Association of Hong Kong Diabetic Nurses
Hong Kong Association of Private Eye Surgeons
23rd Sept 2017

Updates on the Diagnosis and Management of Diabetic Retinopathy

Dr Luk Oi Jing Fiona

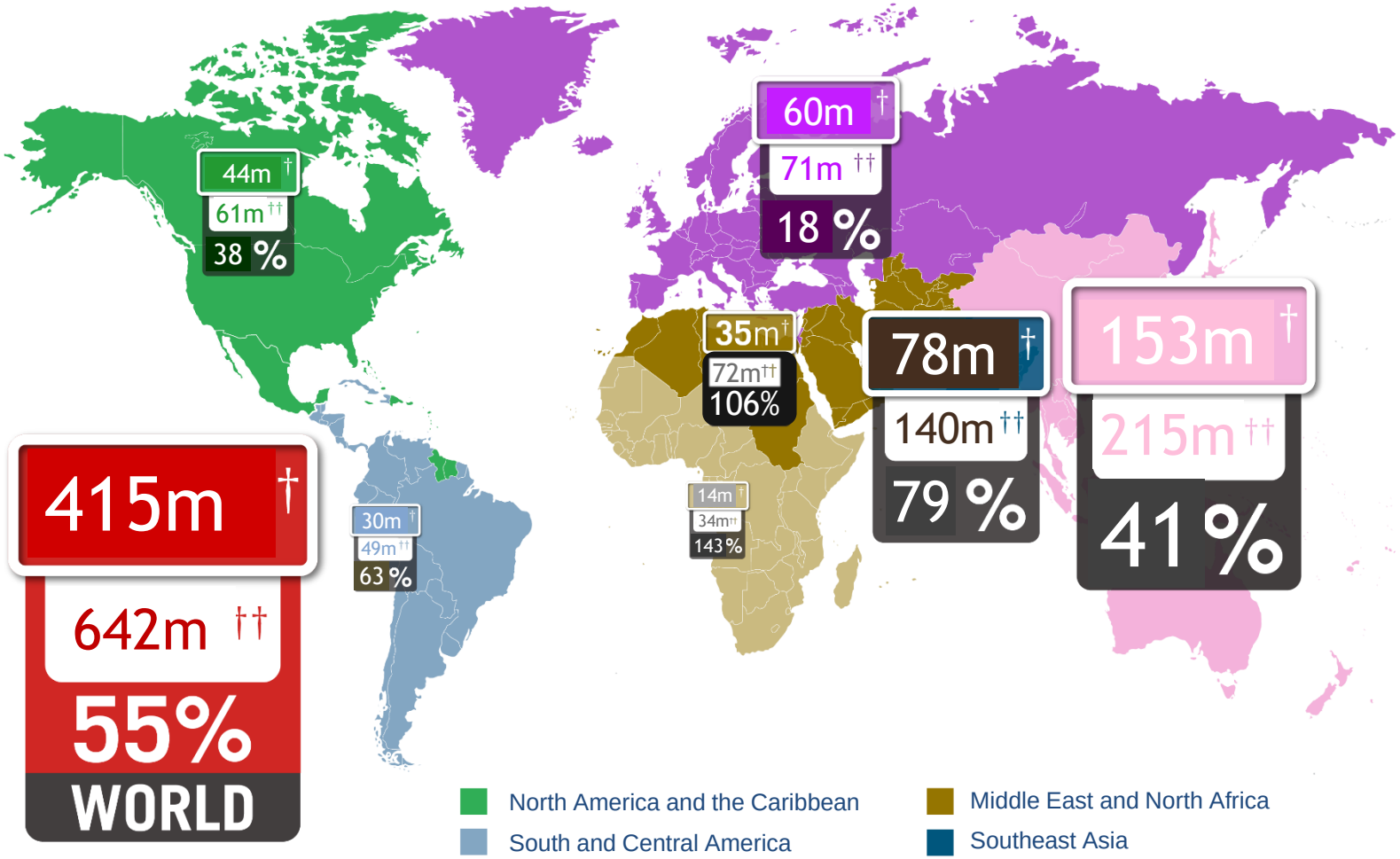
Specialist in Ophthalmology
Premier Medical Centre

Honorary Clinical Assistant Professor
Department of Ophthalmology & Visual Sciences, CUHK

Outline

- Diabetic retinopathy (DMR)
- Diabetic macular oedema (DME)
- Assessment of patients with DMR and DME
- Management of DMR and DME

Global burden of diabetes



† Prevalence in 2015 (millions)
†† Projected prevalence in 2040 (millions)
Projected increase from 2015 to 2040 (%)

International Diabetes Federation. IDF Diabetes Atlas: 7th Edition. 2015.

Major complications of diabetes

Microvascular complications

Retinopathy

A leading cause of blindness in working-age populations[1]

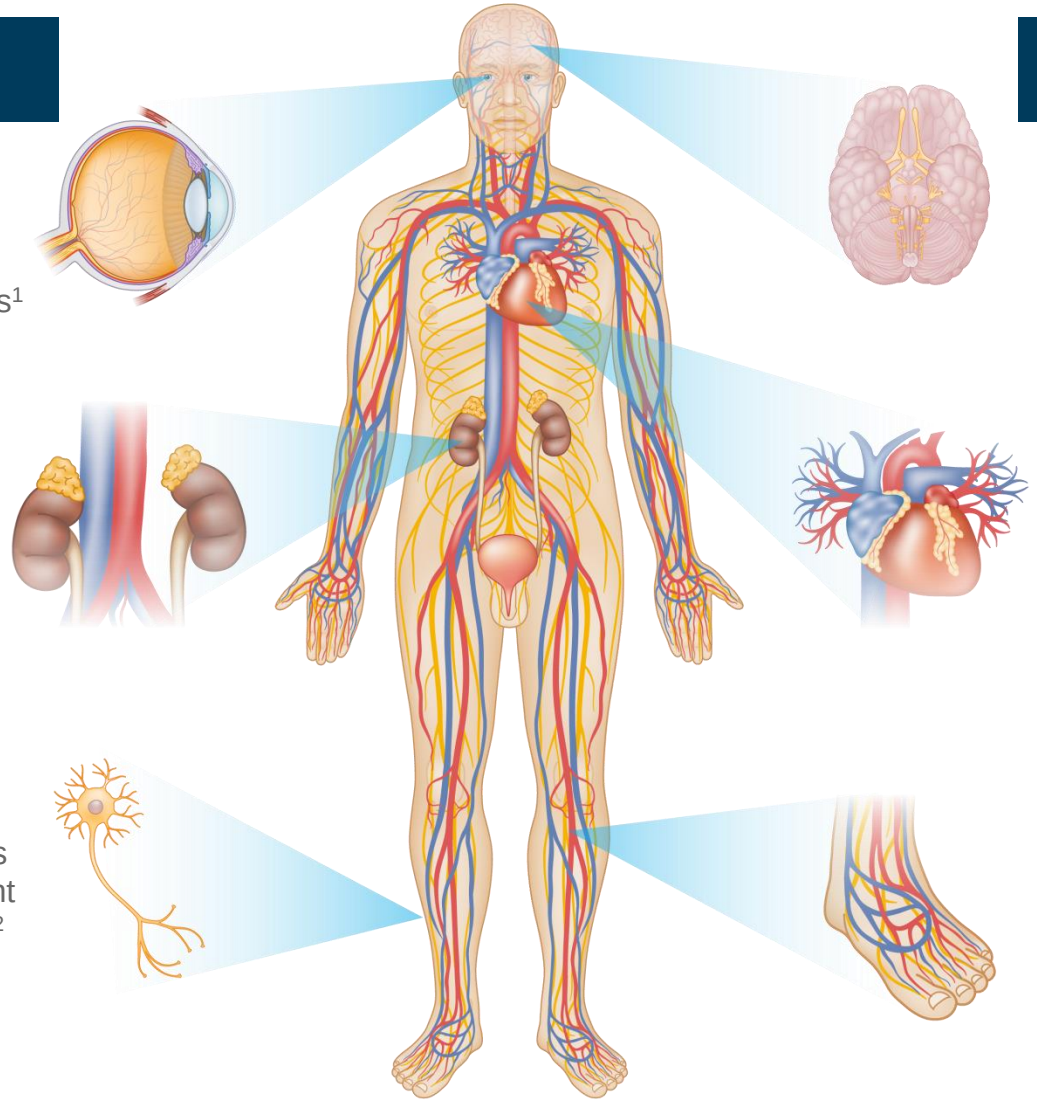
Nephropathy

Responsible for > 40% of new cases of kidney failure[2]

Neuropathy

Mild-to-severe nervous system damage present in 60–70% of patients[2]

*2004 values



Macrovascular complications

Cerebrovascular disease

Cited on 16% of diabetes-related death certificates (patients aged ≥ 65 years)*[2]

Heart disease

Cited on 68% of diabetes-related death certificates (patients aged ≥ 65 years)*[2]

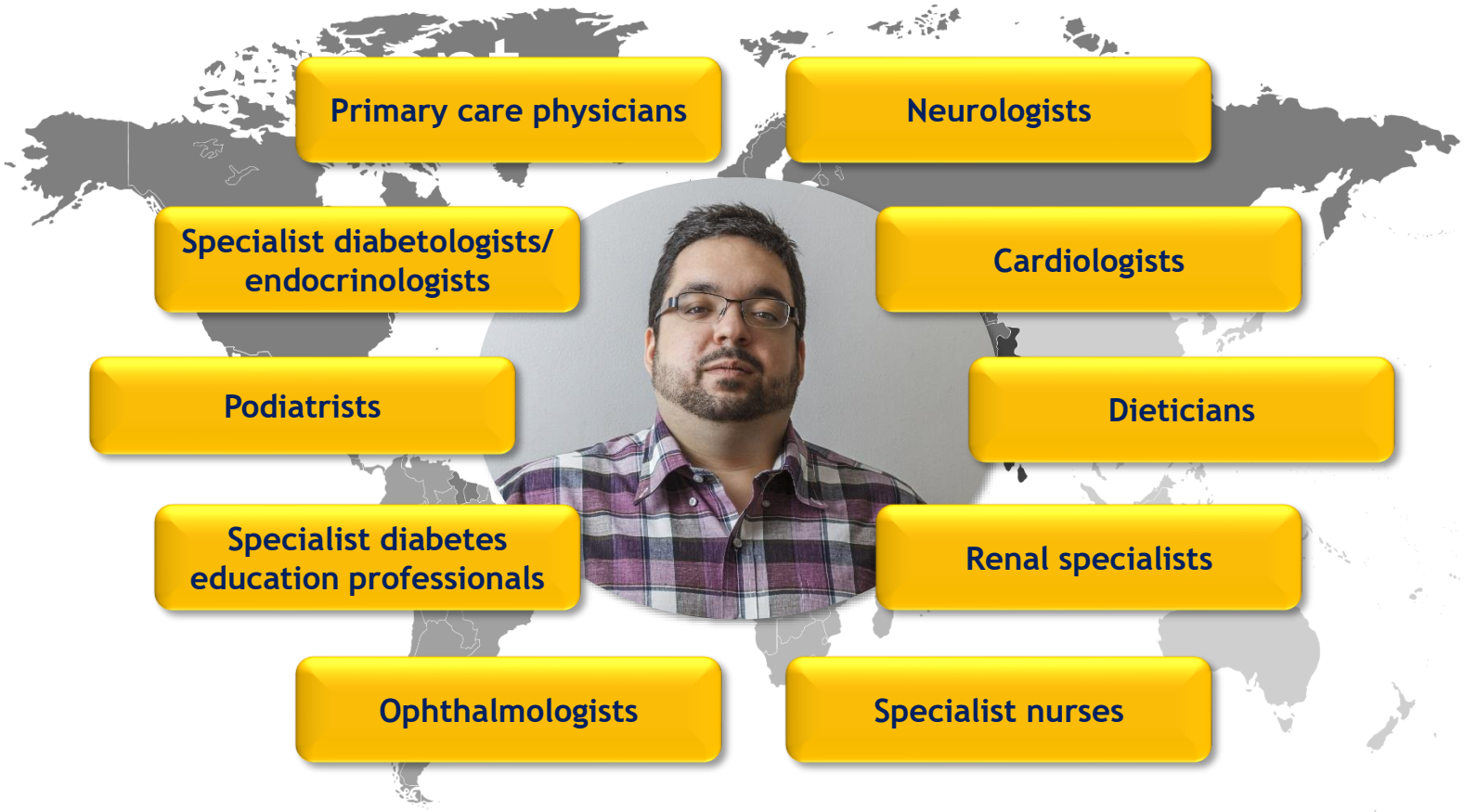
Peripheral vascular disease

Occurs in ~8% of patients with diagnosed diabetes[3] leading cause of non-traumatic lower extremity amputations[2]

1. Ciulla TA, et al. *Diabetes Care*. 2003;26(9):2653–2664; 2. CDC. National Diabetes Fact Sheet, 2011. www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf. Accessed June 19, 2014. 3. Gregg EW, et al. *Diabetes Res Clin Pract*. 2007;77(3):485–488.

A multidisciplinary approach

A team of professionals may be involved in diabetes care

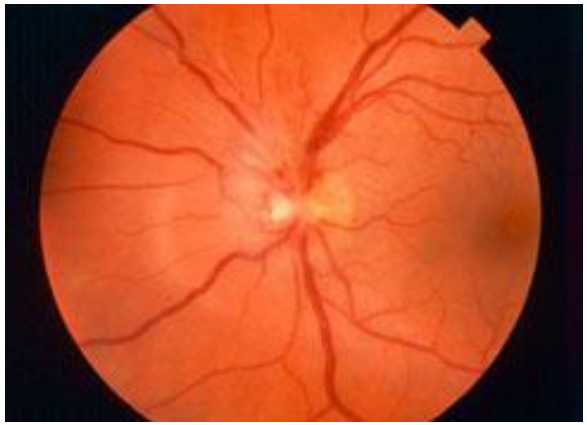


1. National Collaborating Centre for Chronic Conditions (NCCCC). Type 2 diabetes – National clinical guideline for management in primary and secondary care (NICE update). 2008; 2. National Institute for Clinical Excellence (NICE). Type 1 diabetes in adults: Diagnosis and management. 2015.

