cytokine expression.

PASCAL (pattern scanning laser), MP (diode micropulse laser), SDM (subthreshold/subvisible diode micropulse laser).

References:

1. Tomita, *et al. J Clin Med* 2021.
2. Luttrull JK, *et al. Current Diabetes Reviews* 2012.



Anti-vascular endothelial growth factor (VEGF) treatment for DME

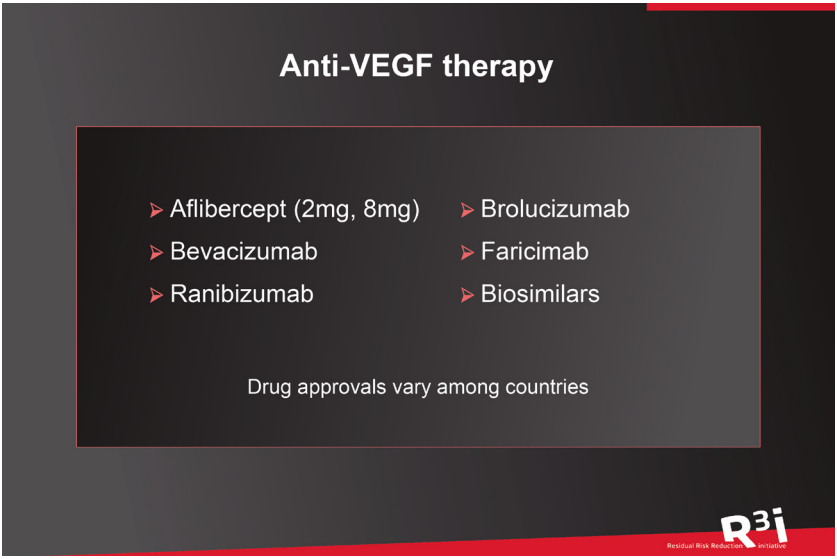
Anti-VEGF agents (aflibercept, ranibizumab, bevacizumab, faricimab, brolucizumab) are effective for center-involved diabetic macular edema, though multiple injections are typically required.

Combination with laser therapy may reduce injection frequency. Potential risks include elevated intraocular pressure, endophthalmitis, cataract formation, retinal damage, and systemic drug exposure.

Treatment selection should consider overall patient health, visual acuity, and central retinal thickness.

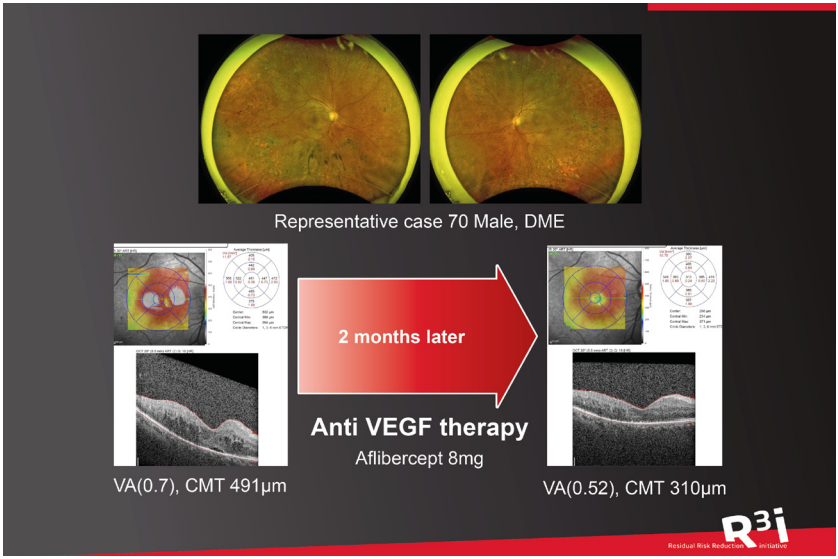
References:

1. Tomita, *et al. J Clin Med* 2021.



Anti-VEGF therapy

Multiple, high-quality clinical trials and systematic reviews have demonstrated that anti-VEGF therapy is more effective in improving vision in eyes with center involved (CI)-DME than monotherapy with focal laser surgery treatment, thus supplanting focal laser surgery as the first-line therapy.

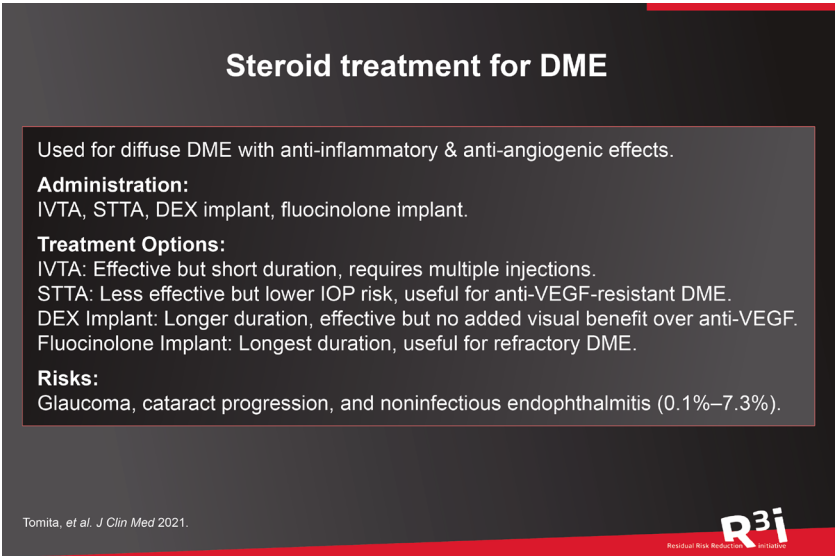


Anti-VEGF therapy

This slide shows a representative case of a 70-year-old male with diabetic macular edema (DME). At baseline, his best-corrected visual acuity (VA) was 0.7 and central macular thickness (CMT) measured 491 µm.

Two months after anti-VEGF therapy with aflibercept (8 mg), VA improved to 0.52, and CMT decreased to 310 µm.

These findings demonstrate both functional (VA) and structural (CMT) improvements, underscoring the effectiveness of anti-VEGF therapy in managing DME.



Steroid treatment for DME

Steroid therapy for diabetic macular edema (DME) provides anti-inflammatory and anti-angiogenic effects, particularly for diffuse DME.

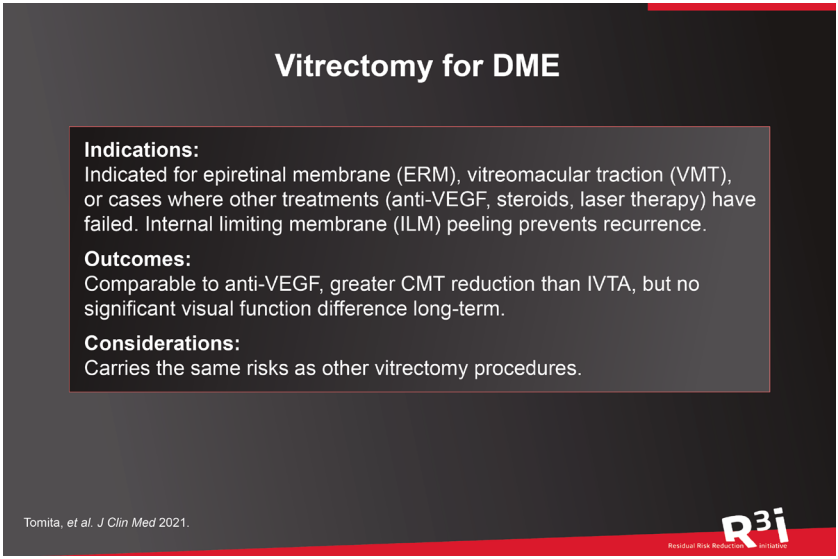
Common delivery methods include intravitreal triamcinolone (IVTA), sub-Tenon triamcinolone (STTA), and dexamethasone or fluocinolone implants.

Although these treatments can be effective—especially in refractory or anti-VEGF-resistant cases—they carry risks of elevated intraocular pressure, cataract progression, and noninfectious endophthalmitis.

Careful patient selection and close monitoring are essential to minimize complications.

