NEW AND EMERGING THERAPIES FOR DIABETIC MACULAR EDEMA (DME)

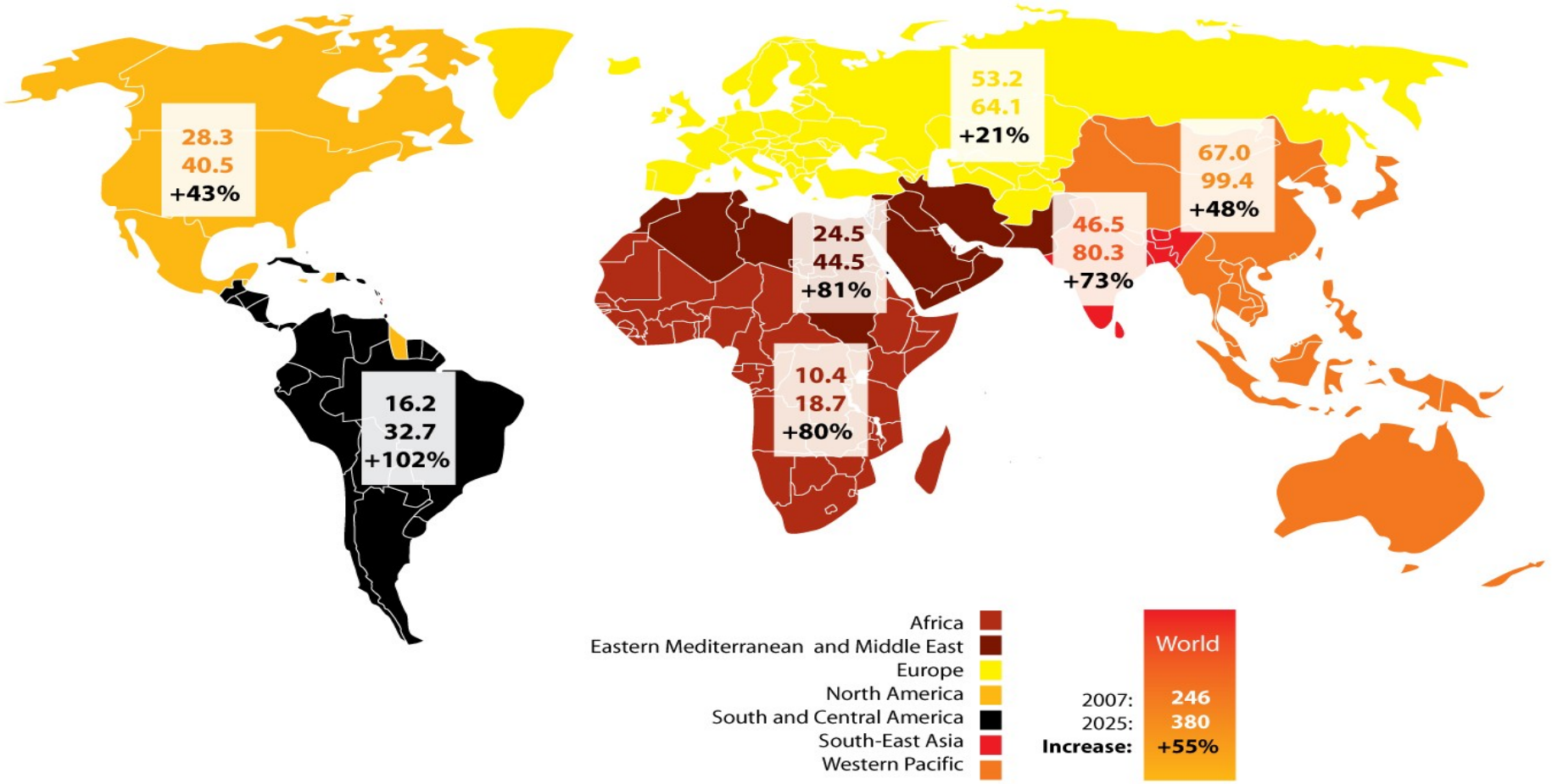
ASIWOME SENEADZA, MD

CONSULTANT EYE SURGEON

RETINA SPECIALIST

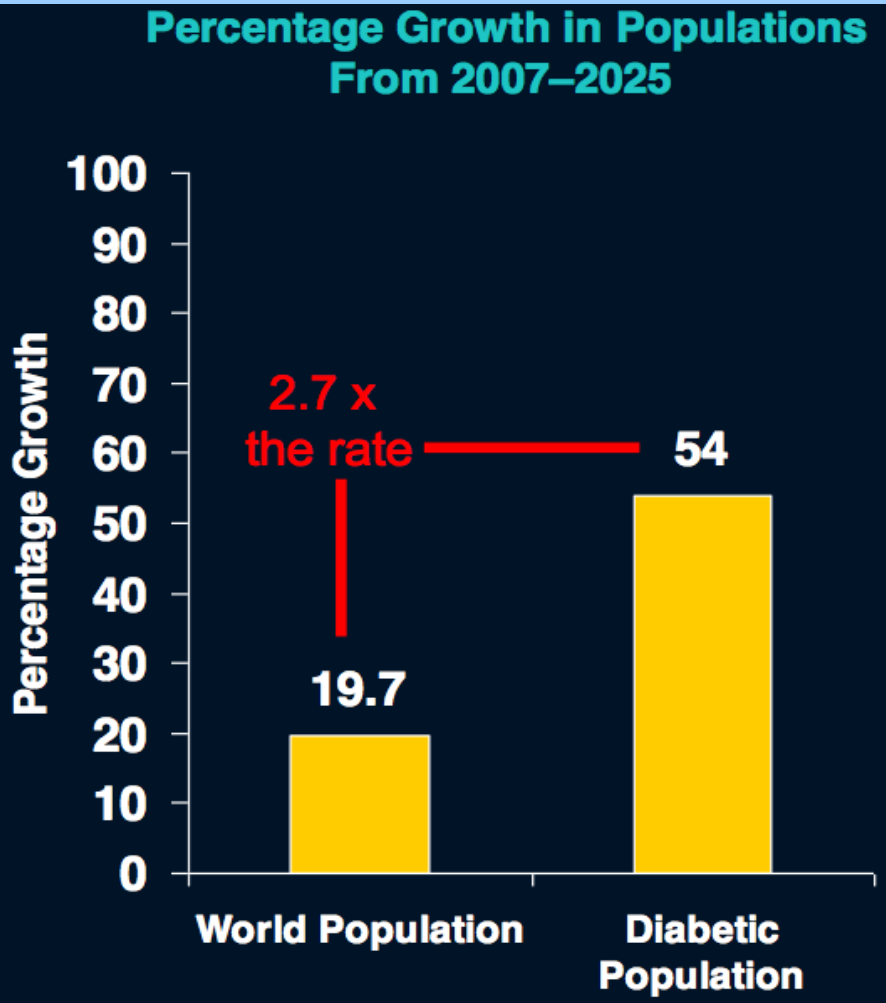
GLOBAL MAGNITUDE OF DIABETICS

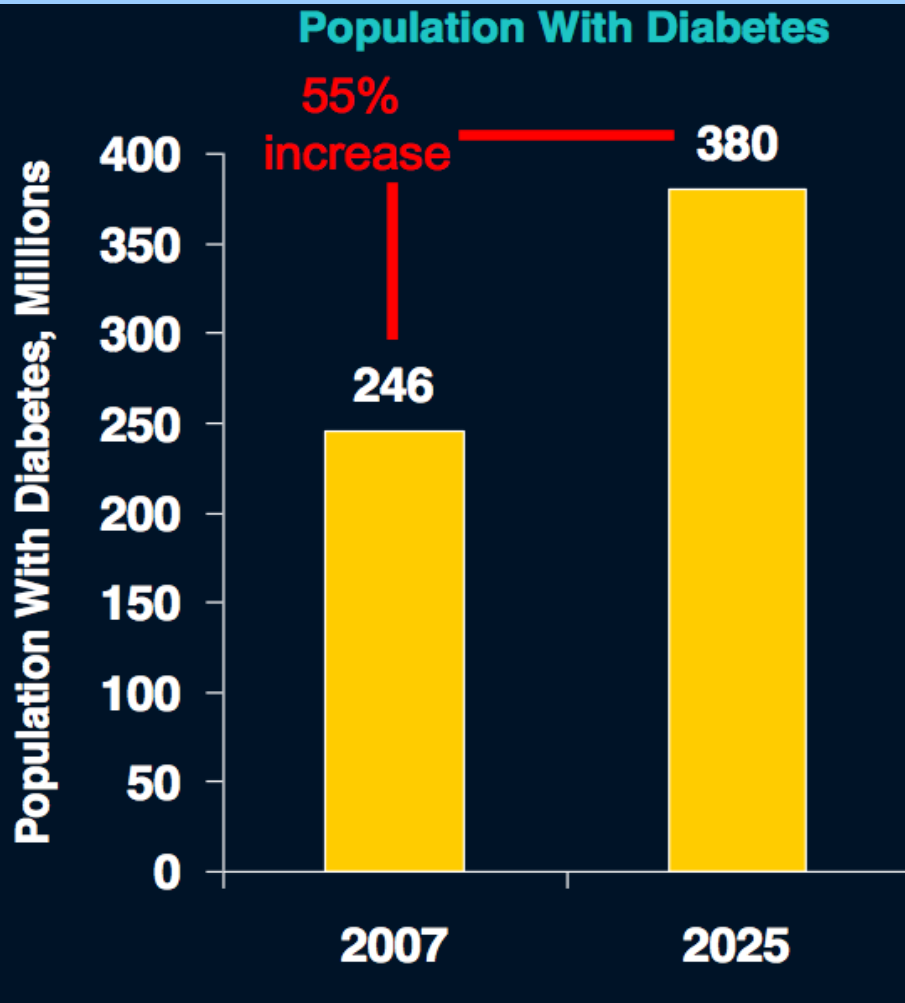
Global projections for the number of people with diabetes (20-79 age group), 2007-2025 (millions)



SOURCE: *DIABETES ATLAS THIRD EDITION.* © INTERNATIONAL DIABETES FEDERATION, 2006

GLOBAL MAGNITUDE OF DIABETICS





Each year another 7 million people develop diabetes

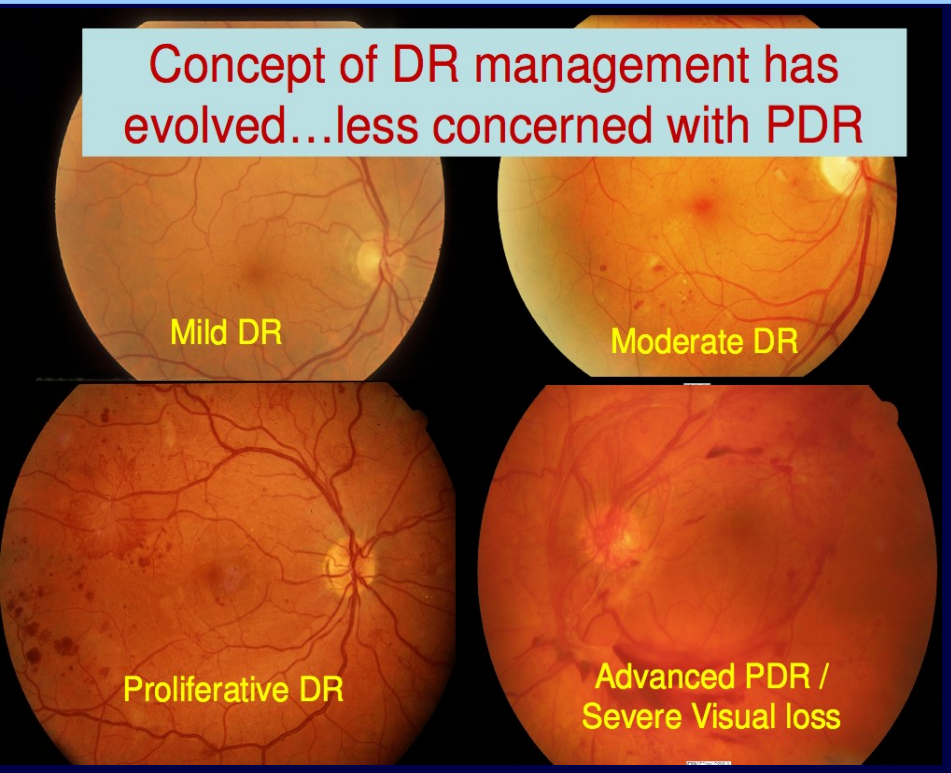
1) *Diabetes Atlas*, 3rd ed, International Diabetes Federation, 2006.

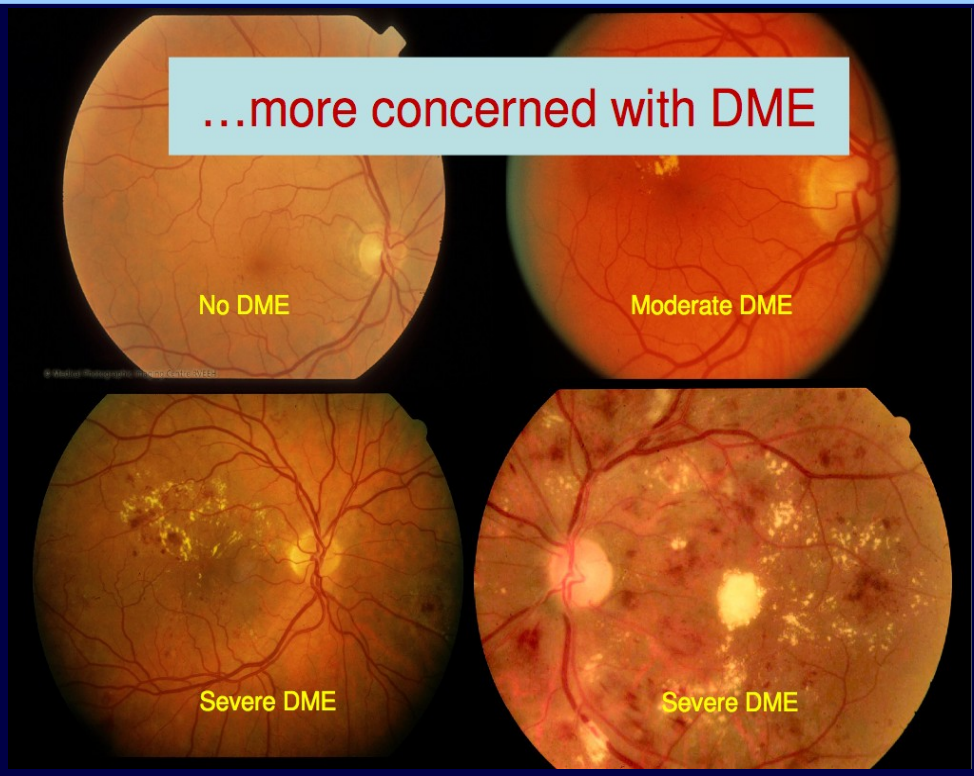
Definition of DME

- Swelling of the retina due to leaking of fluid from blood vessels within the macula in patients with diabetes
- Thickening of the basement membrane and a reduction in the number of pericytes are believed to lead to increased permeability and leakage of plasma constituents in the surrounding retina, resulting in retinal edema

http://www.medterms.com/script/main/art.asp?articlekey=16569. Accessed February 2009

NEED & MAGNITUDE – PARADIGM SHIFT





- Most common complications are microvascular changes
- Diabetic macula edema (DME) is a common cause of blindness in people of working age[2,3] and can develop in both Type 1 and 2 DM
- About 8% of diabetic patients develop DME with visual impairment

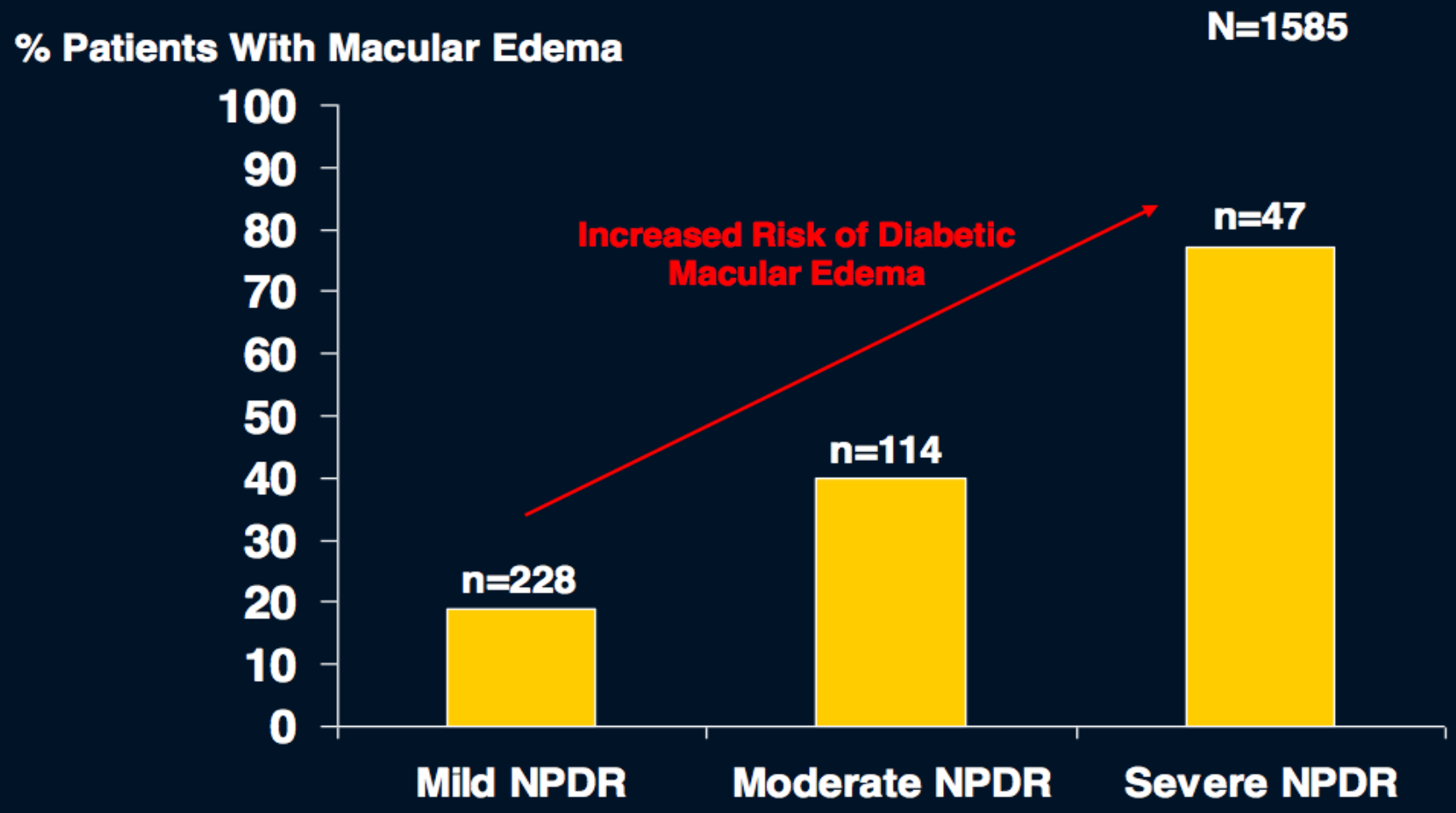
NEED & MAGNITUDE - DME AGAINST PDR

1. Affects ~ 30% of people with diabetes
2. 1 in 4 will lose 15 letters (3 lines) of visual acuity within 3 years

Global prevalence and nos. with DR & DME 2010 and 2030

	% (95% CI)*	No (millions) 2010	No (millions) 2030
Any DR	35.4 (35.2-35.6)	119.6	≈200
PDR	7.2 (7.1-7.3)	20.9	≈25
DME	7.5 (7.4-7.6)	19.1	≈35
VTDR	11.7 (11.6-11.8)	30.5	≈50

DME INCREASES AS NPDR PROGRESSES



NPDR: nonproliferative diabetic retinopathy.

