Preventing Diabetic Retinopathy: The Importance of Connections

Timothy J. Lyons, MD

November 15, 2024

South Carolina FOUNDATION

diabetes free SC

Conflicts

None

South Carolina FOUNDATION

diabetes free SC

Themes, Connections

1. How to connect and translate new research knowledge to effective clinical care
2. How to connect different disciplines so that opportunities are not lost
3. How to connect to past knowledge that may have been forgotten
4. How to connect with health care providers so that they change long-established habits

Talk Outline

1. Diabetic eye disease (retinopathy): pathogenesis and risk fac
2. Preventive measures and current treatments
3. A new role for an old drug?

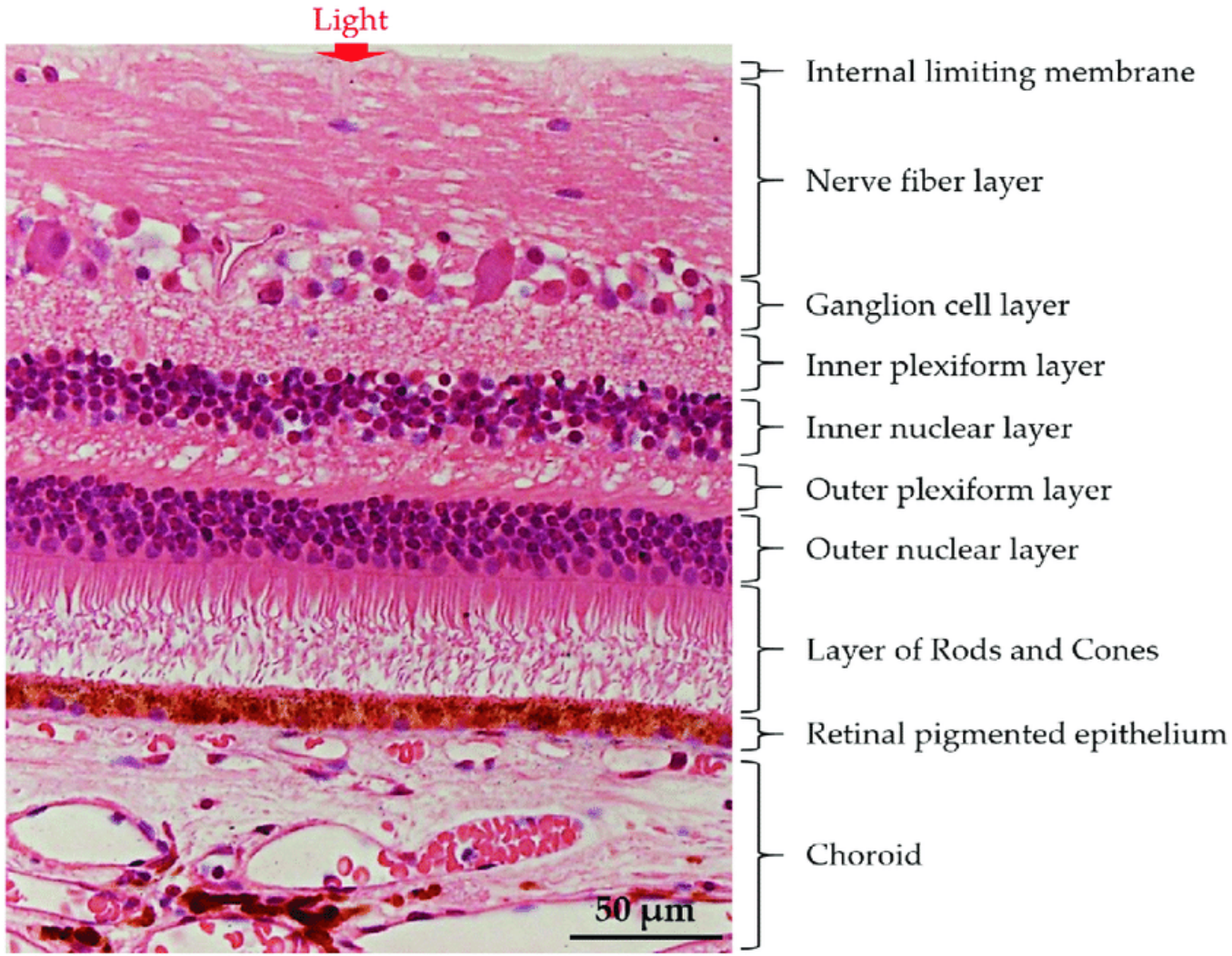
Talk Outline

1. Diabetic retinopathy: pathogenesis and risk factors

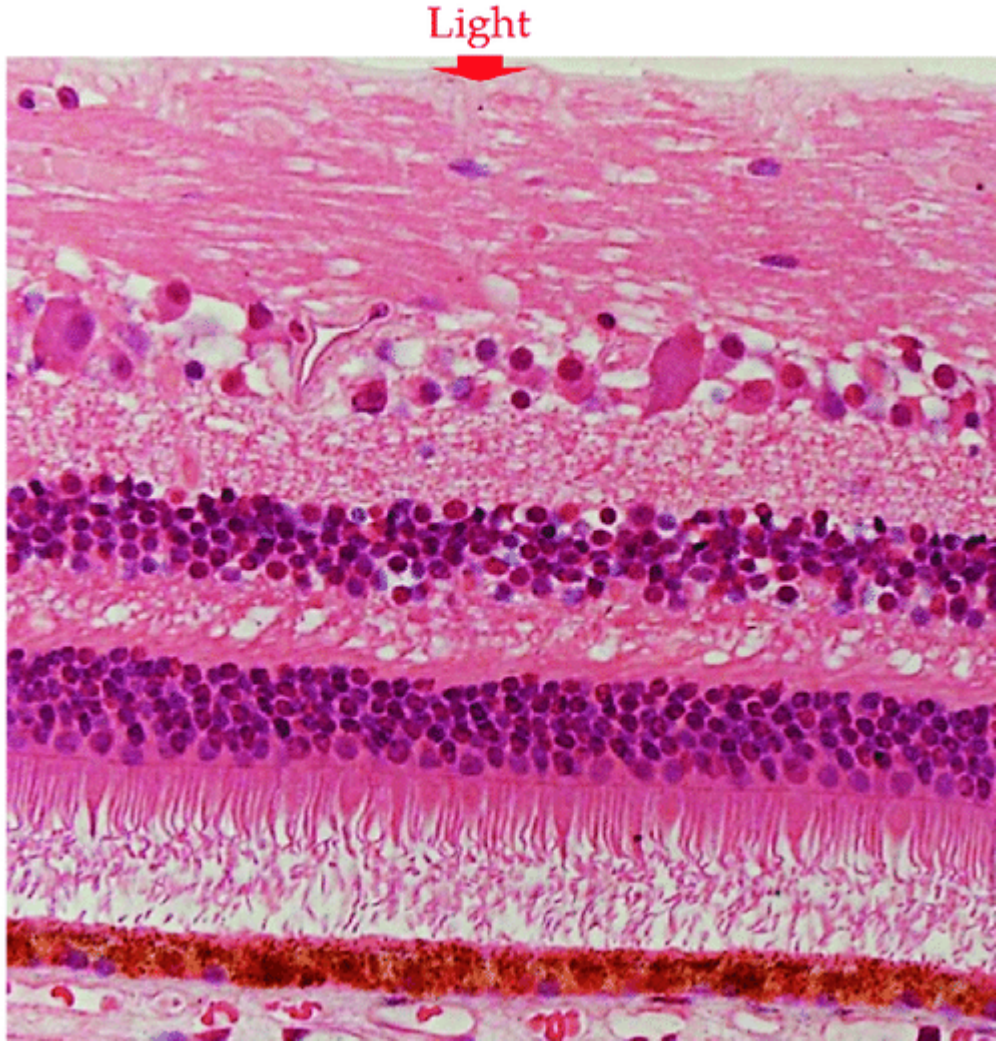
2. Preventive measures and current treatments

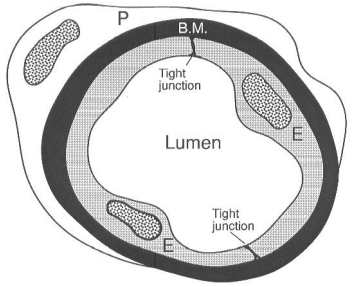
3. A new role for an old drug?