References:

1. Tomita, *et al. J Clin Med* 2021.



Vitrectomy for DME

Vitrectomy for diabetic macular edema (DME) is primarily indicated when mechanical traction from an epiretinal membrane or vitreomacular traction is present, or when medical therapies (e.g., anti-VEGF, steroids) and laser treatment have failed.

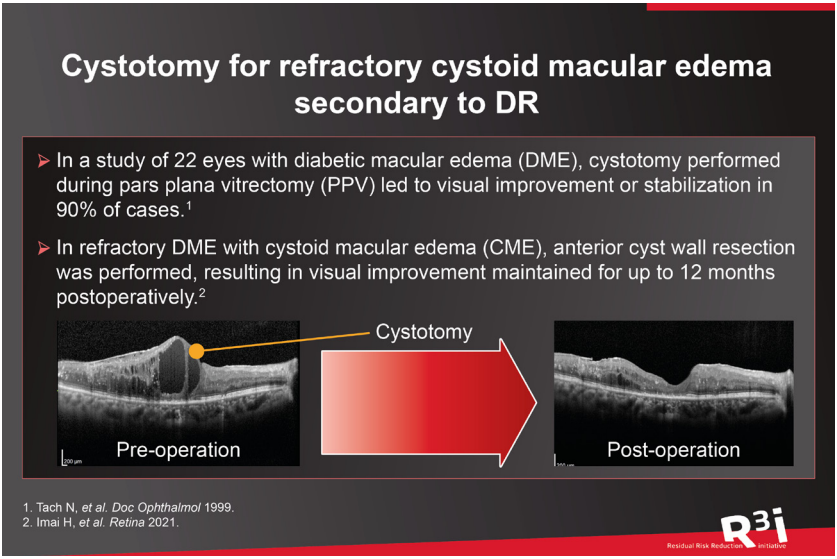
In such cases, pars plana vitrectomy (PPV) can relieve traction and reduce central macular thickness, often with inner limiting membrane (ILM) peeling to prevent recurrence.

While vitrectomy typically achieves rapid anatomical improvement, long-term visual outcomes may not significantly exceed those of intravitreal injections.

Patient selection is key, and standard surgical risks—such as cataract progression, retinal breaks, and endophthalmitis—must be considered.

References:

1. Tomita, *et al. J Clin Med* 2021.



Cystotomy for refractory cystoid macular edema secondary to DR

This procedure is performed for refractory DME that does not respond to anti-VEGF therapy, laser treatment, or conventional vitrectomy.

In some cases, an additional procedure to remove fibrinogen may be included.

Although current reports are retrospective and based on a small number of cases, the effectiveness is promising, and further prospective studies are warranted.

References:

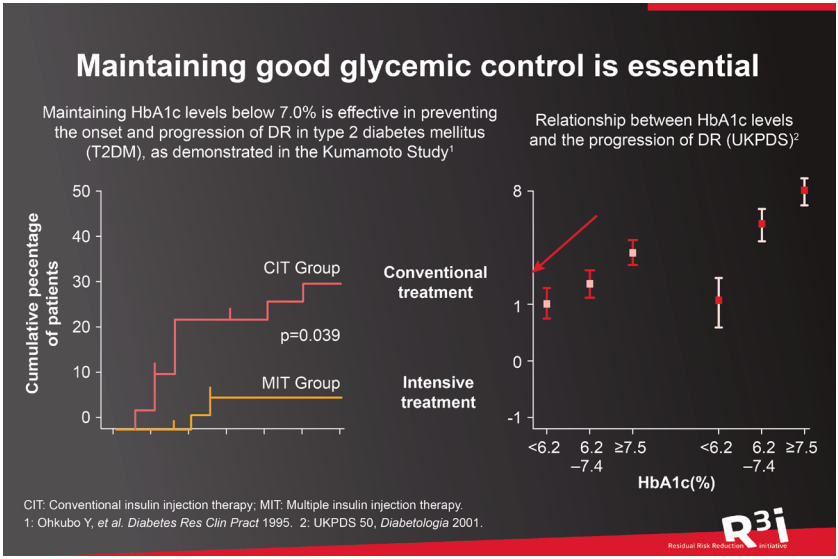
1. Tach N, *et al. Doc Ophthalmol* 1999.
2. Imai H, *et al. Retina* 2021.

Prevention of Diabetic Retinopathy and Future Treatments

SECTION

6

Residual Risk Reduction initiative



Maintaining good glycemic control is essential

It is well known that long-term glycemic control suppresses the progression of diabetic retinopathy (DR). One of the key studies supporting this evidence is the *Kumamoto Study* from Japan.

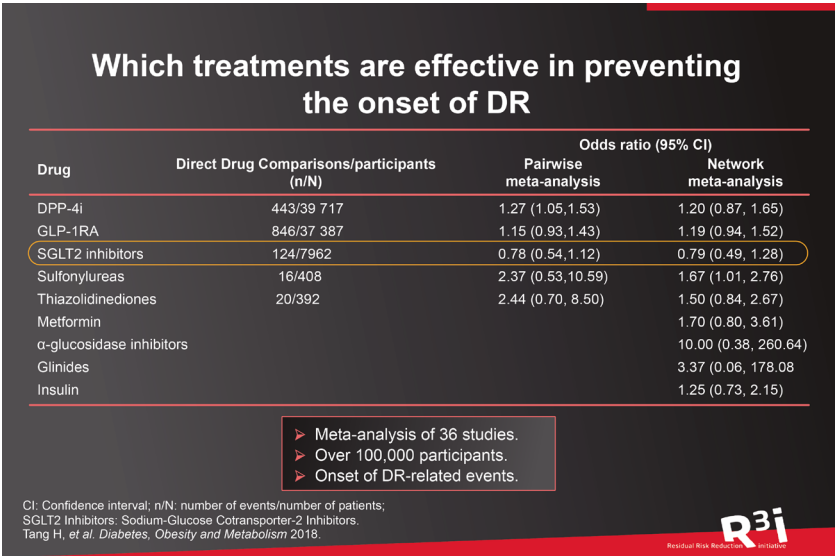
This study demonstrated that, in patients with type 2 diabetes mellitus (T2DM), an intensive insulin therapy group maintaining HbA1c below 7% had a significantly lower risk of DR progression compared to those receiving conventional therapy.

Additionally, the study reported a significant reduction in major vascular events. Furthermore, a report from the UK also showed that an increase in HbA1c levels is associated with a higher risk of DR progression.

The relationship between blood glucose levels and DR is well established, and it is generally accepted that the lower the HbA1c level, the lower the risk of both the onset and progression of DR.

References:

1. Ohkubo Y, *et al. Diabetes Res Clin Pract* 1995.
2. UKPDS 50, *Diabetologia* 2001.



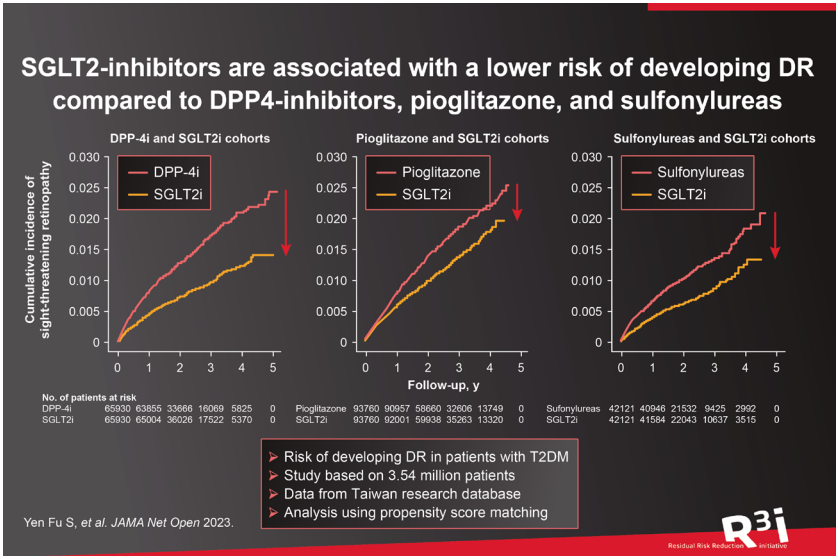
Which treatments are effective in preventing the onset of DR

This **meta-analysis of 36 studies** with **over 100,000 participants** examines the impact of glucose-lowering drugs on **diabetic retinopathy (DR) onset.**

- **SGLT2 inhibitors** show a potential reduction in DR risk (**OR: 0.78–0.79**), but the effect is not statistically significant.
- **Sulfonylureas and thiazolidinediones** may increase DR risk, while **DPP-4 inhibitors, GLP-1 receptor agonists, and insulin** show no significant impact.
- Findings suggest **SGLT2 inhibitors might be beneficial,** but further research is needed to confirm their protective role.

