Prevenzione e cura delle complicanze del Diabete
AMD, Napoli 2017

Retinopatia Diabetica: impatto dei diversi interventi terapeutici sugli end-points visivi solidi

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OSPEDALE SAN RAFFAELE

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Diabetic Retinopathy (DR)

- **DR will triple** (>> DM prevalence, epidemic level)

- **DR frequency**, especially with intensive therapy, lower than reported historically
- **Proliferative DR**: reduction of prevalence and lower risk in more recently diagnosed pts
- **Declining incidence of visual impairment but blindness is still common**

- DR detection/treatment to prevent visual loss are **cost-effective** and result in cost savings

- **Screening**: crucial step
- ~ 40% of diabetic patients receive **guideline-recommended eye care**

Overview of Diabetic Macular Edema

Nancy M. Holekamp, MD

Abstract

Diabetes mellitus (DM) is a rapidly growing epidemic in the United States, and it is expected to affect 592 million individuals within the next 20 years. Diabetic retinopathy (DR) and diabetic macular edema (DME) are the 2 most common ophthalmic complications of DM. DR is the leading cause of blindness among working-age adults around the world, and development of DR is tied to DM disease duration. With the only identifier of early markers of DR being a complete ophthalmic exam, early signs of the disease are asymptomatic. Yearly, or at least every other year, ophthalmic exams are recommended for all patients with DM; but often, individuals with DM have not undergone screening exams and do not have regular eye exams until vision loss has occurred. With spending estimates of $490 million to treat the vision complications of DM, it is clear that DR and DME impose a substantial burden for patients, caregivers, and healthcare systems.

Am J Manag Care. 2016;22:S284-S291

DR

* sight-threathening disease with multifactorial pathogenesis (≠ targets)

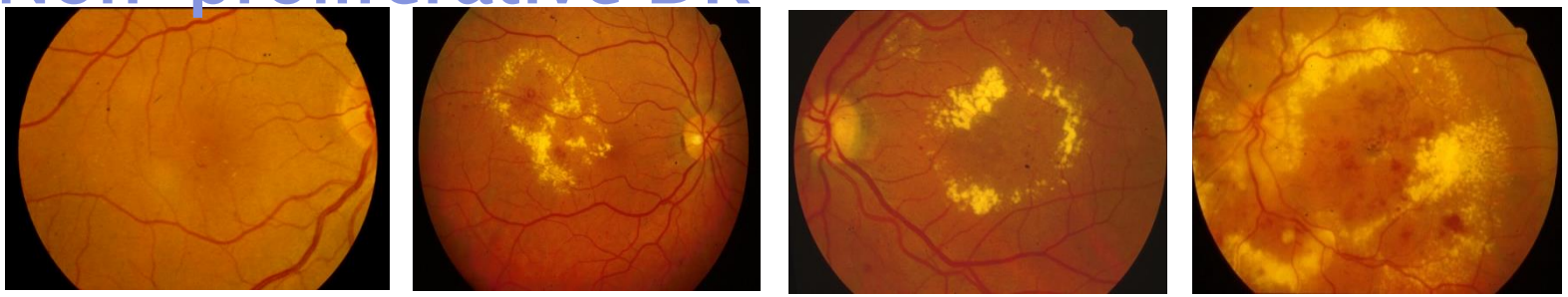
* multidisciplinary approach to managing these complex patients
  → diabetologists & ophthalmologists: common ground

* reducing HbA1c: slower is better

* evolving guidelines, new treatment paradigms with different combined strategy

DR: classification

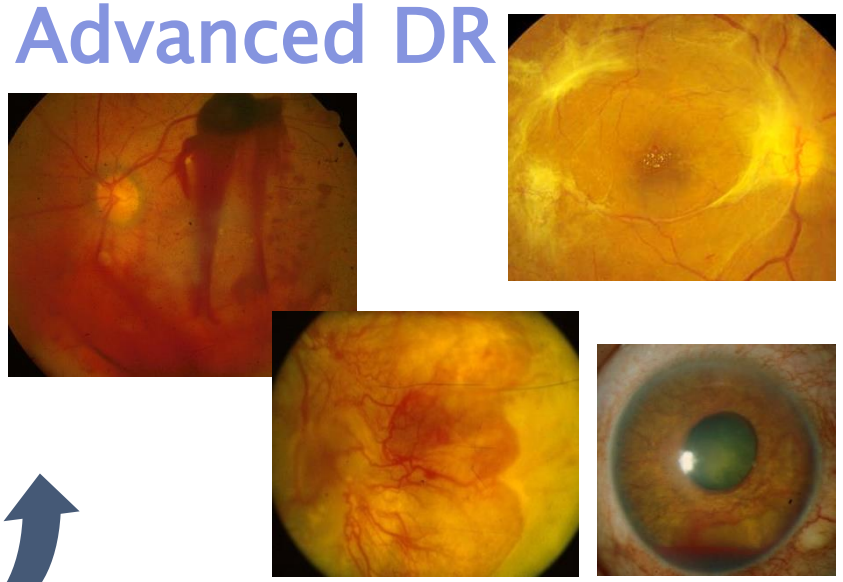
Non-proliferative DR



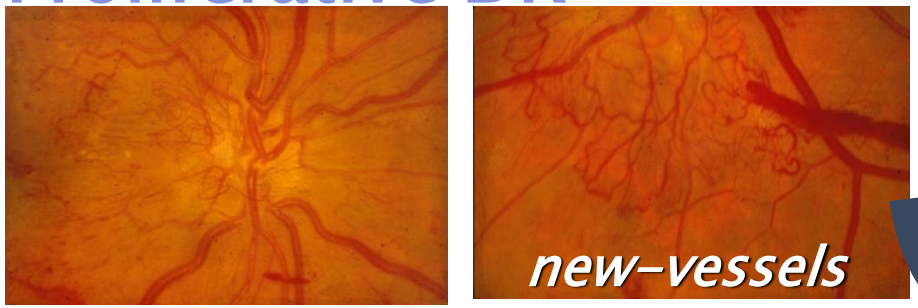
exudation, Diabetic Macular Edema (DME)