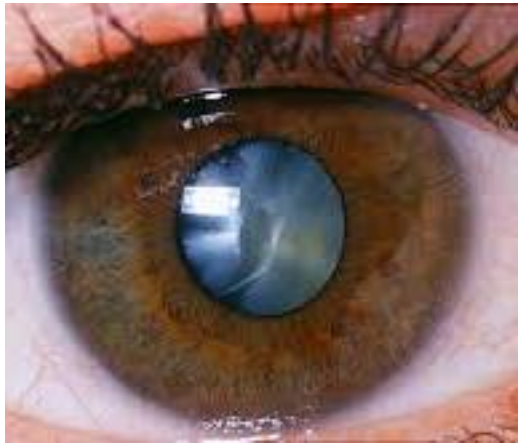
Diabetes and the eye

While some ocular complications are causally linked to hyperglycemia, others may be non-specific recognized associations of diabetes found more readily during routine eye screening













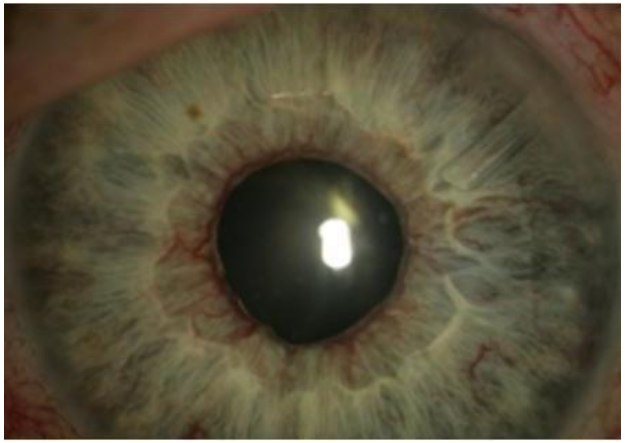
Advanced diabetic eye disease

- End-stage damage from diabetic retinopathy
- Cause of permanent visual impairment and blindness among patients with diabetes
- Routine screening is important in early identification and prevention of the development of advanced disease



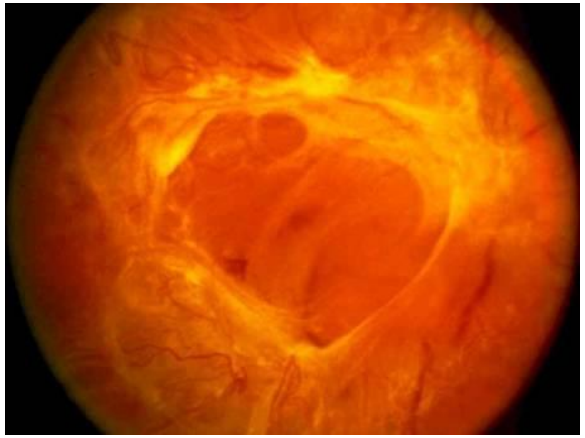
Vitreous/pre-retinal hemorrhage

Image courtesy of Tunde Peto.



Rubeosis iridis

Image courtesy of Samer El-Sherbiny.



Late-stage proliferative diabetic retinopathy with fibrosis

Image courtesy of Nihal Kenawy.

Whitehouse K. Diabetic Retinopathy. Dodson PM (ed.). Oxford University Press; 2008.

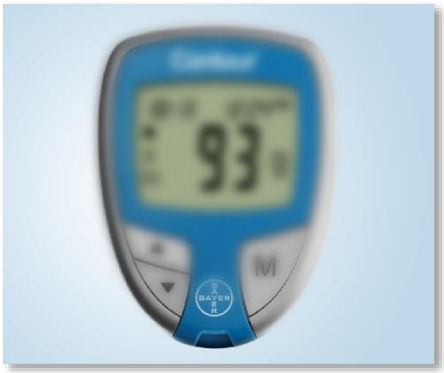
Ophthalmic complications of diabetes that lead to vision loss create numerous challenges

Impact on diabetes self-care:[1]

- Reading medication directions and nutrition labels
- Testing blood glucose levels
- Checking feet for wounds or sores
- Driving to attend physician visits

Economic impact:[2]

- Gaining and maintaining employment
- Time and costs associated with undergoing evaluations and treatment





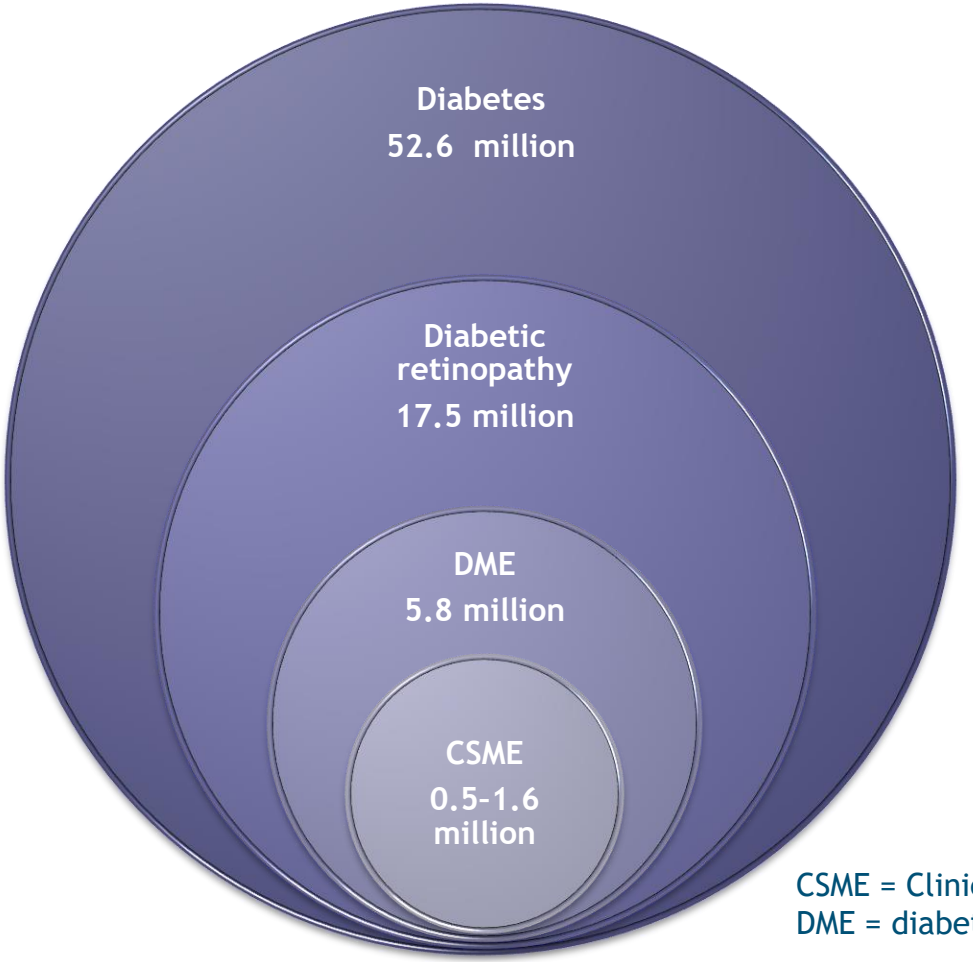


1. Peters CM, et al. ARVO 2012. Poster A645; 2. Chen E, et al. *Curr Med Res Opin.* 2010;26(7):1587–1597.

Diabetic retinopathy (DMR)

Prevalence of DMR

Prevalence rates in Europe in 2011 (millions; extrapolated estimates)



One-third rule:

- Approximately 1/3 of people with diabetes have diabetic retinopathy
- About 1/3 of people with diabetic retinopathy have DME, and 1/3 of these patients have CSME

CSME = Clinically significantly macular edema;
DME = diabetic macular edema.

1. International Diabetes Federation. IDF Diabetes Atlas: 5th Edition. 2011; 2. International Diabetes Federation. IDF Diabetes Atlas: 6th Edition. 2013.

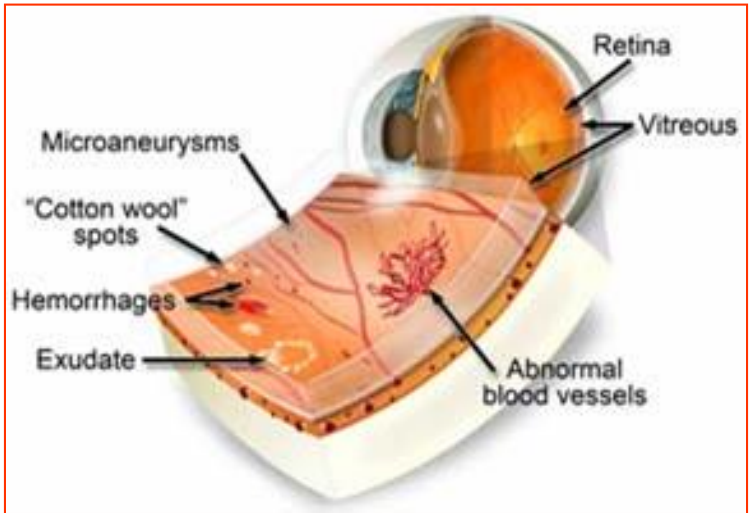
Diabetic retinopathy

- Globally, diabetic retinopathy is the sixth leading cause of blindness
- The condition can be well advanced before symptoms develop
- Key risk factors:
  - Poorly controlled diabetes
  - Chronic hyperglycemia
  - Dyslipidemia
  - Hypertension
  - High body mass index
  - Low levels of physical activity
  - Insulin resistance
  - Age
  - renal disease
  - pregnancy

1. Pascolini D, Mariotti SP. *Br J Ophthalmol*. 2012;96(5):614–618; 2. Clarke M. Diabetic Retinopathy. Dodson PM (ed.). Oxford University Press; 2008; 3. The Royal College of Ophthalmologists. Diabetic Retinopathy Guidelines 2012. 4. Antonetti D, et al. *N Engl J Med.* 2012;366(13):1227–1239; 5. Klein R, Klein BEK. *Retina.* Ryan S, et al, eds. Elsevier 2013

Pathogenesis of Diabetic Retinopathy

- Microvascular disease causing capillary damage
  - Pericytes, endothelial cells
  - Cascade of biochemical and pathophysiological changes, such as superoxide overproduction and the production of sorbitol and advanced glycation end-products
- Leakage of blood constituents into the retina
  - Retinal hemorrhages
  - Retinal edema
  - Lipid exudation



APPROXIMATE EQUIVALENCE OF THE CLASSIFICATION SYSTEMS

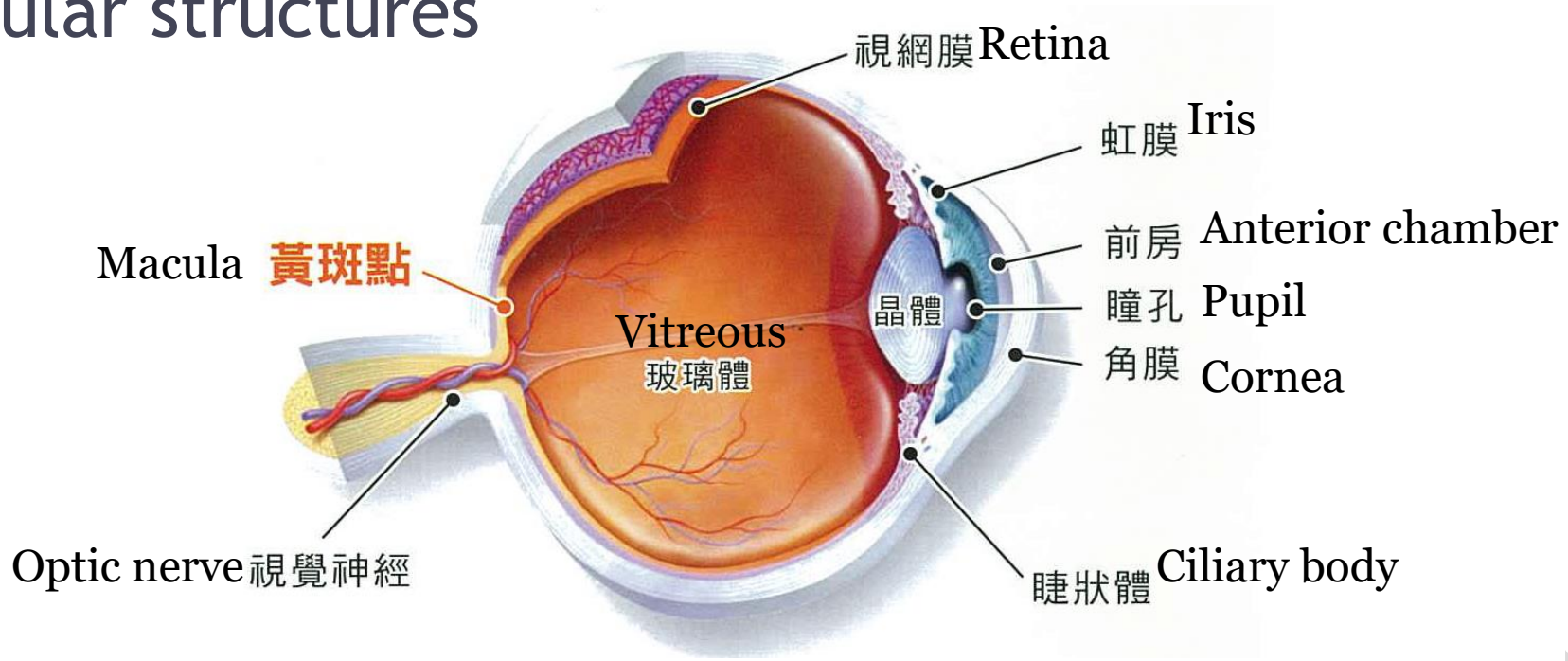
ETDRS	NSC	SDRGS	AAO	RCOphth
10 - None	R0 - None	R0 - None	No apparent retinopathy	None
20 - Microaneurysms only	R1 - Background	R1 - BDR	Mild NPDR	Low risk
35 - Mild NPDR			Moderate NPDR	
43 - Moderate NPDR	R2 - Pre-proliferative	R2 Moderate BDR		High risk
47 - Moderately severe NPDR				
53 A-D - Severe NPDR		R3 - Severe BDR	Severe NPDR	
53 E - Very severe NPDR				
61 - Mild PDR 65 - Moderate PDR	R3 - Proliferative	R4 - PDR	PDR	PDR
71, 75 - High risk PDR 81, 85 - Advanced PDR				

International Classification of DM retinopathy

Non-proliferative DMR	
Mild NPDMR	*only microaneurysms*
Moderate NPDMR	
Severe NPDMR (4:2:1 rule)	*intraretinal haemorrhages in all 4 quadrants, venous beading in 2 quadrants, or intraretinal microvascular abnormalites (IRMA) in 1 quadrant*
Proliferative DMR	
Neovascularisation or preretinal or vitreous haemorrhage	
Diabetic Maculopathy	

Diabetic macular oedema (DME)

Ocular structures



Retina

- A light-sensitive layer of tissue
- Light enters into the eye, strikes the retina and triggers nerve impulses

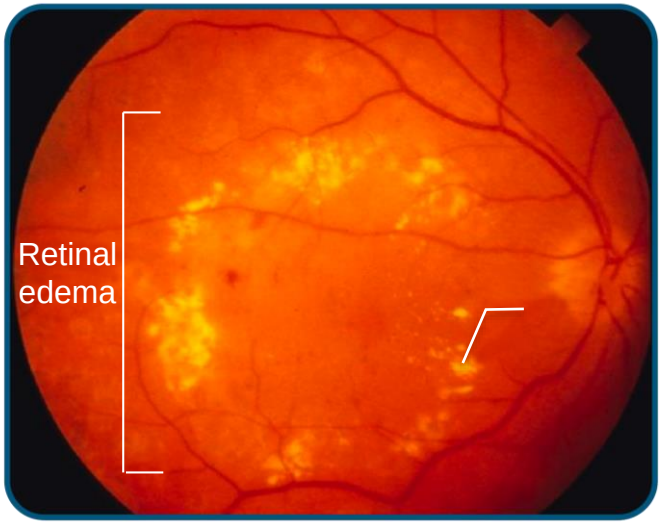
Macula

- Cone photoreceptor predominate and are present at high density
- Responsible for the central, high-resolution, colour vision

Understanding DME

- A microvascular complication of diabetes that is associated with diabetic retinopathy
- The leading cause of moderate-to-severe vision loss in patients with diabetes
- A leading cause of blindness in working-age populations in most developed countries