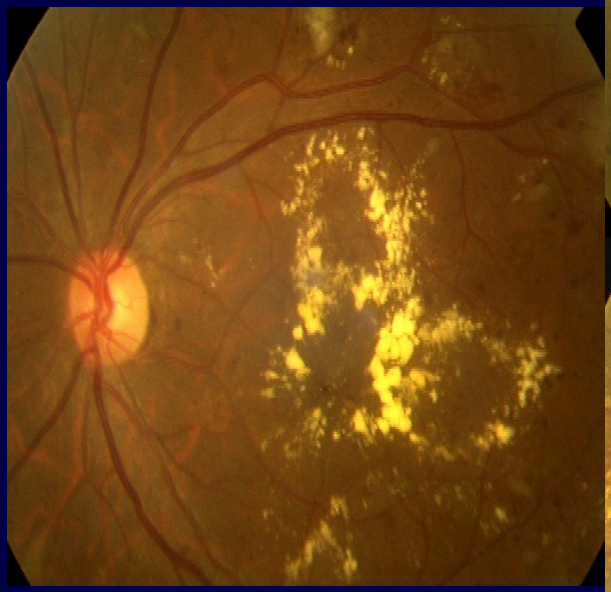
Figure reproduced from Henricsson M et al. *Acta Ophthalmol Scand.* 1999;77:218–223.

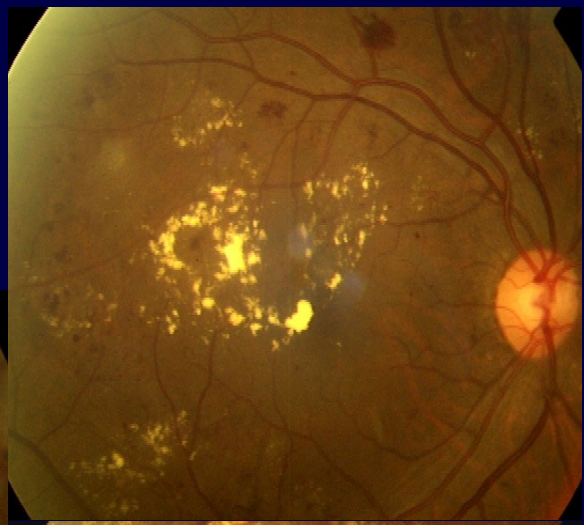
NEED AND MAGNITUDE – DME AFFECTS QoL

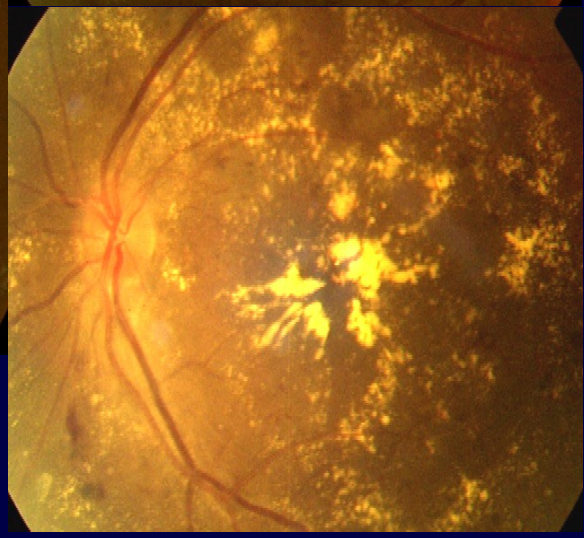
DME Can Significantly Impair Quality Of Life

Difficulty doing daily tasks: –

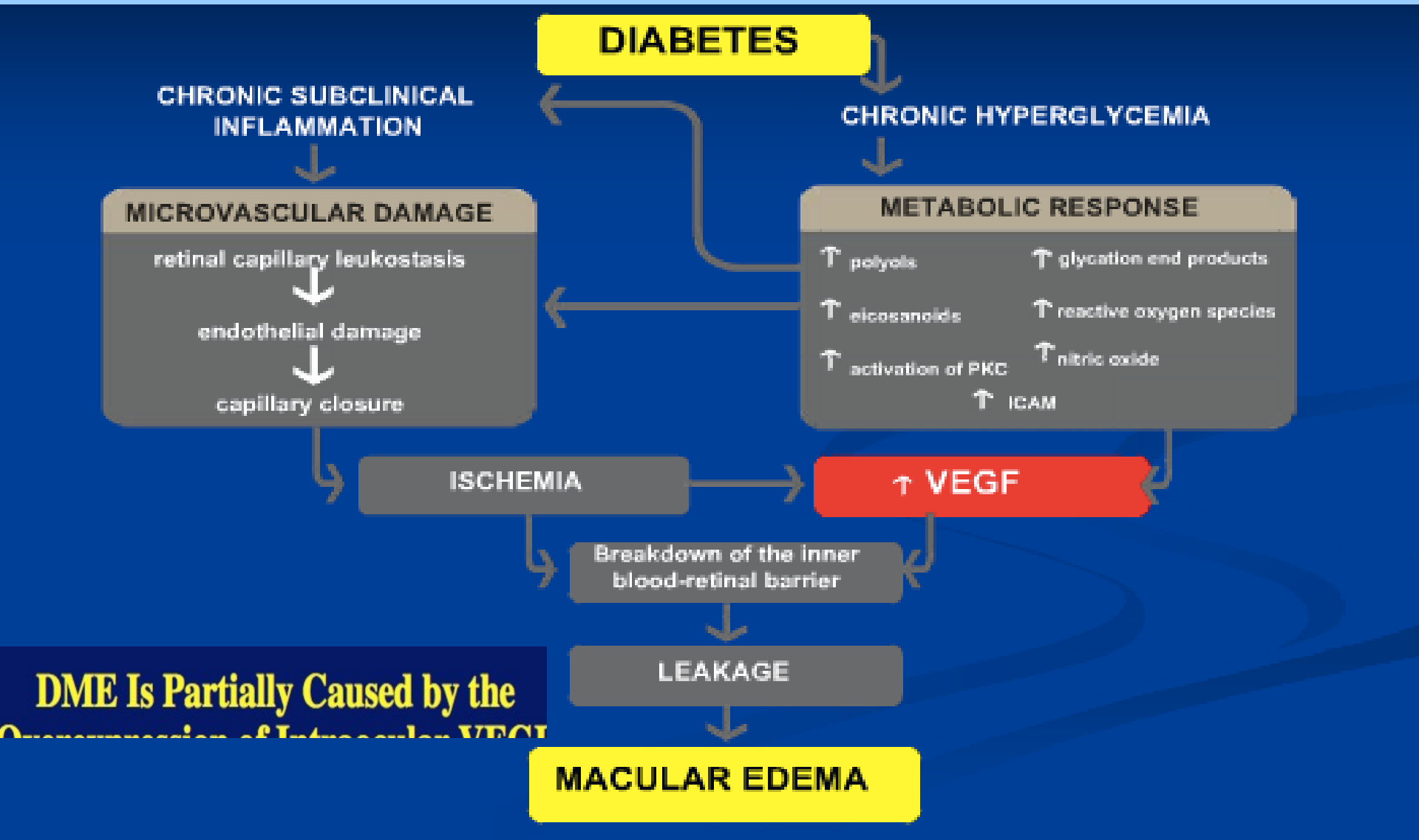
- **Insulin administration,**
- **Self-monitoring blood glucose**
- **Exercise**
- **Cooking**





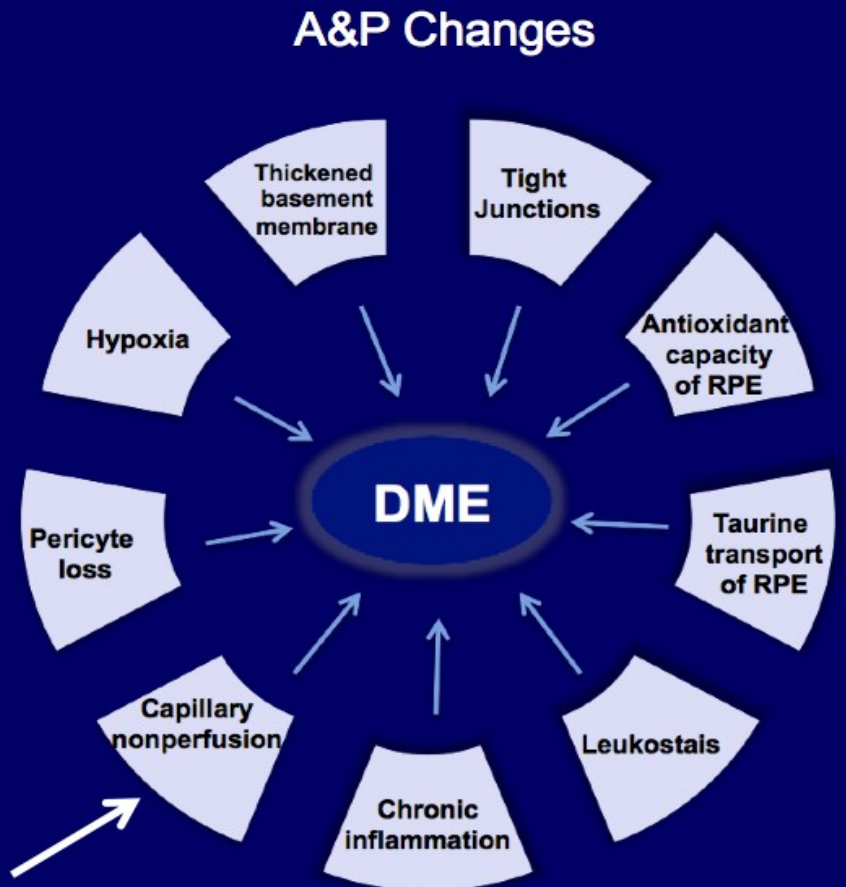


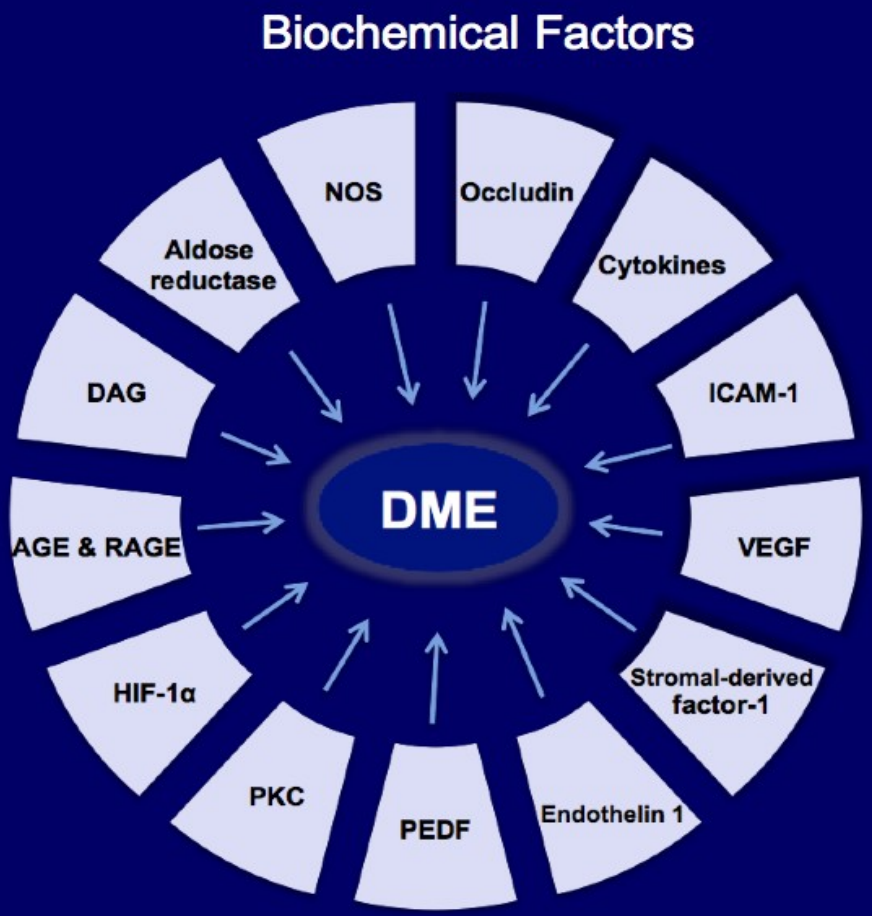
PATHOPHYSIOLOGY



DME Is Partially Caused by the

PATHOPHYSIOLOGY – ANATOMICAL, PHYSICAL AND BIOCHEMICAL MEDIATORS



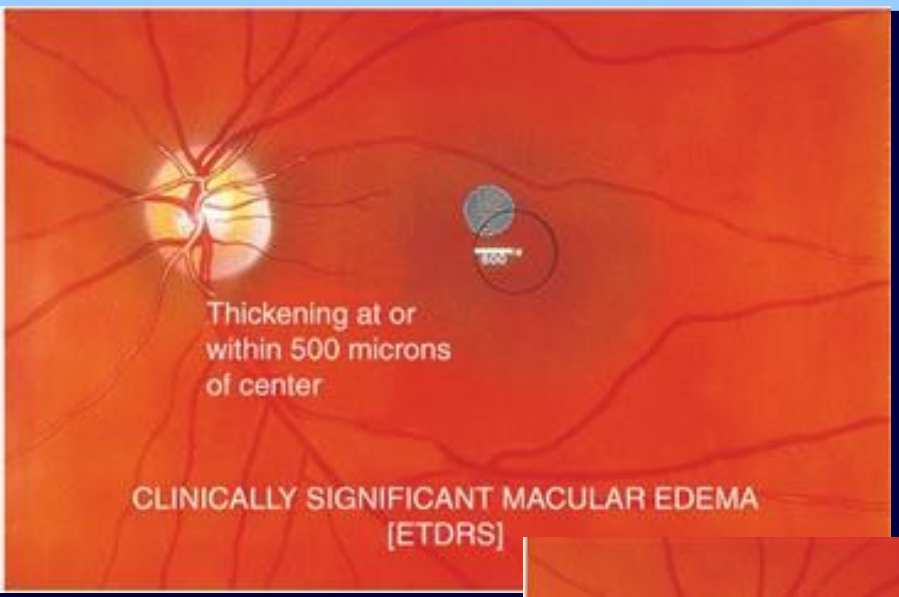


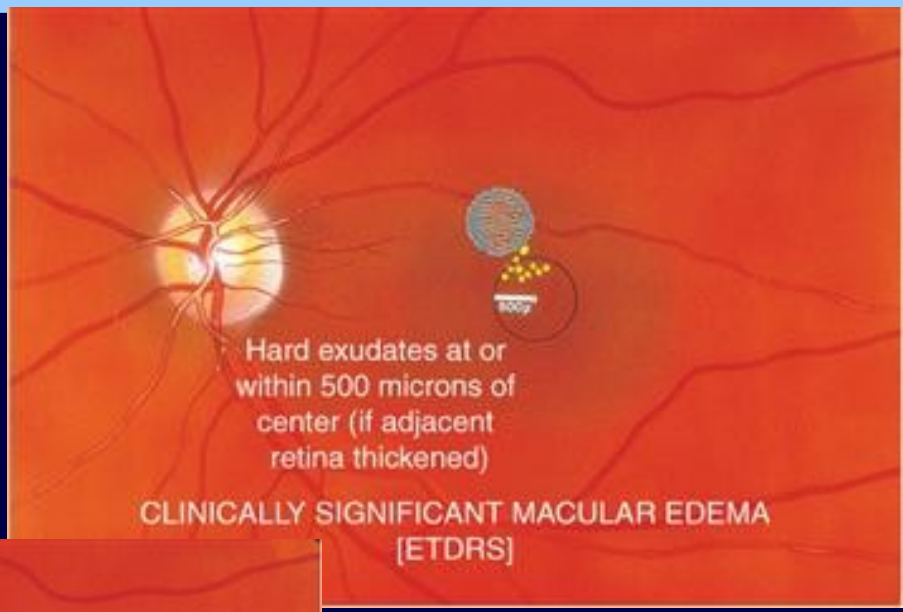
References: Pearson PA. DME treatment options: future therapies—corticosteroids. http://www.atpo.org/documents/handouts/DME.pdf,

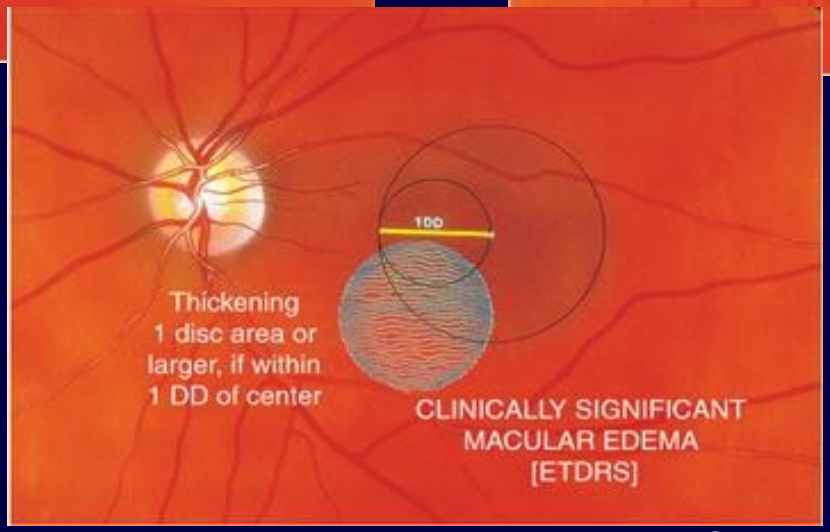
DAG=diacylglycerol; HIF=hypoxia-induced factor; ICAM=intercellular adhesion molecule; NOS=nitric oxide synthase; PEDF=pigment epithelium-derived factor; PKC=protein kinase C; VEGF=vascular endothelial growth factor.