Structure of Retina

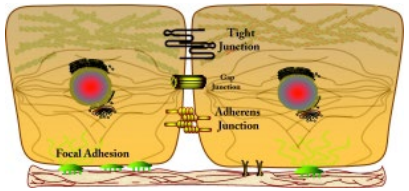


Inner and Outer Blood Retinal Barriers





Inner BRB: tight junctions between capillary endothelial cells in the inner retina



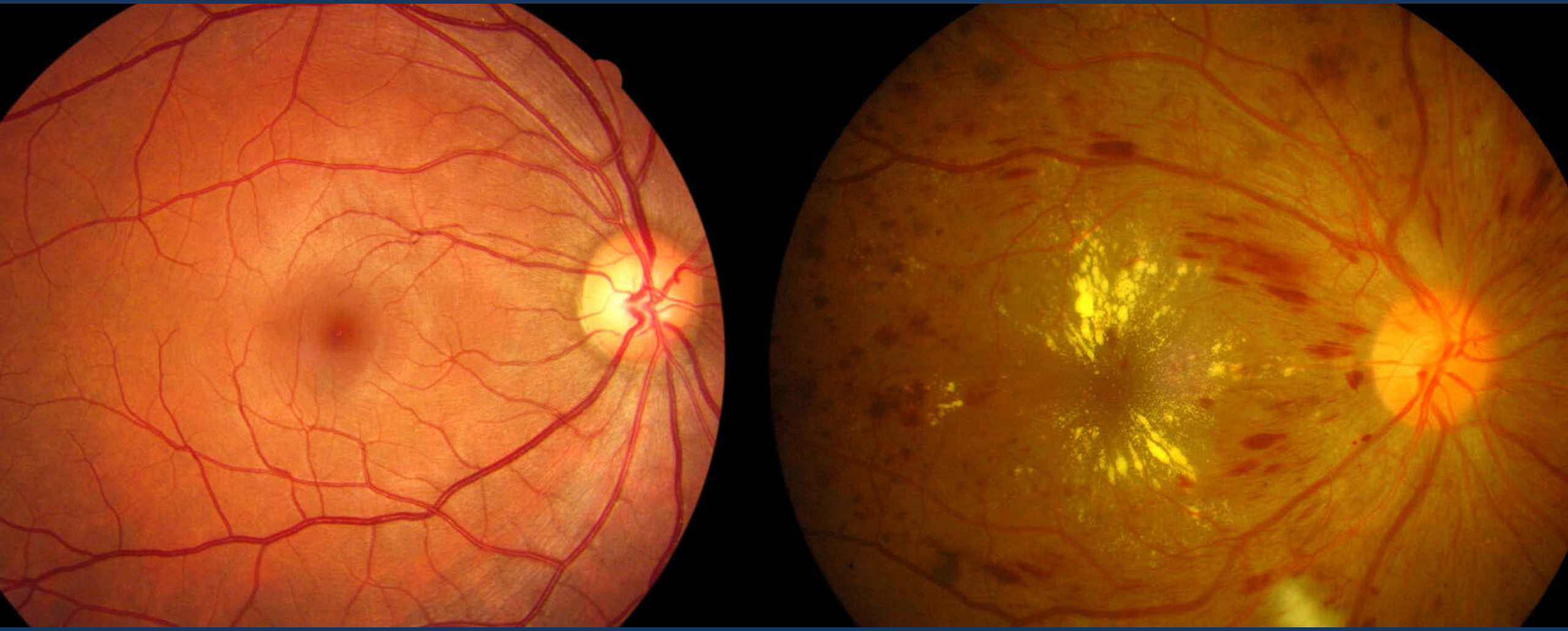
Outer BRB: tight junctions between retinal pigment epithelial cells that form a monolayer defining the outer retinal boundary

Monolayer Barriers and the Complications of Diabetes

- Microvascular complications of diabetes arise in tissues where endothelial and epithelial **barrier functions** are critical
- Diabetes causes barriers to be stressed and compromised for a variety of reasons
- Once breached, vicious cycles of damage may be established (eyes, kidneys, nerves, placenta, gut)
- Cells **not** requiring insulin for glucose uptake are critical to barrier function