References:

1. Tang H, *et al. Diabetes, Obesity and Metabolism* 2018.



SGLT2-inhibitors are associated with a lower risk of developing DR compared to DPP4-inhibitors, pioglitazone, and sulfonylureas

Yen *et al.* analyzed data from **3.54 million T2DM patients** in Taiwan's NHI database, showing that **SGLT2 inhibitors lower the risk of sight-threatening DR** compared to DPP-4 inhibitors, pioglitazone, and sulfonylureas.

Proposed Mechanisms for DR Risk Reduction:

1. Improved **retinal neurovascular coupling and microcirculation**
2. **Suppression of endothelial cell apoptosis**

Study Strengths:

- **Large-scale population data** (95% coverage in Taiwan) minimizing selection bias
- **Robust statistical power** with a large DR case count
- **Sufficient follow-up period** to track DR development

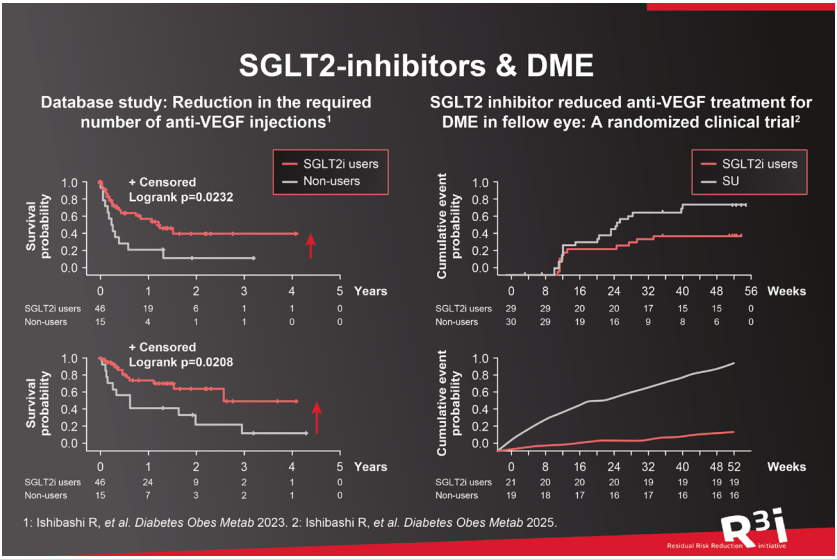
Limitations:

- **Lack of lifestyle factors** (family history, smoking, alcohol, activity)
- **Limited retinal exam data** (fundus, FA, OCT)
- **Ethnic generalizability concerns** (mainly Taiwanese cohort)

These findings suggest **SGLT2 inhibitors may help prevent DR,** but further global studies are needed.

Abbreviations: DPP4i: Dipeptidyl Peptidase-4 Inhibitor, SGLT2i: Sodium-Glucose Cotransporter 2 Inhibitor

References: 1. Yen Fu S, *et al. JAMA Net Open* 2023.



SGLT2-inhibitors & DME

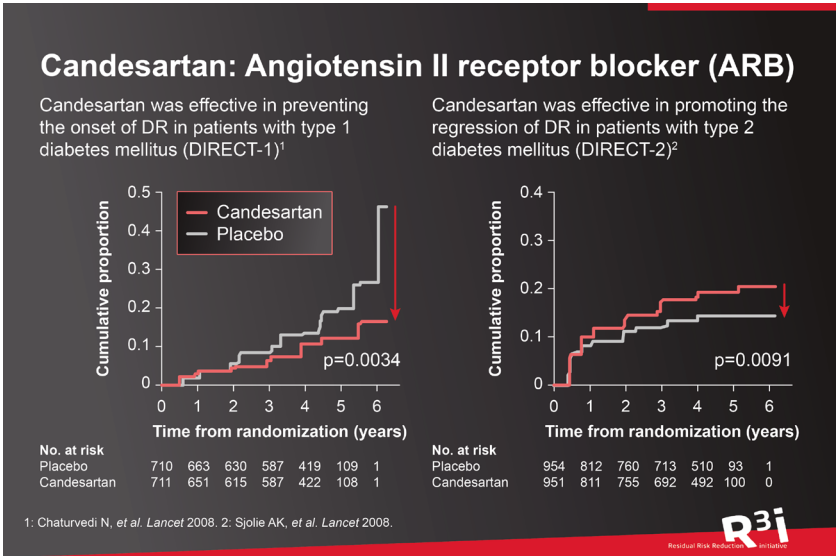
A real-world analysis was conducted using a database from JMDC (Japan Medical Data Center), which aggregates health insurance claims and medical checkup data. This study extracted data with type 2 diabetes who had received anti-VEGF therapy for DME and divided them into two groups based on SGLT2 inhibitor use.

The analysis revealed that patients using SGLT2 inhibitors required fewer anti-VEGF injections, suggesting a potential role for these drugs as a novel treatment option for DME. They also conducted a randomized clinical trial evaluating the use of ranibizumab in combination with luseogliflozin for diabetic macular edema (DME) in patients with type 2 diabetes.

Readministration rates were decreased significantly at the fourth injection in the SGLT2i group ($p = 0.030$, hazard ratio: 0.45, 95% CI 0.22–0.92) (upper right). Additionally, fellow eyes in the SGLT2i group showed fewer injections compared with those in the SU group (1.3 ± 0.6 vs. 3.4 ± 0.8, $p = 0.016$) (lower right).

References:

1. Ishibashi R, *et al. Diabetes Obes Metab* 2023.
2. Ishibashi R, *et al. Diabetes Obes Metab* 2025.



Candesartan: Angiotensin II receptor blocker (ARB)

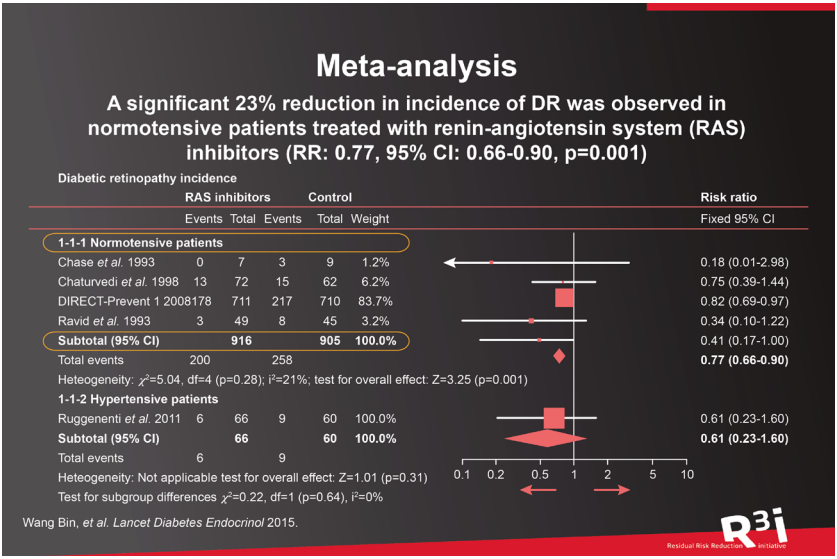
This slide presents findings from the DIRECT studies, which examined the effects of candesartan, an angiotensin II receptor blocker (ARB), on diabetic retinopathy (DR). The results indicate:

- **DIRECT-1 (Left graph):** In patients with type 1 diabetes mellitus, candesartan was effective in preventing the onset of DR compared to placebo.
- **DIRECT-2 (Right graph):** In patients with type 2 diabetes mellitus, candesartan promoted the regression of DR, suggesting a potential role in reversing retinal damage.

These findings suggest that candesartan may have both preventative and therapeutic benefits in diabetic retinopathy without significant adverse effects compared to placebo.