DME CLASSIFICATION

CLASSIFICATION BASED ON SL FINDINGS







DMO

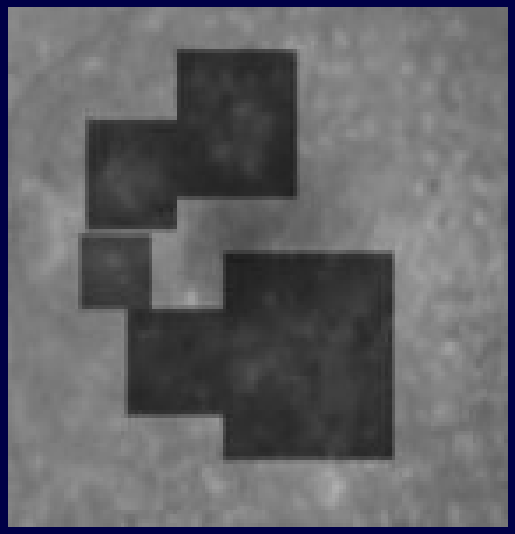
- ***Absent***
- ***Present***
  - ***Clinically significant mo***
  - ***Non clinically significant mo***
    - ***Thickening 1 disc area with different characteristics.***

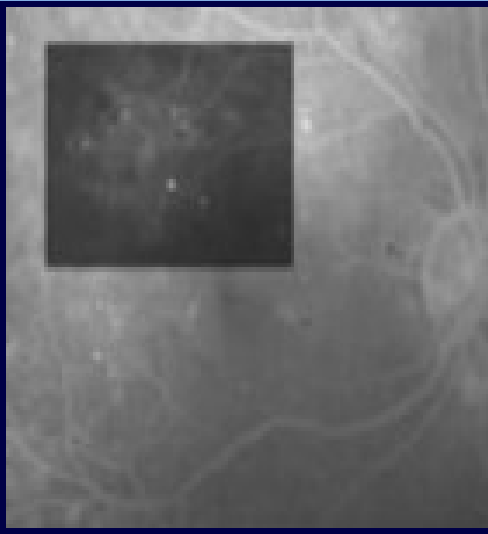
Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. Arch Ophthalmol. 1985;103(12):1796-806.

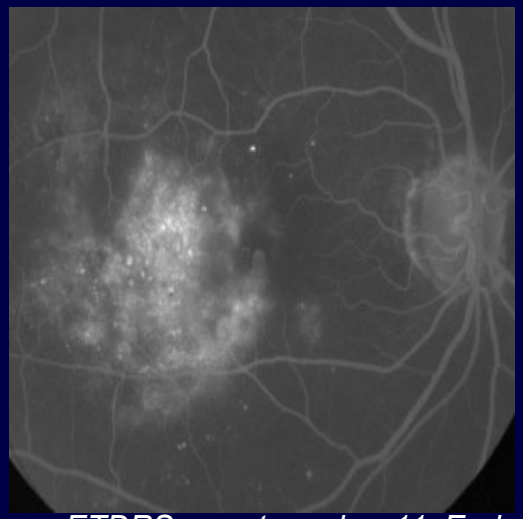
CLASSIFICATION BASED ON FFA FINDINGS

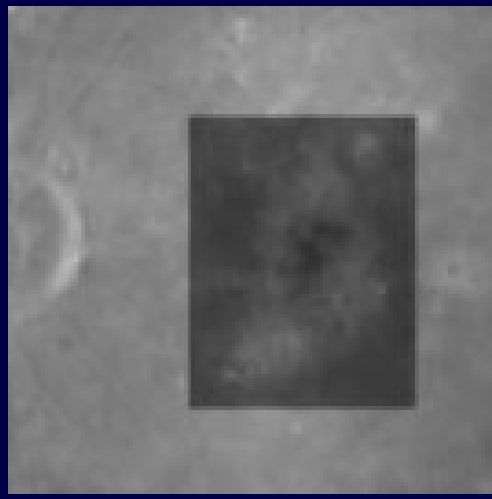
Depending on the location of leakage or loss of blood supply due to capillary loss. DMO can be classified as:

- **Focal maculopathy**: localized leakage (from 1 or more microAn)
- **Diffuse/indeterminate maculopathy**: generalised thickening of the central macula caused by widespread leakage from dilated capillaries.
- **Ischaemic maculopathy**: enlargement and alteration of the FAZ.
- **Mixed maculopathy**: combined pathology, particularly of diffuse oedema and ischaemia.





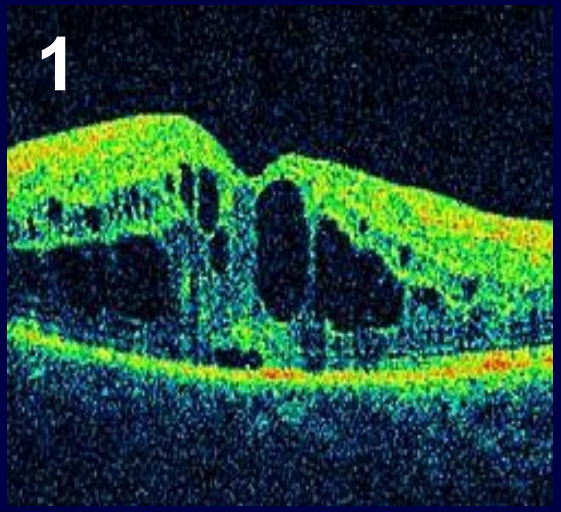


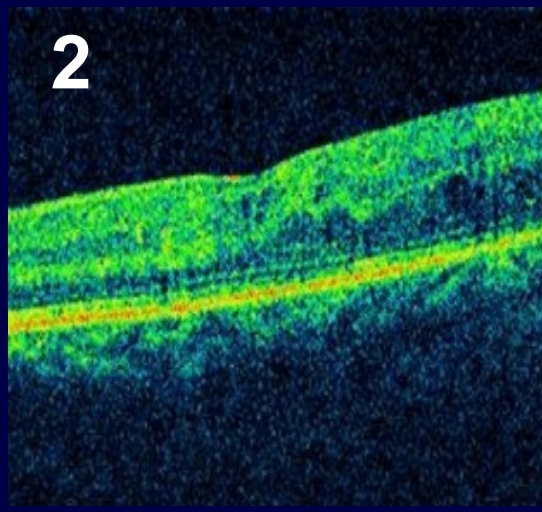


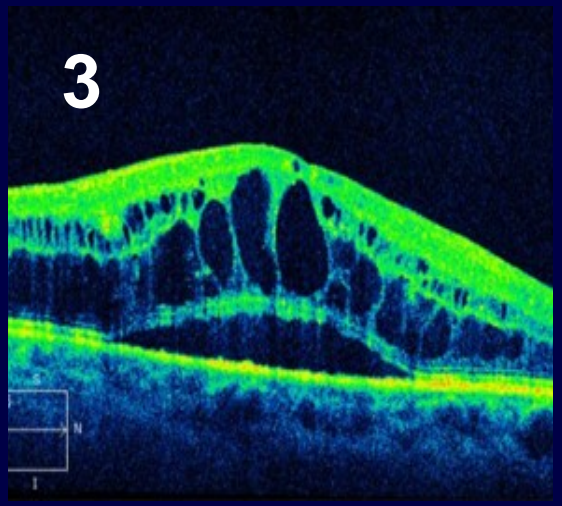
Classification of diabetic retinopathy from fluorescein angiograms. ETDRS report number 11. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology. 1991;98(5):807-22.

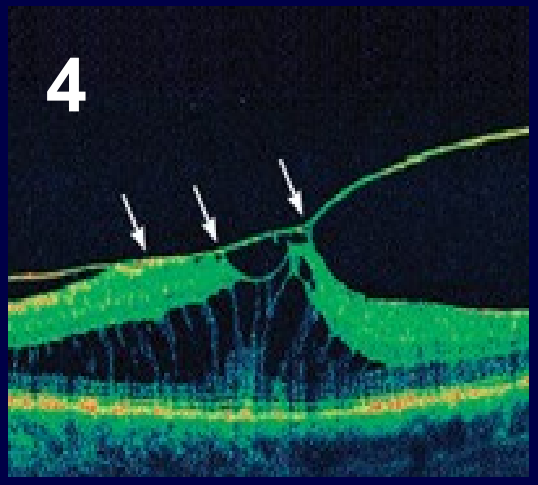
CLASSIFICATION BASED ON OCT FINDINGS

1. CYSTOID MACULAR EDEMA
2. DIFFUSE MACULAR EDEMA– (SPONGELIKE EDEMA)
3. WITH SERIOUS RETAINAL DETACHMENT SRD
4. WITH VITREOMACULAR TRACTION



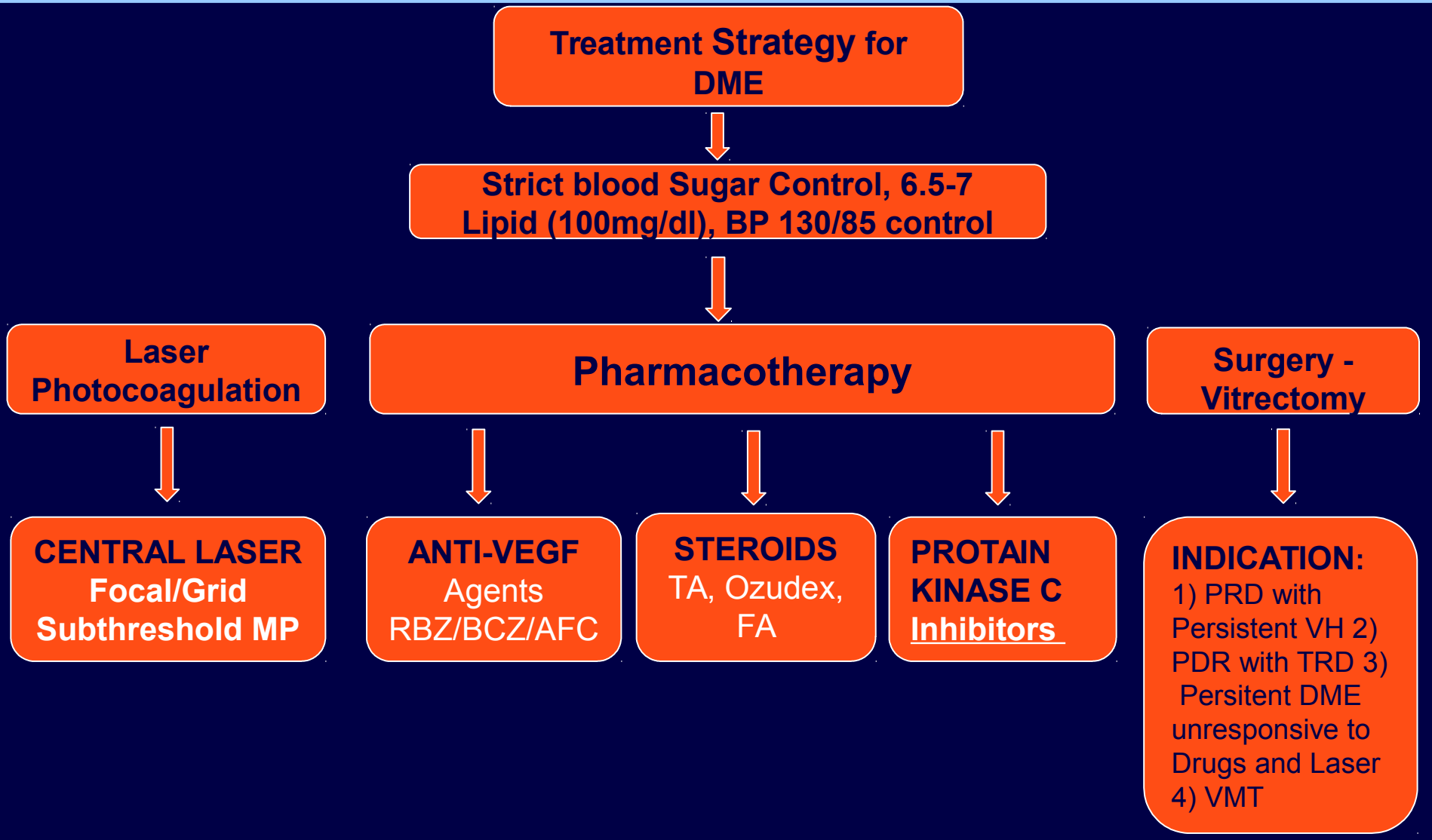






MANAGEMENT – DME

TREATMENT OPTIONS FOR DME



MANAGEMENT OF DME

SYSTEMIC CONTROL – RISK FACTORS

MAIN RISK FACTORS

Modifiable

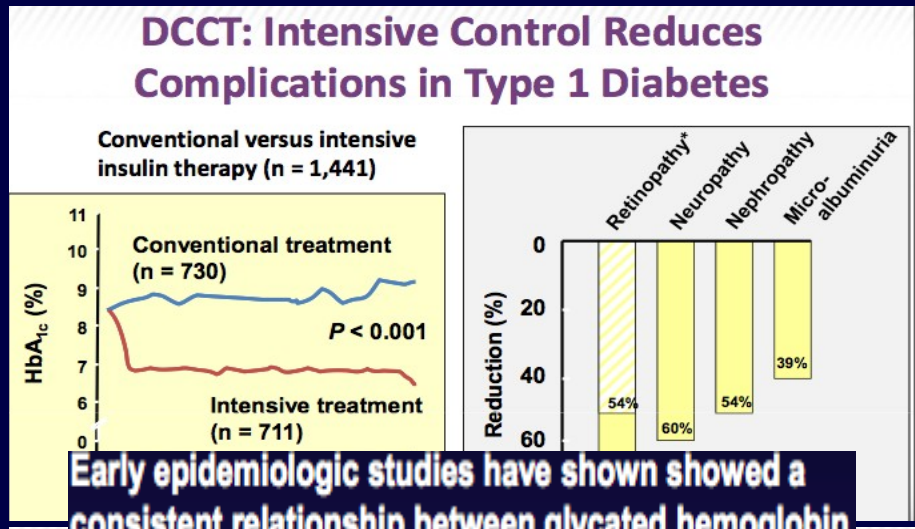
- Metabolic control
- Hypertension
- Hyperlipidemia
- Smoking

Non-Modifiable

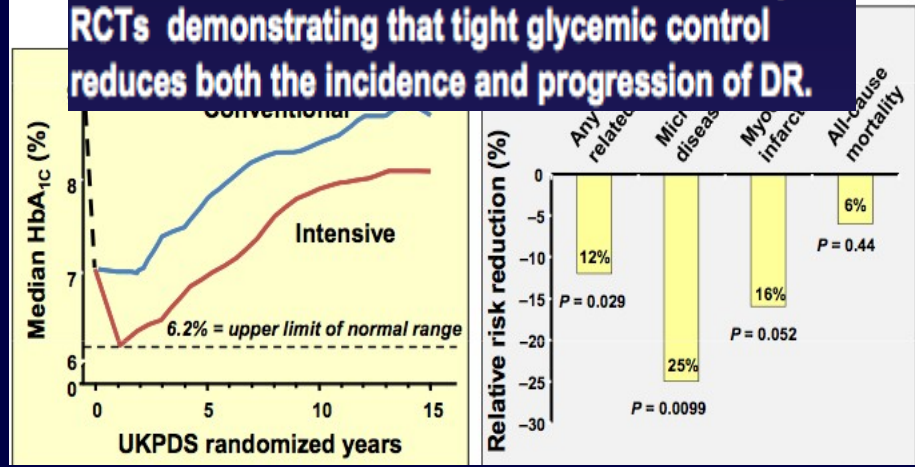
- Type of diabetes
- Duration of diabetes
- Insulin treatment
- Nephropathy
- Pregnancy
- Puberty
- Genetic factors

MANAGEMENT OF DME
SYSTEMIC CONTROL (RF) – MAJOR STUDIES

- Diabetes Control and Complications Trial (DCCT)
  - Type I diabetics (insulin)
- Epidemiology of Diabetes Intervention and Complications Trial (EDIC)
- United Kingdom Prospective Diabetes Study (UKPDS)
  - Type II diabetics
- United Kingdom Prospective Diabetes Study - Hypertension in Diabetes Study (UKPDS-HDS)
- The Wisconsin Epidemiology Study of Diabetic Retinopathy (WESDR)
- Early Treatment Diabetic Retinopathy Study (ETDRS)



Early epidemiologic studies have shown showed a consistent relationship between glycated hemoglobin (HbA1c) levels and the incidence of DR. This important observation has been confirmed in large RCTs demonstrating that tight glycemic control reduces both the incidence and progression of DR.



MANAGEMENT OF DME

SYSTEMIC CONTROL- TREATMENT TARGET TO IMPROVE DIABETES OUTCOMES

Treatment	Outcomes
Aggressive glucose control	Reduces microvascular events; improves lipids
Aggressive weight loss	Improves lipids, glucose, BP, other risk factors
Aggressive lipid-lowering	Reduces CVD event rates; possible effect on retinopathy
Aggressive blood pressure control	Reduces kidney damage, eye damage, and CVD
Anti-thrombosis therapy	Reduces macrovascular event rates

Diabetes Care. 2006;29:S4-S38. Colwell JA, Nesto RW. Diabetes Care. 2003;26:2181-2188.