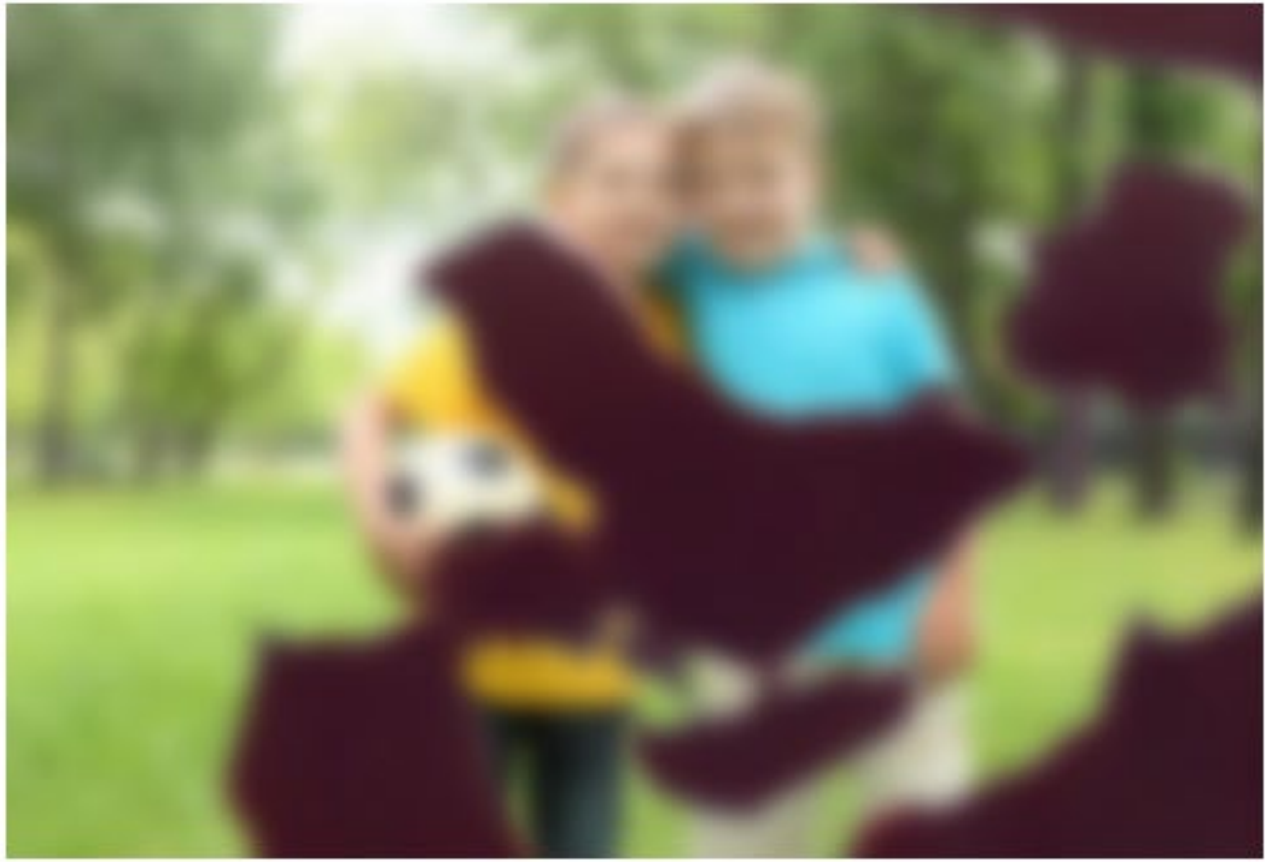
Normal retina

Diabetic retina with hemorrhages, exudates and proliferative changes



Effects of diabetic retinopathy on vision

Normal Vision

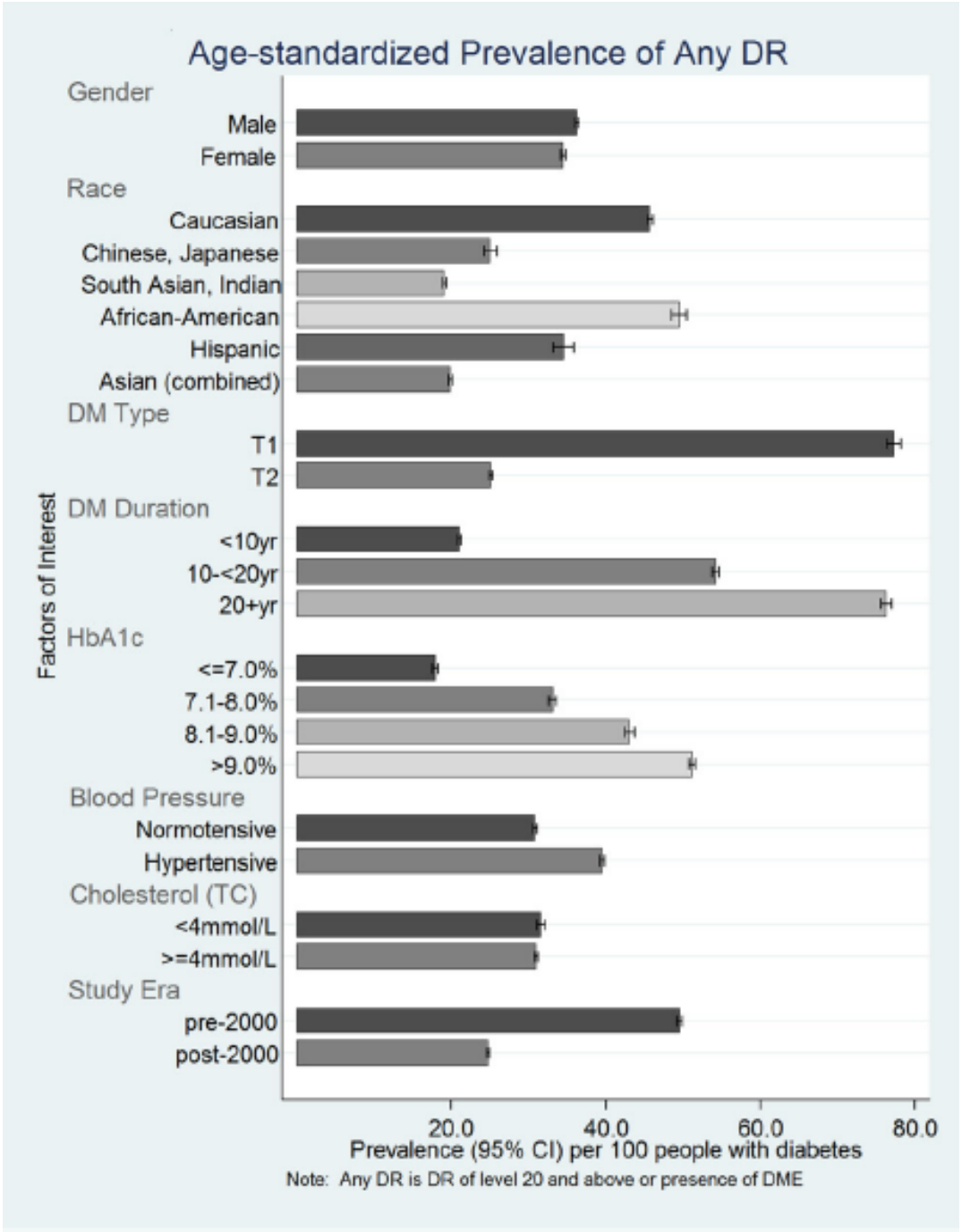


Same scene viewed by a person with Diabetic Retinopathy.

Risk Factors for DR

Modifiable	
1. HbA1c[55]	Decrease in every 1% = reduction in 40% of retinopathy, 25% need for retinal laser and 15% of blindness
2. Systolic Blood Pressure[44,45]	Decrease in every 10 mmHg = reduction in 35% of retinopathy, 35% need for retinal laser and 50% blindness However, two Asian clinic-based studies did not show association of blood pressure with the incidence and progression of DR
3. Hyperlipidemia[73]	DR is associated with triglycerides level whereas DME is associated with LDL, high non-HDL cholesterol and high HDL/LDL ratio
4. Body Mass Index (BMI)[78]	i. Increased waist–hip ratio, BMI >31 kg (men); BMI >32 kg (women) and BMI <20 kg were associated with increased risk of DR development
Non-modifiable	
1. Puberty[88]	Post pubertal period has 30% increased risk of DR development and the onset to any DR was faster (2 years shorter) compared to the prepubertal period
2. Pregnancy[84,85]	i. Pregnancy could increase risk of DR progression by 2.3 times ii. During postpartum period, 29% would have DR regression iii. Pregnant women with retinopathy is at much higher risk of DR progression, with 47% progression and 50% of those required laser treatment