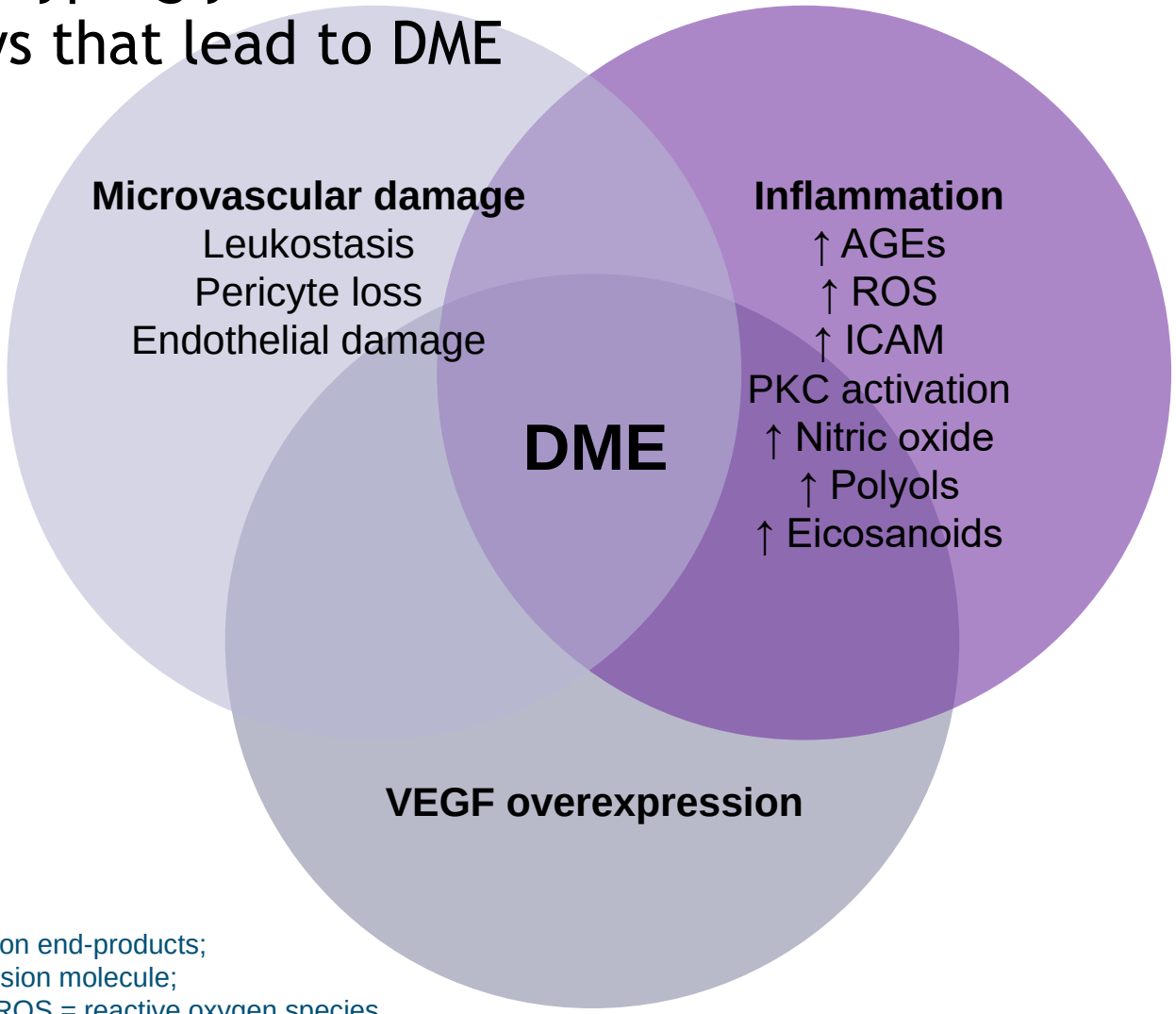
- Clinically significant macular edema (CSME) is the form of DME that is considered to be most vision-threatening



Diabetic macular edema

1. Lobo C, et al. *Optical Coherence Tomography*. Berlin Heidelberg: Springer-Verlag; 2012; 2. Fowler MJ. *Clinical Diabetes*. 2008;26(2): 77–82; 3. International Diabetes Federation. Diabetes & blindness due to DME Q&A. www.idf.org/sites/default/files/Toolkit%2520Q%2526A_FINAL.pdf. Accessed June 19, 2014. Accessed June 4, 2014; 4. Ciulla TA, et al. *Diabetes Care*. 2003;26(9):2653–2664.

Chronic hyperglycemia initiates a number of inter-related pathways that lead to DME



AGEs = advanced glycation end-products;
ICAM = intercellular adhesion molecule;
PKC = protein kinase C; ROS = reactive oxygen species.

Boyer DS, et al. *Ther Adv Endocrinol Metab*. 2013;4(6):151–169.

Diabetic Macular Oedema (DME)

- Retinal thickening within 2 disc diameters of the center of the macula
- Break-down of blood-retinal barrier
- Leakage of plasma constituents

- FOCAL – hard exudates ring caused by leakage from microaneurysms

- DIFFUSE – leakage from microaneurysms, retinal capillaries and arterioles

Clinically Significant Macular Oedema (CSME)

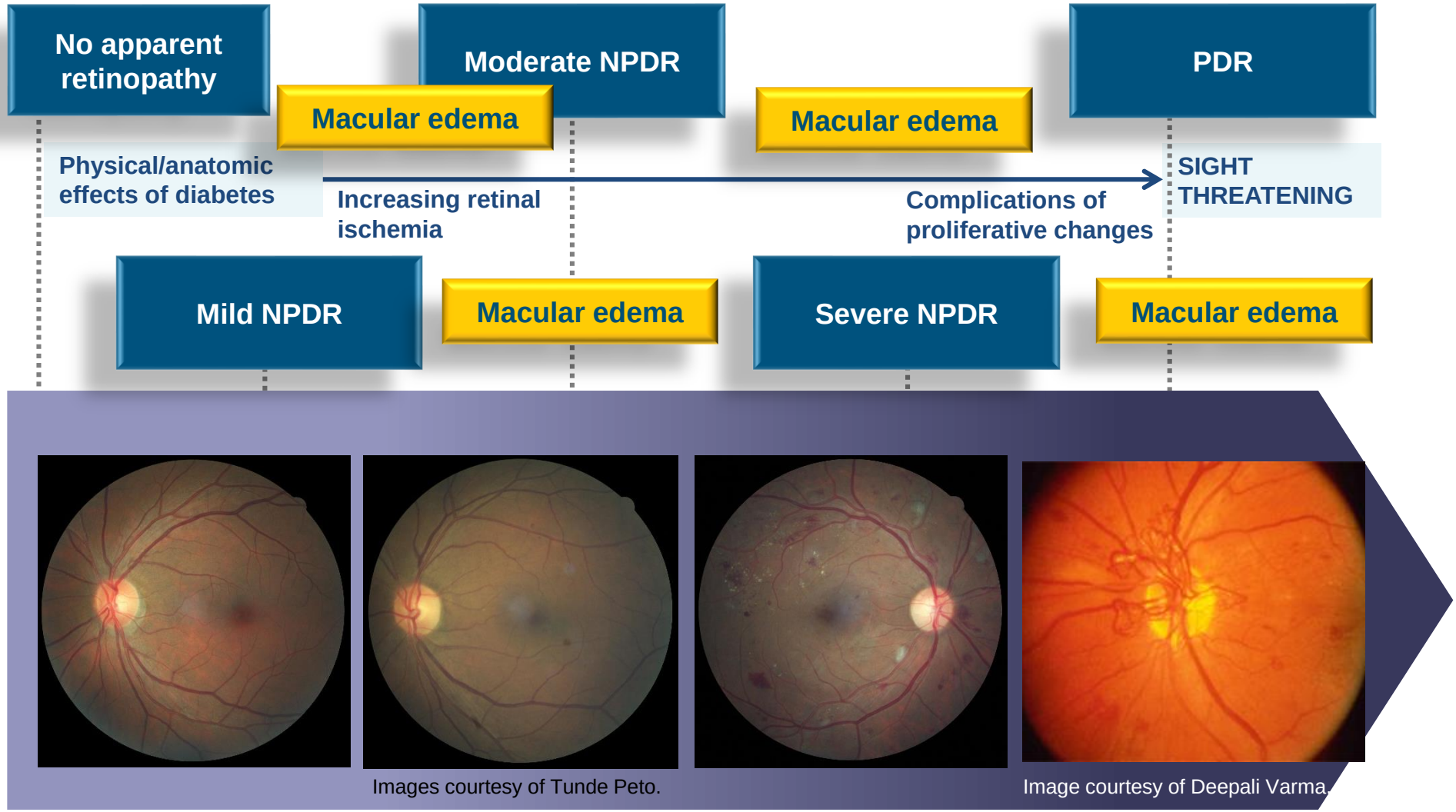
Defined by the Early Treatment Diabetic Retinopathy Study (ETDRS):

- Retinal thickening within 500um of the center of the fovea
- Hard, yellow exudates within 500um of the centre of the fovea with adjacent retinal thickening
- At least 1 disc area of retinal thickening, any part of which is within 1 disc diameter of the centre of the fovea



Image courtesy of Dr Alfredo Garcia Layana.

Progression of diabetic retinopathy

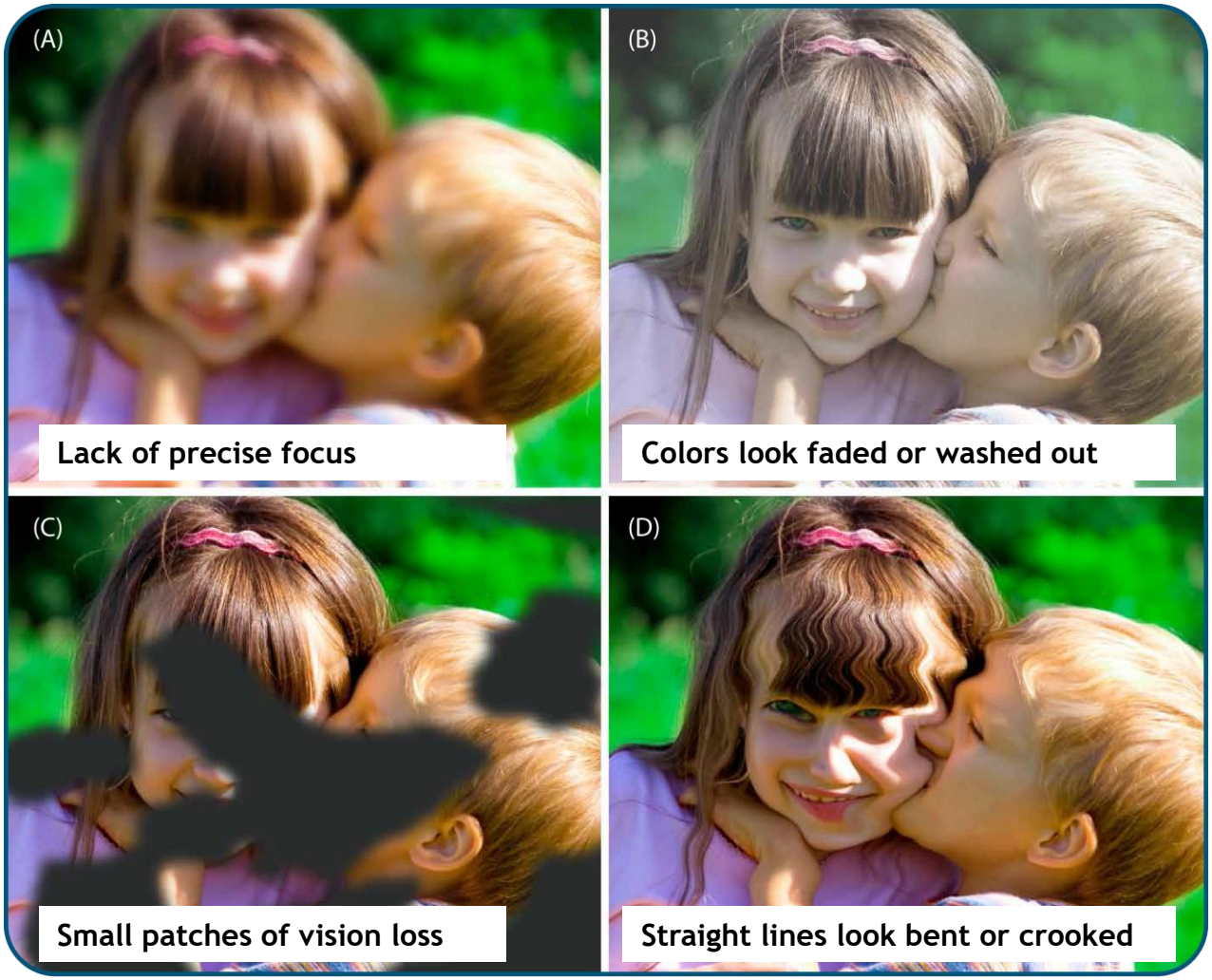


Royal College of Ophthalmology. Diabetic retinopathy guidelines. 2012; Wilkinson CP, et al. *Ophthalmology.* 2003;110(9):1677–1682.

Progression from NPDR to PDR

Stage	Progression to PDR in 1 year
Mild NPDR	<5%
Moderate NPDR	20%
Severe NPDR	50%

Vision loss in DMR and DME



Karim R, Tang B. *Clin Ophthalmol* 2010;4:493–517. Macular Society. Diabetic macular oedema. Available from: www.macularsociety.org/about-macular-conditions/Other-macular-conditions/Diabetic-macular-oedema. Accessed January 2014. EyeSmart. Macular Edema Symptoms. Available from: http://www.geteyesmart.org/eyesmart/diseases/macular-edema-symptoms.cfm. ccessed January 2014.

DME imposes a substantial burden on the diabetic patient

- DME has a negative impact on health-related quality of life (HRQoL) that is related to the degree of visual impairment[1]
- Fear of visual loss is preoccupying and intense for many of these patients[2]
- Loss of vision has been associated with:[3,4]



Those who depend on vision for employment can experience a significant economic burden from DME[5]

1. Davidov E. *Graefes Arch Clin Exp Ophthalmol*. 2009;247:267–272; 2. Luckie R. *Diabet Med*. 2007;24(10):1086–1092; 3. Owen C. *BMC Ophthalmology*. 2006;6:24; 4. Kempen G. *Qual Life Res*. 2012;21:1405–1411; 5. Patel S. ARVO 2013. Available from: http://www.arvo.org/webs/am2013/abstract/sessions/290.pdf. Accessed January 2014.

Ophthalmic screening in patients with diabetes

- Regular and routine ophthalmological screening is essential in patients with diabetes
  - Patients with diabetic retinopathy and DME may still have unchanged vision, but can be at high risk of vision loss
  - When identified, diabetic retinopathy and DME can often be managed to reduce the risk of loss of visual function
- Most guidelines, including those from the AAO and NEI, recommend a comprehensive eye exam at least once a year in patients with diabetes

Diabetes type	Recommended time of first eye examination	Recommended follow-up*
T1DM	3–5 years after diagnosis	Yearly
T2DM	At time of diagnosis	Yearly
Prior to pregnancy (T1DM or T2DM)	Prior to conception and early in the first trimester	No retinopathy to mild or moderate NPDR: every 3–12 months Severe NPDR or worse: every 1–3 months

*Abnormal findings may dictate more frequent follow-up examinations.