Pre-proliferative DR

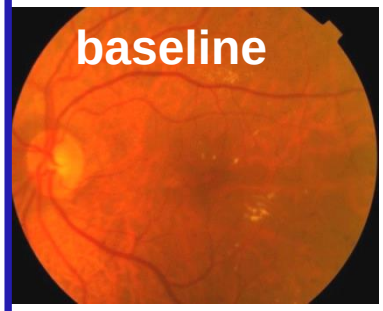
Advanced DR

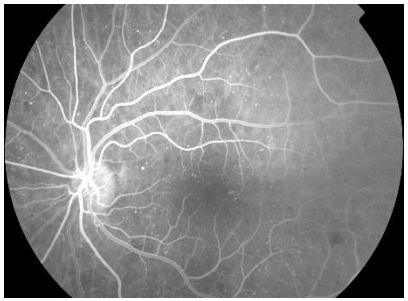


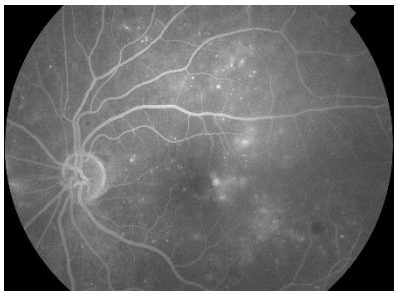
Proliferative DR

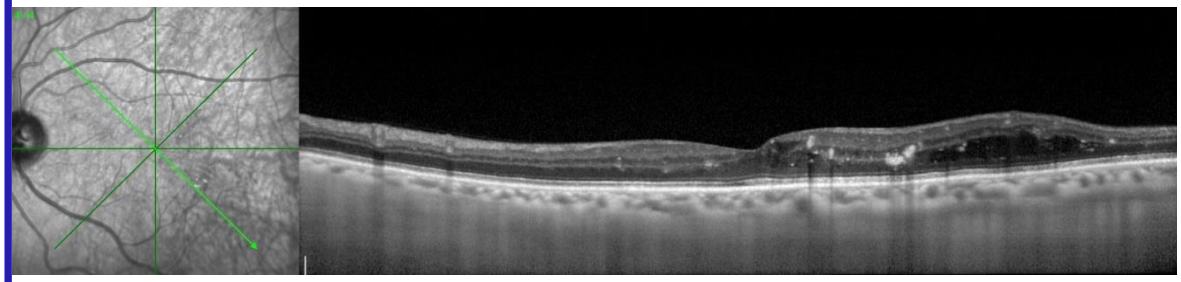


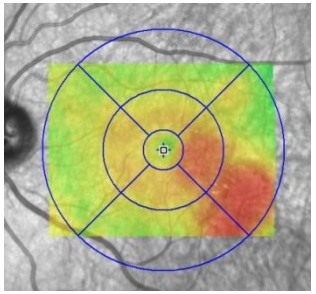
DME: natural history

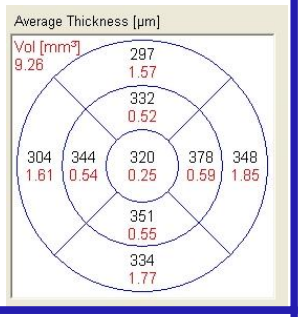


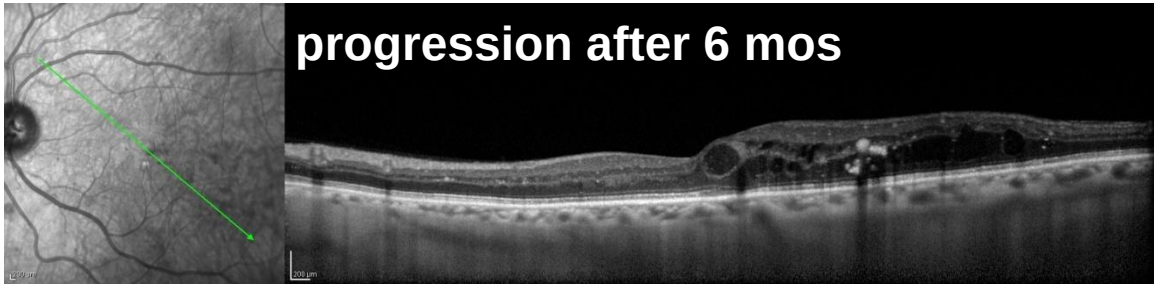


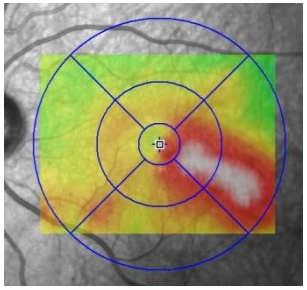


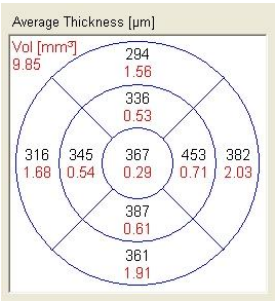


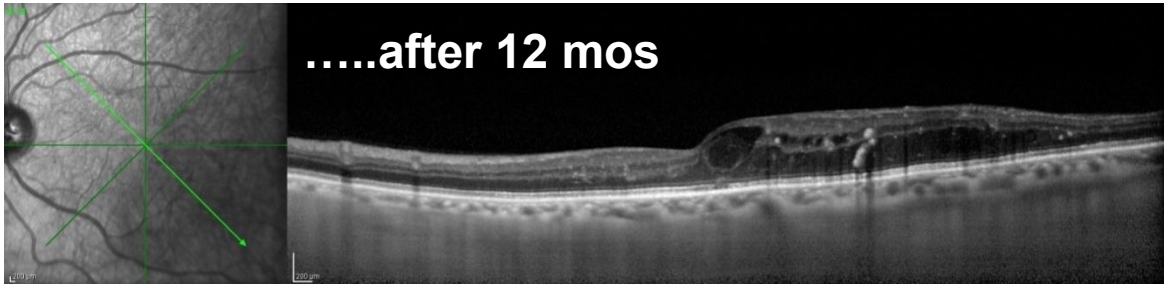


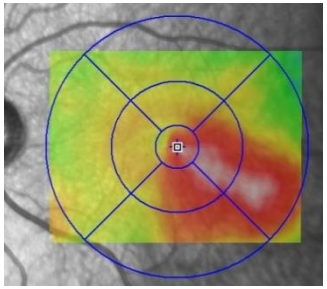


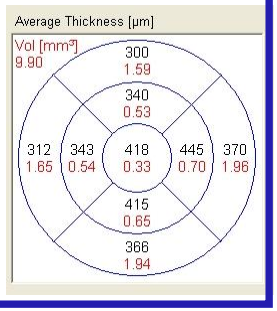












DR: pathogenesis

Hyperglycemia

Anomalies of blood flow

Anomalies of retinal microvessels

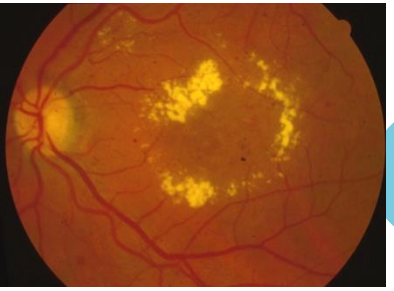
Neuronal anomalies

Inflammation Mediators

↑ VEGF

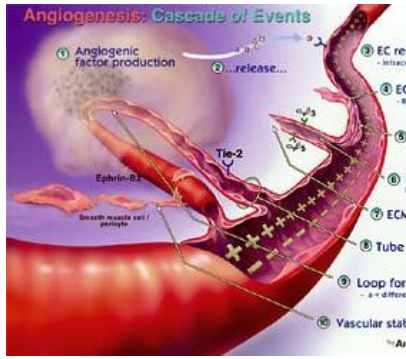
Δ vascular permeability (BRB breakdown)

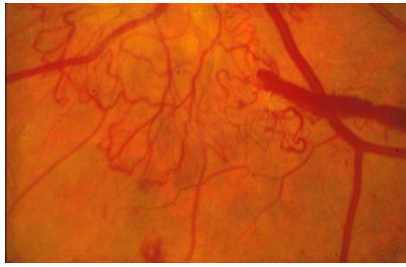
Capillaries obliteration (Ischemia)



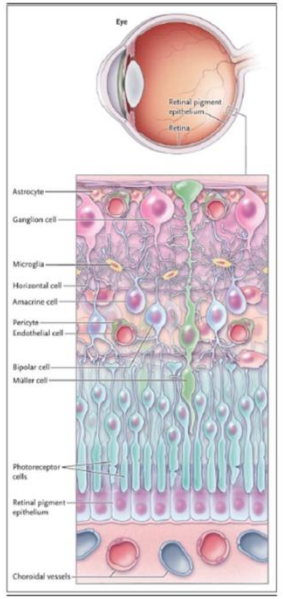
Macular Edema

Retinal New-vessels (Proliferative DR)





The Neurovascular Unit of the Retina.



Rationale for intra-vitreal injections

Vascular Disease
• Diabetes

VEGF
Vascular Endothelial Growth Factor

Inflammatory Mediators

• Vasodilation • Leukostasis • Diapedesis • Permeability • Inflammatory proteins

Breakthroughs in treating DR & DME

Identification of critical roles of:
*** VEGF**
*** Inflammatory mediators**

↓

>> RCTs (efficacy & safety) ➔ **New Therapies**

AntiVEGFs

- (Pegaptanib)
- Bevacizumab
- Ranibizumab*
- Aflibercept*

Steroids

- Triamcinolone Acetonide
- Long-lasting implants (DDS)
  - Desamethasone*
  - Fluocinolone Acetonide*

* on label

AAO 2016– DR Preferred Practice Patterns

TABLE 6 MANAGEMENT RECOMMENDATIONS FOR PATIENTS WITH DIABETES

Severity of Retinopathy	Presence of Macular Edema	Follow-up (Months)	Panretinal Photocoagulation (Scatter) Laser	Focal and/or Grid Laser*	Intravitreal Anti-VEGF Therapy
Normal or minimal NPDR	No	12	No	No	No
Mild NPDR	No	12	No	No	No
	ME	4–6	No	No	No
	CSME†	1*	No	Sometimes	Sometimes
Moderate NPDR	No	12‡	No	No	No
	ME	3–6	No	No	No
	CSME†	1*	No	Sometimes	Sometimes
Severe NPDR	No	4	Sometimes	No	No
	ME	2–4	Sometimes	No	No
	CSME†	1*	Sometimes	Sometimes	Sometimes
Non-high-risk PDR	No	4	Sometimes	No	No
	ME	2-4	Sometimes	No	No
	CSME†	1*	Sometimes	Sometimes	Sometimes
High-risk PDR	No	4	Recommended	No	Alternative[129,130]
	ME	4	Recommended	Sometimes	Usually
	CSME†	1*	Recommended	Sometimes	Usually