Clin. Exp. Ophthalmology 2016; 44: 260–277 doi: 10.1111/ceo.12696



Clin. Exp. Ophthalmology 2016; 44: 260–277
doi: 10.1111/ceo.12696

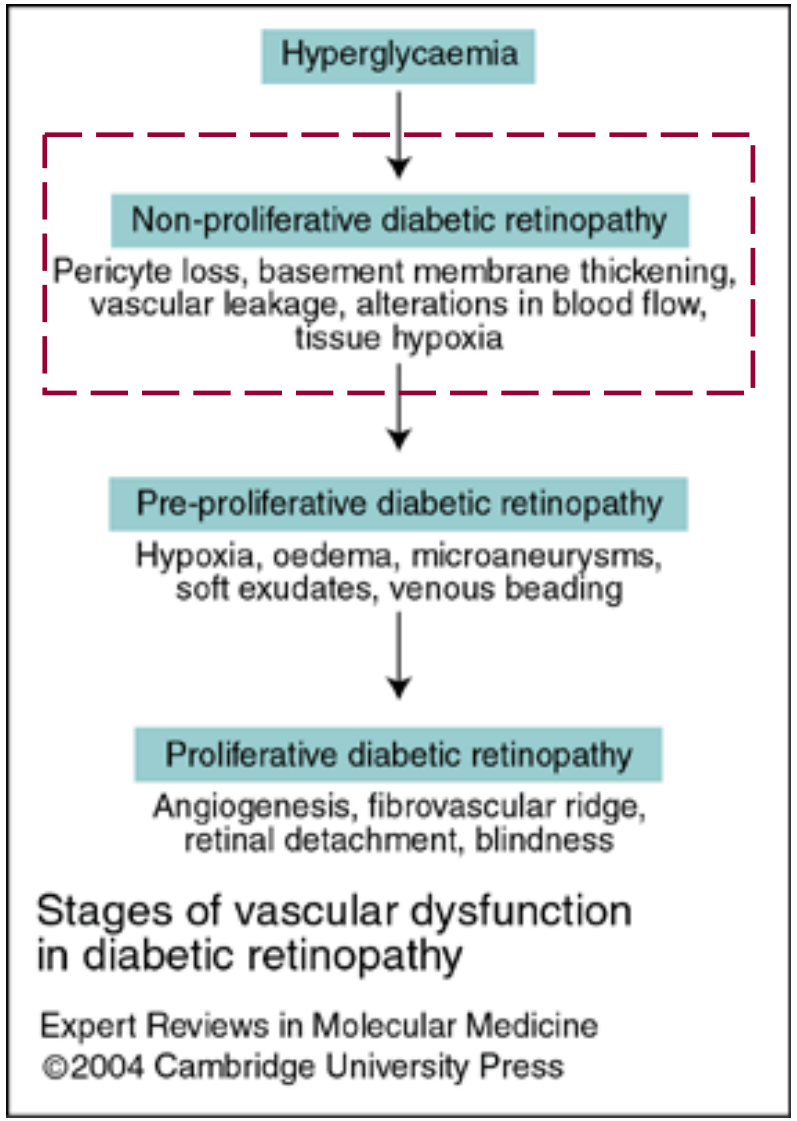
Background

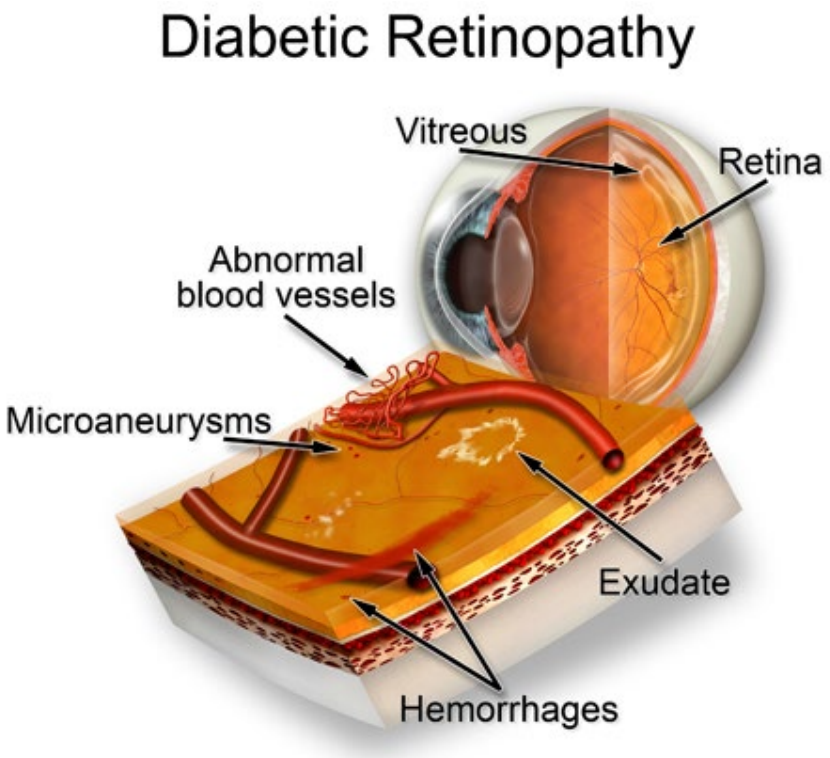
- Diabetes:
- 230 million people worldwide in 2007; predicted 350 million by 2025: actually now ~800 million
- Diabetic retinopathy:
- a leading cause of blindness in adults in developed countries
- 50% by 10 years of diabetes; 90% by 25 years
- ~700,000 have serious diabetic retinal disease in USA
- 12,000-24,000 new cases of blindness each year in USA

Kowluru, RA and Chan PS. Exp Diabetes Res. 2007; 43603.
NCD Risk Factor Collaboration, Lancet, 2023

Diabetes INITIATIVE of South Carolina

Hyperglycemia and DR

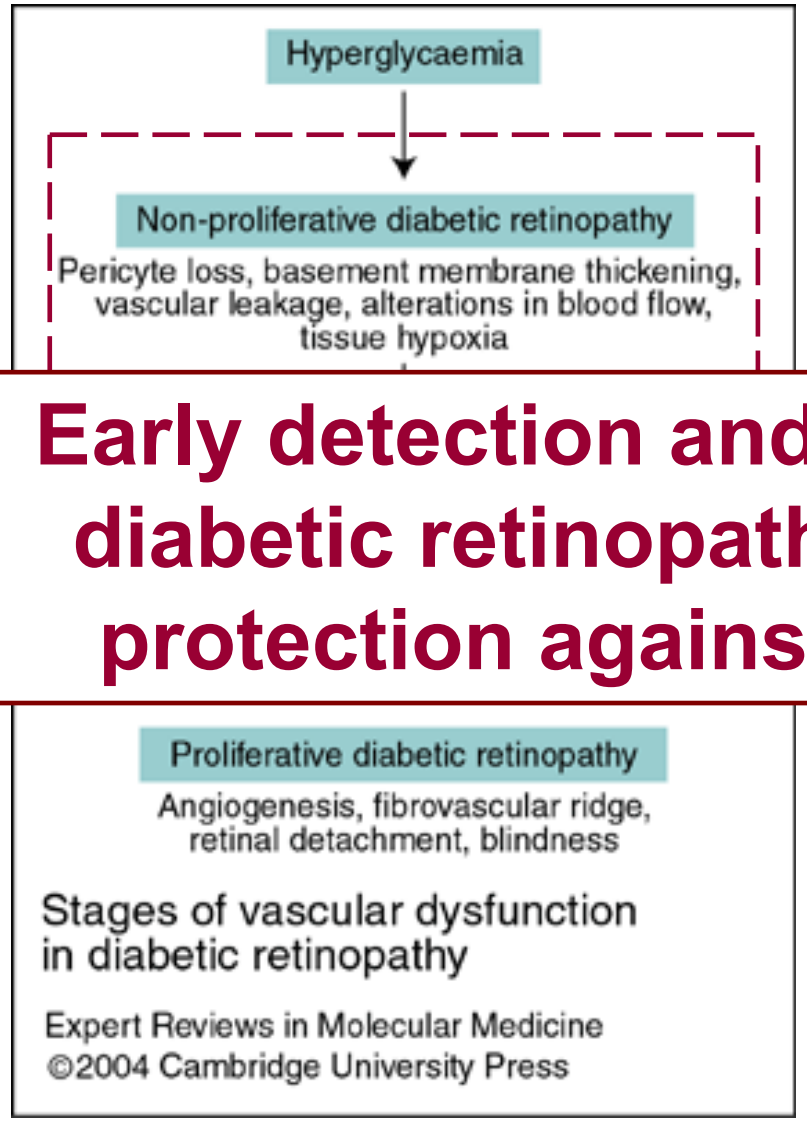




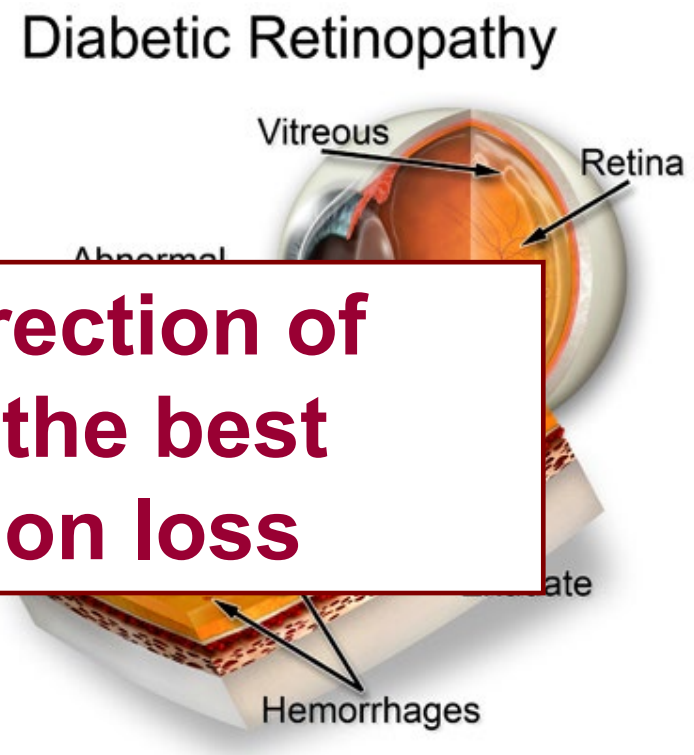
[Ophthalmoscope]

Diabetes INITIATIVE of South Carolina

Hyperglycemia and DR



Early detection and correction of diabetic retinopathy is the best protection against vision loss



[Ophthalmoscope]

Talk Outline

1. Diabetic retinopathy: pathogenesis and risk factors
2. Preventive measures and current treatments
3. A new role for an old drug?