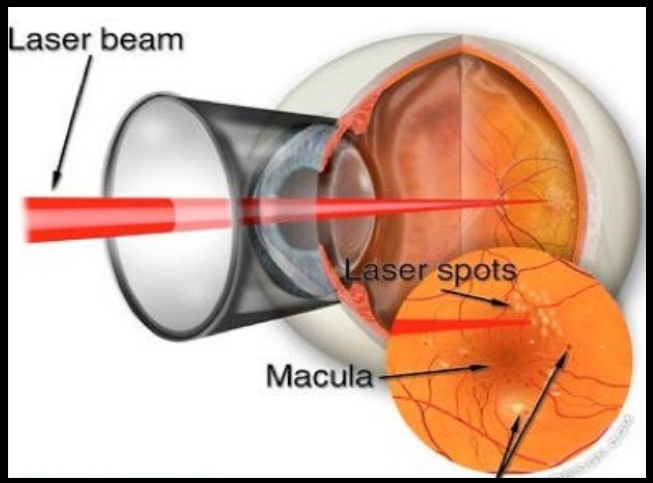
ADA Recommendations for BP & Lipids for People with Diabetes

Parameter	Goal
Blood pressure	<140/80 mm Hg
LDL	<100 mg/dL*
Triglycerides	<150 mg/dL
HDL	>40 mg/dL (men) >50 mg/dL (women)

*LDL <70 mg/dL is a therapeutic option

- Controlled BP <130/80mmHg
  - 51%
- LDL at the goal level <100mg/dl
  - 56%
- A1C at the goal level <7%
  - 53%
- What proportion have met all three?
  - 18.8%

MANAGEMENT OF DME



LASER TRETAMENT

MANAGEMENT OF DME
CURRENT LASER TREATMENT OPTIONS FOR DME

Traditional Conventional Photocoagulation
- Gold Standard
- Navigated Treatment (Navilas)
- Pattern Style (Pascal)

Modified ETDRS
- Direct treatment to microaneurysms and grid to thickened areas only

Mild Macular Grid Laser Technique
- Diffuse widespread area of grid treatment to macula in thick and non-thick areas
- No treatment of microaneurysm

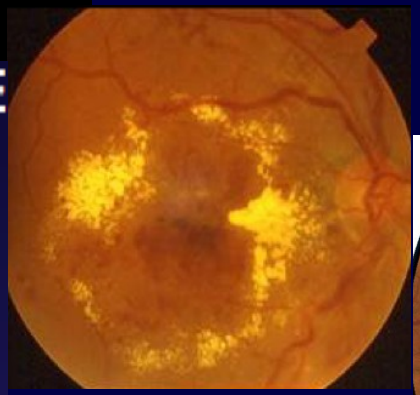
Subthreshold diode micropulse treatment
- Micropulse (IRIDEX, Quantel)
- Endpoint management (Topcon

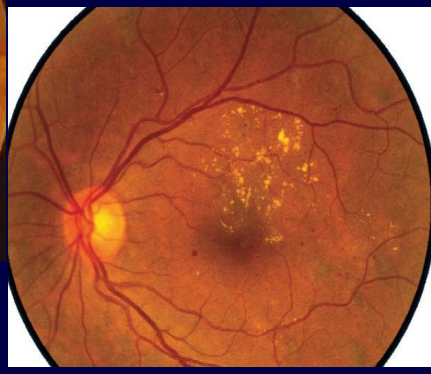
- 810 nm Diode Laser
- Subthreshold treatment of macular region
  - Minimization of "collateral" damage
- Smaller studies showing promise in DME
  - Less chance of scotoma?
  - Better contrast sensitivity?
  - Cost of additional laser?
  - Lack of large randomized clinical trials…

Peripheral Photocoagulation
- Aim is to Reduce VEGF and Cytokine from peripheral Ischaemia
- This will effect reduce DME
- On going study

ETDRS – STUDY FINDINGS

- **Laser photocoagulation reduced the rate of moderate vision loss by 50% in eyes with CSME**
  - 35% of patients in laser-treated group continued to have DME after 1 year
    - 24% at 3 years
  - 40% of patients required retreatment within 1 year
  - Only 3% had > 3 lines of improvement
  - Only 17% had any improvement in vision after 5 years
  - 12% of treated eyes still lost 15 or more ETDRS letters at 3 years



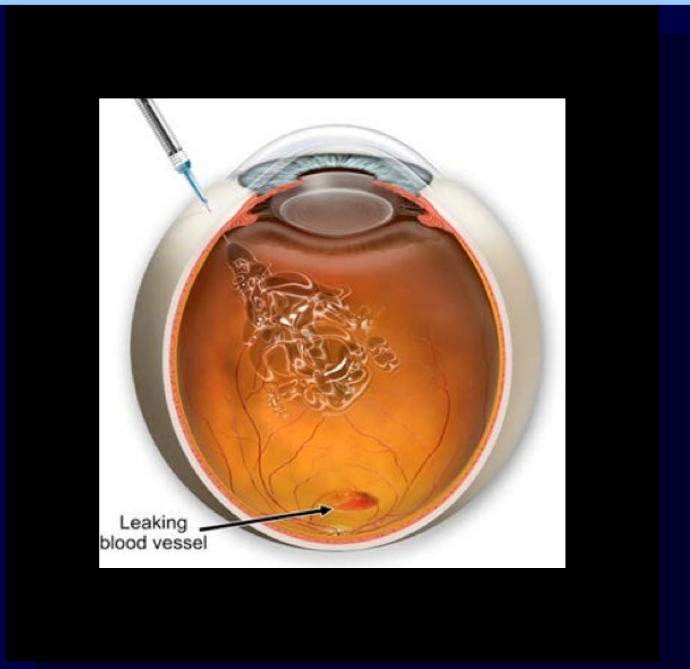


ETDRS

- Overall, decreased moderate visual loss by 50%
  - Treated group 13%
  - Control group 22%

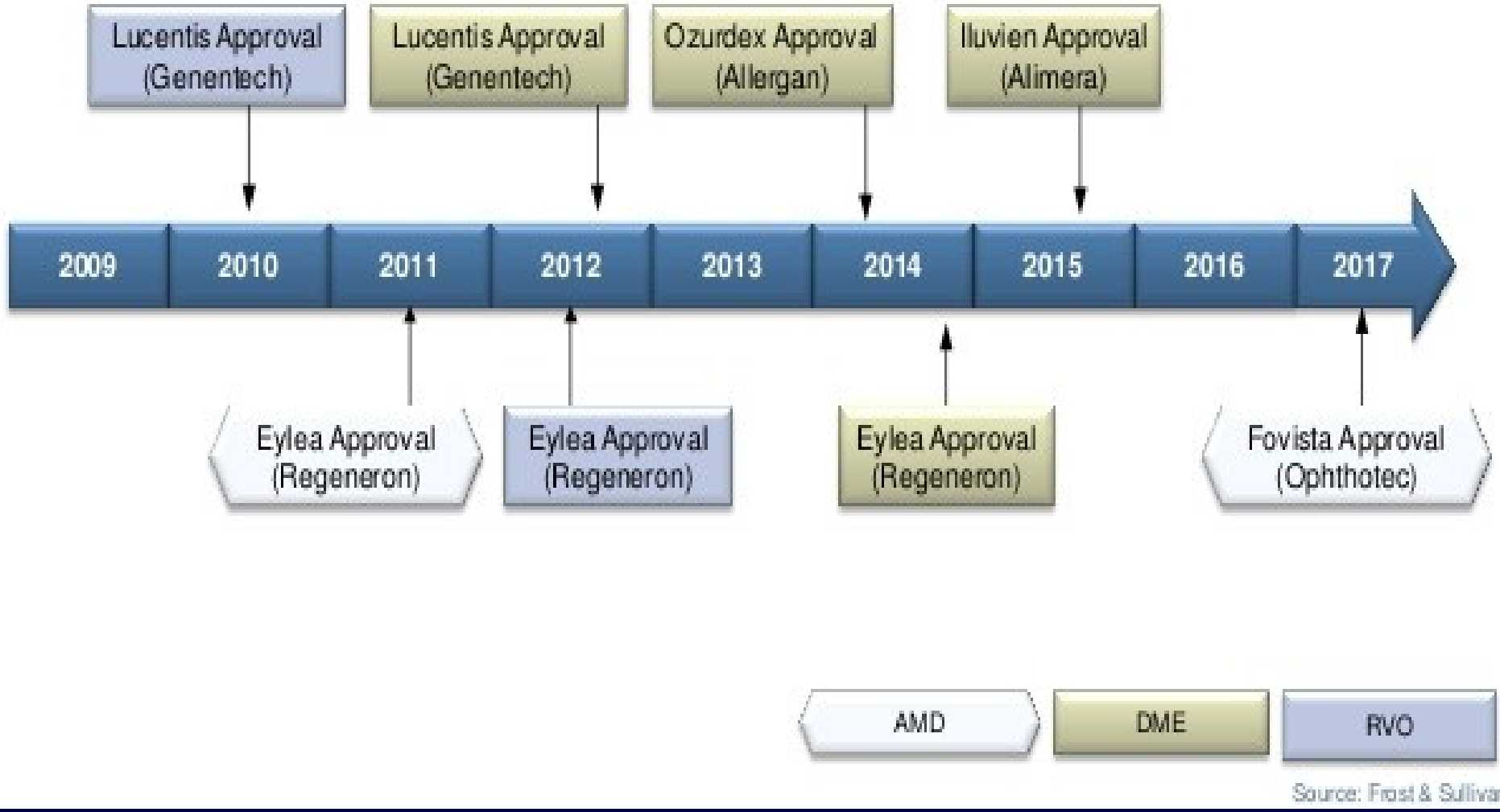
ETDRS Report #1 Arch Ophthalmol 103:1796-806, 1985

MANAGEMENT OF DME



PHARMACOTHERAPY

PHARMACOTHERAPY– FDA TIMELINE APPROVALS FOR IVI

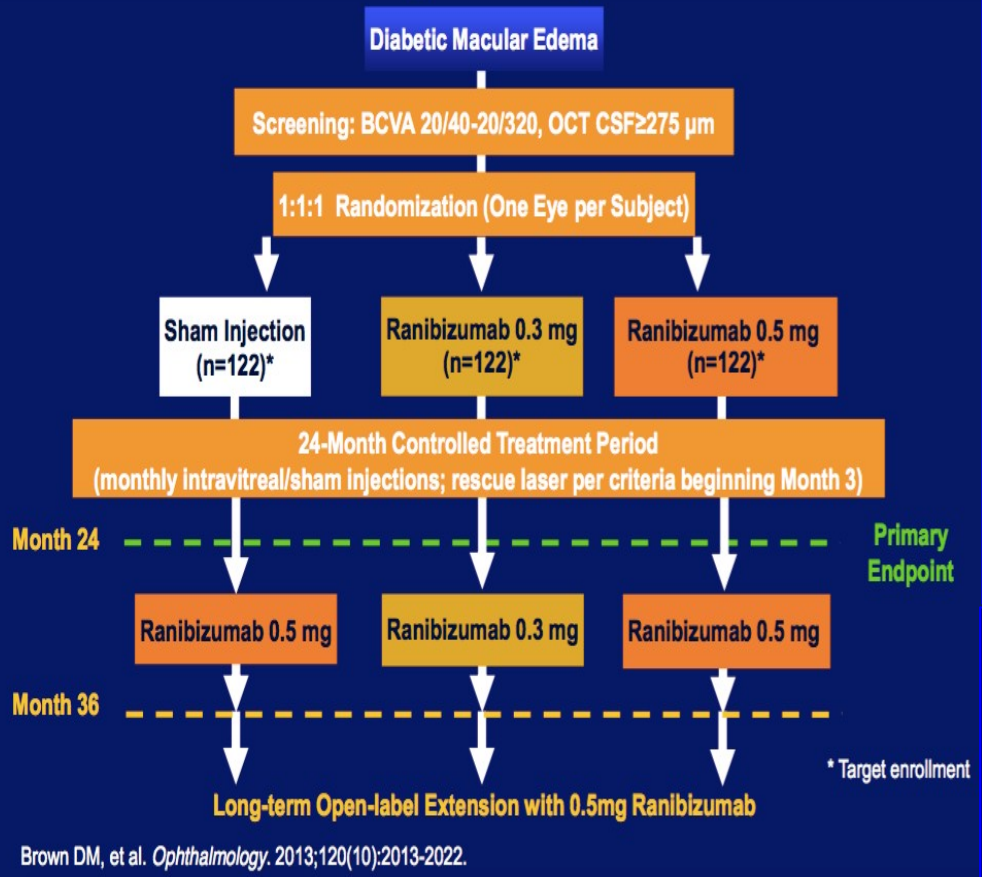


Source: Frost & Sullivan

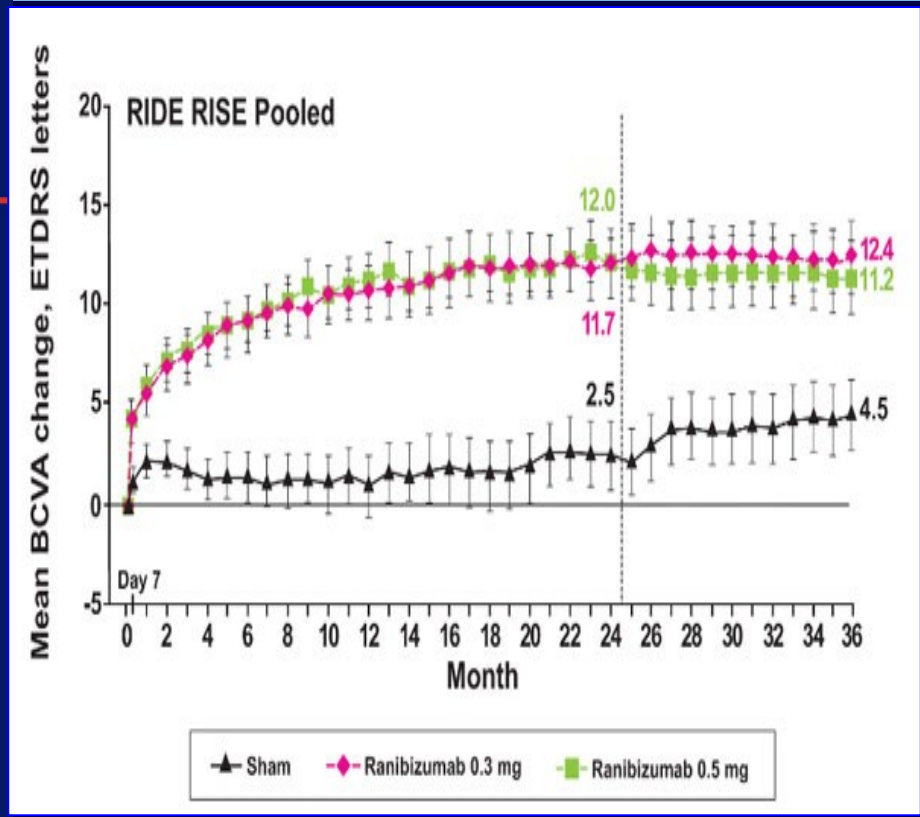
PHARMACOTHERAPY

ANTI-VEGF: RANIBIZUMAB (Lucentis, Genentech) - RIDE AND RISE STUDY

Ranibizumab RIDE & RISE Phase 3 Study Designs



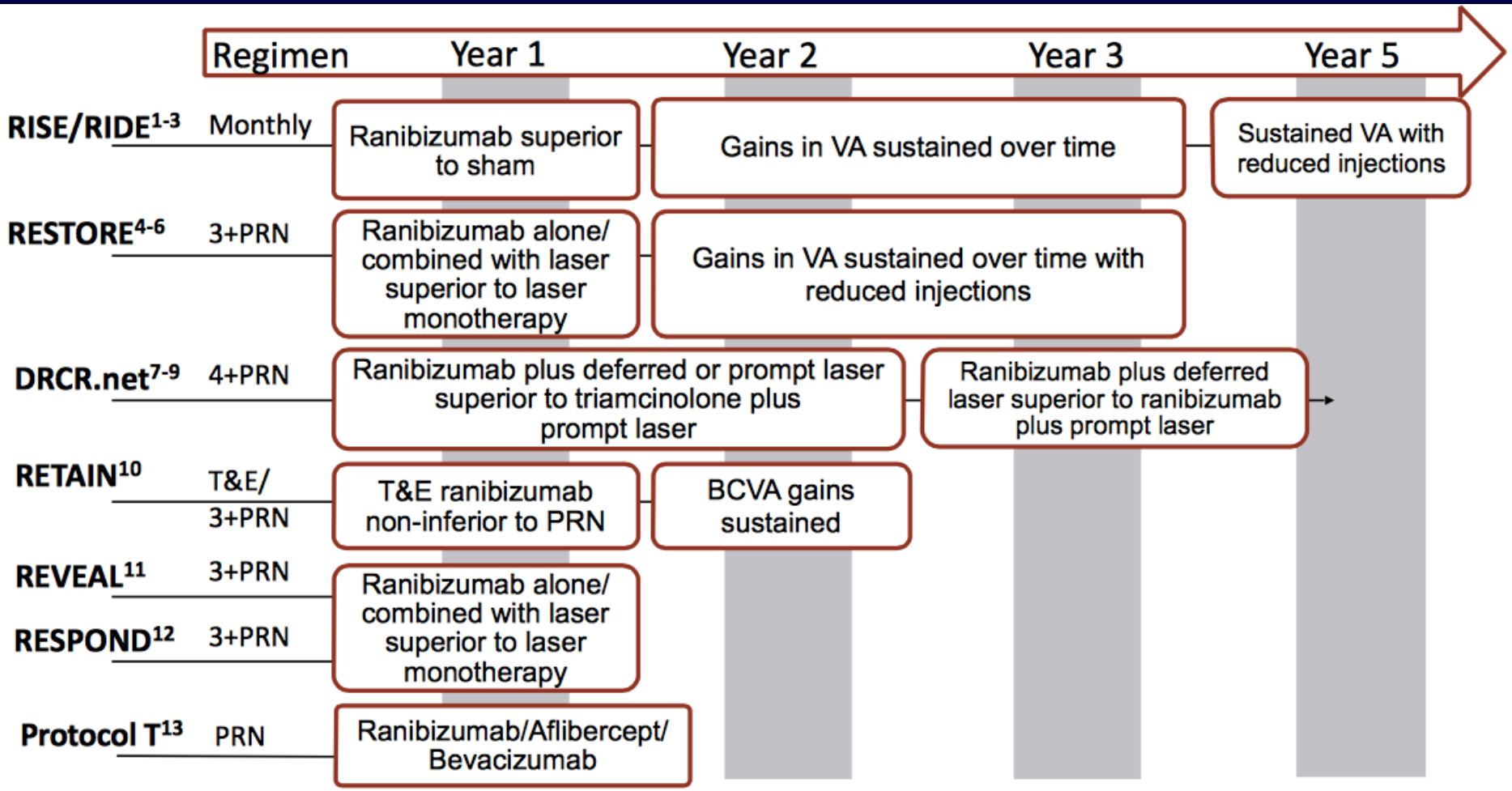
Brown DM, et al. *Ophthalmology*. 2013;120(10):2013-2022.