References:

1. Chaturvedi N, *et al. Lancet* 2008.
2. Sjolie AK, *et al. Lancet* 2008.



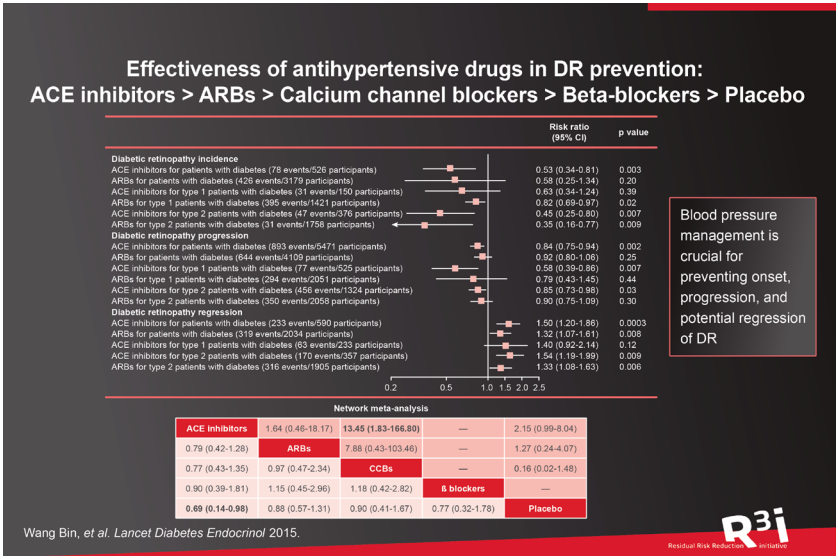
Meta-analysis

This meta-analysis evaluates the effect of renin-angiotensin system (RAS) inhibitors on diabetic retinopathy (DR) incidence. The results indicate a significant 23% reduction in DR incidence among normotensive patients treated with RAS inhibitors (RR: 0.77, 95% CI: 0.66–0.90, p=0.001). However, in hypertensive patients, no significant effect on DR incidence was observed.

These findings suggest a potential DR-preventive effect of RAS inhibitors independent of blood pressure reduction. These findings suggest that RAS inhibition suppresses the progression of DR through mechanisms beyond blood pressure control.

References:

1. Wang Bin, *et al. Lancet Diabetes Endocrinol* 2015.



Effectiveness of antihypertensive drugs in DR prevention: ACE inhibitors > ARBs > Calcium channel blockers > Beta-blockers > Placebo

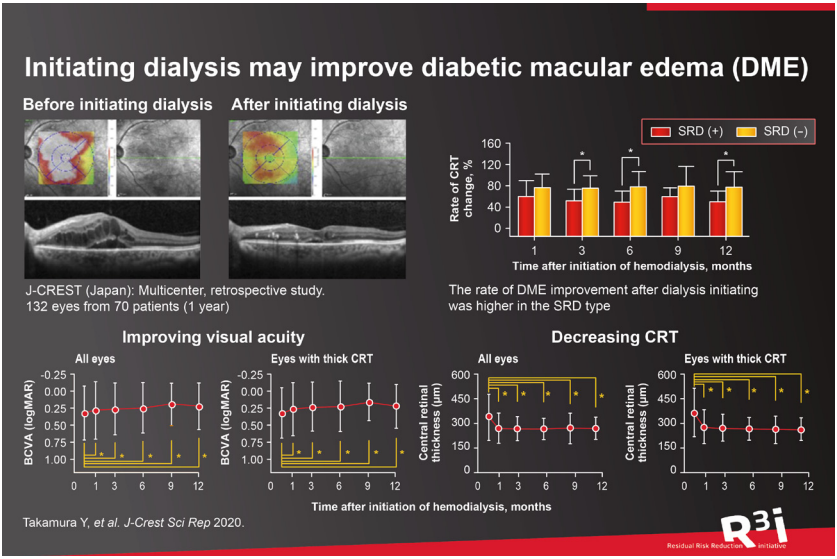
This slide presents a meta-analysis and network meta-analysis evaluating the effectiveness of antihypertensive drugs in preventing diabetic retinopathy (DR). Key findings include:

1. **ACE inhibitors and ARBs** have been consistently shown to reduce the incidence and progression of DR.
2. **Network meta-analysis** suggests that **ACE inhibitors are the most effective** in DR prevention, followed by ARBs, calcium channel blockers, and beta-blockers.
3. **Blood pressure management is crucial** not only for preventing DR onset but also for its progression and potential regression.
4. **Network meta-analysis methodology** allows for both direct and indirect comparisons between different treatment options, providing a comprehensive evaluation of their relative efficacy.

These results highlight the importance of **ACE inhibitors and ARBs** in DR management, supporting their use as first-line antihypertensive agents for diabetic patients at risk of DR.

References:

1. Wang Bin, *et al. Lancet Diabetes Endocrinol* 2015.



Initiating dialysis may improve diabetic macular edema (DME)

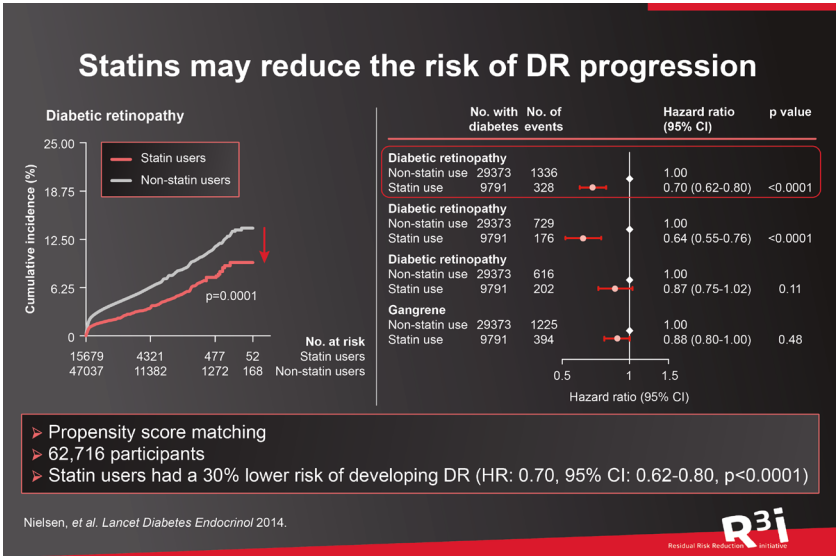
This study from J-CREST (Japan) investigated the impact of initiating dialysis on diabetic macular edema (DME). A retrospective analysis of 132 eyes from 70 patients over one year demonstrated improvements in visual acuity and a significant reduction in central retinal thickness (CRT) after dialysis initiation. Notably, the improvement rate was higher in patients with the serous retinal detachment (SRD) type of DME.

The findings suggest that systemic factors, particularly renal function and fluid regulation via dialysis, play a crucial role in DME pathophysiology.

These results highlight the strong link between kidney function and diabetic retinopathy.

References:

1. Takamura Y, *et al. J-Crest Sci Rep* 2020.



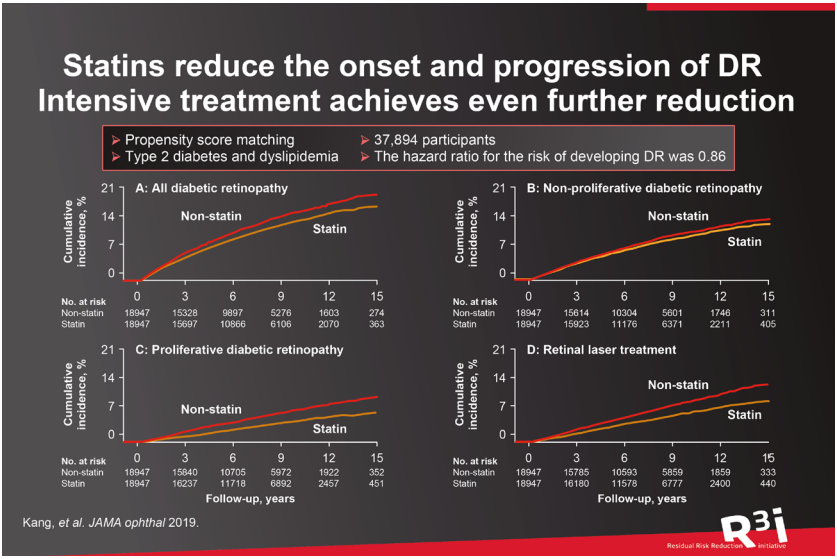
Statins may reduce the risk of DR progression

This slide suggests that statin use may reduce the risk of diabetic retinopathy (DR) progression. Based on a Danish registry study using propensity score matching, the analysis showed that statin users had a 30–40% lower risk of developing DR (HR: 0.70, 95% CI: 0.62-0.80, p<0.0001).