Anti-VEGF = anti-vascular endothelial growth factor; CSME = clinically significant macular edema; ME = non-clinically significant macular edema; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy

* Adjunctive treatments that may be considered include intravitreal corticosteroids or anti-VEGF agents (off-label use, except aflibercept and ranibizumab). Data from the Diabetic Retinopathy Clinical Research Network in 2011 demonstrated that, at two years of follow-up, intravitreal ranibizumab with prompt or deferred laser resulted in greater visual acuity gain and intravitreal triamcinolone acetonide plus laser also resulted in greater visual gain in pseudophakic eyes compared with laser alone.[131] Individuals receiving the intravitreal injections of anti-VEGF agents may be re-examined as early as one month following injection.

† Exceptions include hypertension or fluid retention associated with heart failure, renal failure, pregnancy, or any other causes that may aggravate macular edema. Deferral of photocoagulation for a brief period of medical treatment may be considered in these cases.[132] Also, deferral of CSME treatment is an option when the center of the macula is not involved, visual acuity is excellent, close follow-up is possible, and the patient understands the risks.

‡ Or at shorter intervals if signs approaching those of severe NPDR appear.

Laser Treatment for DME

- Laser treatment improves visual prognosis in diabetic patients
- Focal photocoagulation reduces risk of moderate visual loss by approximately 50%
- Poor prognosis for diffuse CSME despite grid photocoagulation
- Overall, unsatisfactory outcome and several side-effects related to laser photocoagulation

ETDRS report # 1. Arch Ophthalmol, 1985; ETDRS report # 9. Arch Ophthalmol, 1991; Bresnick GH. Ophthalmology 1983; Bresnick GH. Ophthalmology 1986; Lee CM, Olk RJ. Ophthalmology 1991

Limited VA Improvement Induced by Laser

Trial	Mean BCVA change with laser at 1 year
DRCR.net grid laser vs. IVTA	1 letter
DRCR.net mod macular grid	0 letters
DRCR.net ranibizumab vs. prompt/ deferred laser/ IVTA	3 letters
RESTORE	1 letter
BOLT	– 4.6 letters
da Vinci	–1.4 letters

Diabetic Retinopathy Clinical Research network. *Ophthalmology* 2008;115:1447
Diabetic Retinopathy Clinical Research network. *Ophthalmology* 2010;117:1064
Mitchell P *et al. Ophthalmology* 2011 118:615
Michaelides M *et al. Ophthalmology* 2010;117:1078