- ✓ Rapid and sustained =>2 line for 36 months
- ✓ Less visual gain for switch group
- ✓ Pts receiving Rn were less likely to develop PDR.
- ✓ Patients continued to demonstrate improvement in diabetic retinopathy with PRN ranibizumab 60/12

PHARMACOTHERAPY

Phase III evidence supporting the efficacy of Ranibizumab treatments in DME



BCVA, best corrected visual acuity; PRN, *pro re nata*; T&E, treat and extend; VA, visual acuity; VEGF, vascular endothelial growth factor

1. Brown DM, et al. Ophthalmology 2013;120:2013-22; 2. Nguyen QD, et al. Ophthalmology 2012;119:789-801; 3. Morse, LS. 37th Macular Society meeting 2014; 4. Mitchell P, et al. Ophthalmology 2011;118:615-25; 5. Lang GE, et al. Ophthalmology 2013;120:2004-12; 6. Schmidt-Erfurth U, et al. Ophthalmology 2014;121:1045-53; 7. Elman MJ, et al. Ophthalmology 2010;117:1064-77; 8. Elman MJ, et al. Ophthalmology 2011;118:609-14; 9. Elman MJ, et al. Ophthalmology 2012;119:2312-8; 10. Prünte C. AAO 2013; 11. Ohji M. ARVO 2012; 12. Sheidow T. ARVO 2013; 13-Wells JA, et al. NEJM 2015, epub ahead of print; DRCR.net. August 2012. Available from: http://drcrnet.jaeb.org/Studies.aspx?RecID=206 [Accessed 27 October 2014

PHARMACOTHERAPY

ANTI-VEGF: AFLIBERCEPT(Eylea, Regeneron) Vivid (Eu/Japan)/Vista (Us) Studies

Study Design

Randomized, multicenter, double-masked trials in patients with clinically significant DME with central involvement and ETDRS BCVA 20/40 to 20/320
N=406 (VIVID) N=466 (VISTA)

Patients randomized 1:1:1

- IVT Aflibercept 2 mg q4 wks
- IVT Aflibercept 2 mg q8 wks*
- Laser Photocoagulation

Primary endpoint: Mean change in BCVA

Primary Endpoint: Week 52

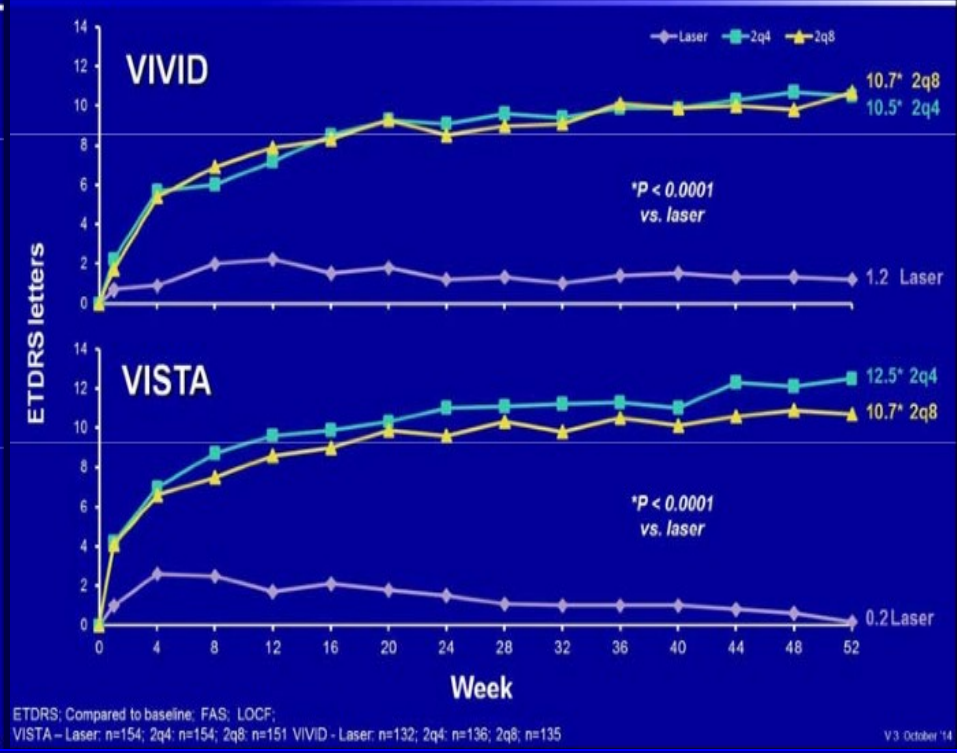
Key Secondary endpoint: Change in DRSS

Continued treatment through Year 3

*After 5 initial monthly doses

V3 October '14

Mean Change in Best-Corrected Visual Acuity



ETDRS; Compared to baseline; FAS; LOCF;
VISTA – Laser: n=154; 2q4: n=154; 2q8: n=151 VIVID - Laser: n=132; 2q4: n=136; 2q8; n=135

V3 October '14

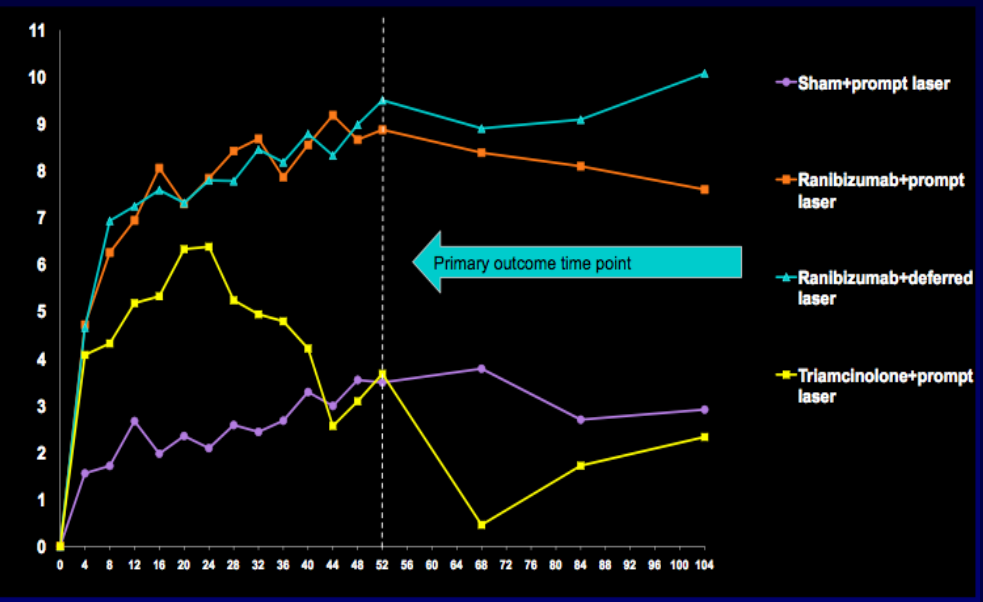
Superior to Laser and Improve BCVA in 6 months
BCVA gain & CST reduction were greater with aflibercept group vrs laser than in the RISE/RIDE trial.

PHARMACOTHERAPY

ANTI-VEGF: RANIBIZUMAB (Lucentis, Genentech) –

DRCR.net Protocol 1: RCT Rb +/-Laser or TA + Laser for DME

Mean Change in Visual Acuity* at Follow-up Visits

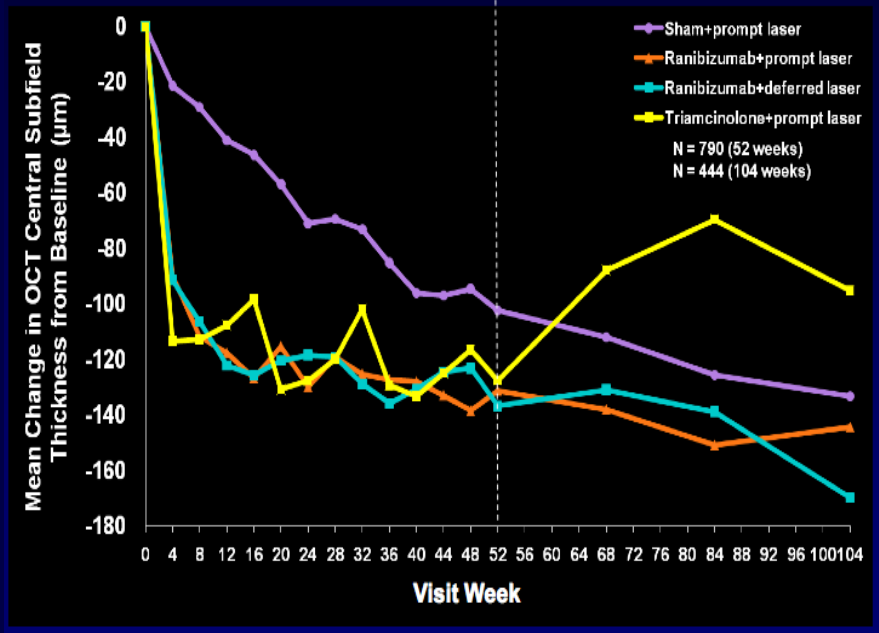


*Values that were ±30 letters were assigned a value of 30

P-values for difference in mean change in visual acuity from sham+prompt laser at the 52-week visit: ranibizumab+prompt laser <0.001; ranibizumab+deferred laser <0.001; and triamcinolone+prompt laser=0.31.

31

Mean Change in Central Subfield Thickening at Follow-up Visits

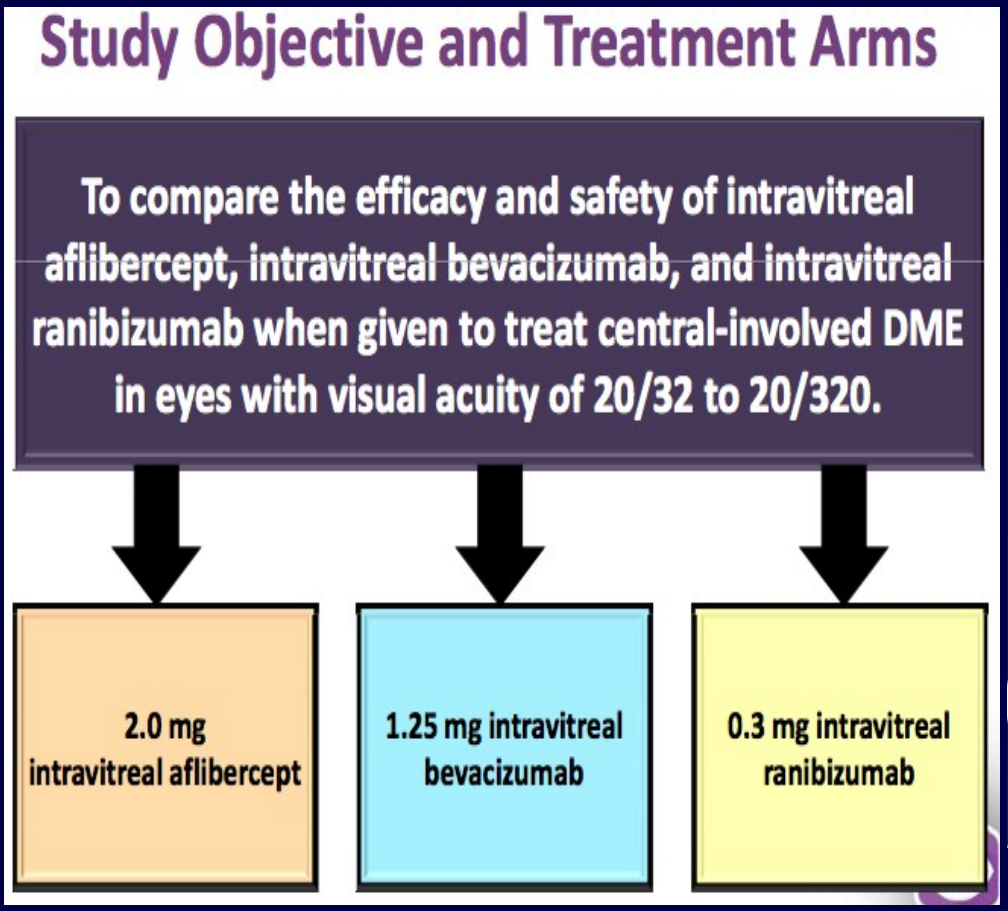


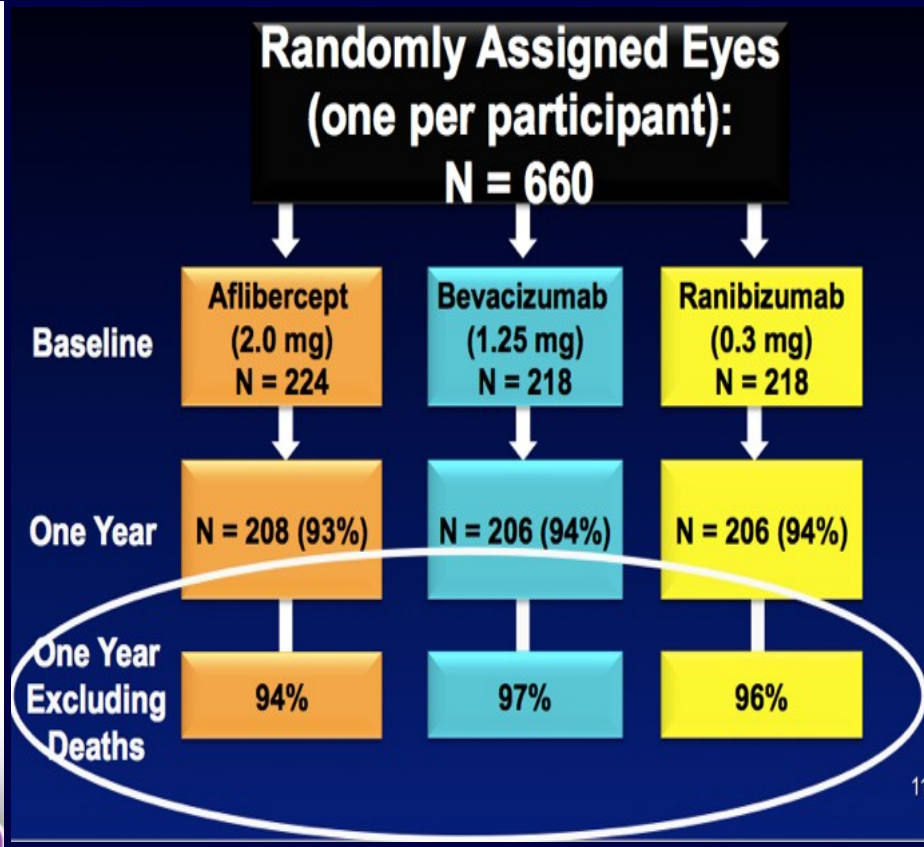
P values are for the difference in mean change in OCT CSF retinal thickness from sham+prompt laser at the 52-week visit: ranibizumab+prompt laser <0.001, ranibizumab+deferred laser <0.001, and triamcinolone+prompt laser <0.001.

33

- Intravitreal ranibizumab with prompt or deferred (≥24 weeks) focal/grid laser had superior VA and OCT outcomes compared with triamcinolone + prompt laser and focal/grid laser treatment alone
- Results were similar whether focal/grid laser was given starting with the first injection or it was deferred >24 weeks
- In the Ranibizumab + deferred laser group, 70% of patients did not have any laser treatment during year one of the study.

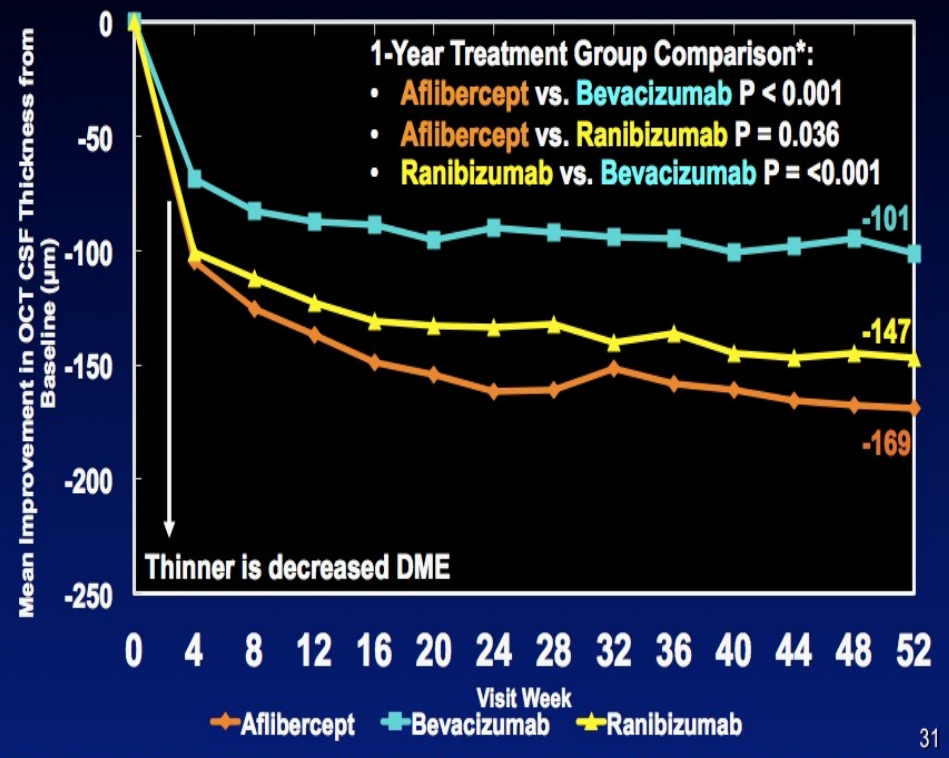
COMPARATIVE EFFECTIVENESS STUDY OF AFLIBERCEPT, BEVACIZUMAB, OR RANIBIZUMAB FOR DME





COMPARATIVE EFFECTIVENESS STUDY OF AFLIBERCEPT, BEVACIZUMAB, OR RANIBIZUMAB FOR DME

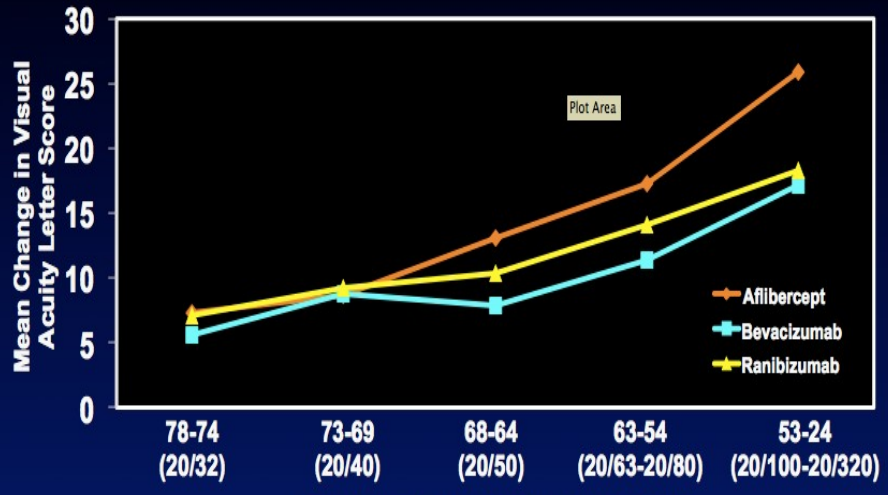
Overall Mean (μm) Change in OCT CST Over Time



31

* *P*-values adjusted for baseline visual acuity, OCT central subfield thickness, and multiple comparisons

Visual Acuity Mean Change: Baseline to 1 Year



N =					
Aflibercept	54	52	36	29	37
Bevacizumab	41	63	35	38	29
Ranibizumab	46	59	32	37	32