This study suggests that statins may contribute to DR prevention and progression delay, potentially due to their anti-inflammatory and vascular protective effects.

References:

1. Nielsen, *et al. Lancet Diabetes Endocrinol* 2014.



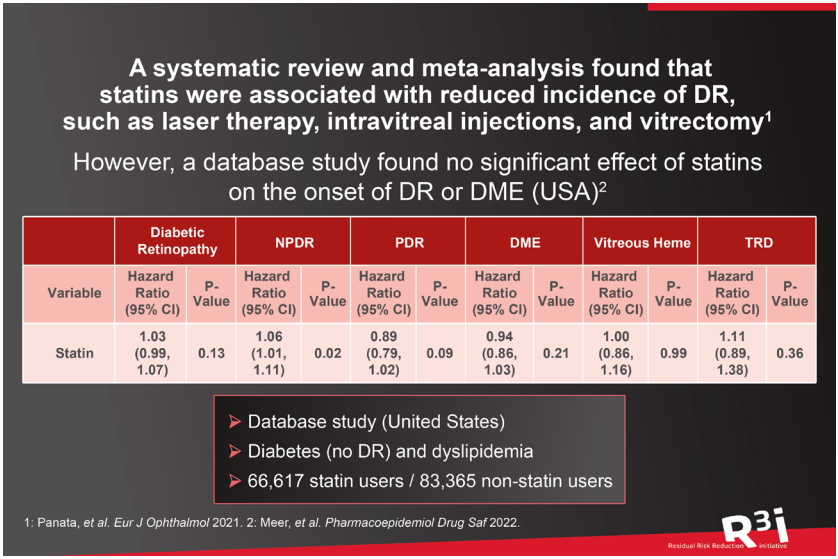
Statins reduce the onset and progression of DR

This figure illustrates the cumulative incidence of diabetic retinopathy (DR) in patients with type 2 diabetes and dyslipidemia, comparing statin users with non-users over a 15-year follow-up period. Data were derived from a cohort of 37,894 individuals using propensity score matching. Statin use was associated with a significant reduction in the onset and progression of DR, as well as in the need for retinal laser treatment.

Figure A shows the cumulative incidence of any diabetic retinopathy. Statin users had a significantly lower incidence compared to non-users (Hazard Ratio [HR], 0.86; 95% Confidence Interval [CI], 0.81–0.91; $P < 0.001$).
Figure B demonstrates the incidence of nonproliferative diabetic retinopathy. Statin therapy was associated with a modest but statistically significant reduction in risk (HR, 0.92; 95% CI, 0.86–0.99; $P = 0.03$).
Figure C presents the incidence of proliferative diabetic retinopathy. Statin users showed a markedly lower risk compared to non-users (HR, 0.64; 95% CI, 0.58–0.70; $P < 0.001$), indicating a robust protective effect against severe retinal disease.
Figure D shows the cumulative incidence of retinal laser treatment, an indicator of advanced diabetic retinopathy. Statin use was associated with a significantly reduced need for such intervention (HR, 0.71; 95% CI, 0.65–0.77; $P < 0.001$).

These findings suggest that statins not only reduce the risk of cardiovascular events in patients with diabetes but may also confer a protective effect against the development and progression of diabetic retinopathy.

References: 1. Kang, *et al. JAMA ophthal* 2019.



	Diabetic Retinopathy		NPDR		PDR		DME		Vitreous Heme		TRD	
Variable	Hazard Ratio (95% CI)	P-Value	Hazard Ratio (95% CI)	P-Value	Hazard Ratio (95% CI)	P-Value	Hazard Ratio (95% CI)	P-Value	Hazard Ratio (95% CI)	P-Value	Hazard Ratio (95% CI)	P-Value
Statin	1.03 (0.99, 1.07)	0.13	1.06 (1.01, 1.11)	0.02	0.89 (0.79, 1.02)	0.09	0.94 (0.86, 1.03)	0.21	1.00 (0.86, 1.16)	0.99	1.11 (0.89, 1.38)	0.36

A systematic review and meta-analysis found that statins were associated with reduced incidence of DR, such as laser therapy, intravitreal injections, and vitrectomy

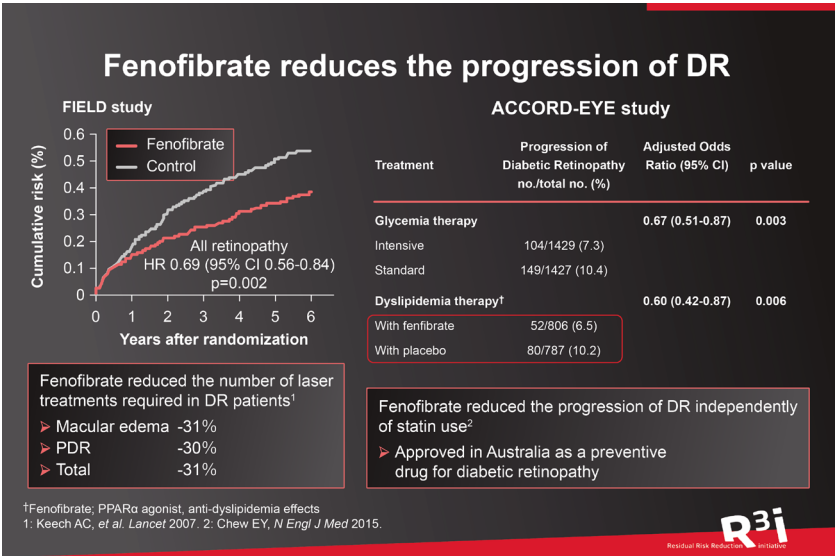
A systematic review and meta-analysis by Panata *et al. Eur. J. Ophthalmol* 2021, demonstrated that statin use was associated with a reduced incidence of diabetic retinopathy (DR) and its complications, including the need for laser photocoagulation, intravitreal injections, and vitrectomy. These findings support a potential protective role of statins in DR progression.

However, a large-scale database study conducted in the United States, Meer *et al. Pharmacoepidemiol Drug Saf* 2022, reported no significant association between statin use and the onset or severity of DR or diabetic macular edema (DME). The study included 66,617 statin users and 83,365 non-users, all with diabetes and dyslipidemia but no prior history of DR at baseline.

As shown in the table, the hazard ratio (HR) for developing any diabetic retinopathy among statin users was 1.03 (95% CI, 0.99–1.07; P = 0.13), indicating no significant difference. While a statistically significant increase was observed for nonproliferative DR (HR, 1.06; 95% CI, 1.01–1.11; P = 0.02), no significant associations were found for proliferative DR, DME, vitreous hemorrhage, or tractional retinal detachment.

These discrepant findings highlight the need for further research to clarify the role of statins in DR prevention, particularly considering differences in study design, population characteristics, and confounding factors.

References: 1. Panata, *et al. Eur J Ophthalmol* 2021.
2. Meer, *et al. Pharmacoepidemiol Drug Saf* 2022.



Fenofibrate reduces the progression of DR

Large-scale clinical trials, including the FIELD and ACCORD studies, have demonstrated that fenofibrate reduces the need for laser treatment and slows the progression of diabetic retinopathy (DR), independent of statin use. These findings led to its approval in Australia as a preventive drug for DR.