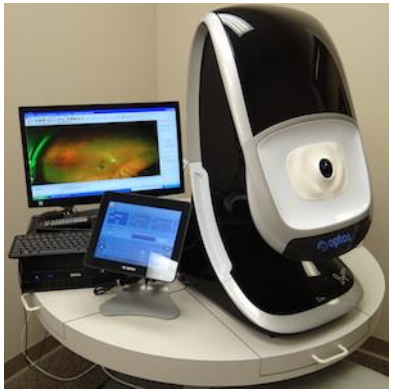
1. American Diabetes Association. *Diabetes Care*. 2013;36(Suppl 1):S11–66; 2. American Academy of Ophthalmology. Diabetic Retinopathy Preferred Practice Pattern. 2016.

Fundoscopy

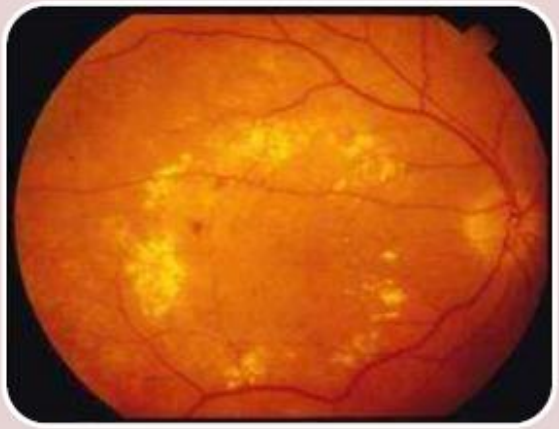




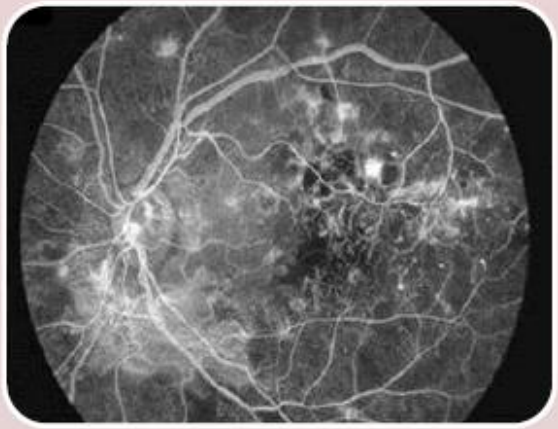




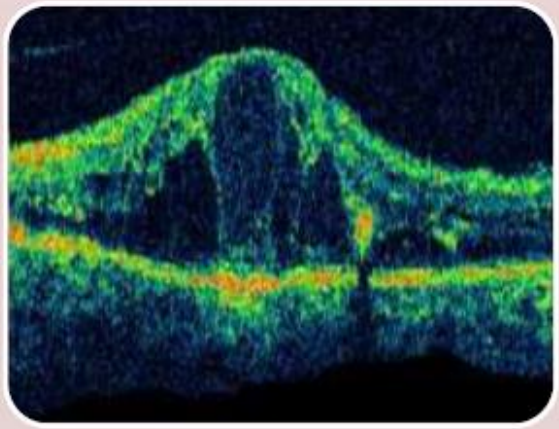
Retinal Imaging Quantifies Disease, Progression, and Treatment Response



Colour fundus photo



Fundus fluoroscein angiography



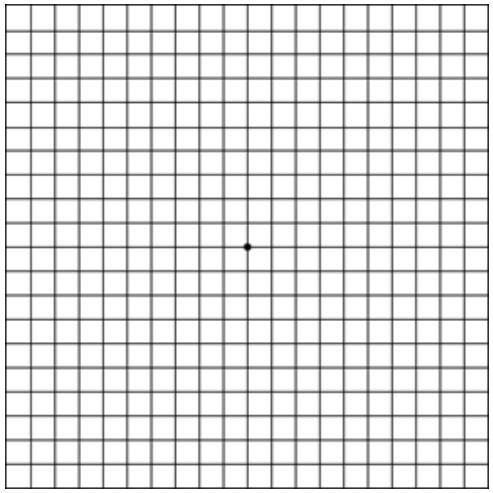
Optical coherence tomography

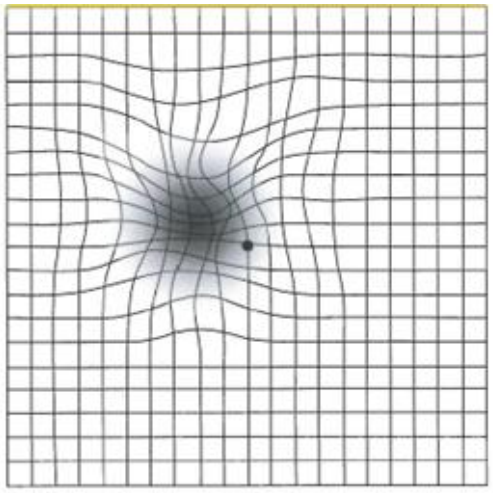
Visual acuity



- Snellen Visual Acuity Charts
  - Distance vision
- Rosenbaum Near Vision Screener
- Placed at around 30cm from patient' s eyes
- Must have spectacles on, especially if they have presbyopia
- Check one eye at a time (fellow eye well covered)

Check for any distorted vision





- 「阿姆斯勒方格表」檢查 (Amsler Grid Test)
- Must have glasses on, especially in patients with presbyopia
- The test must be carried out in a well-lit room
- One eye is tested at a time.
- Patient is asked to focus on the central dot and to note if any distortion or blurring

Slit lamp exam



Measurement of intra-ocular pressure





Management of DMR and DME

Systemic treatment

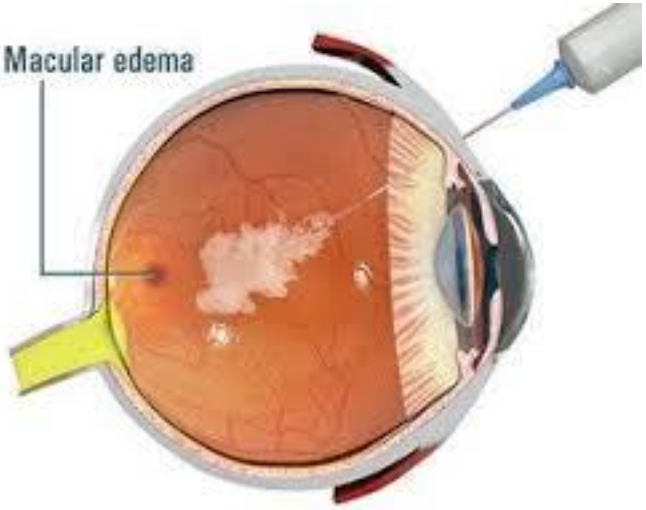
- Control of systemic condition
  - Glycaemic control
  - BP control
  - Lipid control
  - Reduce obesity
- Lifestyle modification
  - Quit smoking

Local treatment

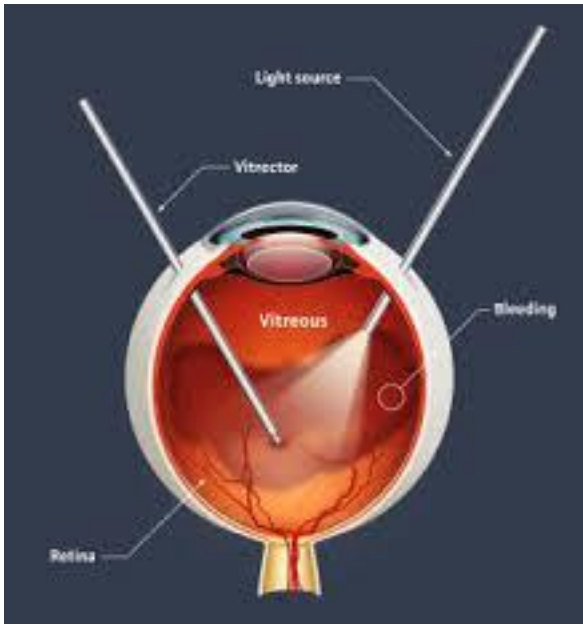
Laser therapy



Intraviteal injection

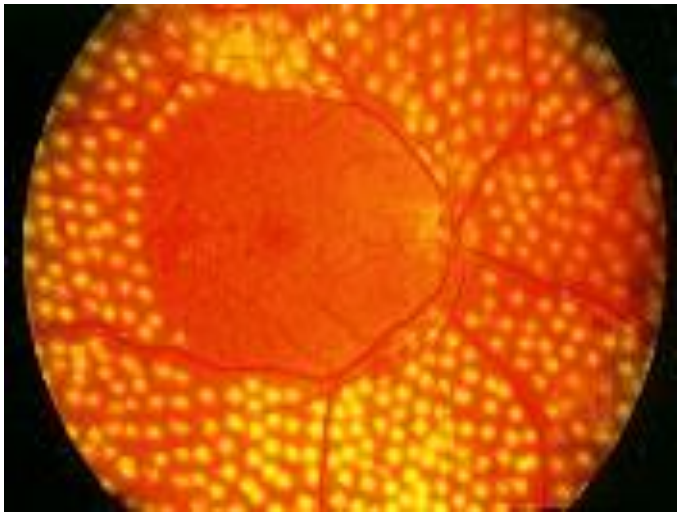


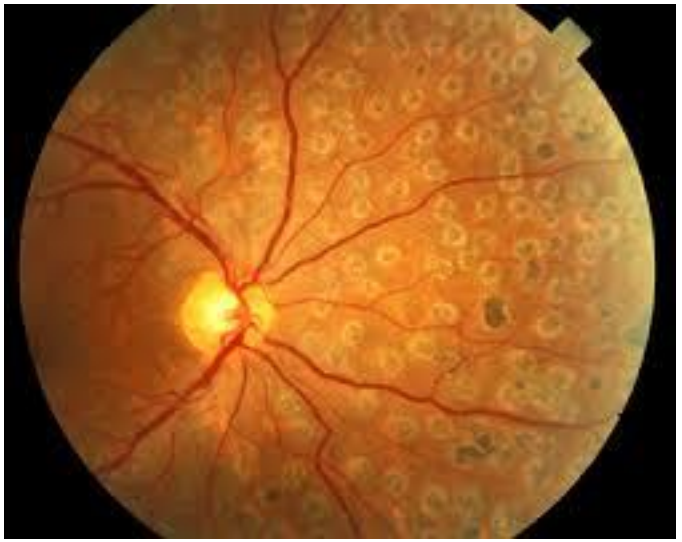
Vitreoretinal surgery



Pan-retinal photocoagulation (PRP)

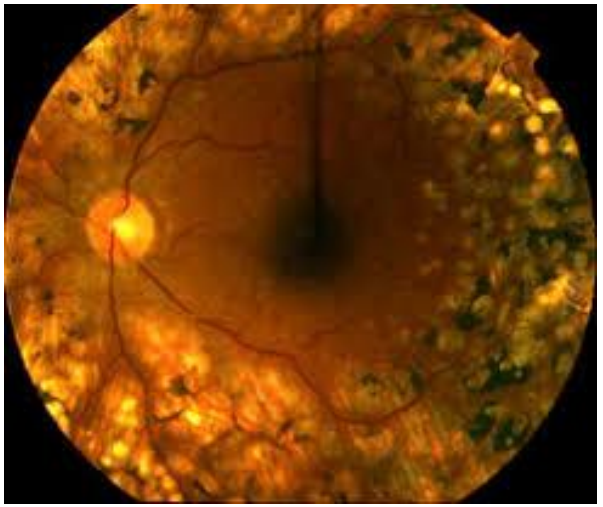
- Generally recommended as a treatment for proliferative diabetic retinopathy (PDR)
- Reduce risk of severe visual loss by 60% in 2 years
- Involves the delivery of a large number of laser ‘burns’ to destroy peripheral ischemic retinal tissue
- Can be delivered over several sessions or in a single session



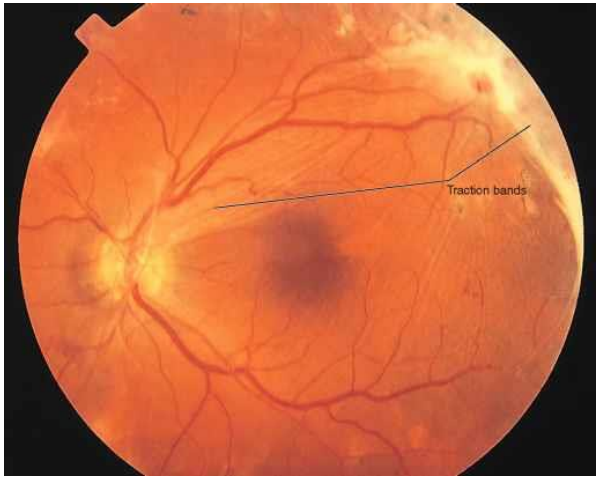


Pan-retinal photocoagulation (PRP)

- Acute loss of visual acuity of ≥ 2 lines may occur in treated eyes in the first few weeks after PRP, and vision then typically returns to baseline levels
  - By 1 year after treatment, the benefits of treatment are considered to outweigh the adverse effects associated with PRP



- Secondary macular oedema
- Increase traction from fibrovascular proliferation during NV regression
- Side effects : reduced vision, constricted visual field, reduced colour and contrast sensitivity



Macular laser

- Focal and/or grid laser
- Indication: CSME

- Early Treatment Diabetic Retinopathy Study (EDTRS)
- Reduce risk of moderate visual loss by 50% at 3 years

- Mechanism is unclear
  - Stimulation of RPE
  - Closure of leaking microaneurysms
  - Induction of endothelial cell proliferation
  - Alteration of cytokines and growth factors in RPE



Macular laser

- Treatment area: area of retinal thickening 500-3000 um from the center of the macula, but not within 500um of the disc
- Burn size: 50 um
- Duration: 50-100ms

- Focal laser: Mild gray-white burn
- Grid laser: barely visible burn

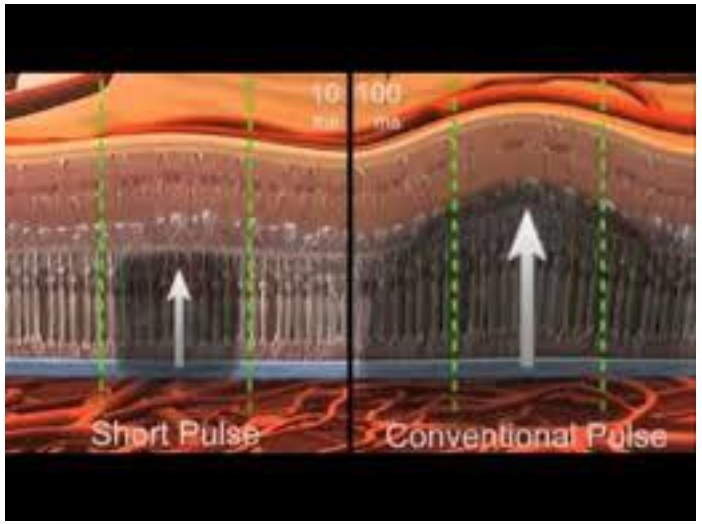
- Side effects: central scotomas, decreased colour vision

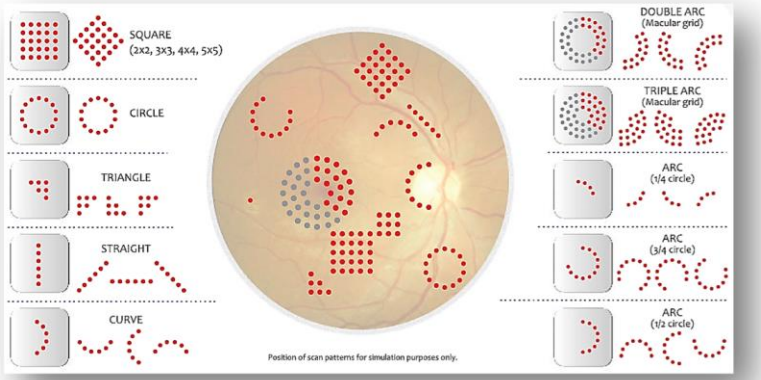


Pattern scanning laser

- Blumenkranz et al. Retina 2006; 26(3): 370-6
- Rapid application of multiple laser spots in an array with shorter pulse duration of 10-30ms