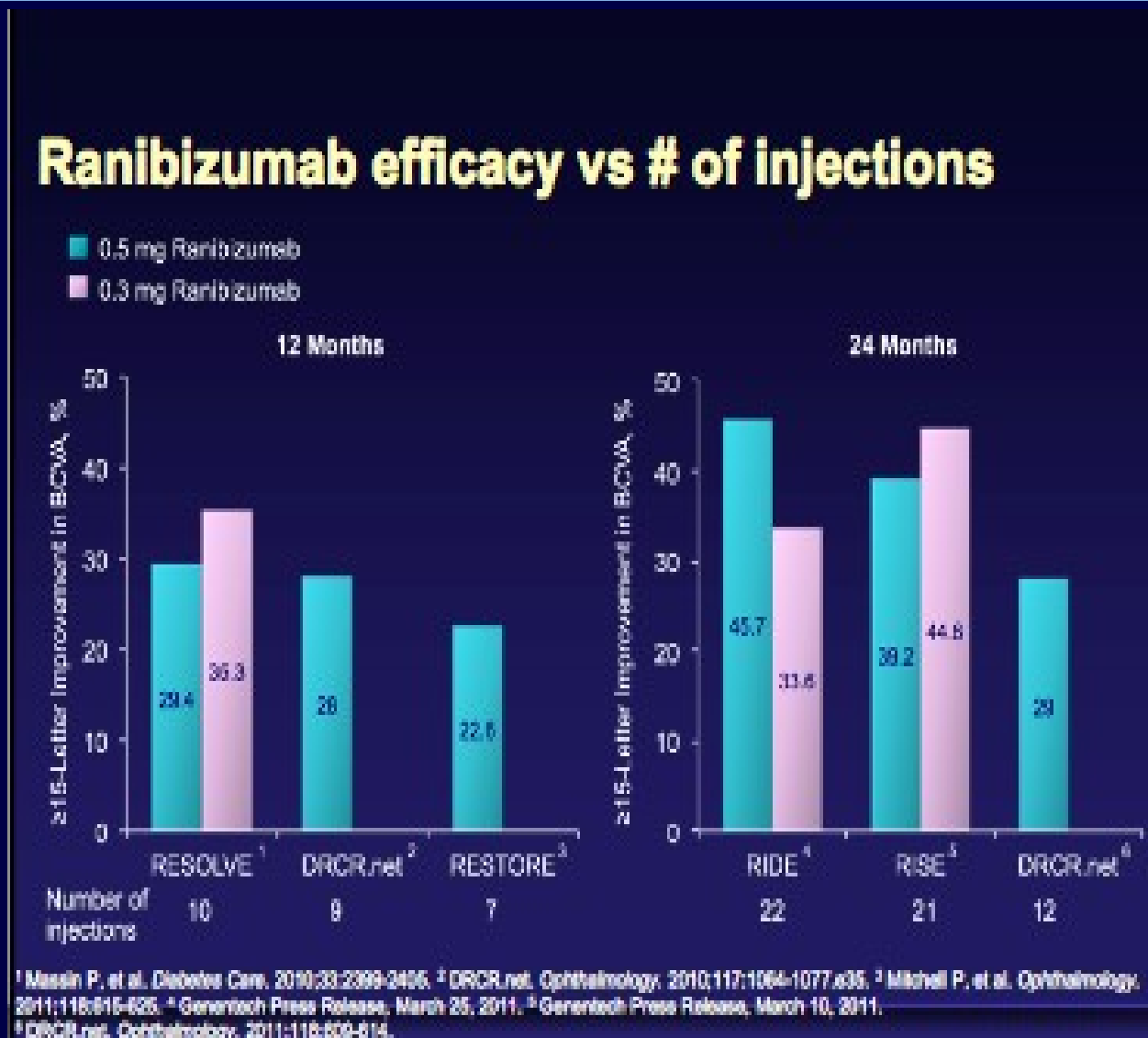
- All three anti-VEGF agents are effective treatments for DME causing vision impairment
- When initial visual acuity loss is mild, on average there is little difference in visual acuity at 1-year.
- aflibercept is more effective at improving vision.

ANTI-VEGF: RESULTS SIMILAR ACCROS SEVERAL STUDIES

Anti VEGF more Likely to improve Vision than Laser

- 40-60% of Anti-VEGF patients gained 2 lines vision vs. 0-15% of Laser only patients
- Average improvement 8-10 letters of Anti-VEGF vs. 0-2 letters for laser alone

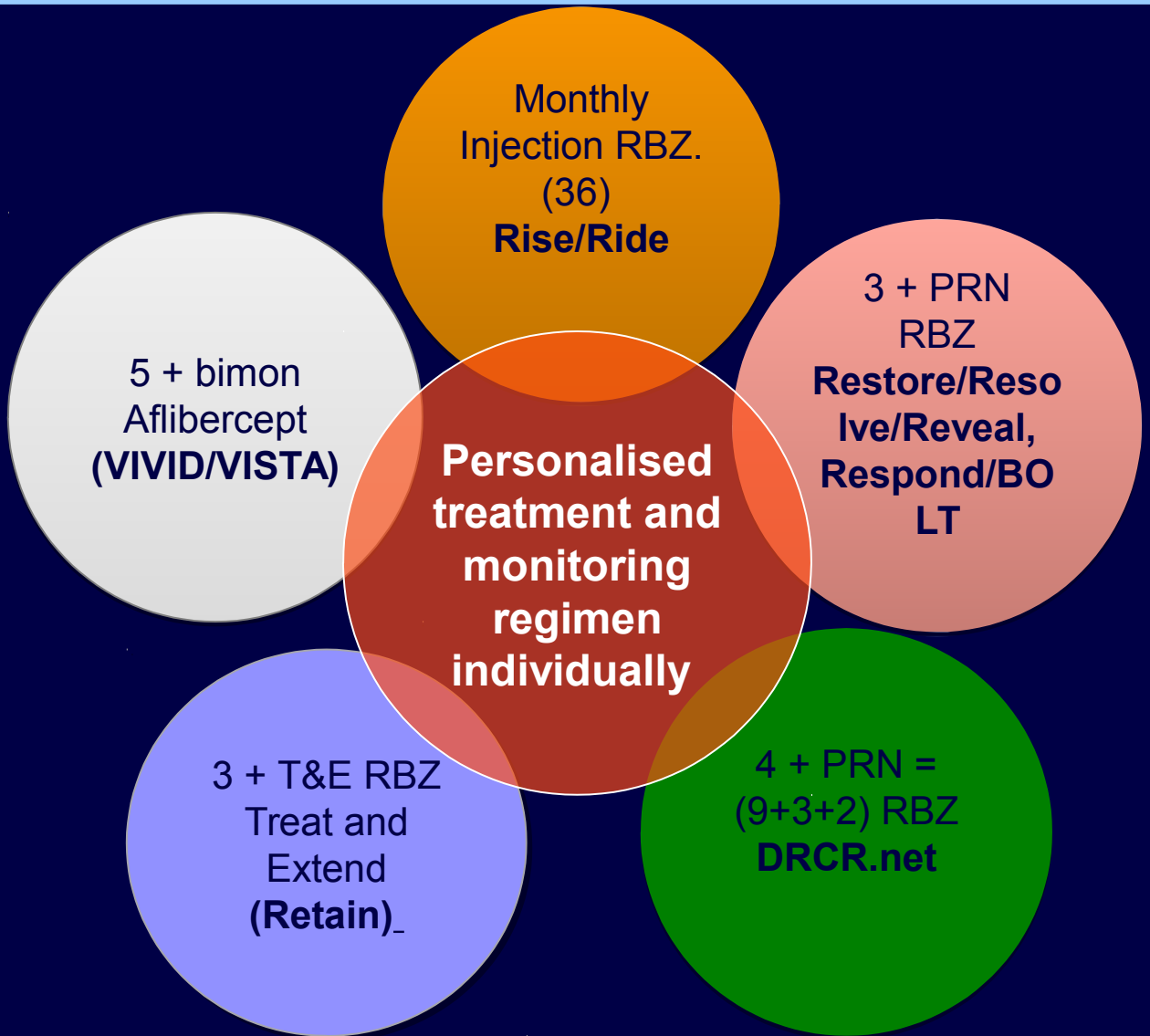
Anti-VEGF agents have fewer side effects than steroids: Cataract & Glaucoma



[1] Massin P, et al. Diabetes Care. 2010;33:2399-2405. [2] DRCR.net. Ophthalmology. 2010;117:1064-1077.e35. [3] Mitchell P, et al. Ophthalmology. 2011;118:615-625. [4] Genentech Press Release, March 25, 2011. [5] Genentech Press Release, March 10, 2011. [6] DRCR.net. Ophthalmology. 2011;118:609-614.

PHARMACOTHERAPY

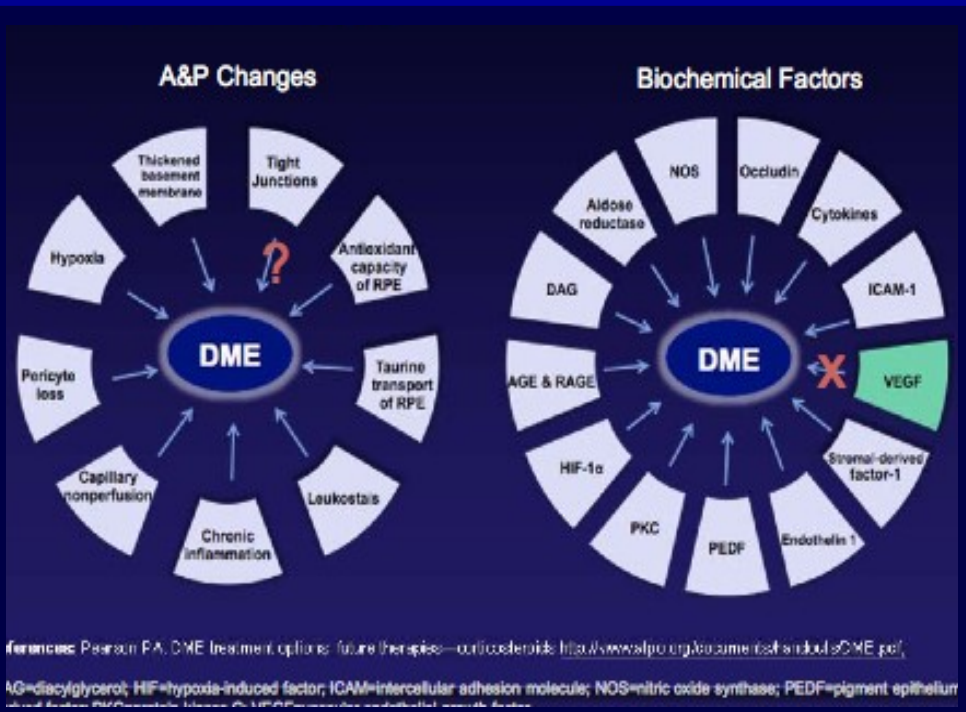
ANTI-VEGF: TREATMENT PROTOCOL OPTIONS

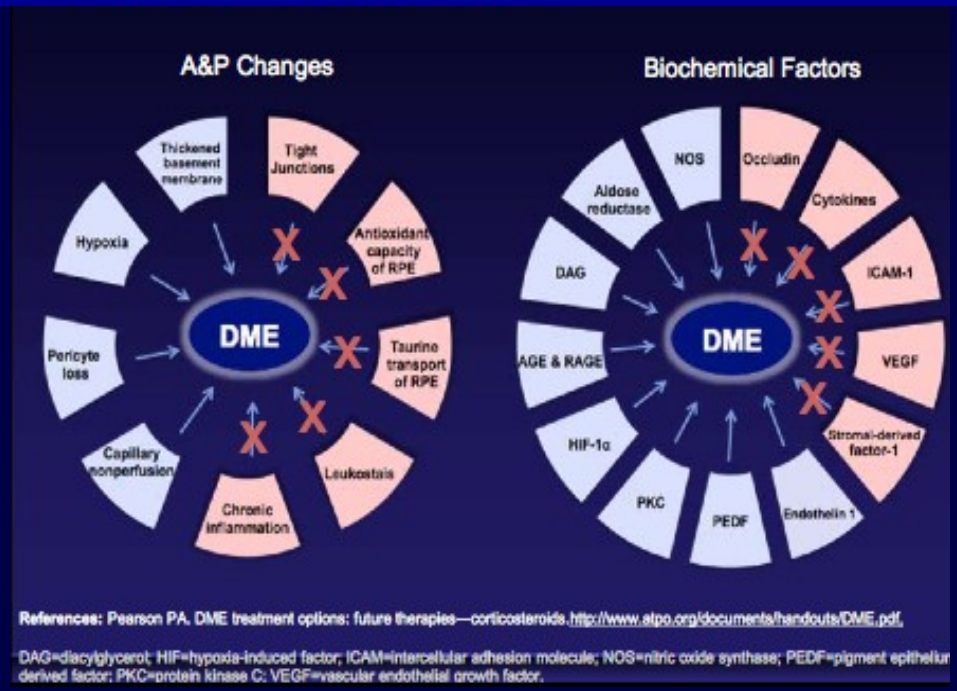


CORTICOSTEROIDS

PATHOPHYSIOLOGY OF DME

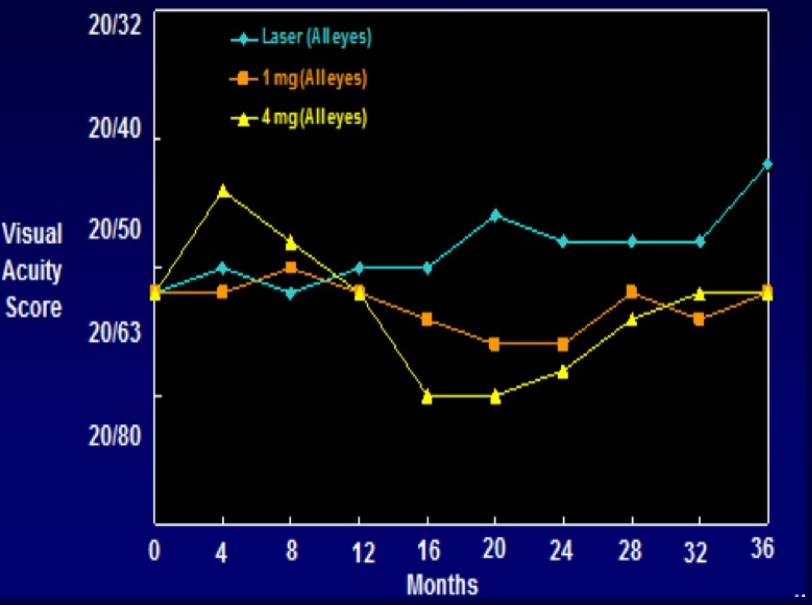
Early focal leakage is primarily VEGF-driven, but when it advances to diffuse leakage, leading to fibrosis, pigmentary alterations, and loss of PRs, the equation changes. The process is now primarily inflammation driven,



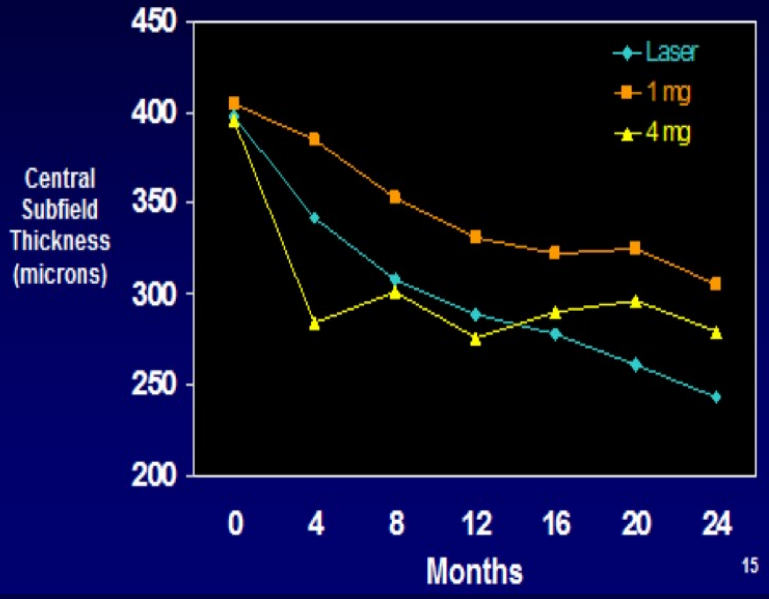


STERIODS – TRIAMCINOLONE
DRCR.net Protocol B: RCT Comparing TA vrs Focal/Grid Laser for DME

Mean Visual Acuity Over 3 Years in All Eyes



Median OCT Central Subfield Thickness in Laser and IVT Treated Eyes



15

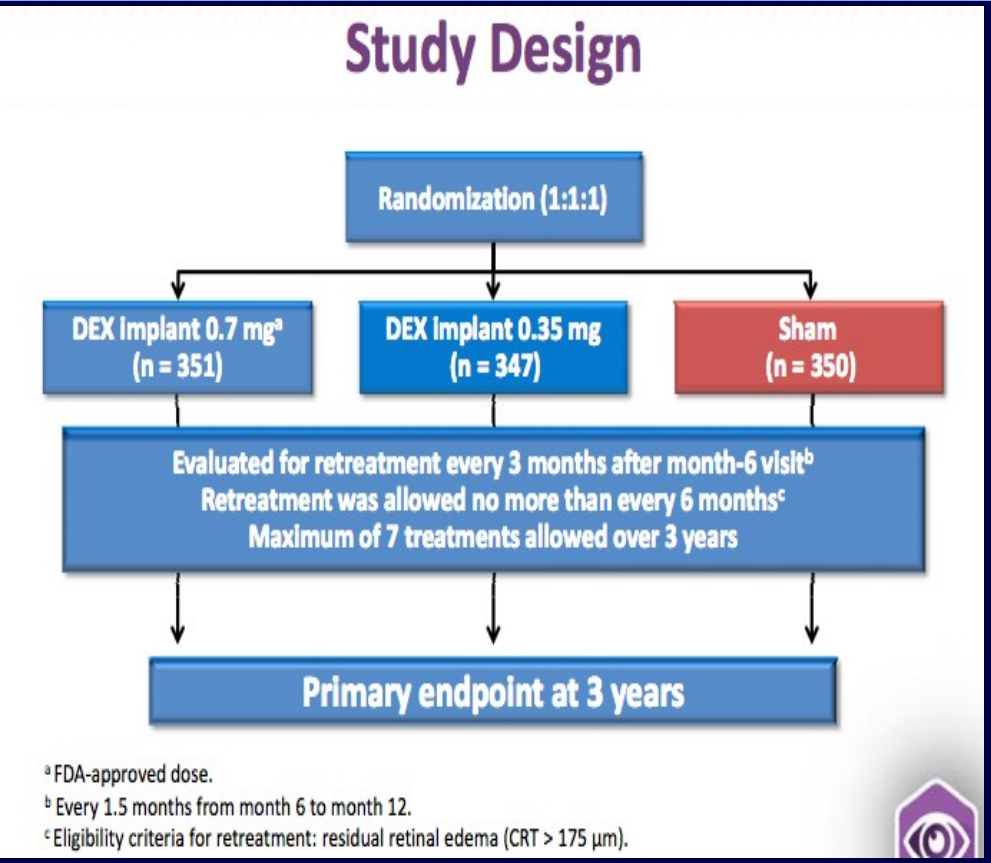
- By 2 years, there was a greater VA benefit and fewer side effects (IOP and cataract) in laser group compared with the IVT groups
- 3 year results similar to the 2 year results
- OCT results mirrored VA results