VA deterioration despite Laser

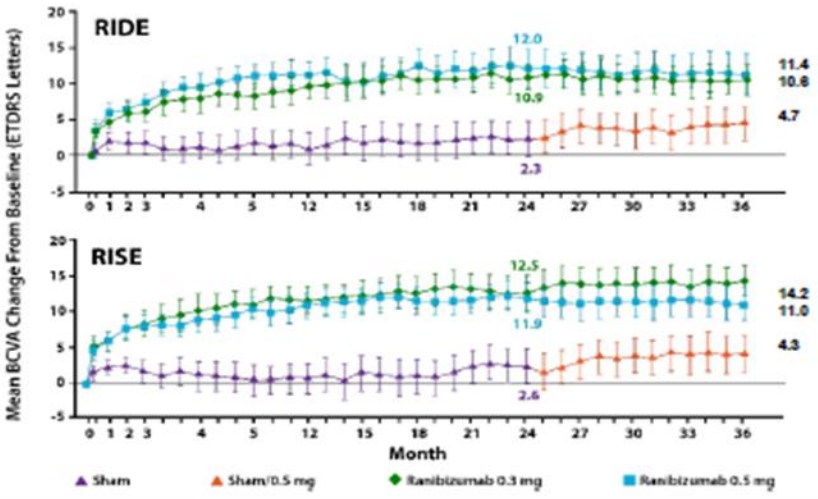
Trials with 1 year data	2-line loss with laser	3-line loss with laser
DRCR.net: grid laser vs. IVTA	17%	13%
DRCR.net: mod macular grid	~13%	7–10%
DRCR.net: ranibizumab vs prompt/ deferred laser/ IVTA	13%	8%
RESTORE	13%	8%
BOLT: bevacizumab vs laser	Not reported	26%

Diabetic Retinopathy Clinical Research network. *Ophthalmology* 2008;115:1447-59e10
Diabetic Retinopathy Clinical Research network. *Ophthalmology* 2010;117:1064-77
Mitchell P *et al. Ophthalmology* 2011 118:615
Michaelides M *et al. Ophthalmology* 2010;117:1078

VA gain with intra-vitreal anti-VEGFs

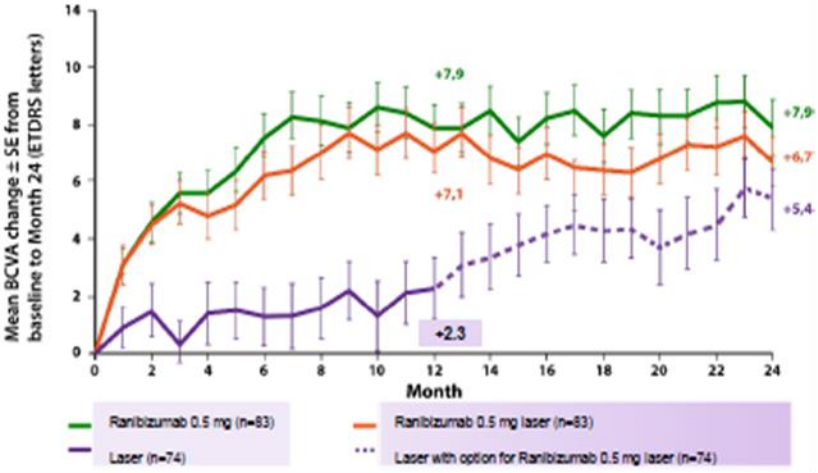
RISE, RIDE[1]

Ranibizumab better than sham all throughout 3 years



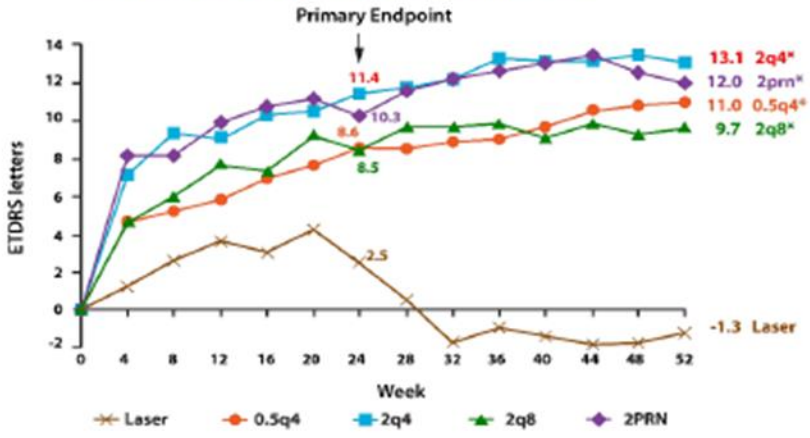
RESTORE[2]

Better VA w/ ranibizumab than laser alone or combination



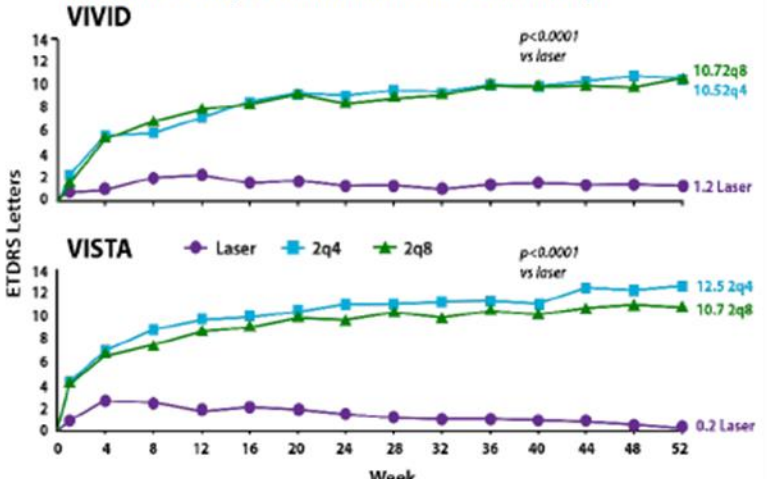
DA VINCI[3]