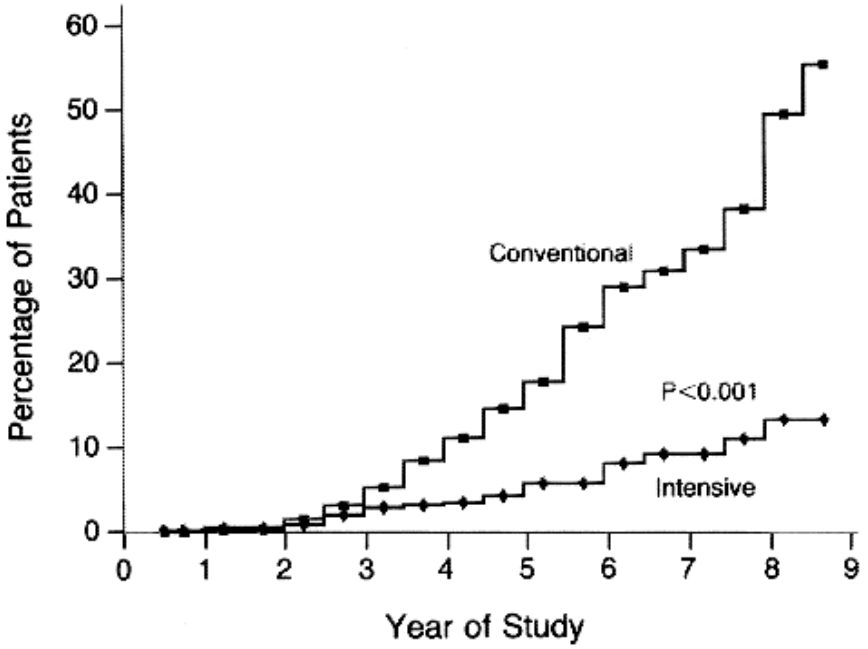
Diabetes INITIATIVE of South Carolina

Prevention, Treatment

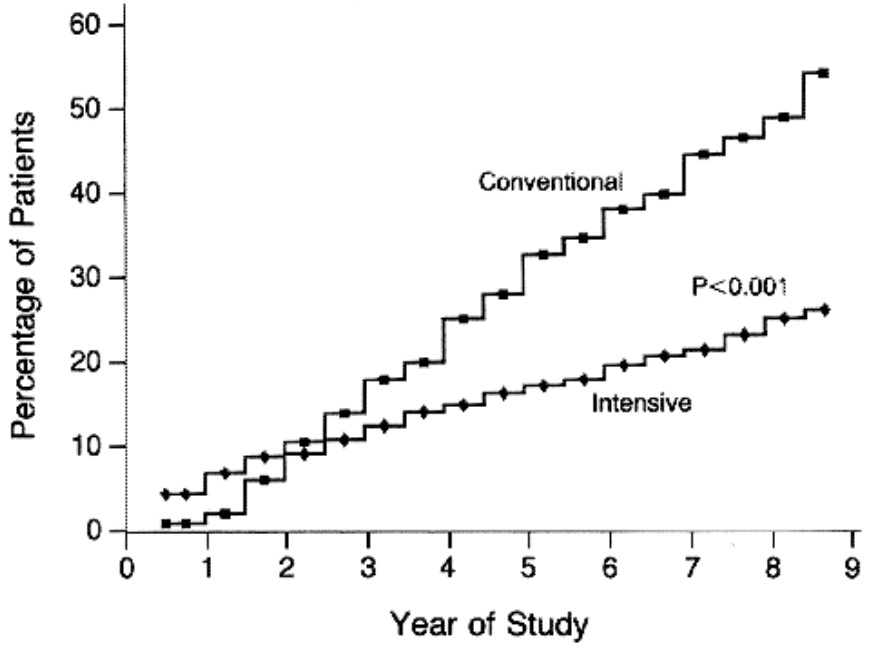
- Control risk factors, especially blood sugar, blood pressure
- For advanced, sight-threatening disease, laser ablation of abnormal new vessels, intra-ocular injections to inhibit new vessel formation, vitrectomy (all late and invasive)
- Until now, no specific, targeted treatment to block progression of early-stage disease.

Diabetes INITIATIVE of South Carolina

Results: Cumulative Incidence of a Sustained Change (3 steps, 6 months) in Retinopathy in DCCT



Primary-prevention cohort
76% reduction



Secondary-intervention cohort
54% reduction

New Engl J Med 1993;329:977-986

Talk Outline

1. Diabetic retinopathy: pathogenesis and risk factors
2. Preventive measures and current treatment
3. A new role for an old drug?

Diabetes INITIATIVE of South Carolina

Forgotten History: Fibrates

Brit. J. Ophthal. (1969) **53,** 9

Present status of clofibrate therapy in ophthalmology

J. NOLAN AND J. F. CULLEN
Department of Ophthalmology, Royal Infirmary, Edinburgh

Clofibrate reduces serum lipid levels, interferes with blood clotting, and may possibly alter aqueous humour dynamics. It has been used in the treatment of hard retinal exudates, retinal vascular occlusion, lipidosis oculi, and certain types of glaucoma.

Effects of Clofibrate on DR

Table I *Comparison of exudate results found in various series (see text) in percentage of total*

Result	*Treated*				*Control*			
	Edinburgh 5 yrs	*Duncan and others*	*Houtsmuller*	*Harrold and Marmion*	*Edinburgh 5 yrs*	*Duncan and others*	*Houtsmuller*	*Harrold and Marmion*
Improved	49	57	69	43	14	16	15	4
No change	42	39	20	53	66	56	37	80
Worse	9	4	11	4	20	28	48	16
Total eyes	106	46	23	60	70	50	19	60
Observation period (yrs)	5	3	3	1	5	3	3	1

Table II *Results after 5 years' observation (eyes)*

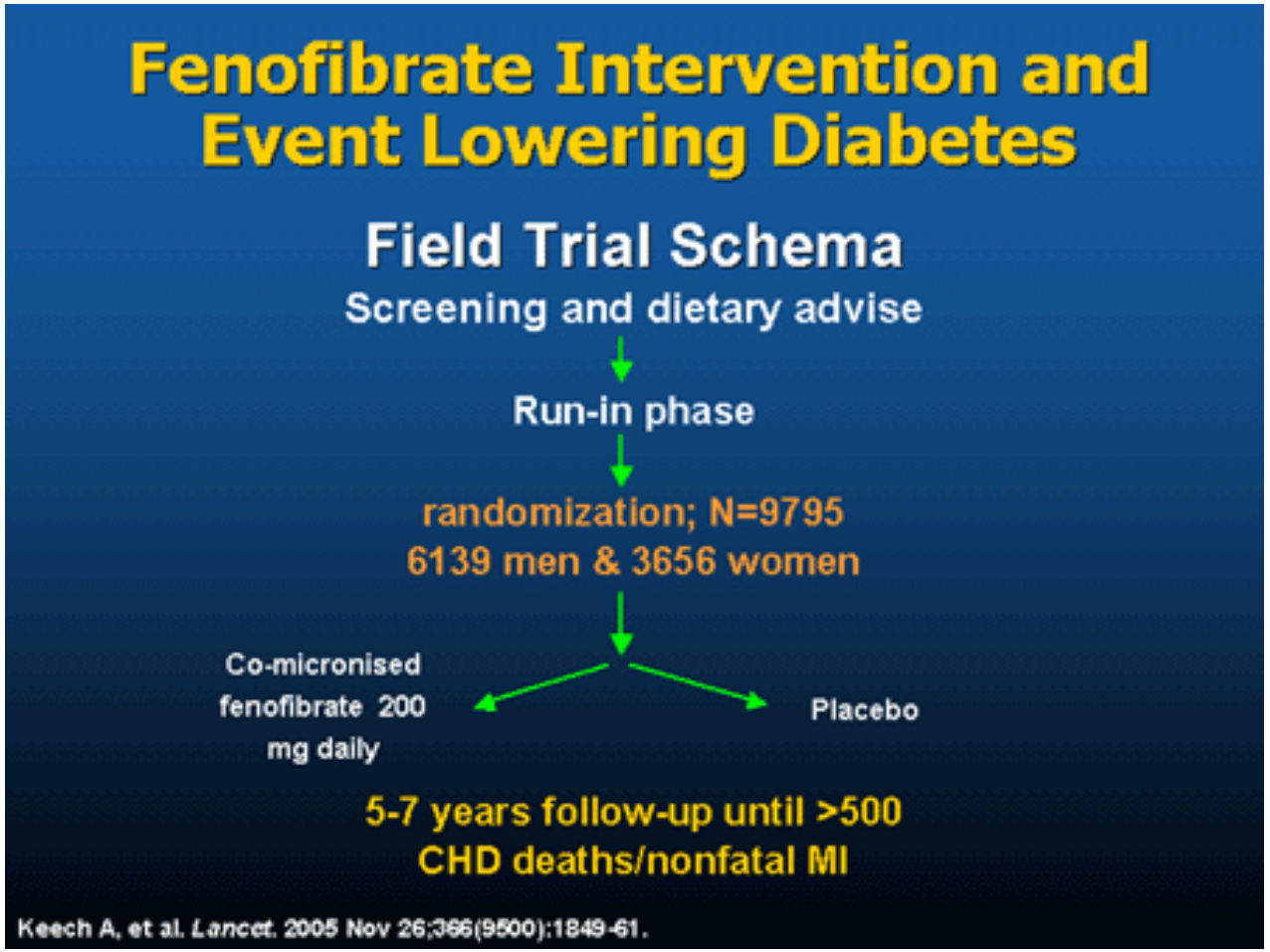
Symptoms	*Exudates*			*Haemorrhages*			*Visual acuity*		
Results	*Improved*	*No change*	*Worse*	*Improved*	*No change*	*Worse*	*Improved*	*No change*	*Worse*
Treated No.	52	44	10	0	84	22	18	63	25
Control	10	46	14	0	56	14	2	44	24
Treated Per cent.	49	42	9	0	79	21	17	60	23
Control	14	66	20	0	80	20	3	63	34

Nolan J, Cullen JF. Present status of clofibrate therapy in ophthalmology. Br J Ophthalmol. 53: 9-15, **1969**

Fenofibrate

- Peroxisome proliferator-activated receptor (PPAR) – nuclear receptors
- PPAR α regulates lipid metabolism mainly in the liver and skeletal muscle
- Fenofibrate: PPAR α agonist
- Effect of fenofibrate on circulating lipids:
  - Triglycerides ↓↓↓
  - VLDL cholesterol ↓↓
  - LDL cholesterol ↓
  - Apo B ↓
  - HDL cholesterol ↑

FIELD: Primary endpoints were cardiovascular



Patients aged 50 – 75 years
Type 2 diabetes

Randomized to Fenofibrate 200mg/day vs. placebo.