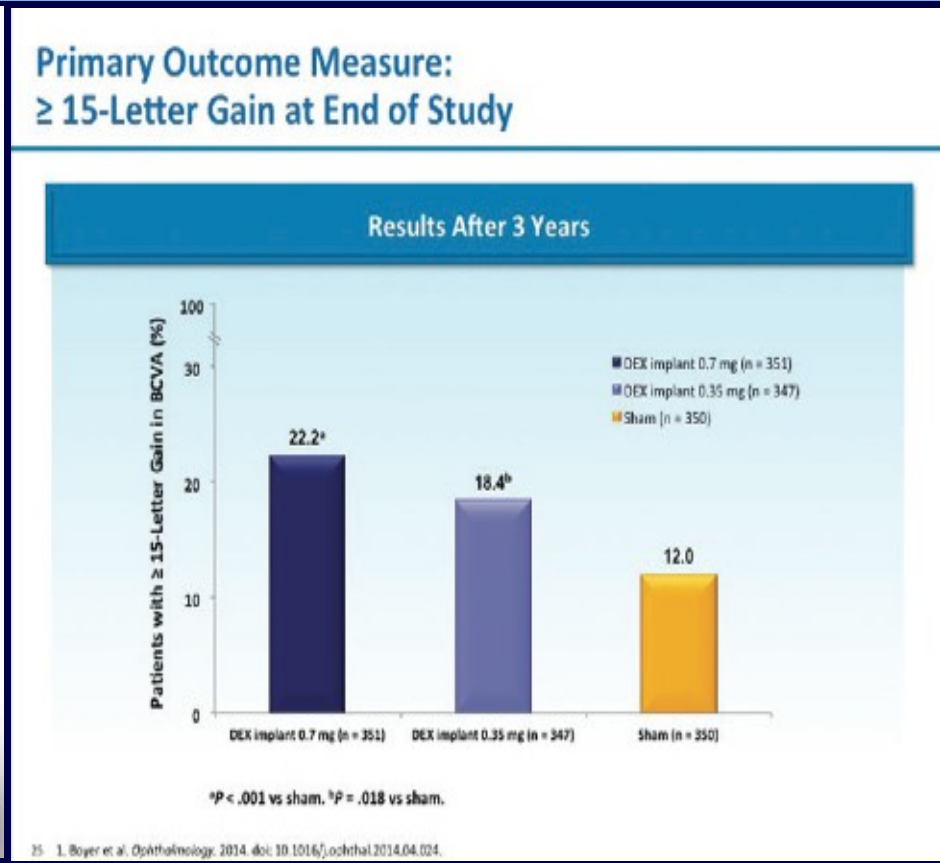
- Focal/grid currently still most effective treatment for patients with DME and is the benchmark against which other new treatments for DME should be compared in clinical trials for DME

DRCR.net

National Eye Institute
NATIONAL INSTITUTES OF HEALTH

STERIODS: DEXAMETHASONE (OZUDEX) – MEAD Study - Dex Inplant Study

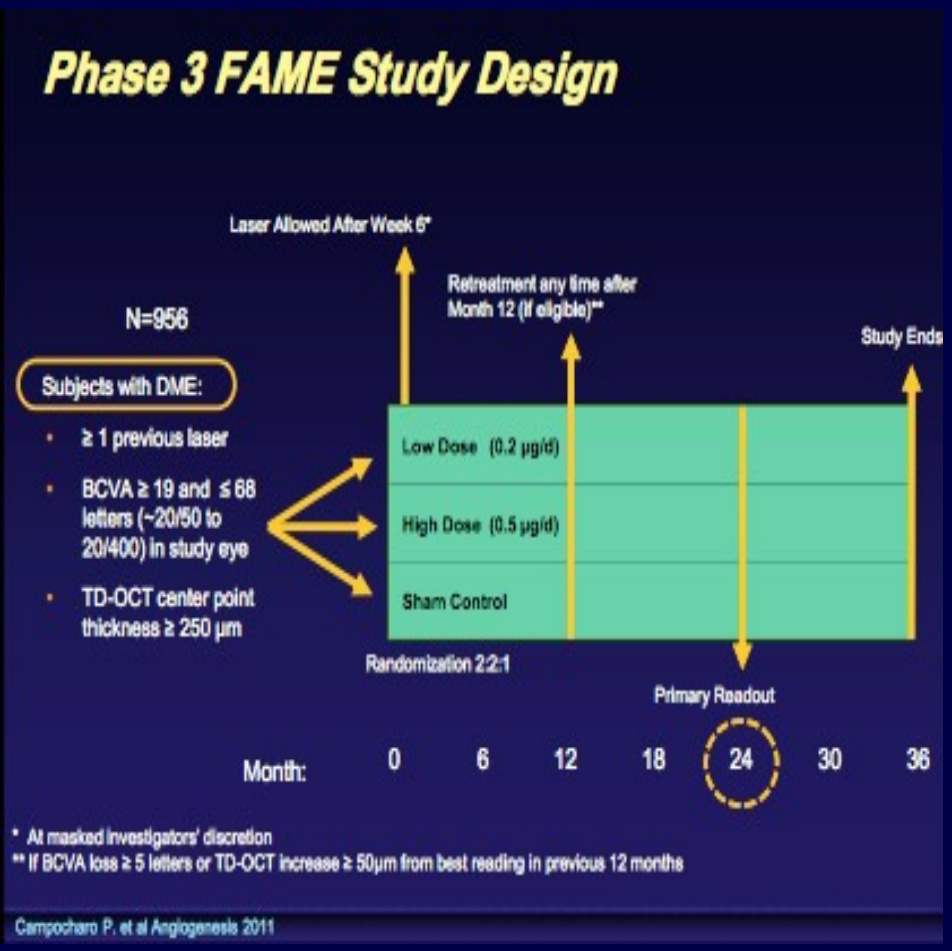


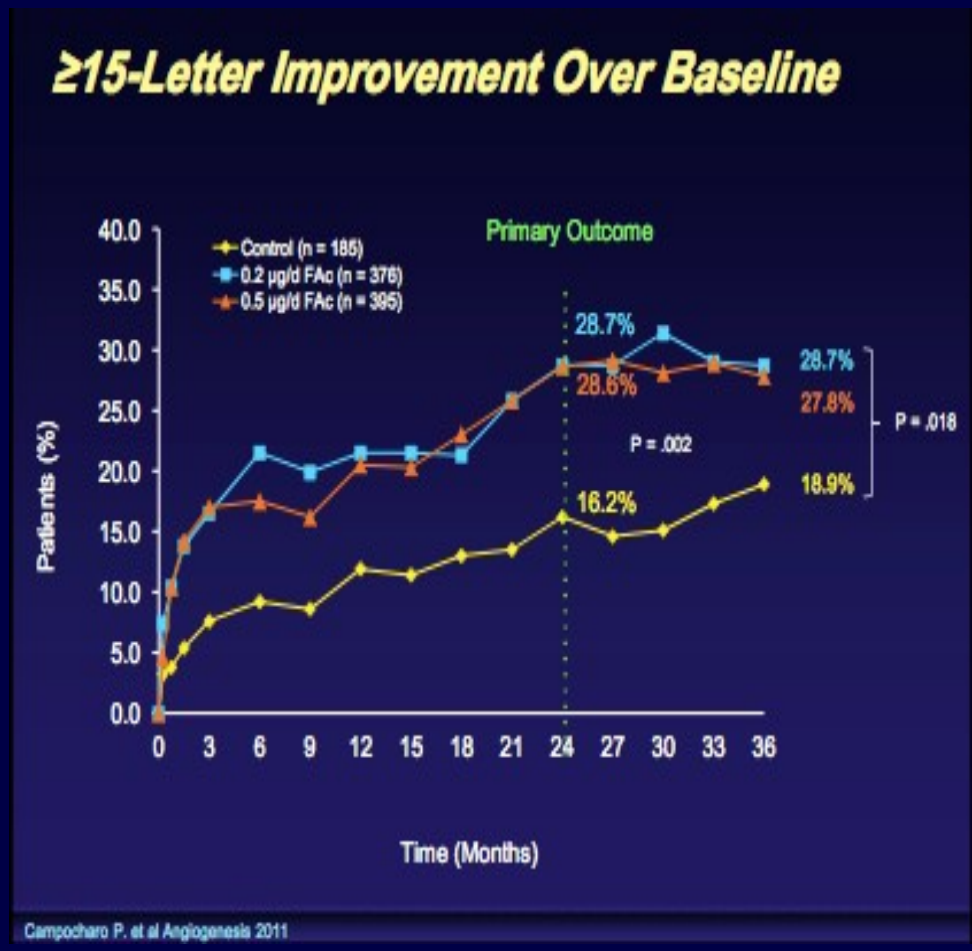


CATARACT 59%, GLAUCOMA 41%, GLS 0.7%

Patients in the dexamethasone group were more likely than placebo patients to have at least a 15-letter improvement from baseline. Less cat and glaucoma

STERIODS - FLUOCINOLONE ACETONIDE - IIUVIEN (ALIMERA) – PHASE 3 FAME STUDY





- Rapid and Significant VA/CST improvement
- Cataract 82%, Glaucoma 38-42%, GS 4.8-8.1

It releases a submicrogram daily dose of fluocinolone for about 3 years.

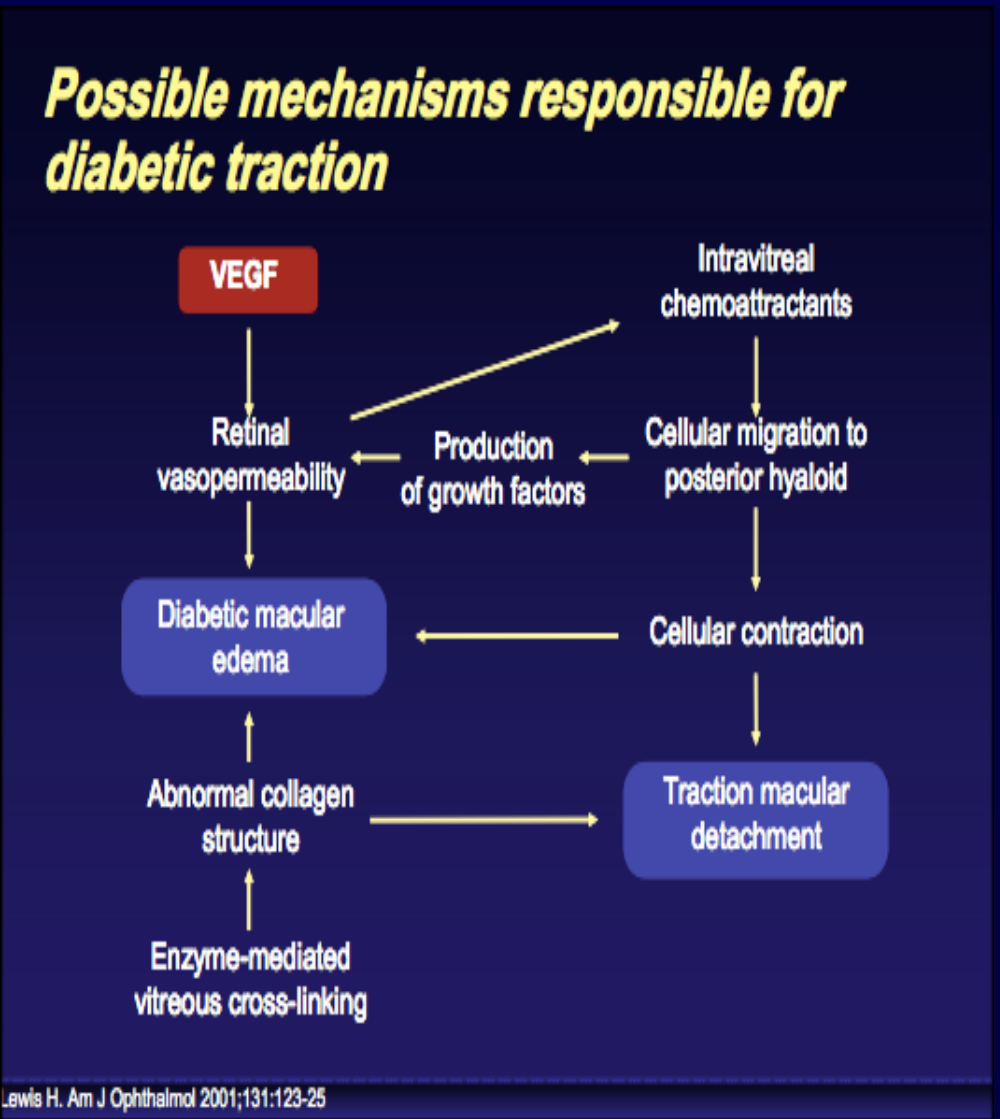
Advantages of Steroid

- Less Frequent Dosing
- Treat Inflammatory Component
- Okay in Pregnancy
- No Systemic Risk
- Some Patients Respond Dramatically, Even if No Response to Anti-VEGF Agent
- Ozurdex Helpful in Vitrectomized Patient

Disadvantages of Steroid

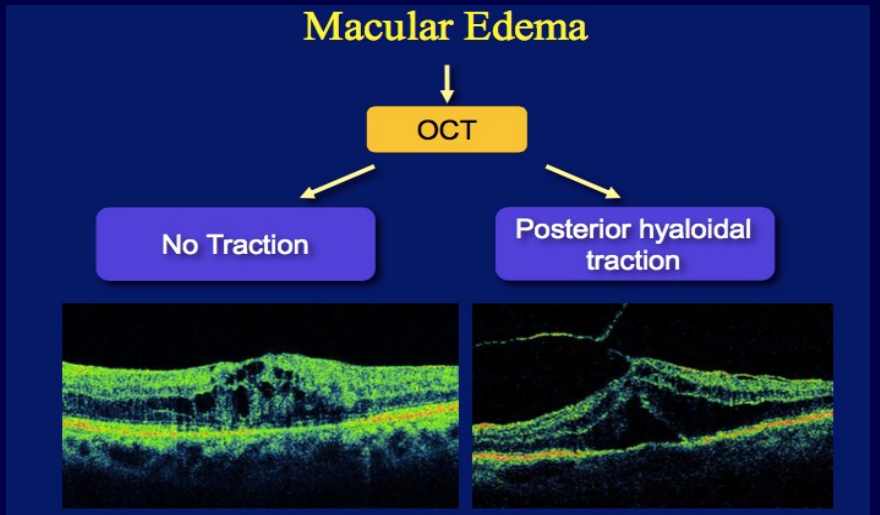
- Cataract
  - Virtually 100%, Significant Problem Within One Year
- Glaucoma
  - 40% Require Therapy (60 % Do Not)
  - Filter or Surgical Removal of Steroid Can be Necessary

VITRECTOMY: Pathophysilogy



Improved oxygenation

- Removal of harmful growth factors
- Removal of tractional forces
- Usually reserved for refractory cases

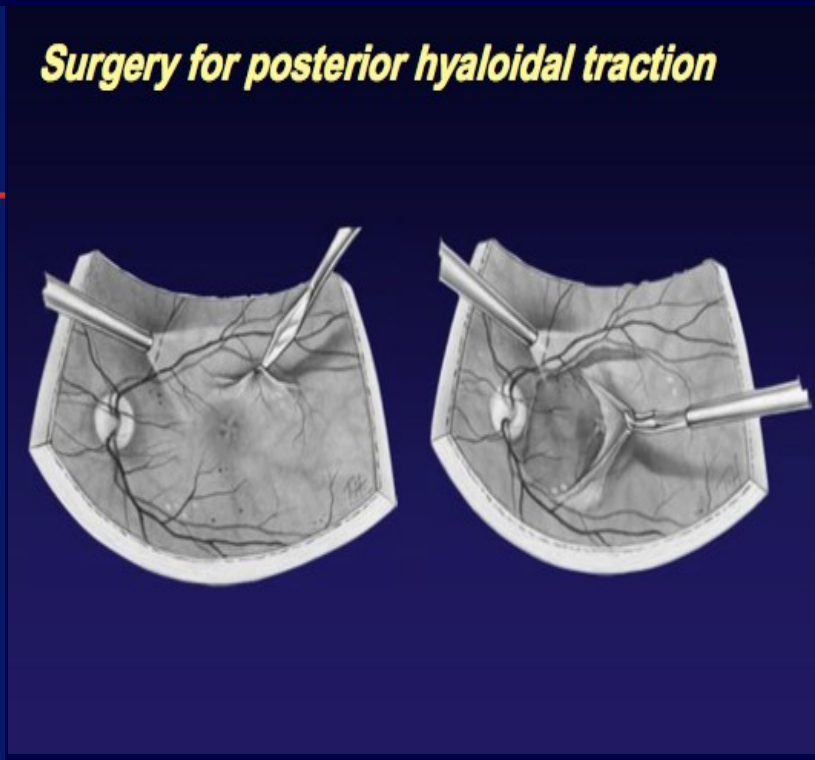


VITRECTOMY:

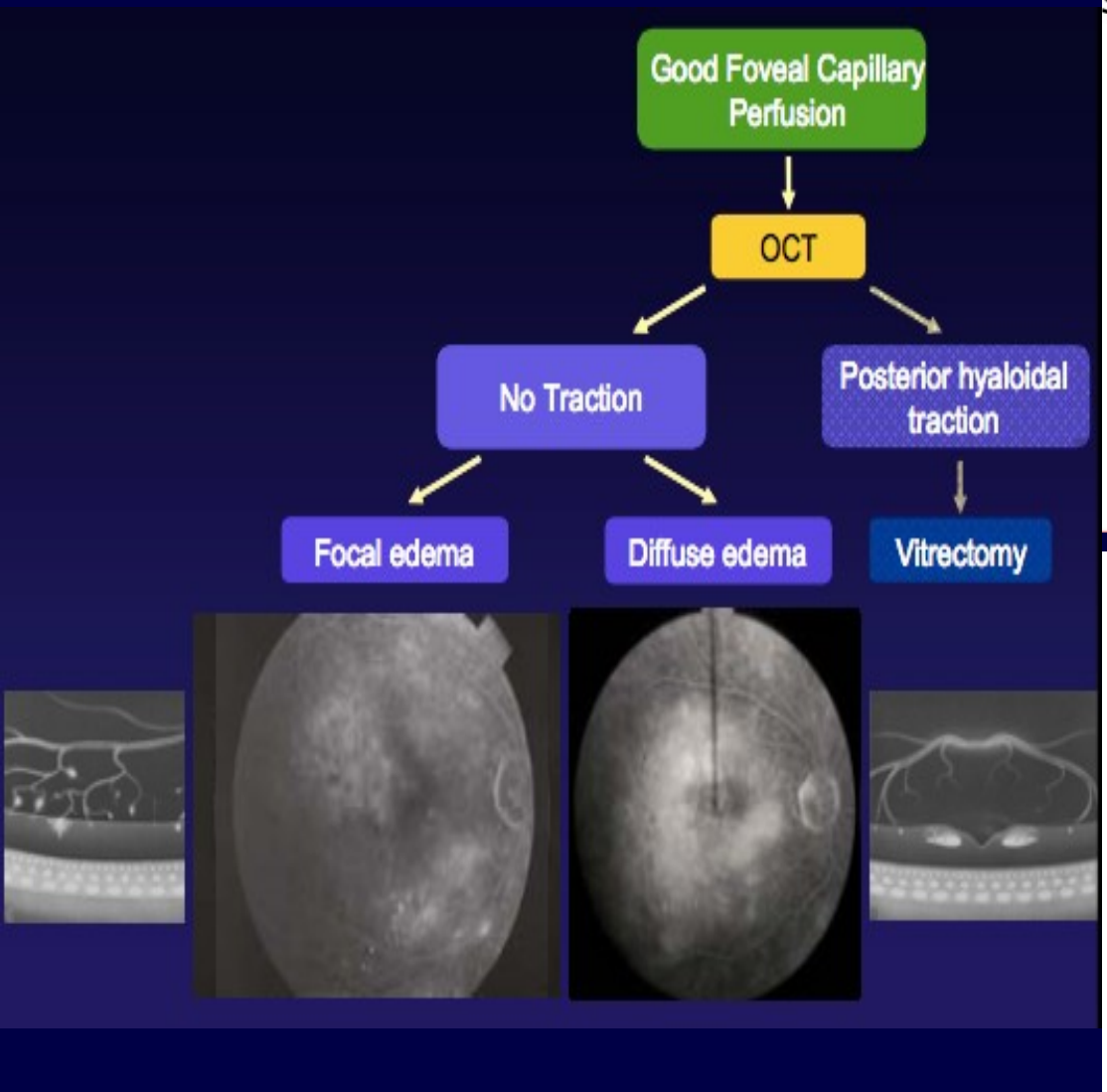
Vitrectomy for DME and Traction Associated with PHT

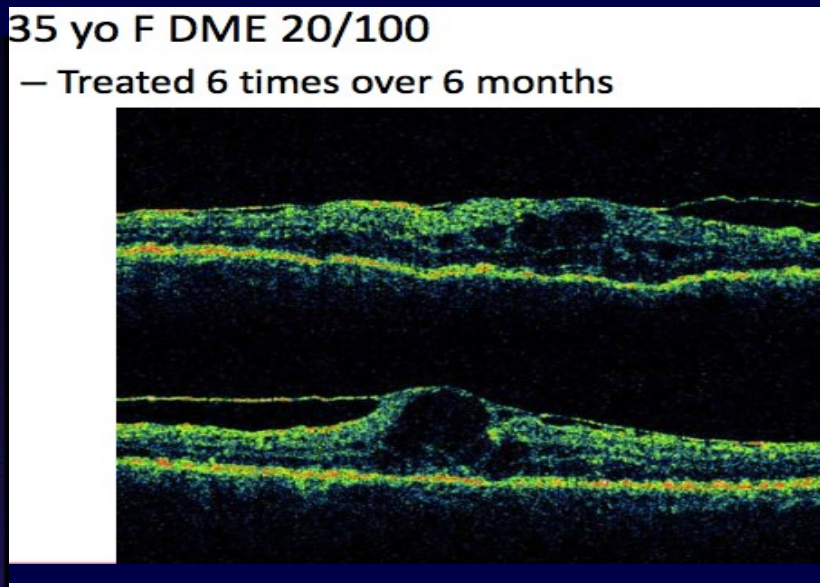
Authors	Year	Eyes (No.)	Previous Macular Laser (%)	Complete Resolution of DME (%)	Improvement in Visual Acuity ≥ 2 lines (%)
Lewis et al.	1992	10	90	80	60
Van Effenterre et al.	1993	22	64	45	86
Harbour et al.	1996	7	57	57	57
Pendergast et al.	2000	55	85	82	49
Gandorfer et al.	2000	12 *	50	50	92

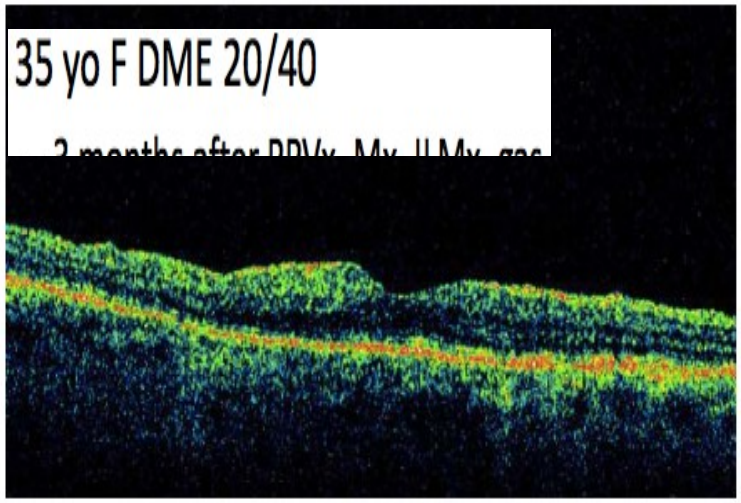
* 2 eyes without posterior hyaloidal traction

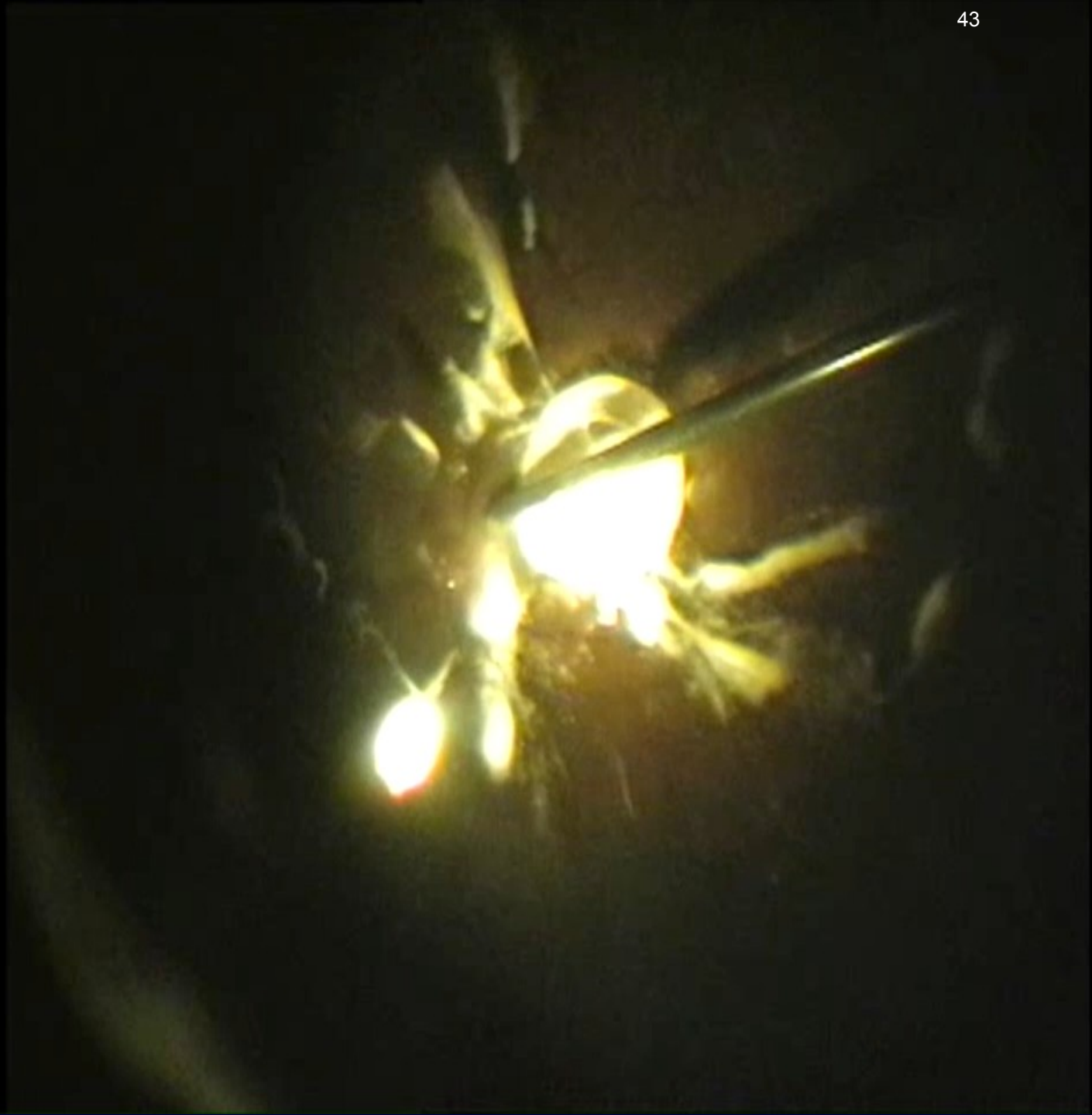


VITRECTOMY:


Good Foveal Capillary Perfusion
OCT
No Traction
Posterior hyaloidal traction
Focal edema
Diffuse edema
Vitrectomy


35 yo F DME 20/100
– Treated 6 times over 6 months


35 yo F DME 20/40

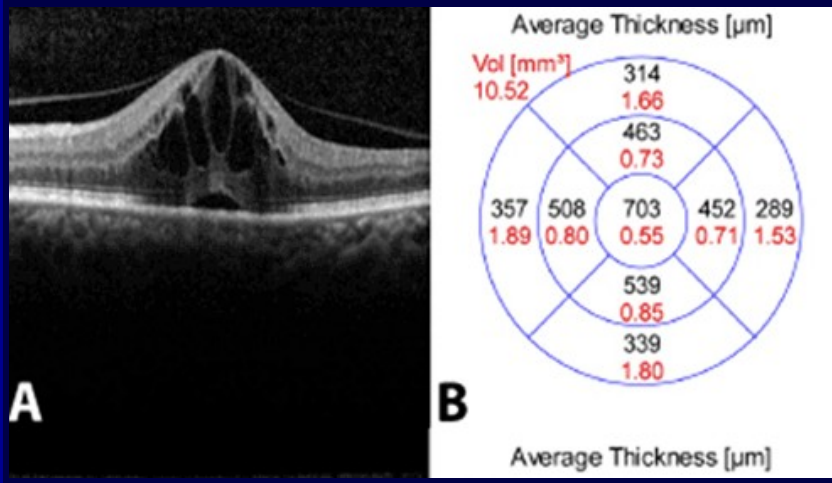


SUMMARY

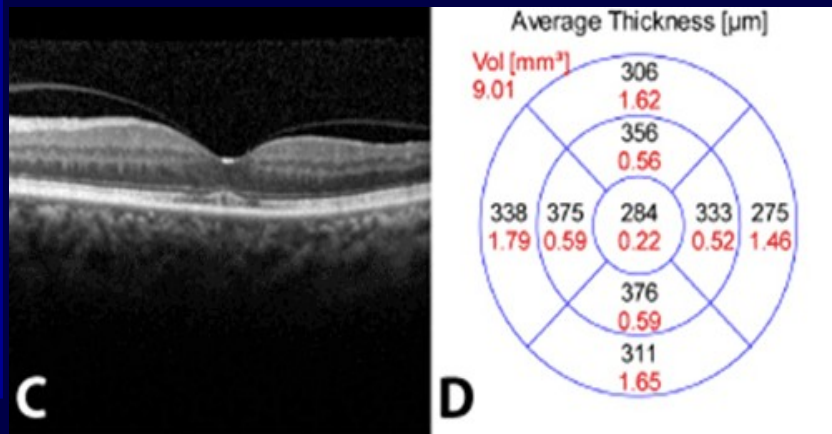
KEY POINTS FOR MANAGING DIABETIC MACULAR EDEMA (DME)

1. What is the Vision
2. Is the Centre of The Fovea Involved
   - CSF – 315 Heidelberg, 250 Stratus, 300 Cirrus
3. Ocular Risk Factors: Lens Status, Glaucoma, Steroid Responder, PDR
4. Systemic Risk Factors: Stroke, Heart Attacks, Surgery, Ulcers
5. Ability to Follow Up
6. Affordability - Who is Paying
7. Do not treat All edema – Can Follow up mild edema

Before Anti-VEGF



After Anti-VEGF



SUMMARY

THE OPTIONS – ANTIVEGF, STERIODS, LASER

ANTI-VEGF INJECTION

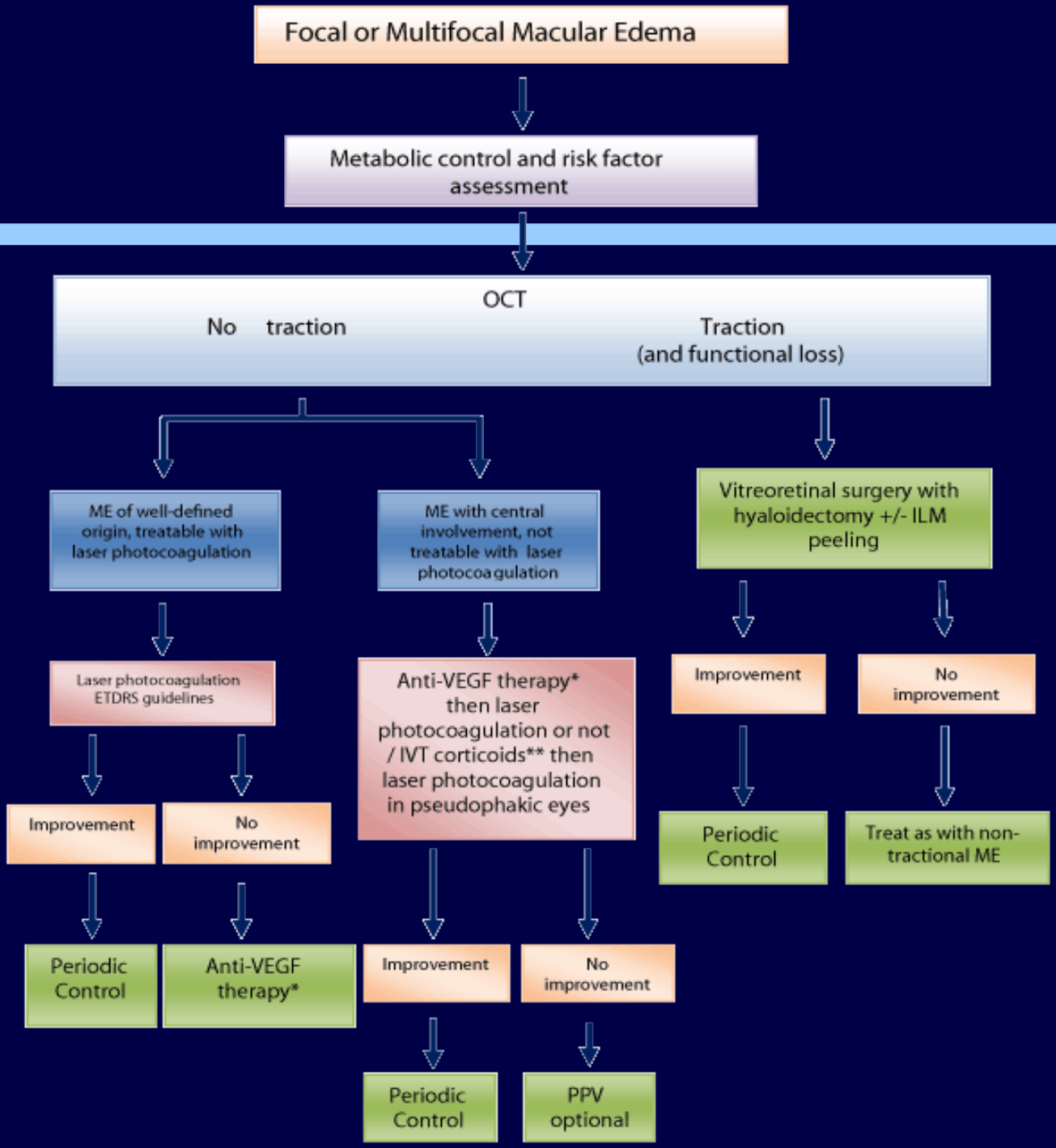
1. Centre Involving Edema
2. Decreased Vision 6/9 or Worse
3. First Line – Anti VEFG Agent (Most Efficacious and Safest)
4. Consider the various Option – DRCR.net, Restore, Rise and Ride, Vista and ViVID

INTRAOCULAR STEROIDS

1. Anti-VEGF Failure - Significant Edema (Chronic edema) & Poor VA after 6 injection and Laser Tx.
2. Pseudophakic or Planed Lens Sx
3. Recent Cataract Surgery (CME)
4. Systemic Side Effect to Anti-VGF – Stroke, Heart Attacks, Surgery, Non healing Wound, Pregnancy

CENTRAL LASER

1. Edema Threatening but not Involving the Central Macular
2. Prior to PRP, CSX Worsening Vision,
3. Poor Compliance
4. Uncertain Follow up
5. Cost Burden


Focal or Multifocal Macular Edema
Metabolic control and risk factor assessment
OCT
No traction
Traction (and functional loss)
ME of well-defined origin, treatable with laser photocoagulation
ME with central involvement, not treatable with laser photocoagulation
Vitreoretinal surgery with hyaloidectomy +/- ILM peeling
Laser photocoagulation ETDRS guidelines
Anti-VEGF therapy* then laser photocoagulation or not / IVT corticoids** then laser photocoagulation in pseudophakic eyes
Improvement
No improvement
Improvement
No improvement
Periodic Control
Anti-VEGF therapy*
Improvement
No improvement
Periodic Control
Treat as with non-tractional ME
Periodic Control
PPV optional

SUMMARY
PROGRESS AND GAPS

1. DME (not PDR) is now the major cause of vision loss
2. Screening of DR remains patchy globally.
3. Control of systemic risk factors DR is under-utilized
4. Limitations of laser treatment are now clearer and role of laser as gold standard treatment is questioned
5. Anti-VEGF treatment is superior to laser for DME and may be first line therapy, but incur significant costs and resources
6. No clear uniformed definition of DME using OCT
7. Lack of biomarker of treatment response for DME

WHAT WE KNOW – PROGRESS AND GAPS

1. Is there a difference in prevalence of PDR vs DME in terms of vision loss in resource rich vs. resource poor countries?

2. Are high risk groups different in resource rich vs. resource poor countries?

3. Should evidence-based systemic control (e.g., HbA1c and BP levels) and patient education efforts be different in resource rich vs resource poor countries?

- **Have we defined DR and DME properly?** Are current definitions too focused on DR and not on DME?

- **What is missing in our management of DR and DME?** What are the critical gaps? Are we (NGOs vs industry) properly focused on priority needs?

- **Are we incorporating technology (e.g., automated DR screening) in our management?**