- Advantages:
  - Shorter treatment duration
  - Increased safety
  - Uniform and precise spot placement
  - Accurate subthreshold grid-pattern placement
  - Reduced pain
  - Reduced visual field defect





Pattern scanning laser

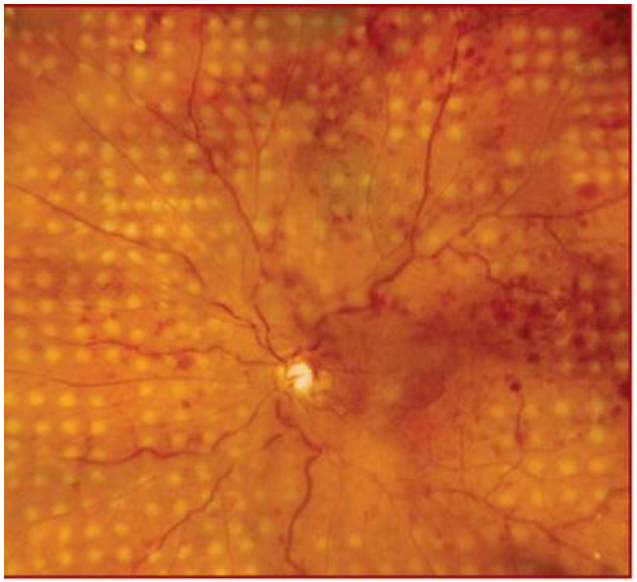
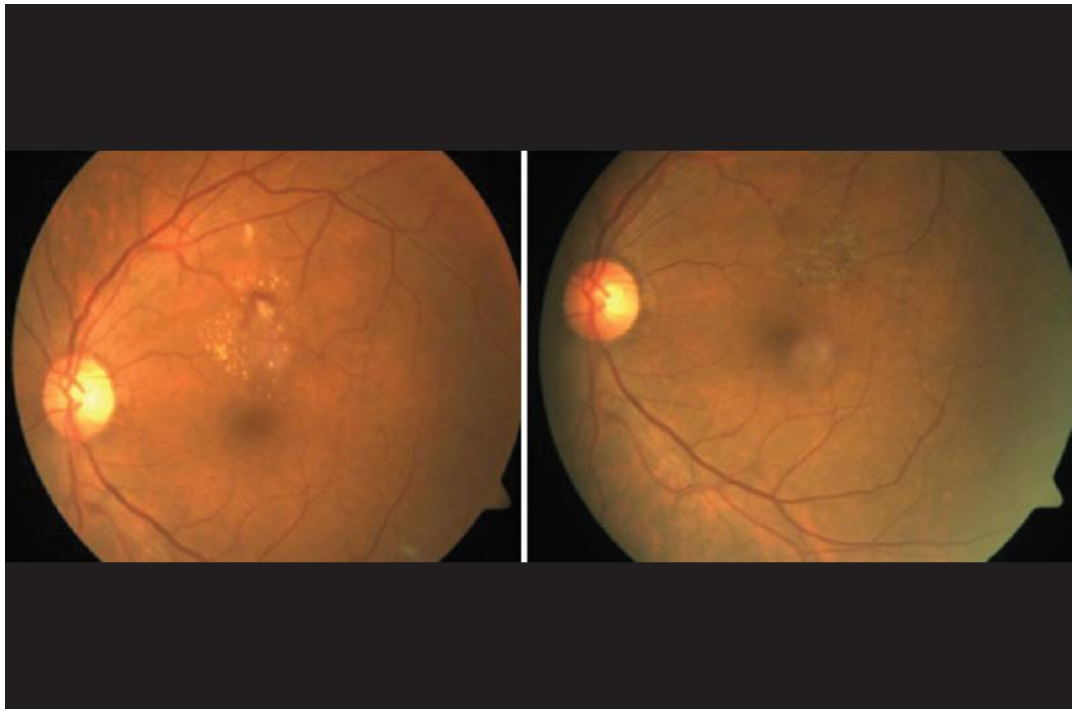


Photo courtesy of Carlos Mateo, MD

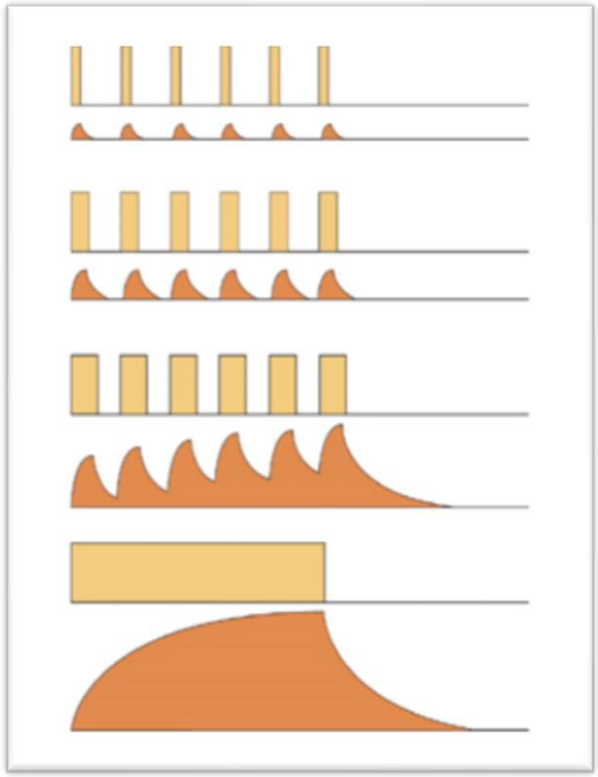
In PRP, with 6 x 6 or 7 x 7 array, the total treatment time in a single treatment session may be reduced from approximately 25min to 3-5 min.



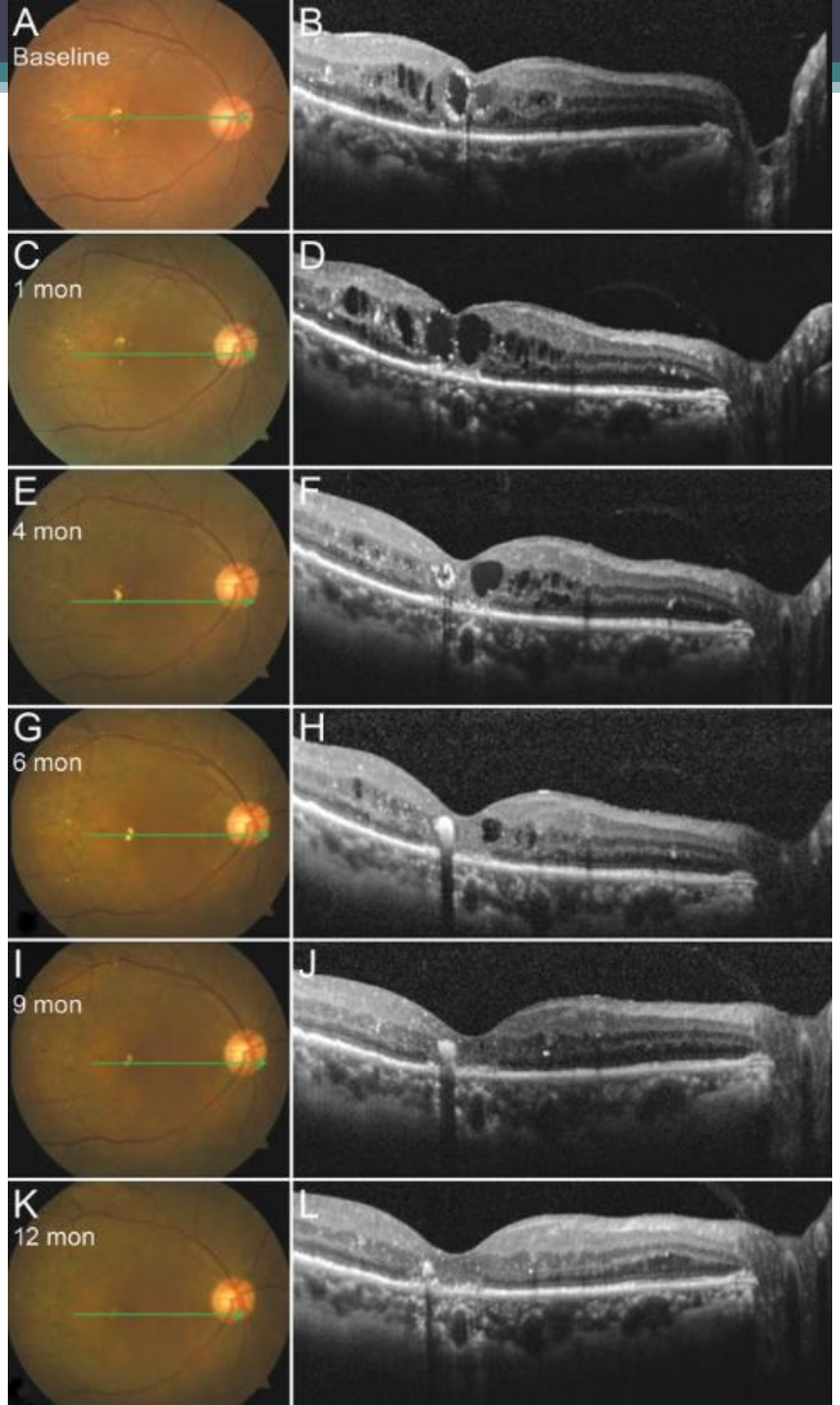
Ind J Ophthalmol 2016; 64(1): 14-25

Subthreshold diode micropulse laser (SDM)

- Diode laser 810nm
- Micropulse technique
  - Laser is delivered in ultrashort pulses (microseconds) that are shorter than the thermal relaxation time of the target tissue
  - Cycles of on time and off time for the full duration of laser spot (100-300ms)
- Low-intensity, high-density laser applications
- No visible scar by fundoscopy, red free imaging, FFA, ICG, OCT or FAF
- Limit laser burns to RPE without damaging outer retina
- As effective as conventional macular laser in treatment of CSME



Ophthalmic surg lasers imag retina 2016;47(11) 985-990
Br J Ophthalmol 2009; 93(10):1341-4
Invest Ophthalmol Vis Sci 2001; 52(7):4314-23



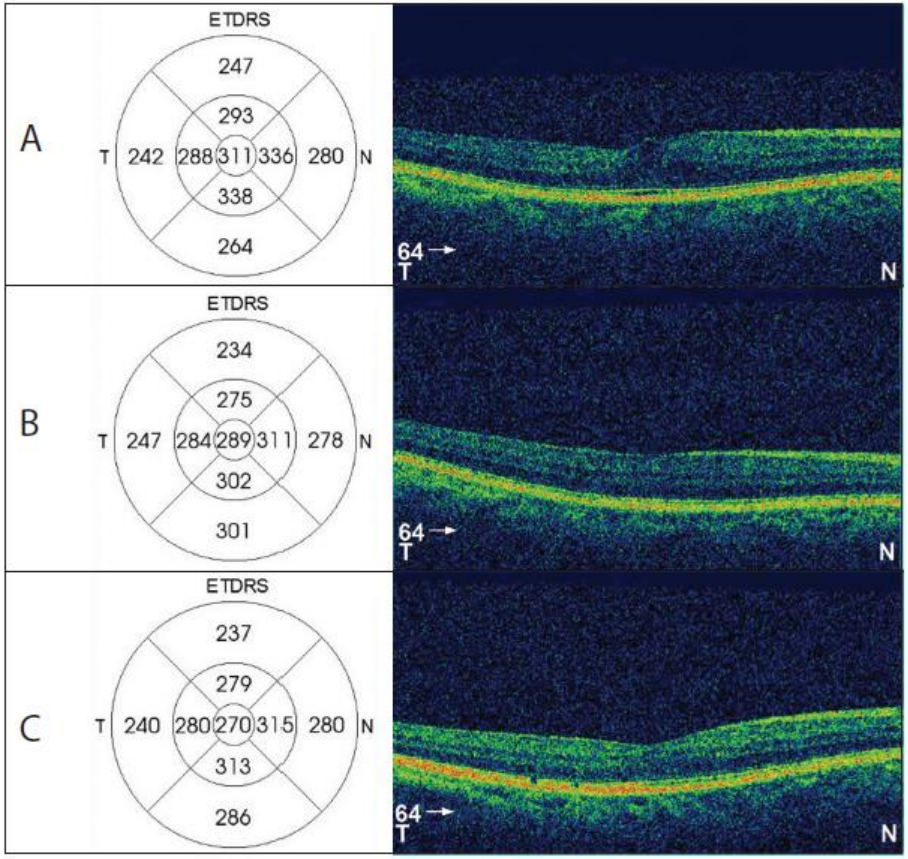
63/F

- 577nm yellow laser
- 15% duty cycle
- Exposure time 20ms
- Spot diameter 100um
- Laser pulses in a confluent, repetitive manner with a 3 x 3 pattern mode

Korean J Ophthalmol 2014;28(5):379-385

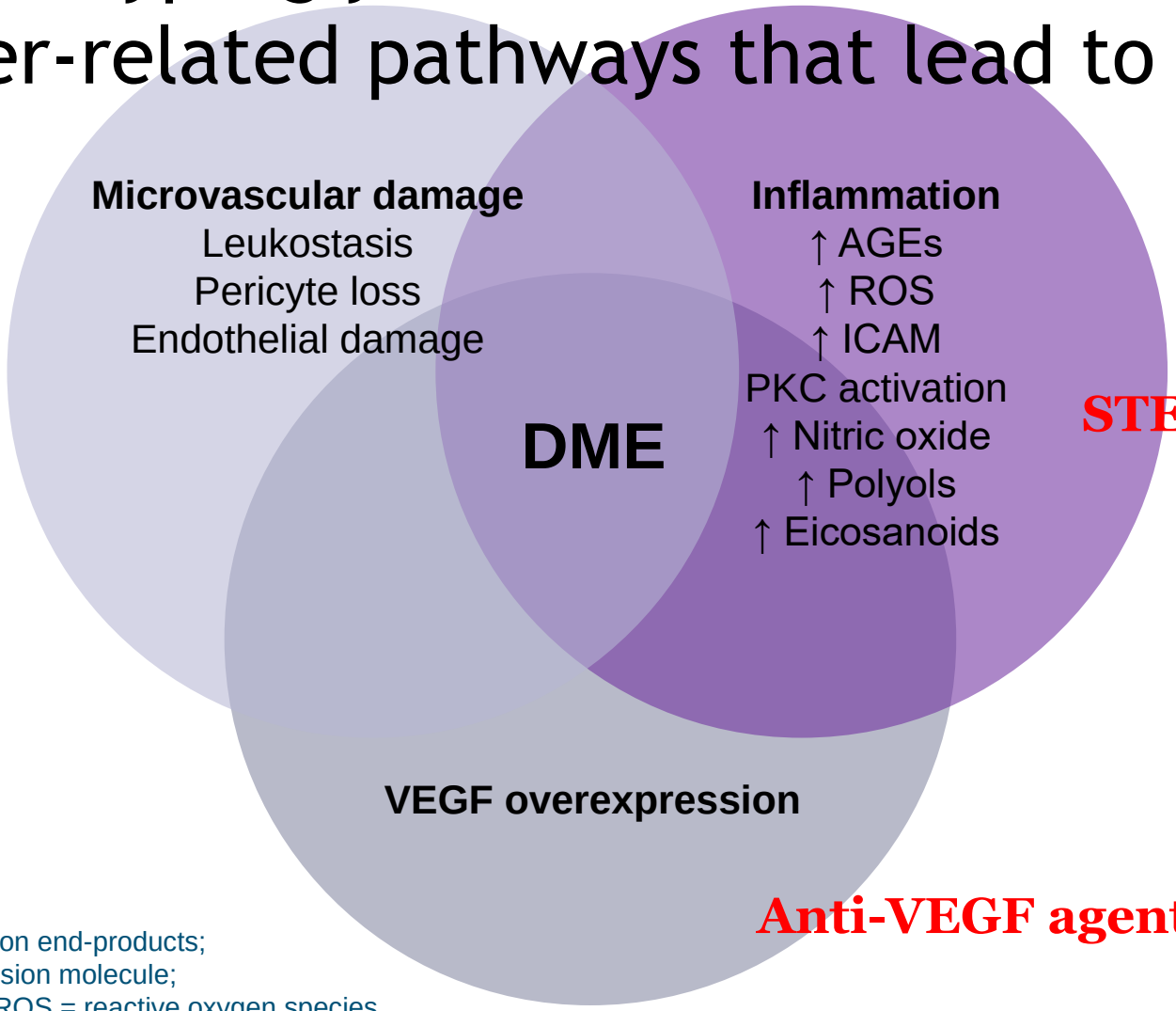
Subthreshold micropulse laser for DME

- Severity of macular oedema influences the effectiveness of laser
- Patients with CFT greater than 400um do not respond well



Ophthalmic surg lasers imag retina 2016;47(11) 985-990
Eye (Lond) 2014 Dec;28(12):1418-24.