Primary End-Point: CHD deaths + non-fatal MI

<u>Need for laser Rx for DR, progression to albuminuria, amputation were tertiary endpoints</u>

Retinal photographs obtained in a subset, n=1012

FIELD Eye Study (Tertiary Outcome Analysis)

Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial

A C Keech, P Mitchell, P A Summanen, J O'Day, T M E Davis, M S Moffitt, M-R Taskinen, R J Simes, D Tse, E Williamson, A Merrifield, L T Laatikainen, M C d'Emden, D C Crimet, R L O'Connell, P G Colman, for the FIELD study investigators*

Summary

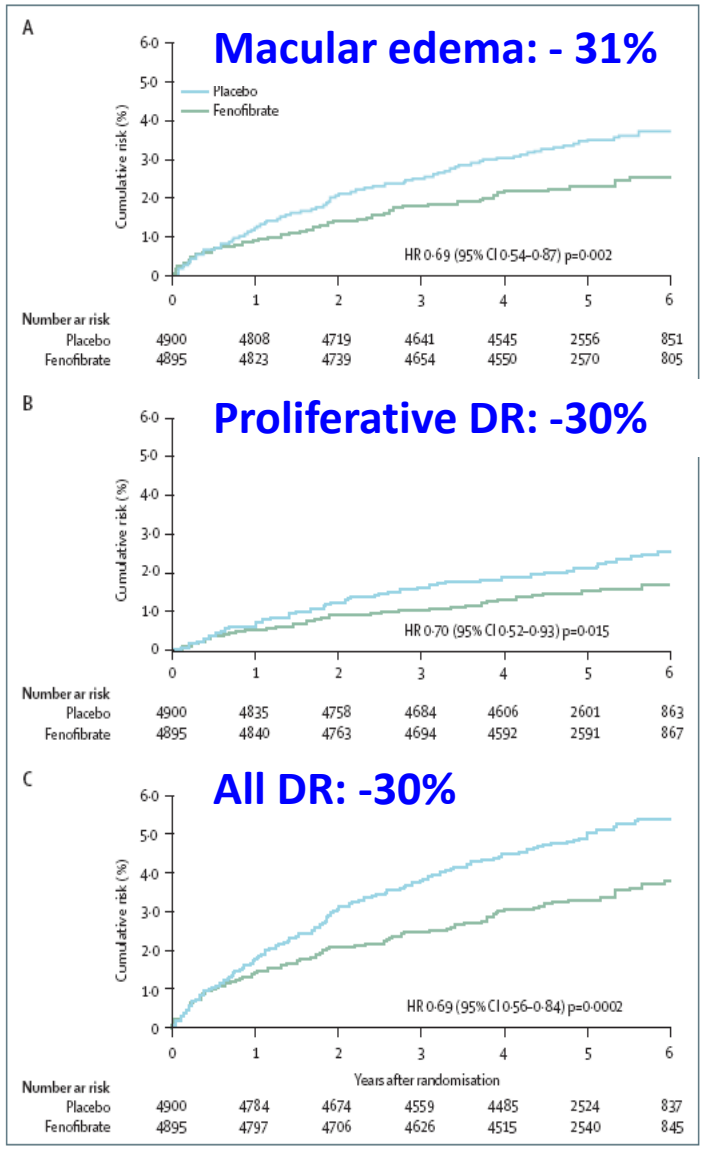
Background Laser treatment for diabetic retinopathy is often associated with visual field reduction and other ocular side-effects. Our aim was to assess whether long-term lipid-lowering therapy with fenofibrate could reduce the progression of retinopathy and the need for laser treatment in patients with type 2 diabetes mellitus.

Lancet 2007; 370: 1687–97

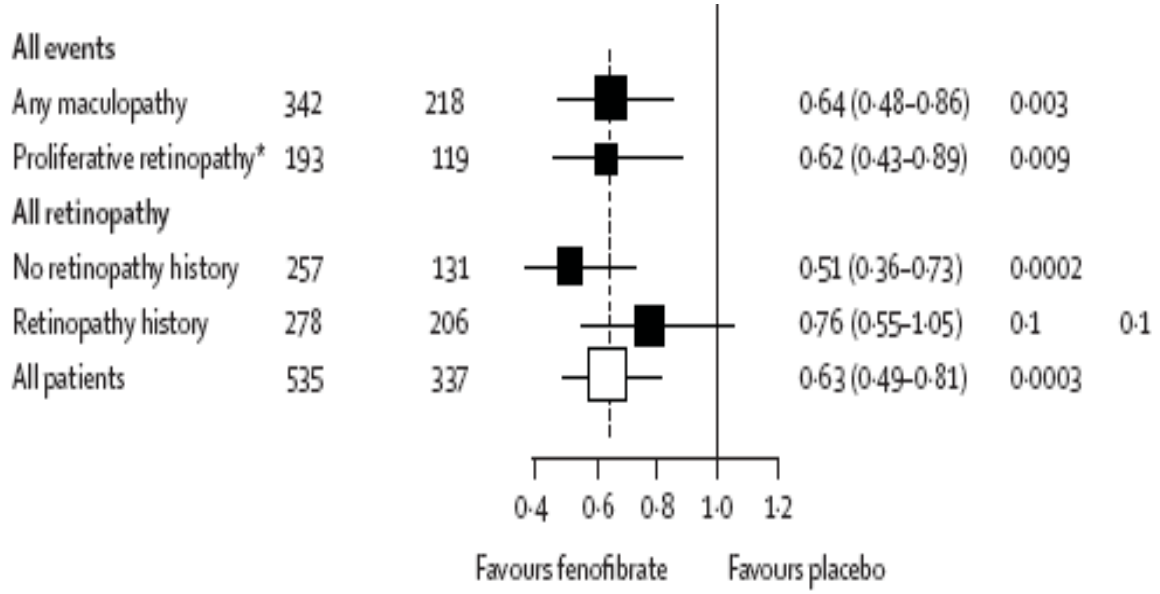
Published Online
November 6, 2007
DOI:10.1016/S0140-

Keech A et al, Lancet. 370: 1687-97, 2007

FIELD: fenofibrate reduced need for laser treatment



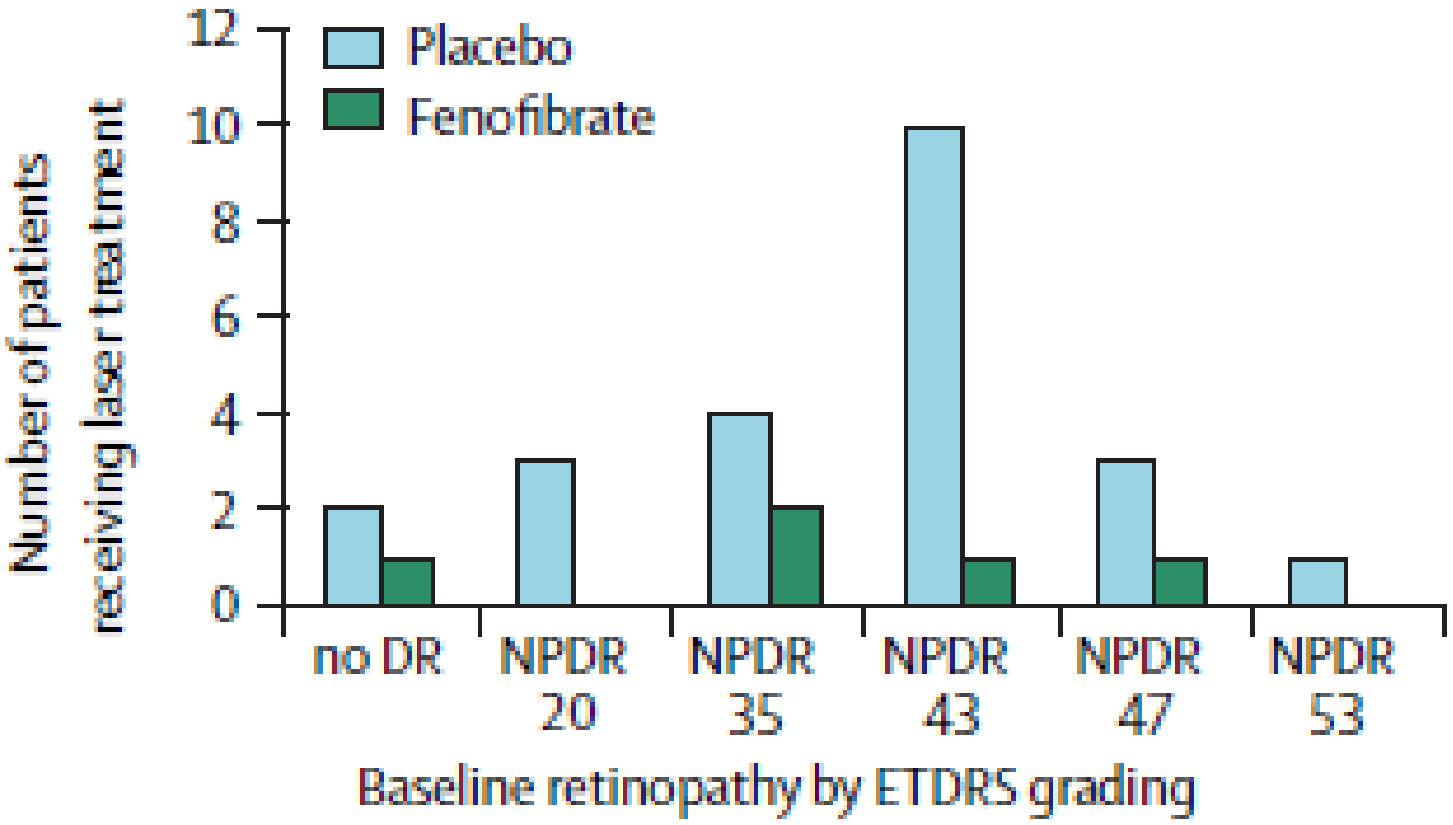
Need for laser treatment
37% reduced with fenofibrate; p=0.0003