Improved VA over laser in all regimens

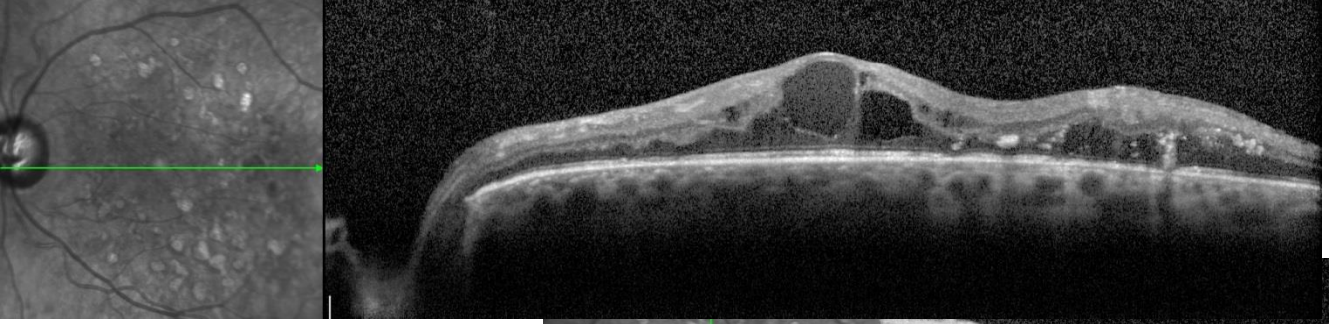


VIVID, VISTA[4]

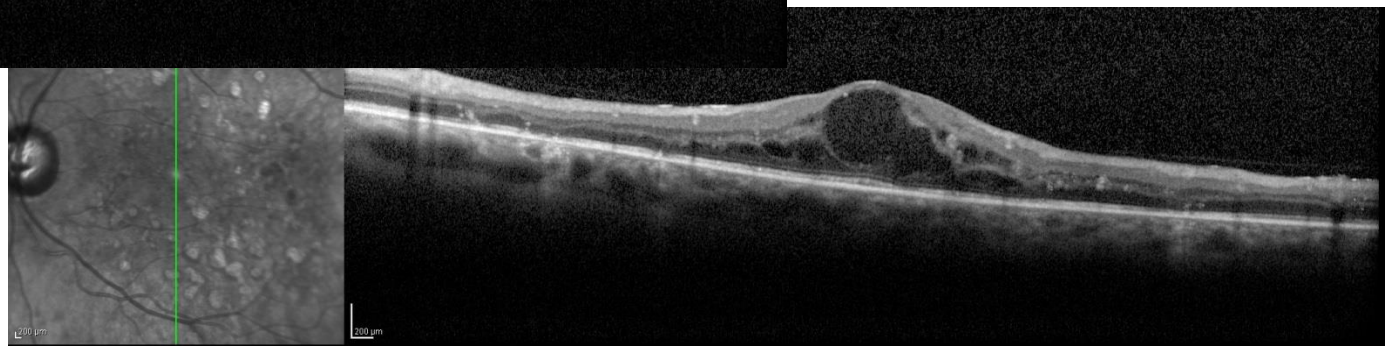
Minimal VA improvement w/ laser vs aflibercept

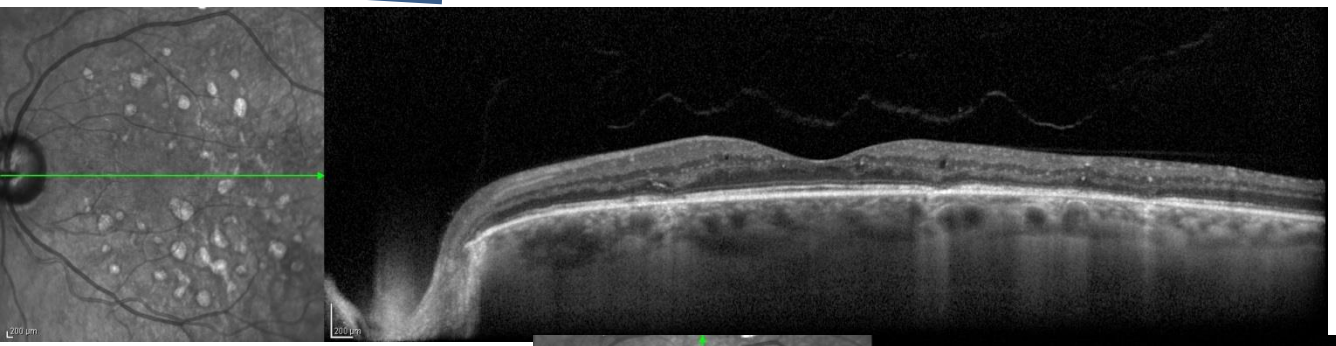


1.Brown DM et al Ophthalmology 2013;120:2013-22; 2.Schmidt-Erfurth U et al. Ophthalmology 2014;121:1045-53; 3. Do DV et al. Ophthalmology 2012;119:1658-65; 4. Brown DM e-poster presented at Retina Society 2013



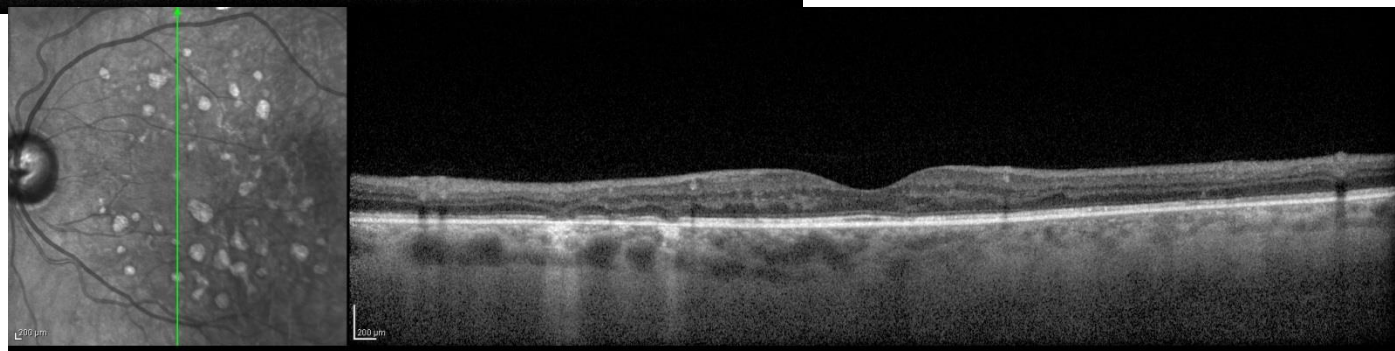
baseline





after 100 weeks:

- 5 IV anti-VEGF monthly
- 7 PRN (pro re nata)



DME management: changing trends over the past decade

- **Intra-vitreal drugs**: significant inprovements in visual/anatomical outcomes (RCTs)
- Several **safe drugs** on-label ➔ replacing laser as mainstay treatment
- IV: beneficial role in DR (regression, < risk of progression)
- better **QoL** : goal for treating
- To understand the burden that treatment selection has on patients and on health care system: crucial

➔ beyond the clinical trials ?