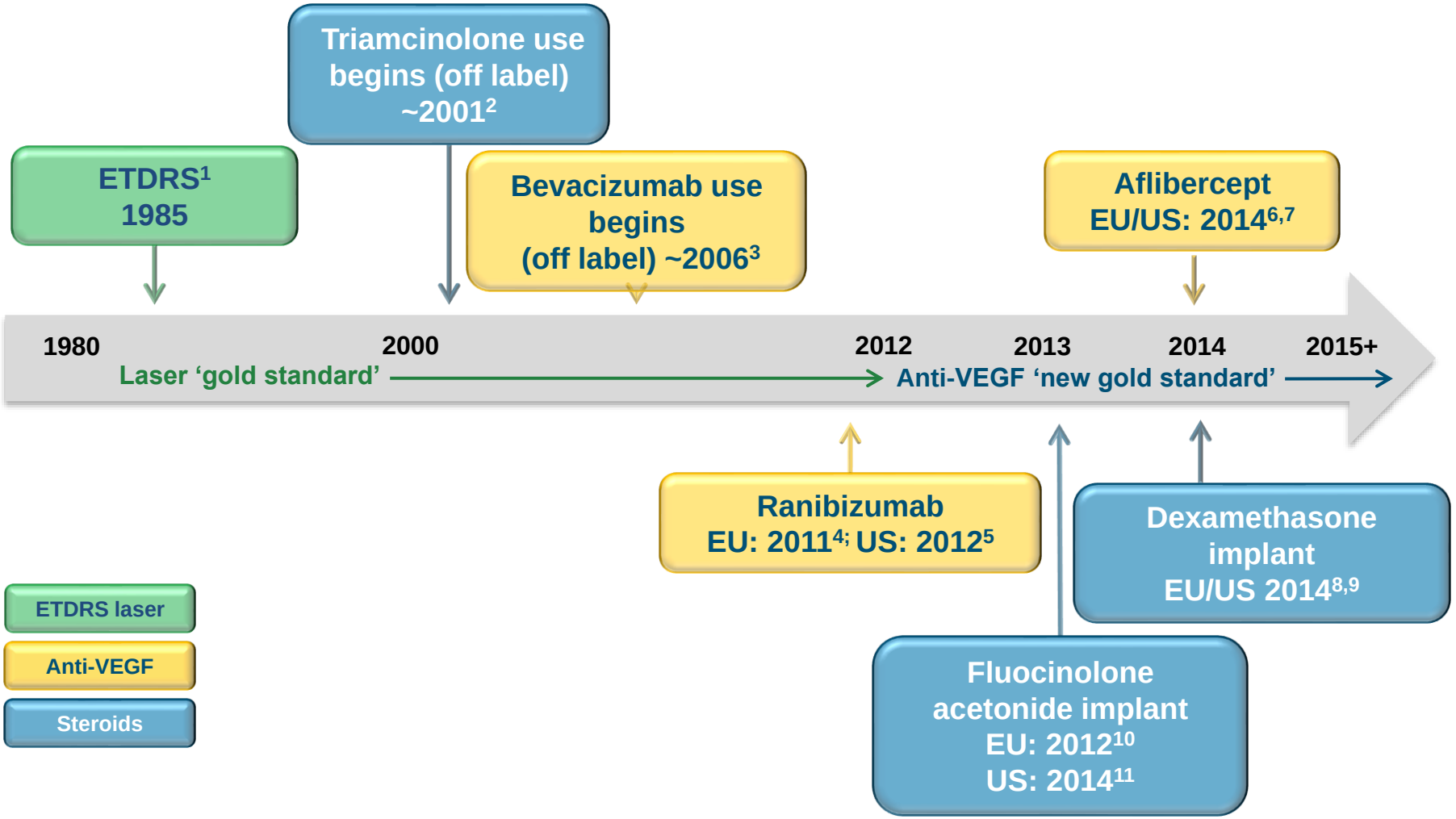
Chronic hyperglycemia initiates a number of inter-related pathways that lead to DME



AGEs = advanced glycation end-products;
ICAM = intercellular adhesion molecule;
PKC = protein kinase C; ROS = reactive oxygen species.

Boyer DS, et al. *Ther Adv Endocrinol Metab*. 2013;4(6):151–169.

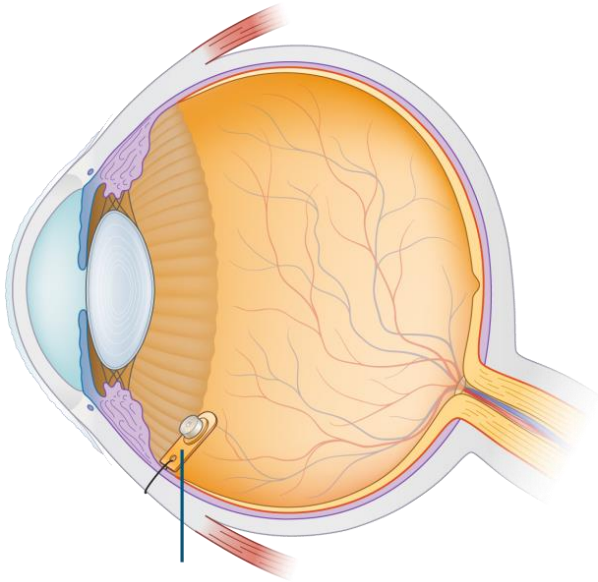
Pharmacological treatment of DME



Dates shown are the dates regulatory approval was obtained.

Role of steroids in DME

- Steroids reduce the activity of inflammatory cytokines and growth factors such as VEGF that are elevated in DME[1]
- Three synthetic glucocorticoids
- **Intravitreal steroid injection:**
  - Triamcinolone acetonide (Kenalog®, Triesence®)
    - off-label
    - Typically effective for up to 3 months
    - Repeated injections may be needed to maintain treatment benefit
- **Extended-release steroid implants:**
  - Dexamethasone (Ozurdex®)
  - Fluocinolone acetonide (Retisert®, Iluvien®)
    - Implants are surgically inserted into the vitreous body, allowing regular release of steroid for up to 3 years



Intravitreal steroid implant device

1. Funatsu H, et al. *Ophthalmology*. 2009;116(1):73–79; 2. Schwartz SG, et al. *Curr Ophthalmol Rep*. 2013;1(3):144-149.

Role of steroids in DME

- Steroids have demonstrated efficacy, alone and in combination, for the treatment of DME[1]
- Steroid therapy is considered for patients with:[2-4]
  - Recalcitrant DME
  - Pseudophakic eyes
- A reduction in treatment frequency with long-acting steroids can make this therapeutic approach appealing for some patients[1]
- However, the frequency of secondary cataracts and increased intraocular pressure as adverse effects are important treatment considerations[1]

1. Schwartz SG, et al. *Curr Ophthalmol Rep*. 2013;1(3):144–149; 2. American Academy of Ophthalmology Preferred Practice Pattern – Diabetic Retinopathy – Updated 2016; 3. Schmidt-Erfurth U, et al. Ophthalmologica. 2017;237(4):185-222; Cheung GC, et al. Clin Exp Ophthalmol. 2017 May 30. doi: 10.1111/ceo.12999

Anti-VEGF treatments for DME

- Bevacizumab (Avastin®)
  - Humanized, recombinant monoclonal antibody with high affinity for VEGF-A[1]
  - Approved in numerous markets for the systemic treatment of various cancers, and used extensively off-label for several ocular diseases, including DME[1,2]
- Ranibizumab (Lucentis®)
  - Humanized fragment of the same mouse parent monoclonal antibody as bevacizumab; specifically binds VEGF-A[3]
- Aflibercept (EYLEA®)
  - Fully human, recombinant fusion protein that binds VEGF-A and placental growth factor (PlGF)[4]

1. Roche. Avastin Summary of Product Characteristics. 2016; 2. Karmel M. www.aao.org/publications/eyenet/201001/feature.cfm; 3. Gupta N, et al. *Open Ophthalmol J*. 2013;7:4–10; 4. Bayer. EYLEA Hong Kong Prescribing Information . 2017.

Ranibizumab: Key phase III studies in DME

	RISE and RIDE	RESTORE	RETAIN	REVEAL	DRCR Protocol I
Treatment groups	RBZ 0.3 mg monthly RBZ 0.5 mg monthly Sham injection monthly	RBZ 0.5 mg PRN* + sham laser RBZ 0.5 mg PRN* + laser Laser + sham injection	RBZ 0.5 mg T&E RBZ 0.5 mg T&E + laser RBZ 0.5 mg PRN	RBZ 0.5 mg PRN* + sham laser RBZ 0.5 mg PRN* + laser Laser + sham injection	RBZ 0.5 mg PRN + prompt laser RBZ 0.5 mg PRN + deferred laser** TMC 4 mg + prompt laser Laser + sham injection PRN
Primary endpoint assessment	24 months	12 months	12 months	12 months	12 months
Mean change in BCVA (ETDRS letters)	RBZ 0.3 mg: 10.9–12.5 RBZ 0.5 mg: 11.9–12.0 Sham: 2.3–2.6	RBZ: 6.8 RBZ + laser: 6.4 Laser: 0.9	RBZ T&E: 6.8 RBZ T&E + laser: 6.8 RBZ PRN: 7.4	RBZ: 6.6 RBZ + laser: 6.4 Laser: 1.8	RBZ + prompt laser: 9 RBZ + deferred laser: 9 TMC + laser: 4 Laser: 3
Mean average change in BCVA (ETDRS letters)	N/A	RBZ: 6.1 RBZ + laser: 5.9 Laser: 0.8	RBZ T&E: 6.1 RBZ T&E + laser: 5.9 RBZ PRN: 6.2	RBZ: 5.9 RBZ + laser: 5.7 Laser: 1.4	N/A

*After 3 monthly loading doses; ** ≥ 24 weeks.
N/A: Not available; RBZ: ranibizumab; T&E: Treat and extend; TMC: triamcinolone.

Aflibercept: Key trials in DME

DA VINCI (Phase II)
- Investigated different dosing regimens of aflibercept versus macular laser photocoagulation[1]

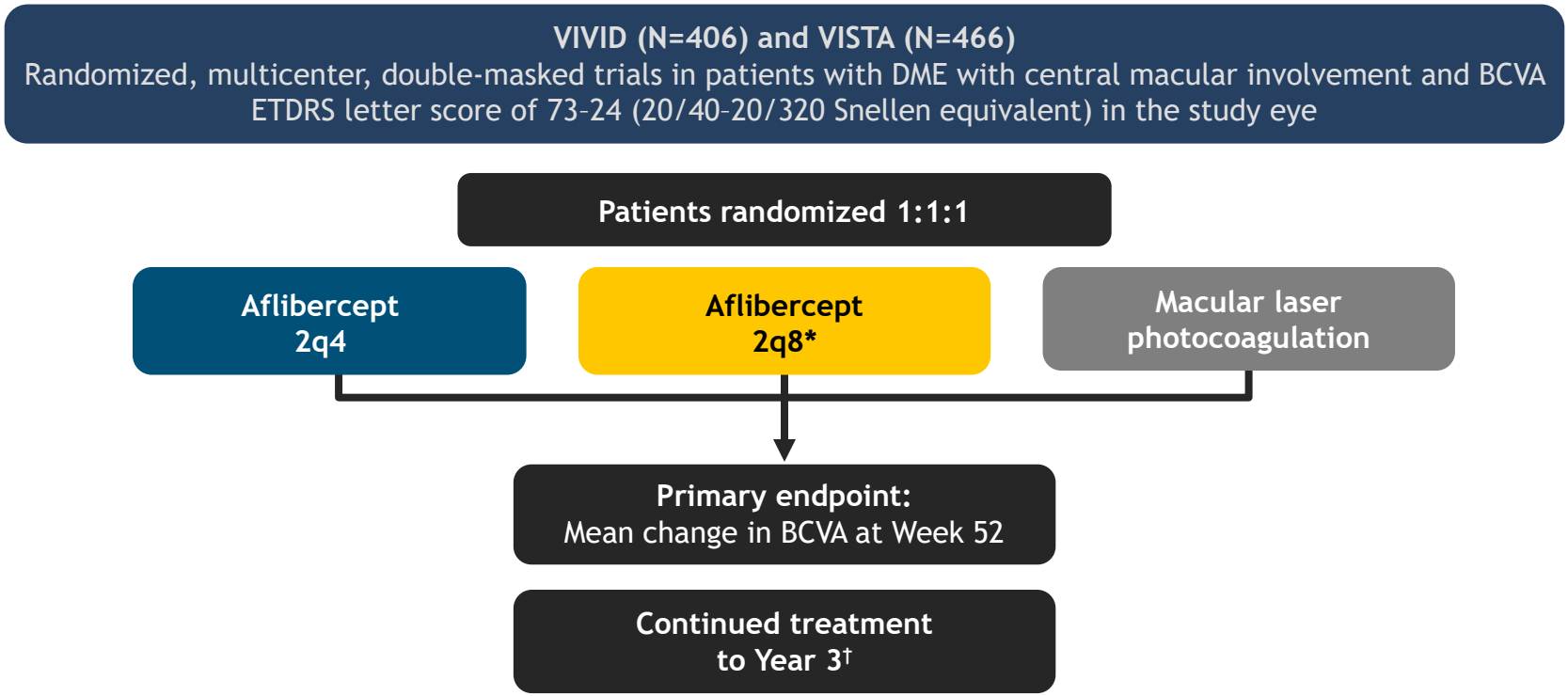
VIVID^{DME} and VISTA^{DME} (Phase III)
- Designed to investigate the efficacy and safety of repeated doses of aflibercept versus macular laser photocoagulation; both 3-year studies[2]