- Broad-based:both types of diabetes, patients with and without retinopathy at baseline
- Achieved rapidly (within 8 months)
- Independent of and additive to glycemic control

Keech A et al, Lancet. 370: 1687-97, 2007

FIELD substudy: fenofibrate effective regardless of baseline DR



N = 1012

Keech A et al, Lancet. 370: 1687-97, 2007

Action to Control Cardiovascular Risk in Diabetes (ACCORD)

ACCORD Eye

Effects of intensive management of:

Glycemia
Lipids
Blood Pressure

On DR progression & moderate vision loss

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Medical Therapies on Retinopathy Progression in Type 2 Diabetes

The ACCORD Study Group and ACCORD Eye Study Group*

ABSTRACT

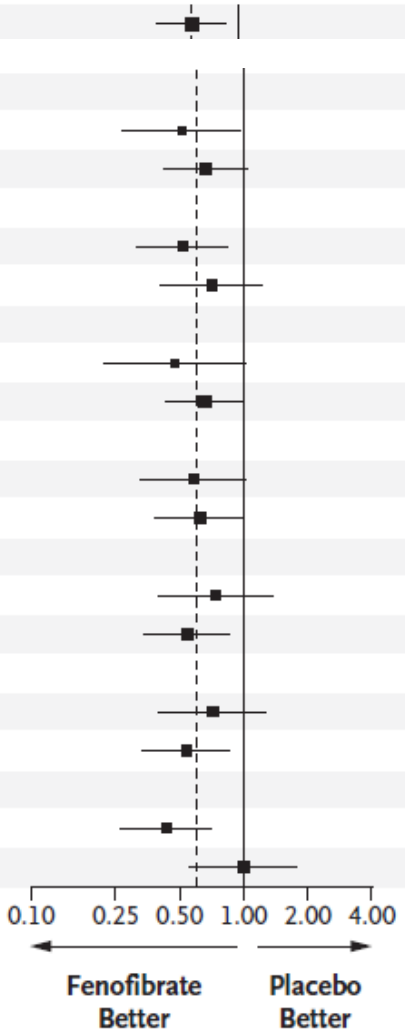
BACKGROUND

We investigated whether intensive glycemic control, combination therapy for dyslipidemia, and intensive blood-pressure control would limit the progression of diabetic retinopathy in persons with type 2 diabetes. Previous data suggest that these systemic factors may be important in the development and progression of diabetic retinopathy.

New Engl. J. Med. 363:233-244, 2010

ACCORD Eye

Subgroup	Fenofibrate	Placebo
	no. with retinopathy progression/total no. (%)	
Overall	52/806 (6.5)	80/787 (10.2)
Race		
Nonwhite	16/222 (7.2)	31/234 (13.2)
White	36/584 (6.2)	49/553 (8.9)
Duration of diabetes		
≥10 yr	28/358 (7.8)	47/353 (13.3)
<10 yr	24/442 (5.4)	33/427 (7.7)
Age		
≥65 yr	11/250 (4.4)	19/220 (8.6)
<65 yr	41/556 (7.4)	61/567 (10.8)
Smoking status		
Nonsmoker	21/313 (6.7)	35/333 (10.5)
Previous or current smoker	31/492 (6.3)	45/454 (9.9)
BMI		
<30	20/296 (6.8)	24/267 (9.0)
≥30	32/510 (6.3)	56/520 (10.8)
Glycemia therapy		
Intensive	21/400 (5.2)	29/406 (7.1)
Standard	31/406 (7.6)	51/381 (13.4)
Retinopathy at baseline		
Some	27/405 (6.7)	56/412 (13.6)
None	25/401 (6.2)	24/375 (6.4)