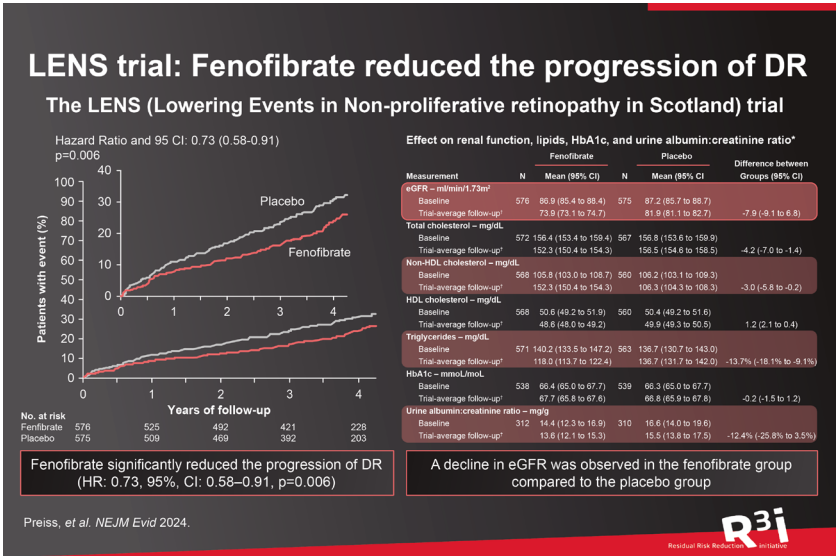
Fenofibrate, a fibrate-class lipid-lowering agent, has gained sustained attention due to its potential protective effects on DR. The FIELD study (2007) first highlighted its benefits, showing that fenofibrate reduced the risk of laser treatments for DR as a secondary outcome. However, variations in statin use among participants raised concerns.

The ACCORD-EYE study was conducted to address this issue, specifically analyzing fenofibrate's effects in patients already on statin therapy. The results confirmed that fenofibrate independently suppressed DR progression.

These findings have since spurred extensive research into the underlying mechanisms using animal and cellular models. As a result, fenofibrate is now prescribed in Australia for DR prevention.

References:

1. Keech AC, *et al. Lancet* 2007.
2. Chew EY, *N Engl J Med* 2015.



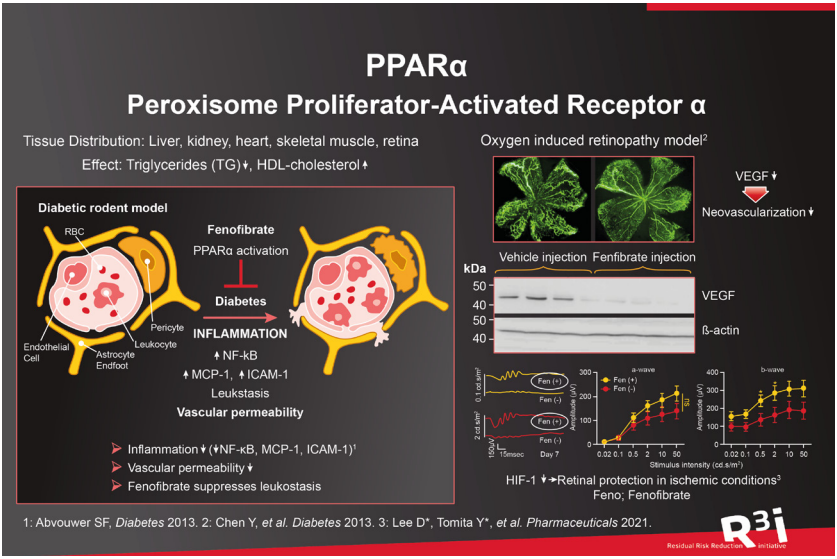
LENS trial: Fenofibrate reduced the progression of DR

Recently, clinical trials specifically designed to investigate the ocular effects of fenofibrate have also demonstrated that fenofibrate reduced the progression of DR.

However it also showed that fenofibrate reduced renal function, so it's challenging to use it for DR patients with dysfunction of kidney.

References:

1. Preiss, *et al. NEJM Evid* 2024.



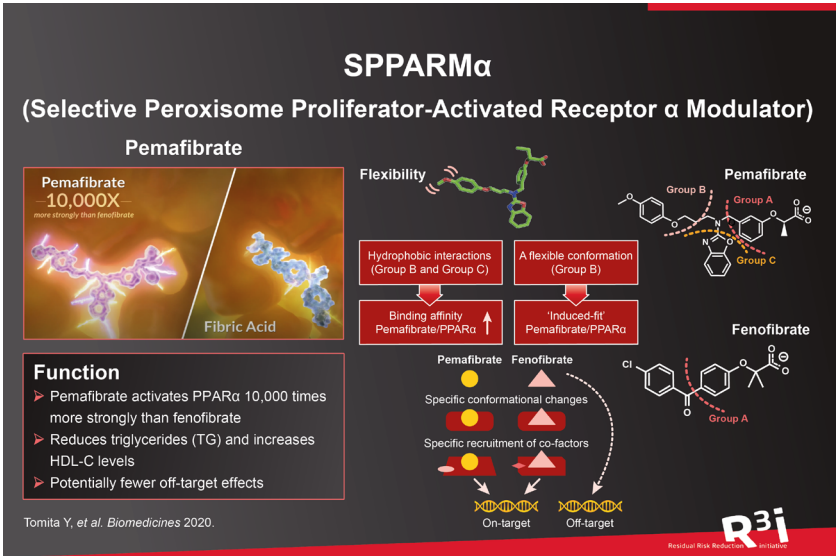
PPARα
Peroxisome Proliferator-Activated Receptor α

Fenofibrate activates peroxisome proliferator-activated receptor alpha (PPARα), which is expressed in many tissues. It lowers serum triglycerides and increases HDL cholesterol. Several studies have demonstrated that fenofibrate reduces inflammation and vascular permeability in the retinas of diabetic mouse models.

Fenofibrate also exerts anti-angiogenic effects by suppressing VEGF, a key mediator of pathological neovascularization in the retina. Previously, our group showed that fenofibrate protected the retina from ischemia by downregulating hypoxia-inducible factor-1 (HIF-1), a key regulator of VEGF.

References:

1. Abvouwer SF, *Diabetes* 2013.
2. Chen Y, *et al. Diabetes* 2013.
3. Lee D*, Tomita Y*, *et al. Pharmaceuticals* 2021.



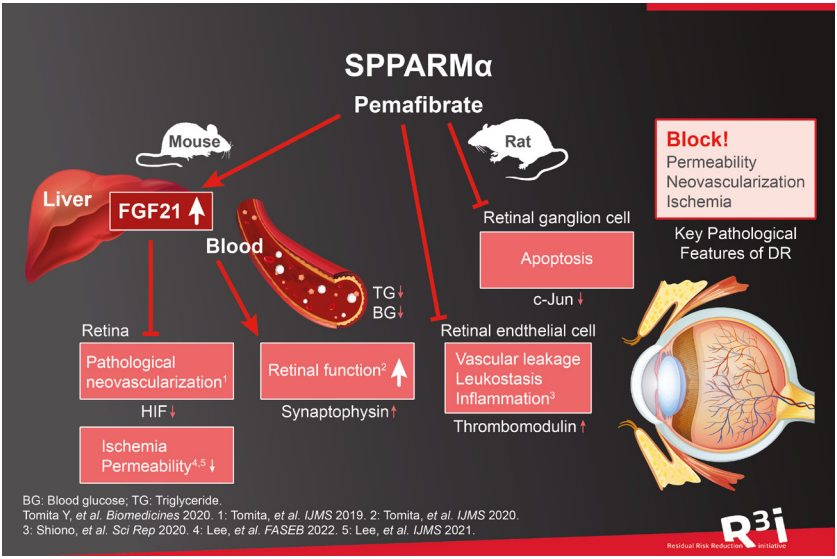
SPPARMα (Selective Peroxisome Proliferator-Activated Receptor α Modulator)

This slide highlights **pemafibrate**, a **selective PPARα modulator** (**SPPARMα**) approved in Japan for dyslipidemia management. Its unique molecular structure enables it to activate PPARα up to **10,000 times more potently** than fenofibrate.

As a result, pemafibrate l**owers serum triglycerides and increases HDL cholesterol** while having **fewer off-target effects,** thereby potentially reducing adverse events compared to conventional fibrates.