Real-world in AntiVEGF & Steroids era ?
own drawbacks & concerns

- temporary anatomical response
- frequent re-treatments necessary
- suboptimal response
- VEGF/other factors resistance

➔ preferred agent/optimal therapeutic regimen ?

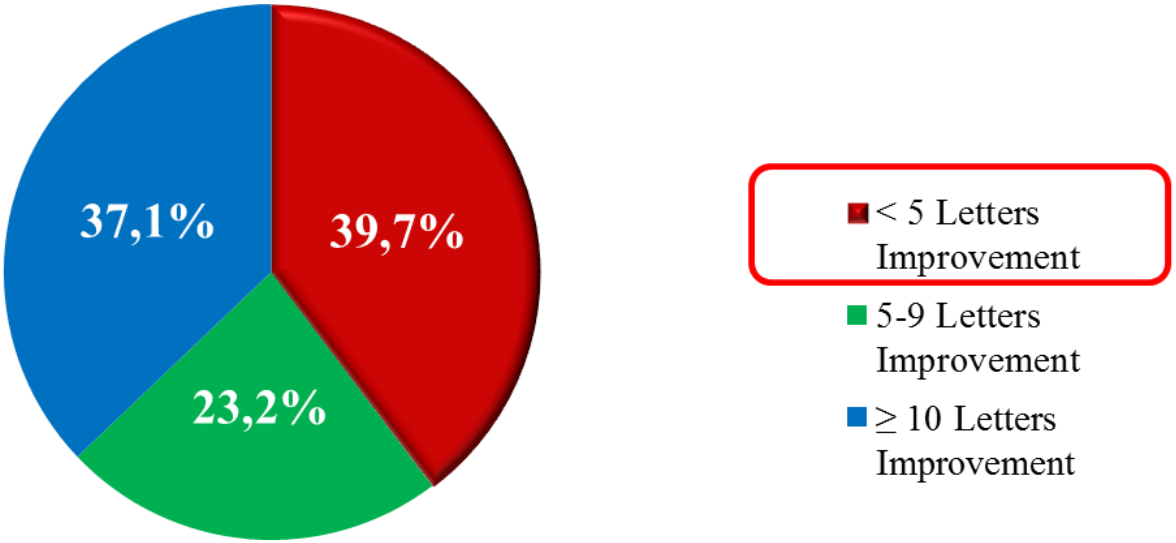
not settled

Long-term response (3yrs) to Anti-VEGF therapy for DME can be predicted after 3 injections

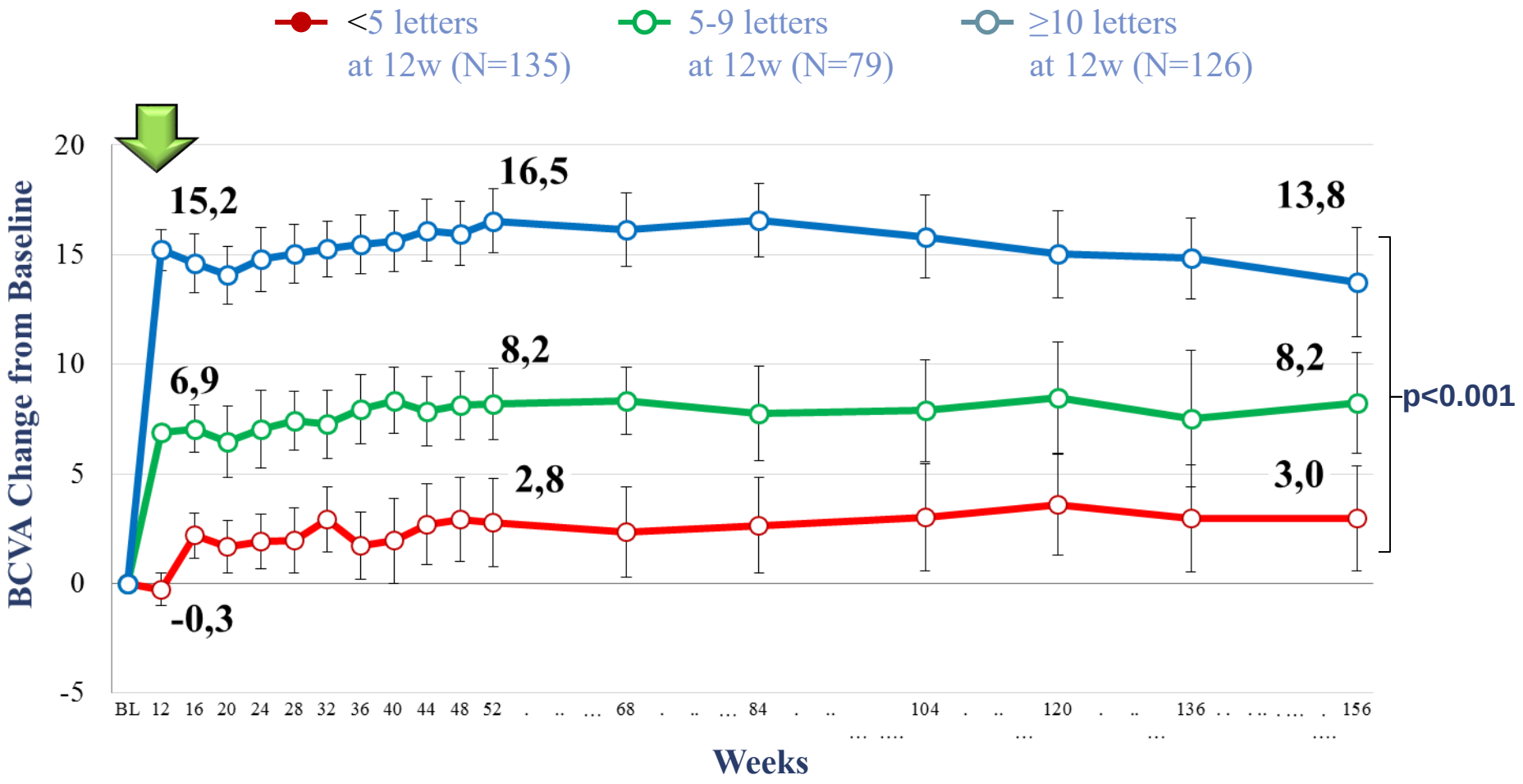
An Analysis of the Protocol I Data -DRCRnet-

To assess whether early BCVA response to Ranibizumab after 3 injections (12 weeks) can predict long-term treatment outcomes in Diabetic Macular Edema

Stratification into 3 cohorts at 12 weeks



EYES WITH <5 LETTER GAIN AFTER 3 INJECTIONS SHOWED LIMITED ADDITIONAL IMPROVEMENT FOR THE STUDY DURATION (3 YEARS)



Studi clinici vs *Real World Data:* perchè outcomes visivi così diversi?