VIVID^{East} (Phase III)
- Same design as VIVID and VISTA, but with a total duration of 52 weeks[3]

VIVID^{Japan} (Phase III)
- Designed to evaluate the safety and tolerability of aflibercept in Japanese patients to support the regulatory submission of aflibercept in Japan[4]

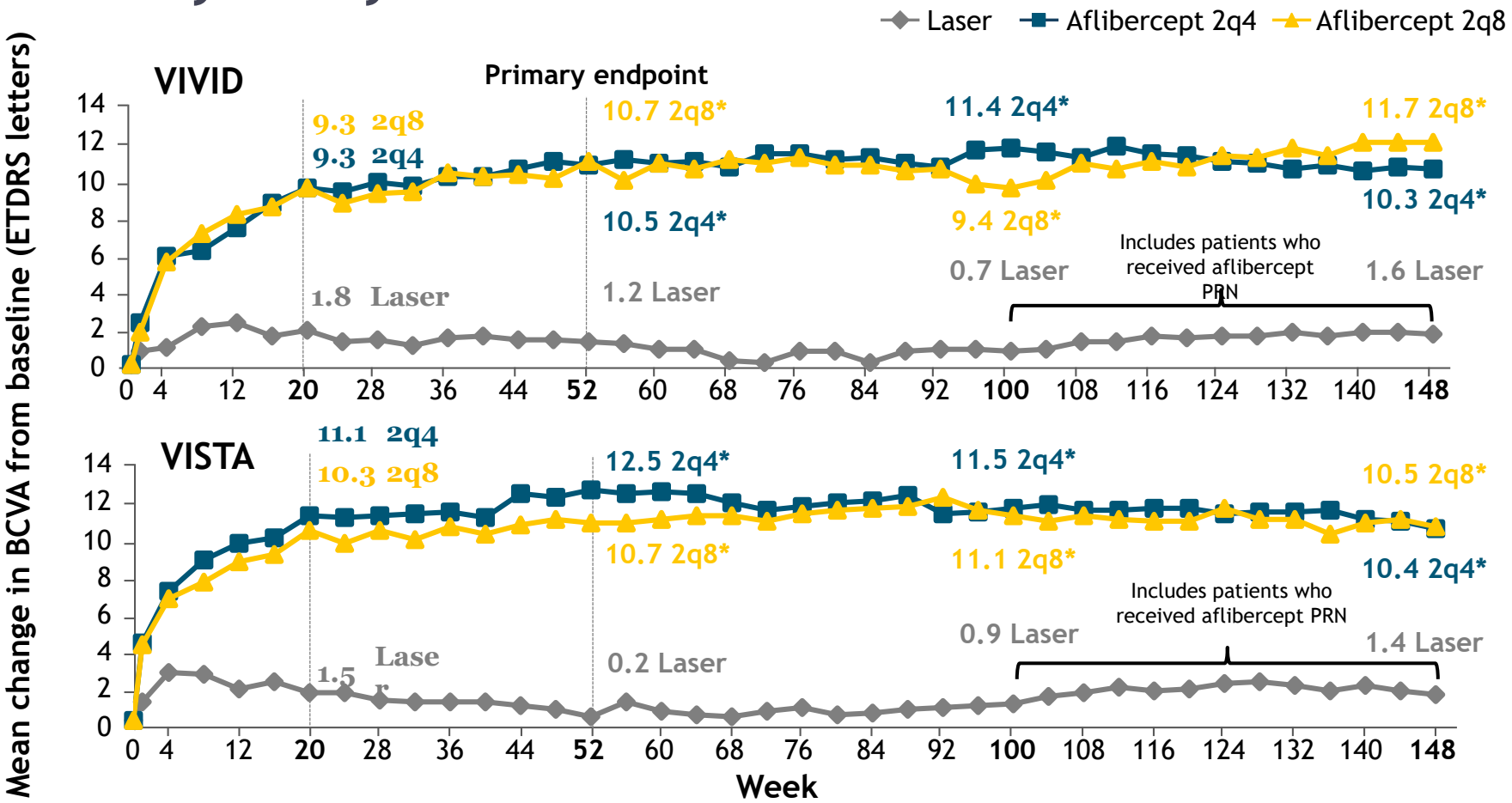
1. Do DV, et al. *Ophthalmology*. 2011;118(9):1819–1826; 2Korobelnik J-F et al. Ophthalmology 2014; 121 (11): 2247–2254.; 3. Clinicaltrials.gov. http://clinicaltrials.gov/ct2/show/NCT01783886. Accessed June 13, 2014; 4. Clinicaltrials.gov. http://clinicaltrials.gov/ct2/show/NCT01512966. Accessed June 13, 2014.

VIVID and VISTA: Study design



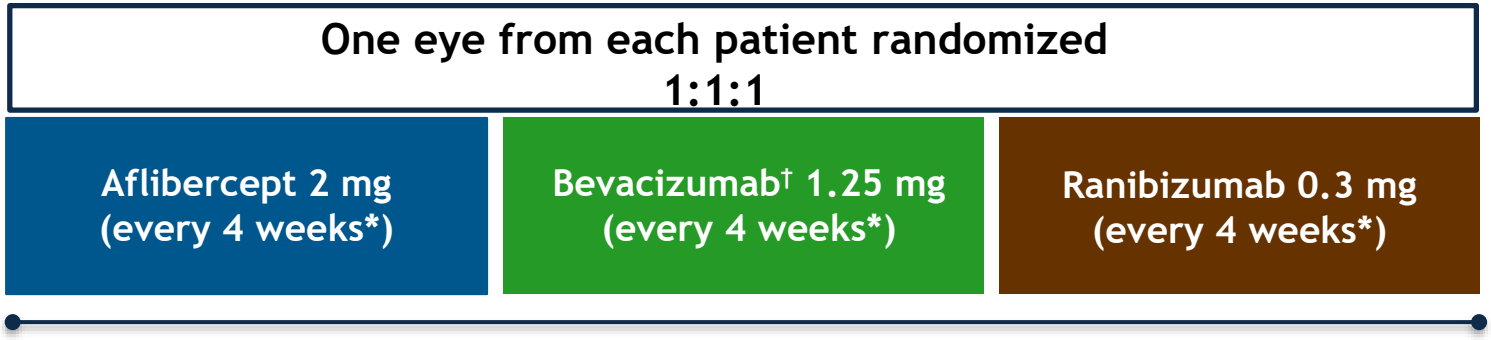
*Following 5 initial monthly doses. †Patients in the laser group were eligible to receive aflibercept 2 mg PRN during Year 3.
2q4, 2 mg every 4 weeks; 2q8, 2 mg every 8 weeks; BCVA, best corrected visual acuity; DME, diabetic macular edema; ETDRS, Early Treatment Diabetic Retinopathy Study; PRN, *pro re nata* (as needed).
Korobelnik J-F *et al*. *Ophthalmology* 2014; 121 (11): 2247–2254.

Mean change in BCVA to Week 148: Primary analysis[1–3]



*P<0.0001 vs. laser. VIVID: control n=132; 2q4 n=136; 2q8 n=135. VISTA: control n=154; 2q4 n=154; 2q8 n=151. Full analysis set; LOCF, censoring measurements after rescue treatment was given. 2q4, 2 mg every 4 weeks; 2q8, 2 mg every 8 weeks, following 5 initial monthly doses; BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; LOCF, last observation carried forward; PRN, *pro re nata* (as needed). 1. Korobelnik J-F *et al*. *Ophthalmology* 2014; 121 (11): 2247–2254. 2. Brown DM *et al*. *Ophthalmology* 2015; 122 (10): 2044–2052. 3. Heier JS *et al*. *Ophthalmology* 2016; 123 (11): 2376–2385.

The DRCR.net Protocol T study compared efficacy of aflibercept and ranibizumab for visual impairment due to DME[1,2]

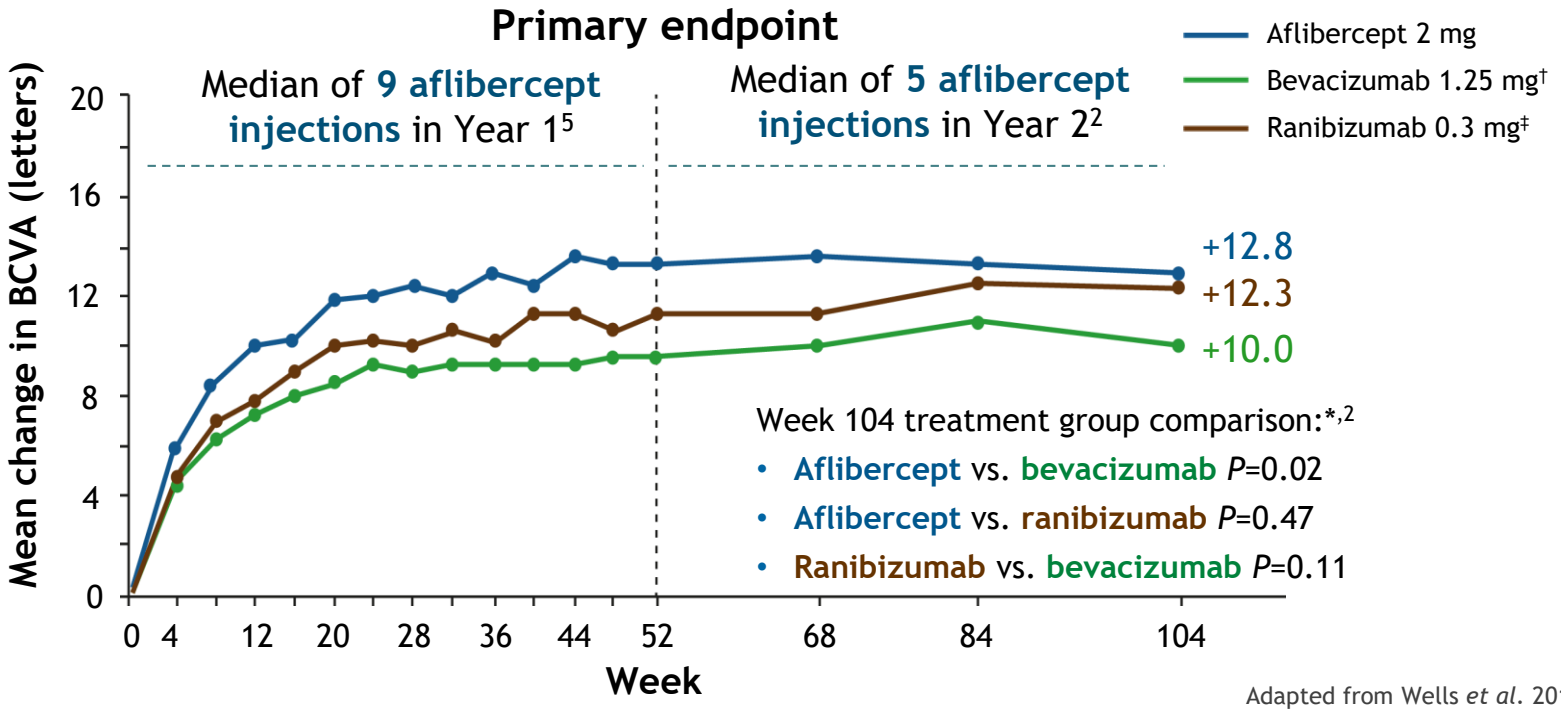


Primary endpoint: Mean change in VA at 1 year, adjusted for baseline VA using intention-to-treat principle

(Year 2: Visits occur every 4–16 weeks depending on disease status and treatment)

*Treatment decision based on OCT and VA criteria. †Bevacizumab is not licensed for the treatment of visual impairment due to DME.
DME, diabetic macular edema; DRCR.net, Diabetic Retinopathy Clinical Research Network; OCT, optical coherence tomography; VA, visual acuity.
1. Diabetic Retinopathy Clinical Research Network. *N Engl J Med* 2015; 372 (13): 1193–1203. 2. Wells JA *et al*. *Ophthalmology* 2016; 123 (6): 1351–1359.

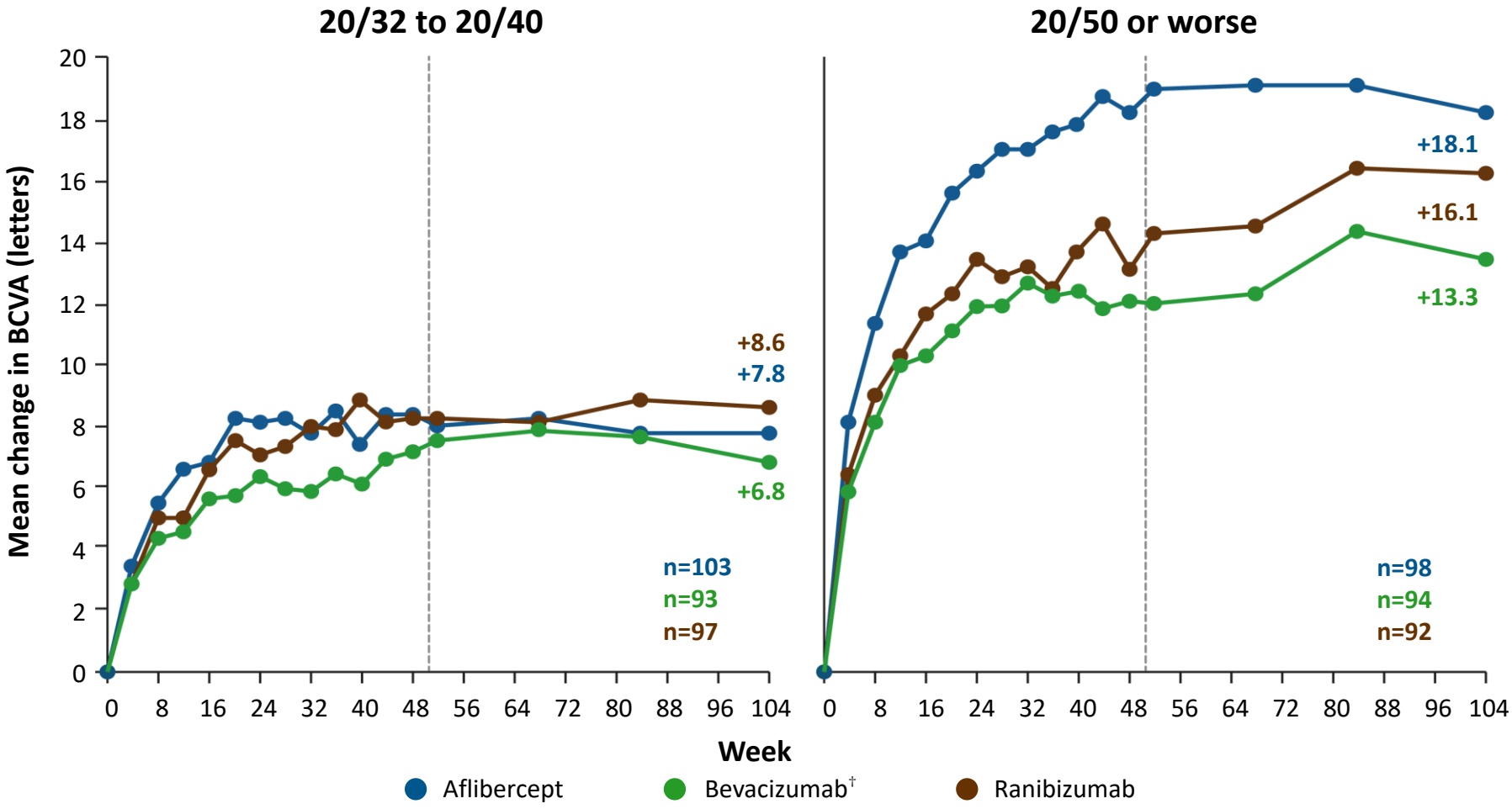
Visual outcomes with aflibercept were maintained in Year 2, with fewer injections than in Year 1



Adapted from Wells *et al*. 2016

**P*-values adjusted for baseline VA and multiple comparisons. †Bevacizumab is not licensed for the treatment of visual impairment due to DME. ‡The licensed dose for ranibizumab in Hong Kong is 0.5 mg; please consult your local prescribing information. Patient numbers at Year 2: aflibercept = 201, bevacizumab = 185, ranibizumab = 191. BCVA, best corrected visual acuity; VA, visual acuity. 1. Wells JA *et al*. *Ophthalmology* 2016; 123 (6): 1351–1359. 2. Wells JA *et al*. *Ophthalmology* 2016; 123 (6): 1351–1359 – supplementary appendix. 3. Korobelnik J-F *et al*. *Ophthalmology* 2014; 121 (11): 2247–2254. 4. Brown DM *et al*. *Ophthalmology* 2015; 122 (10): 2044–2052. 5. Diabetic Retinopathy Clinical Research Network. *N Engl J Med* 2015; 372 (13): 1193–1203 – supplementary appendix.