References:

1. Tomita Y, *et al. Biomedicines* 2020.



SPPARMα
Pemafibrate

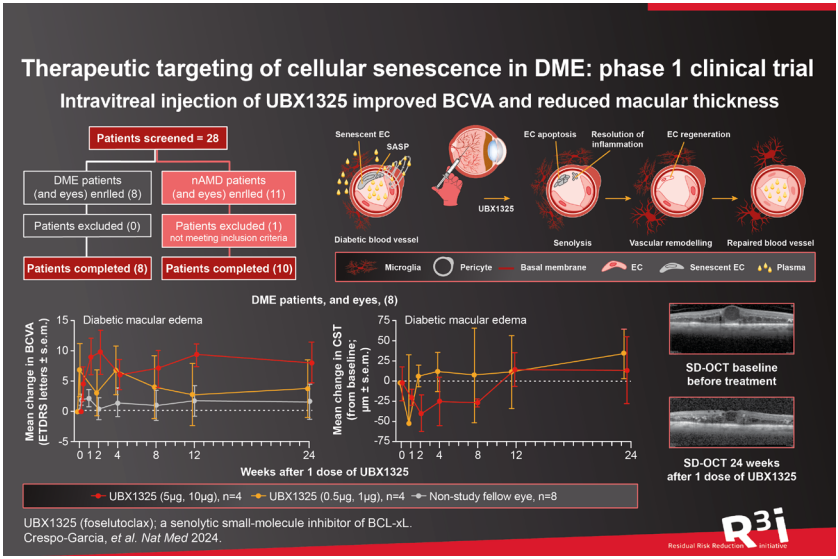
This slide illustrates **pemafibrate's** potential to block three key pathological processes in diabetic retinopathy: **vascular permeability, neovascularization, and ischemia.** Pemafibrate elevated **FGF21 levels**, which helped **prevent pathological neovascularization,** reduce **retinal ischemia,** and **maintain retinal function.**

Another group similarly reported that pemafibrate suppressed **vascular leakage, inflammation,** and **apoptosis** in a rat model.

These findings collectively suggest that pemafibrate effectively targets multiple pathways involved in DR progression.

References:

Tomita Y, *et al. Biomedicines* 2020.
1. Tomita, *et al. IJMS* 2019.
2. Tomita, *et al. IJMS* 2020.
3. Shiono, *et al. Sci Rep* 2020.
4. Lee, *et al. FASEB* 2022.
5. Lee, *et al. IJMS* 2021.



Therapeutic targeting of cellular senescence in DME: phase 1 clinical trial

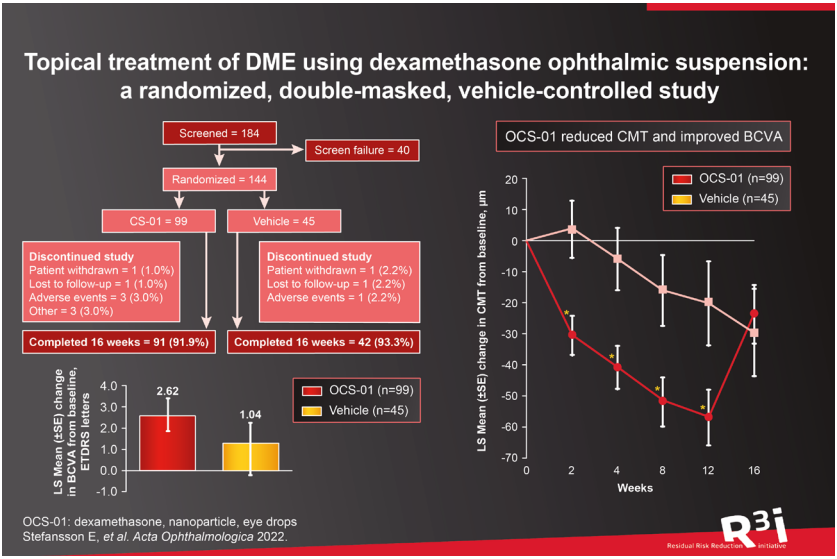
(**A**) Patient Flow Diagram.
A total of 28 patients were screened. Of these, 8 patients with diabetic macular edema (DME) each received a single intravitreal injection of UBX1325. Best-corrected visual acuity (BCVA; C) and central subfield thickness (CST; D) were measured (mean ± s.e.m.) over a 24-week follow-up period. CST data reflect measurements in the study eye only, as a standardized central reading was not performed for the fellow eye.

(**B**) Representative SD-OCT Imaging.
Shown here are baseline (top) and 24-week (bottom) SD-OCT images from a patient who demonstrated a 108-µm reduction in CST and an 11-letter improvement in BCVA (ETDRS) by the end of the study.

(**E**) Schematic of the Senescence Hypothesis in DME.
During diabetes, senescent endothelial cells (ECs) accumulate in retinal vessels, perpetuating microinflammation and blood–retina barrier (BRB) breakdown, ultimately compromising visual function. UBX1325, a small-molecule BCL-xL inhibitor, selectively eliminates these senescent cells (senolysis), thereby promoting vascular remodeling and restoration of retinal integrity.

References:

1. Crespo-Garcia, *et al. Nat Med* 2024.



Topical treatment of DME using dexamethasone ophthalmic suspension: a randomized, double-masked, vehicle-controlled study

Study Design:

- **Objective:** To evaluate the efficacy of OCS-01 (topical dexamethasone) in diabetic macular edema (DME).
- **Design:** Multicenter, double-masked, randomized Phase 2 trial.
- **Participants:** 144 patients with DME (OCS-01: n=99, Vehicle: n=45), treated for 12 weeks (1 drop, 3 times daily).

Key Findings:

- **CMT Reduction:** OCS-01 significantly reduced central macular thickness (−53.6 µm vs. −16.8 µm, p=0.0115, 12 weeks).
- **Visual Acuity Improvement:** OCS-01 showed a trend toward better BCVA(best corrected visual acuity) improvement (+2.6 vs. +1.0 ETDRS letters, p=0.125, 12 weeks)
- **Safety:** Well tolerated, with intraocular pressure elevation as the most common adverse event.

Conclusion:

OCS-01 effectively reduces macular thickness and may improve vision, particularly in patients with lower baseline BCVA. A Phase 2/3 study is ongoing to confirm these findings in a larger patient population.

References:

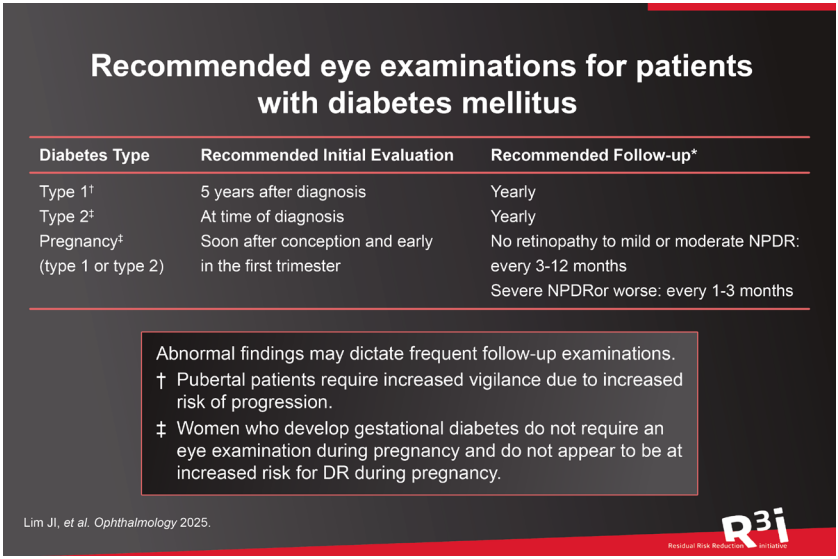
1. Stefansson E, *et al. Acta Ophthalmologica* 2022.

Others

SECTION

7

Residual Risk Reduction initiative



Recommended eye examinations for patients with diabetes mellitus

In type 1 diabetes, retinopathy risk correlates with the duration of disease and tends to accelerate during puberty, though vision-threatening changes are uncommon before that stage. Annual examinations are generally advised starting 5 years after the initial diagnosis.