Popolazioni diverse da quelle degli studi

trattamento iniziato tardivamente rispetto all'insorgenza dei sintomi

Afferenza non tempestiva al centro

Lunghe liste di attesa

Insufficiente numerosità del personale medico

Diagnosi incomplete

Budget di farmaco insufficiente

Sistemi di prenotazione non efficienti

Difficoltà di accesso alla sala operatoria

Vantaggi e limiti delle attuali terapie del DME:

gestione differente nella real life vs RCTs

LUMINOUS: a Novartis-sponsored study observing the effectiveness and safety of Ranibizumab in clinical practice in AMD, DME, and RVO

Table 3. Visual acuity outcomes at 12 months , studio LUMINOUS

	DME	
	Treatment naïve (N=128, n=40)	Prior treated (RBZ) (N=178, n=59)
Baseline Visual Acuity* (ETDRS letters)	56.0	62.7
12 month Visual Acuity	60.5	65.9
Change in letter score (at month 12)	**+4.5**	**+3.2**
Mean number of injections at month 12	3.2	3.8
Mean number of visits at month 12	5.0	6.9

- I risultati degli studi con anti-VEGF spesso non possono essere replicati nella pratica clinica
- Burden della gestione ne limita l'efficacia

I pazienti con DME in real-life ricevono un numero inferiore di iniezioni di Ranibizumab e ottengono un guadagno più basso di AV rispetto a quanto riportato negli studi clinici randomizzati

Souied EH, Gekkiev B, Bretagne A *et al.* Poster presentation at the Association for Research in Vision and Ophthalmology Annual Meeting; May 3–7, 2015; Denver, CO. Abstract 1417-A0112.

Vantaggi e limiti delle attuali terapie del DME:

numero di accessi
(visite di monitoraggio e visite per il trattamento)

… Anti-VEGF & Steroids era

- increased burden and frequency of visits

1862 pts: 3±2 visits/year ➔9±2/year

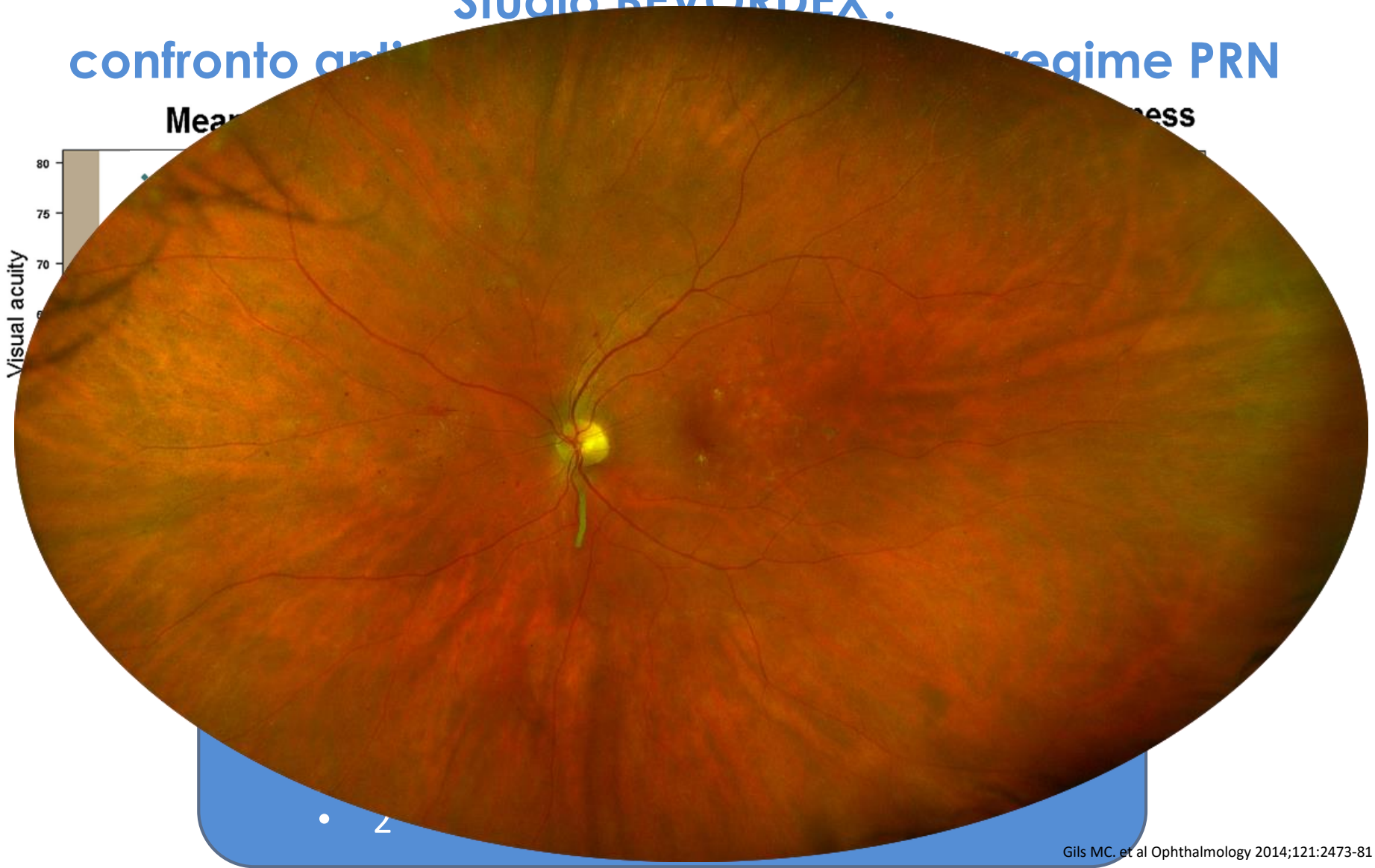
➔ significant rise in health-care costs

➔ strategy to reduce treatment burden ?