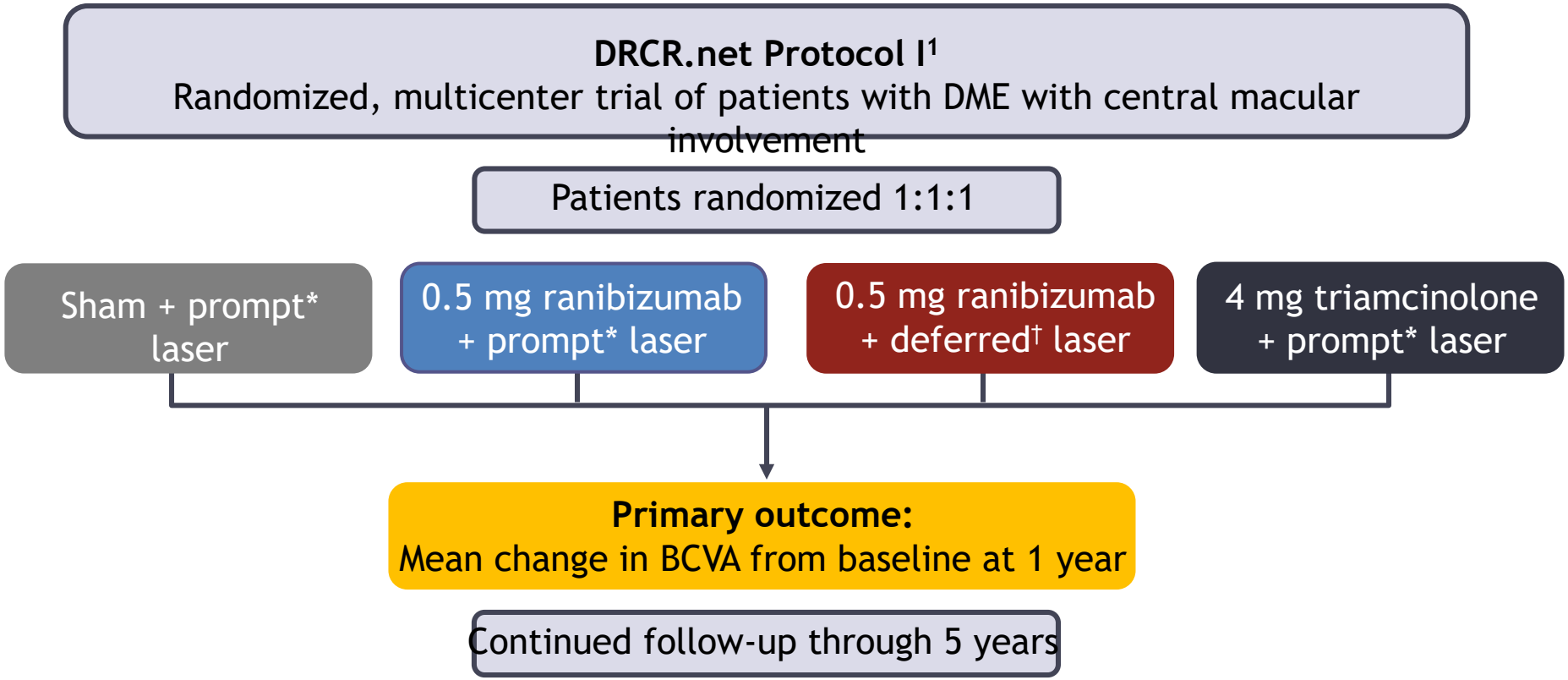
Mean change in VA over 2 years: By baseline VA subgroup



†Bevacizumab is not licensed for the treatment of visual impairment due to DME.
BCVA, best corrected visual acuity; DME, diabetic macular edema; VA, visual acuity.
Wells JA *et al*. *Ophthalmology* 2016; 123 (6): 1351–1359.

Long term management of DME with anti-VEGF

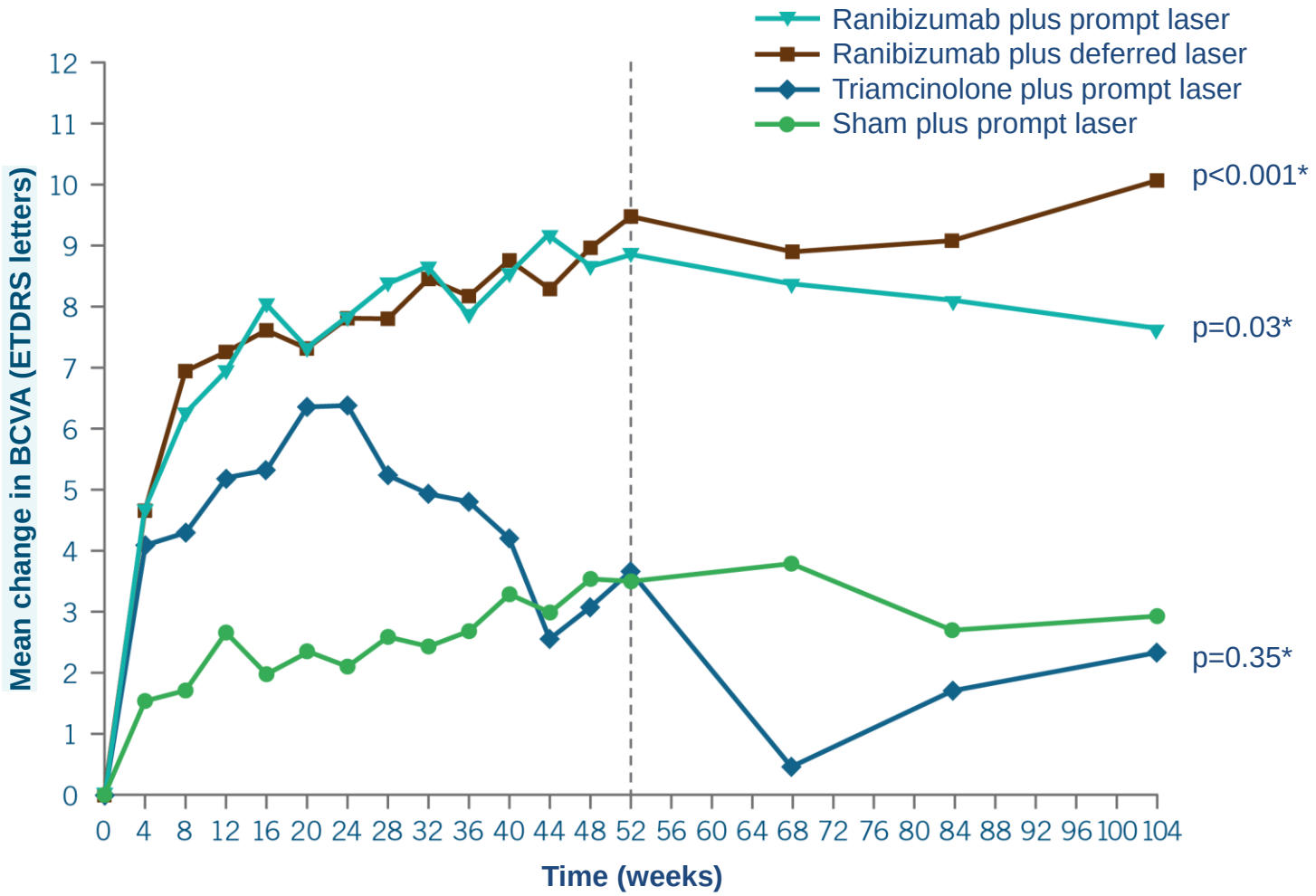
Protocol I: Study design



- Patients randomized to the triamcinolone + laser group were given the opportunity to initiate very deferred‡ ranibizumab plus continued laser (if indicated)[2]

*Within 3–10 days. †≥24 weeks. ‡Between 1.5 and 3 years following enrollment.
BCVA, best corrected visual acuity; DME, diabetic macular edema; DRCR.net, Diabetic Retinopathy Clinical Research Network.
1. Diabetic Retinopathy Clinical Research Network. *Ophthalmology* 2010; 117 (6): 1064–1077. 2. Bressler SB *et al*. *Am J Ophthalmol* 2016; 164: 57–68.

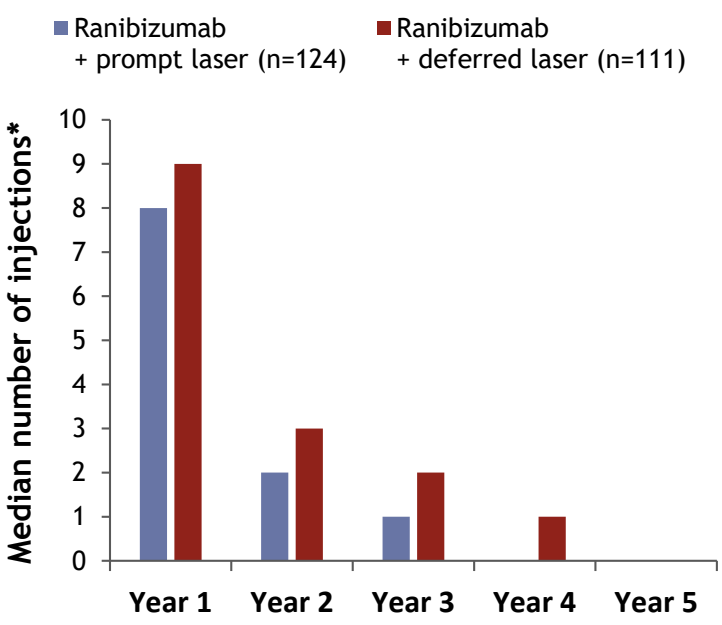
DRCR.net Protocol I: Mean change in BCVA over 104 weeks

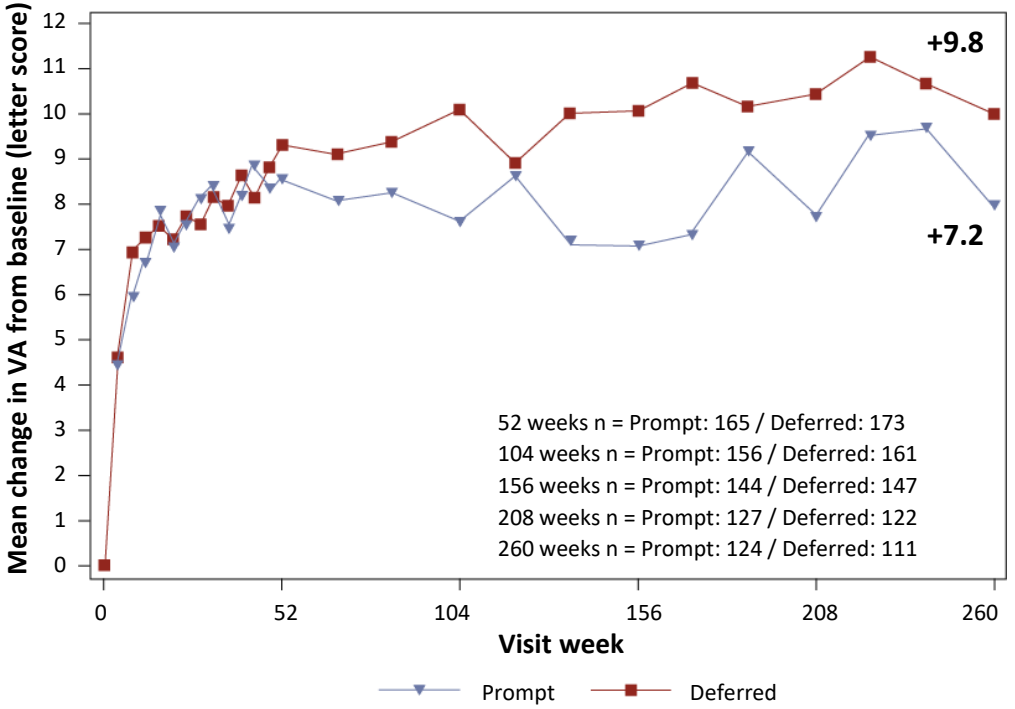


*Versus sham plus prompt laser.

Elman MJ, et al. *Ophthalmology*. 2011;118(4):609-614.

Protocol I: Ranibizumab injection number and change in VA over 5 years





Most eyes treated with ranibizumab and either prompt or deferred laser maintained first-year vision gains over 5 years, with little additional treatment after 3 years

*Only eyes that completed the 5-year visit.
VA, visual acuity.
Elman MJ *et al. Ophthalmology* 2015; 122 (2): 375–381.

Recommendations on DME management based on key clinical trials

- Anti-VEGF therapy should be given as a first-line treatment for patients with centre-involved DME with vision loss[2-5]
- Choice of anti-VEGF agent depends on baseline vision[2,4,5]
- Early intensive therapy with anti-VEGF agents is important to reduce long term burden[2,5]
- Laser treatment may be considered in non-centre-involving DME[2-5]
- Corticosteroid may be considered in non-responders to anti-VEGFs, or in pseudophakic or postvitrectomy eyes[4,5]

1. Strain WD, et al. Diabetes Res Clin Pract. 2017 Apr;126:1-9; 2. International Council of Ophthalmology Guidelines for Diabetic Eye Care Update 2017; 3. American Academy of Ophthalmology Preferred Practice Pattern – Diabetic Retinopathy – Updated 2016; 4. Cheung GC, et al. Clin Exp Ophthalmol. 2017 May 30. doi: 10.1111/ceo.12999; 5. Schmidt-Erfurth U, et al. Ophthalmologica. 2017;237(4):185-222

In reality:

- Clear published evidence on the use of pharmacologic treatment for DME
- Actual clinical usage dictated by practical considerations like medication availability, affordability and waiting times
- Delay in treatment may cause poor outcome

Summary

- Most patients are asymptomatic until they develope advanced DMR
- To prevent irreversible visual loss, early diagnosis of DMR and DME through regular screening and timely referral helps to ensure prompt treatment
- Control of systemic condition is essential while patients are having more treatment options
- Laser therapy are evolving with increased efficacy and minimzing adverse effects
- Pharmacological treatment with anti-VEGF and steroids have shown to improve visual function and quality of life in patients with DME

Thank you