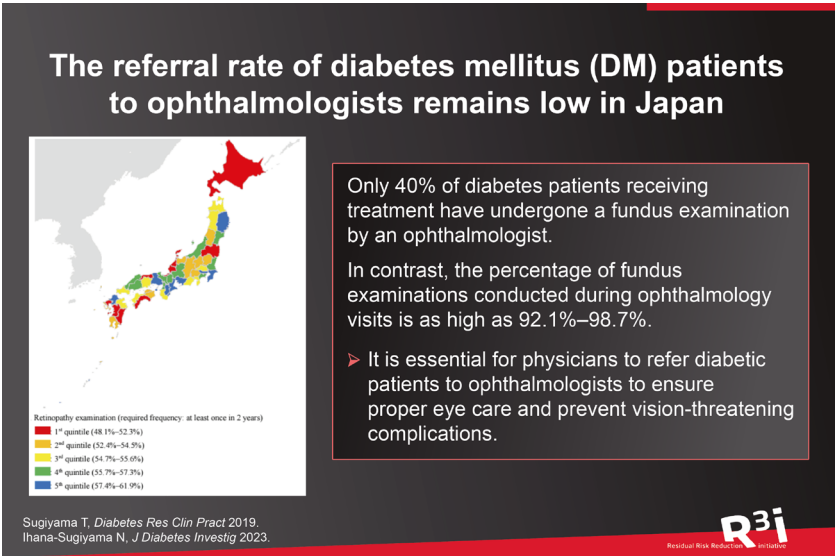
In type 2 diabetes, retinopathy may already be present at the time of diagnosis due to an often indeterminate onset, necessitating a comprehensive examination at diagnosis and at least yearly thereafter.

During pregnancy, preexisting diabetes can lead to retinopathy progression, so patients should be examined and counseled before conception or early in the first trimester, with follow-up intervals based on disease severity. Women with gestational diabetes alone typically do not require specific ophthalmic evaluation during pregnancy.

After each examination, clinicians should discuss findings with the patient, classify both eyes by retinopathy severity and macular edema, and determine the appropriate timing for interventions and future follow-up.

Abbreviations: NPDR = nonproliferative DR

References: 1. Lim JI, *et al. Ophthalmology* 2025.



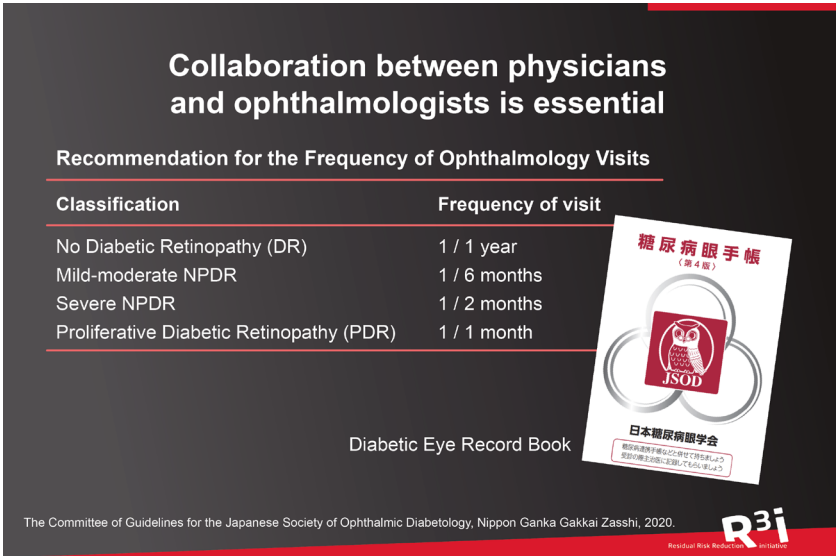
The referral rate of diabetes mellitus (DM) patients to ophthalmologists remains low in Japan

Based on a large-scale database study, only about 40% of treated diabetes patients in Japan undergo a fundus examination by an ophthalmologist, whereas 92.1–98.7% of those who visit an ophthalmologist actually receive this exam. This gap suggests that many diabetic patients are not being referred for specialized eye care, potentially delaying early detection and treatment of diabetic retinopathy.

Consequently, timely referral from primary care or other specialties to ophthalmologists is crucial, as is reinforcing the need for regular eye examinations to prevent vision-threatening complications.

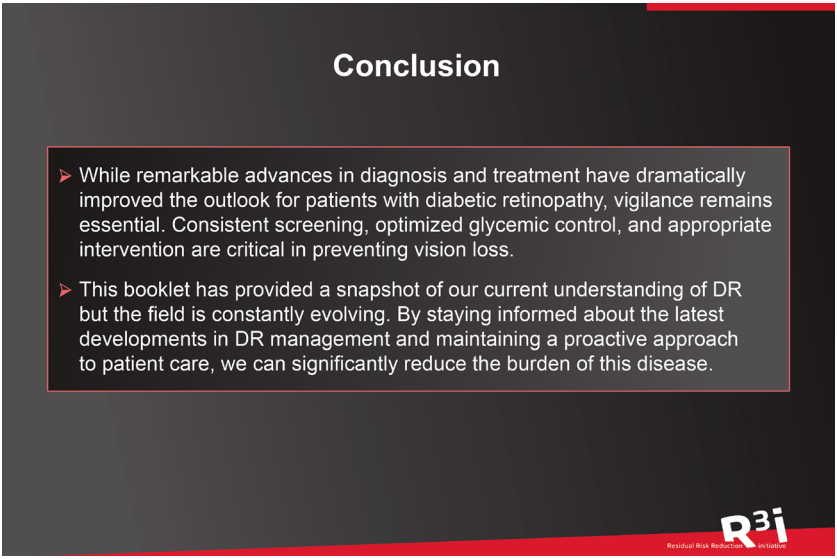
References:

1. Sugiyama T, *Diabetes Res Clin Pract* 2019.
2. Ihana-Sugiyama N, *J Diabetes Investig* 2023.



Collaboration between physicians and ophthalmologists is essential

The **Diabetic Eye Record Book** is an essential tool for managing diabetic retinopathy (DR) in patients with diabetes. It allows for better communication between healthcare providers, ensuring timely eye examinations and appropriate interventions.



Conclusion

While *remarkable* advances in diagnosis and treatment have dramatically improved the outlook for patients with diabetic retinopathy, vigilance remains essential. Consistent screening, optimized glycemic control, and appropriate intervention are critical in preventing vision loss.

This booklet has provided a snapshot of our current understanding of DR but the field is constantly evolving. By staying informed about the latest developments in DR management and maintaining a proactive approach to patient care, we can significantly reduce the burden of this disease.

Abbreviations

ACE	Angiotensin-converting enzyme
ARB	Angiotensin II receptor blocker
BCVA	Best corrected visual acuity
BRB	Blood-retina barrier
CKD	Chronic kidney disease
CRT	Central retinal thickness
CST	Central subfield thickness
DME	Diabetic macular edema
DM	Diabetes mellitus
DR	Diabetic retinopathy
DRD	Diabetic retinal disease
DRN	Diabetic retinal neurodegeneration
eGFR	Estimated glomerular filtration rate
ERG	Electroretinogram
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein angiography
FFA	Fundus Fluorescein Angiography
FGF	Fibroblast growth factor
GLP-1	Glucagon-like peptide-1
GIP	Glucose-dependent insulinotropic polypeptide
HIF	Hypoxia-inducible factor
ICDR	International Clinical Diabetic Retinopathy
ILM	Inner limiting membrane
IOP	Intraocular pressure

IVTA	Intravitreal triamcinolone acetonide
MAFLD	Metabolic dysfunction-associated fatty liver disease
NPA	Non-perfusion area
NPDR	Non-proliferative diabetic retinopathy
NVG	Neovascular glaucoma
OCT	Optical coherence tomography
OCTA	Optical coherence tomography angiography
PDR	Proliferative diabetic retinopathy
PDGF	Platelet-derived growth factor
PKC	Protein kinase C
PPARα	Peroxisome proliferator-activated receptor alpha
PRP	Panretinal photocoagulation
RAS	Renin-angiotensin system
SDM	Subthreshold diode laser micropulse photocoagulation
SGLT2i	Sodium-glucose cotransporter 2 inhibitor
SMC	Smooth muscle cell
SPPARMα	Selective peroxisome proliferator-activated receptor alpha modulator
SRD	Serous retinal detachment
STTA	Sub-Tenon triamcinolone acetonide
TRD	Tractional retinal detachment
TRP	Targeted retinal photocoagulation
VA	Visual acuity
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
VTDR	Vision-threatening diabetic retinopathy


R3i
Residual Risk Reduction initiative