Jusufbegovic D et al: Retina 2015

Vantaggi e limiti delle attuali terapie del DME: numero di iniezioni

Studio BEVORDEX : confronto gli… …regime PRN



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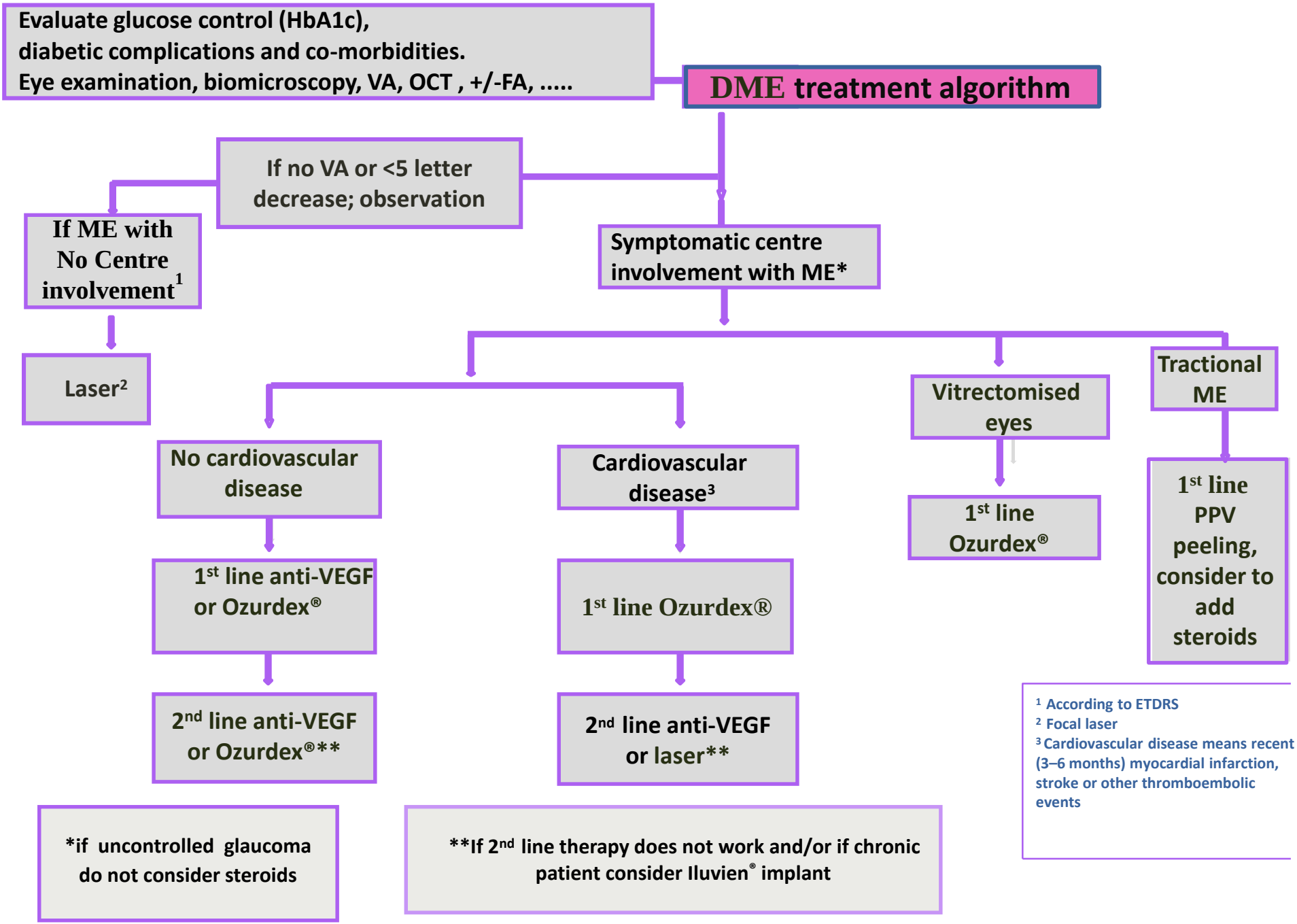
Gils MC. et al Ophthalmology 2014;121:2473-81



Proposed by A. Loewenstein, Tel Aviv University, Israel

? : first-line

Anti-VEGFs

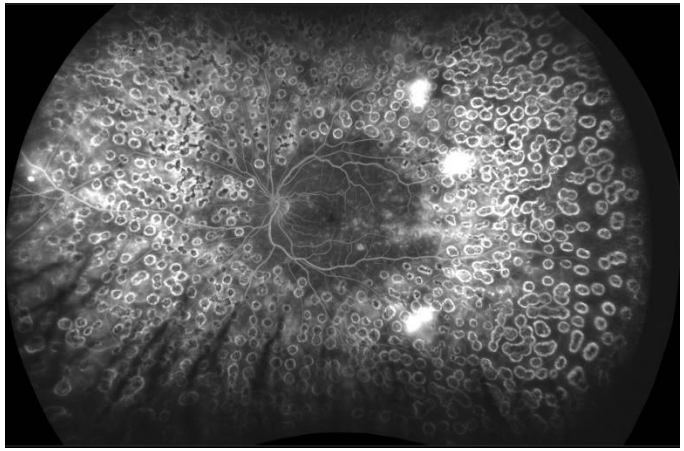
- no recent cardiovascular events (3–6 months) or high-risk
- younger patient
- clear lens
- uncontrolled glaucoma

Steroids

- recent cardiovascular events (3–6 months) or high-risk
- patient vitrectomised
- patient with risk of non-compliance
- patient insufficiently responsive to non-corticosteroid therapy
- patient pseudo-phakic

Proposed by A. Loewenstein, Tel Aviv University, Israel

DR:
aim of treatment management



- managing the sight-threatening complications
  → improving long-term vision

- reduce burden of illness
  → tailored treatment regimens in follow-up reduces chances of over/under-treatment

- laser has still an important role

- patient-centric approach
  → **minimizing impact on Quality of Life (QoL)**

Cosa vuol dire adottare il trattamento idoneo per clinico e paziente?

Non accontentarsi dei risultati iniziali ma continuare fino a raggiungere i migliori risultati stabili

Personalizzare la terapia sulle basi delle esigenze del singolo paziente

Concentrare gli sforzi sulla fase di induzione per conferire il massimo beneficio, che si ripercuoterà anche sul risultato finale

Effettuare miglioramenti organizzativi per consentire un trattamento tempestivo e idoneo

..... grazie !

Financial Disclosures

- Allergan
- Bayer
- Novartis