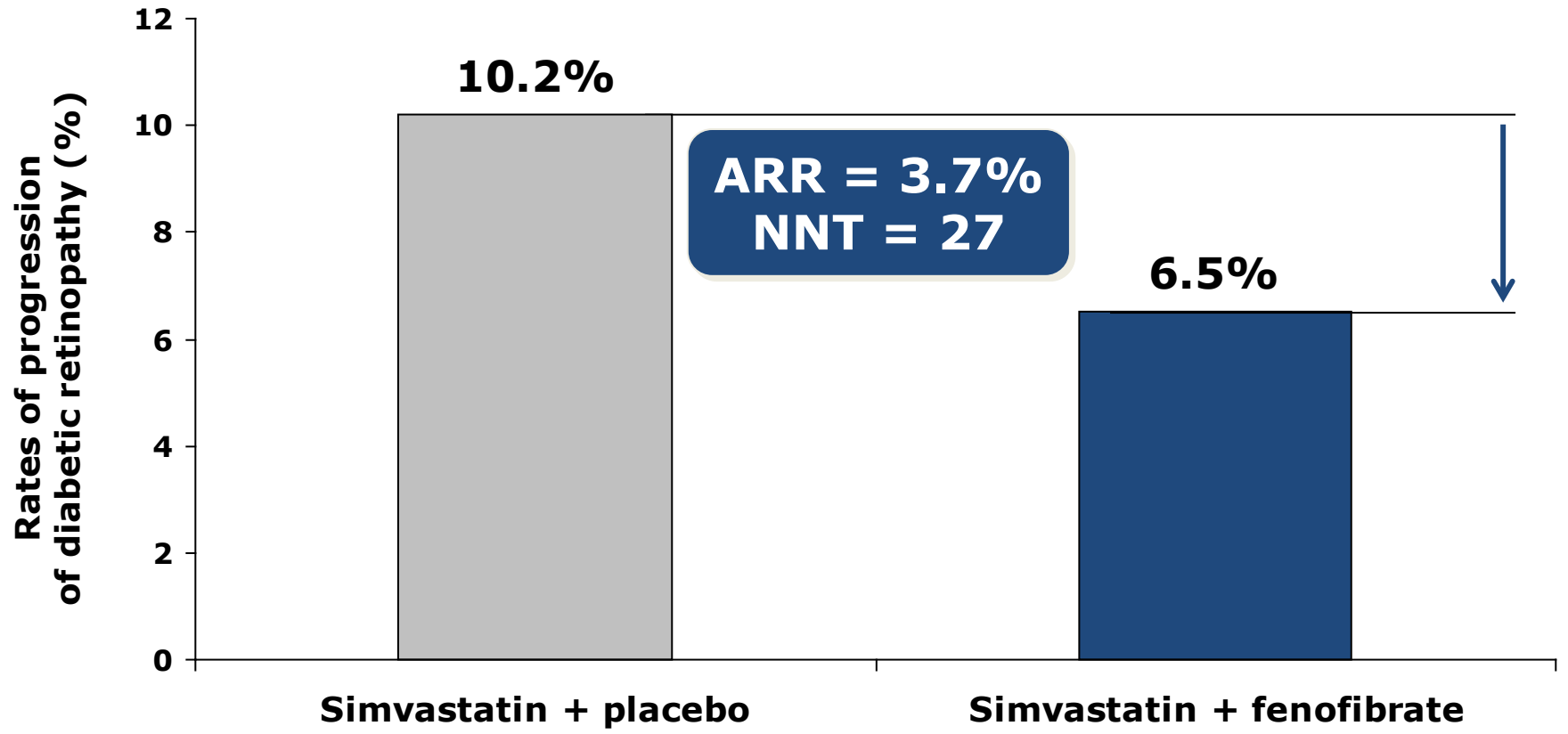


P<0.006

ACCORD Eye: N = 2856.
ETDRS 3-step progression

ACCORD Study Group. Chew et al. NEJM 363: 233-244, 2010

ACCORD: Fenofibrate added to simvastatin reduced progression of DR by **40%**



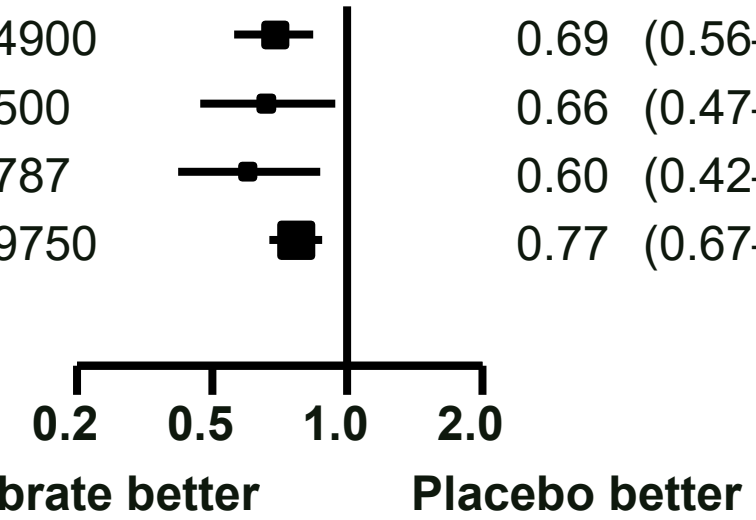
-40%
p=0.006
OR 0.60
(95% CI 0.42-0.87)
N = 2,856

ACCORD-EYE Lipid Arm

New Engl. J. Med. 363:233-244, 2010

Retinopathy data in cardiovascular trials of fenofibrate

Trial	Year	Fenofibrate (Event/N)	Placebo (Event/N)	Result (95% CI)
FIELD (retinal laser)	2007	164/4895	238/4900	0.69 (0.56–0.84)
FIELD sub-study (post hoc composite)	2007	53/512	75/500	0.66 (0.47–0.94)
ACCORD Eye (composite)	2010	52/806	80/787	0.60 (0.42–0.87)
Trial meta-analysis (retinal laser)	2022	391/9754	501/9750	0.77 (0.67–0.88)



As these results emerged from subsidiary analyses of cardiovascular trials with non-significant effects on cardiovascular outcomes, they should be considered hypothesis-generating

Keech et al, Lancet 2007; 370: 1687-97
ACCORD Study Group, NEJM, 2010;363:233-44
Preiss et al, Diabetes Care 2022;45:e1-e2

2024: The LENS Study
Retinopathy as the Primary End-Point

LENS: **L**owering **E**vents in **N**on-proliferative retinopathy in **S**cotland

NEJM Evidence

Published June 21, 2024

DOI: 10.1056/EVIDoa2400179

ORIGINAL ARTICLE

Effect of Fenofibrate on Progression of Diabetic Retinopathy

David Preiss, Ph.D., F.R.C.Path., M.R.C.P.,[1] Jennifer Logue, M.D., F.R.C.Path., M.R.C.P.,[2] Emily Sammons, D.Phil.,[1] Mohammed Zayed, M.B.Ch.B., M.Sc., M.R.C.G.P.,[1] Jonathan Emberson, Ph.D.,[1] Rachel Wade, M.Sc.,[1] Karl Wallendszus, M.Sc.,[1] Will Stevens, Ph.D.,[1] Rosanna Cretney, Ph.D.,[1] Simon Harding, F.R.C.Ophth.,[3] Graham Leese, Ph.D.,[4] Gemma Currie, Ph.D., M.R.C.P.,[5] and Jane Armitage, F.R.C.P., F.F.P.H.,[1] for the LENS Collaborative Group*

FUNDED BY

NIHR | National Institute for Health and Care Research

OXFORD POPULATION HEALTH

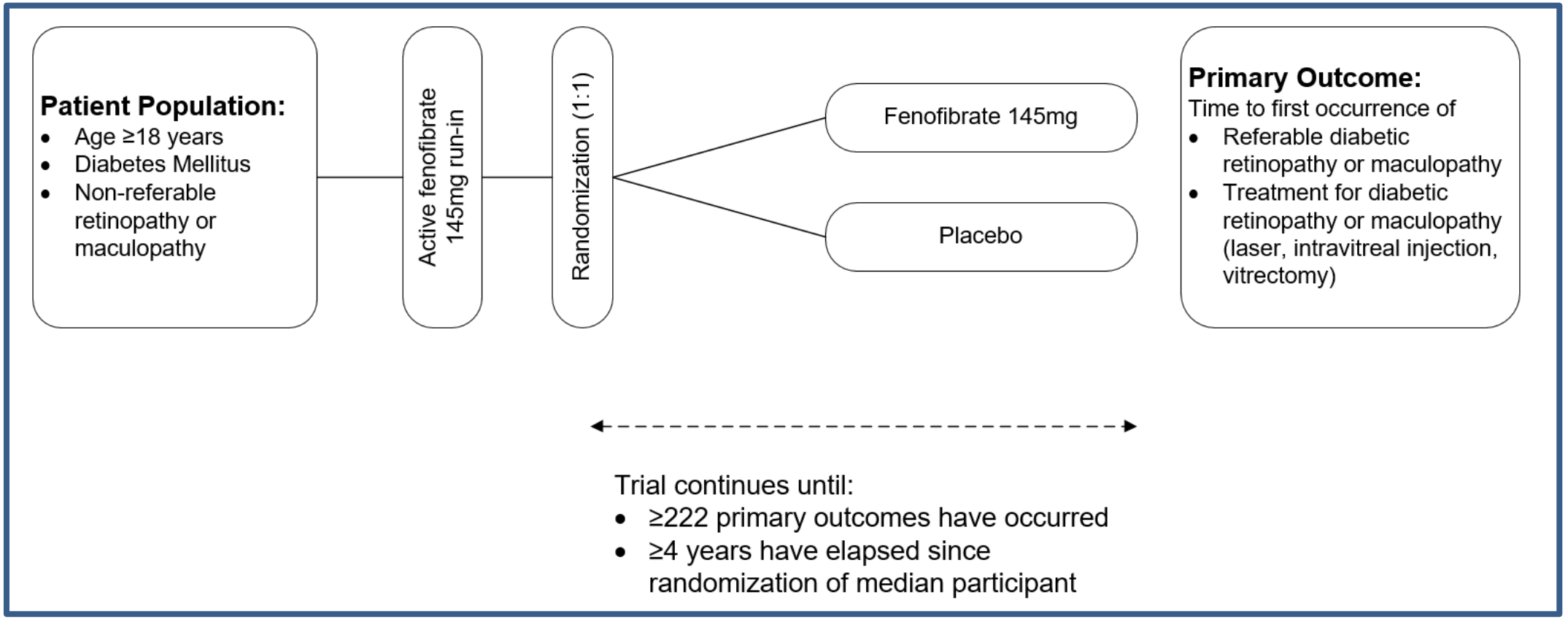
UNIVERSITY OF OXFORD

CTSU

Scotland's national Diabetic Eye Screening program

- *Purpose* identify potentially vision-threatening disease
- 340,000 (6.2% of the population) people with diabetes in Scotland
- Regular (6-24 monthly) retinal screening offered to everyone with diabetes (aged ≥12 years)
- Visual acuity recorded
- 45-degree single, macula-centered, color image of each eye
- Staged mydriasis
- Slit lamp examination arranged if images not gradable
- Images graded in 10 centres:
  - Image analysis software and trained graders
  - Biannual quality assurance program

LENS: Study Design



- **Trial design:** randomized double-masked placebo-controlled trial in Scotland
- **Study treatment:** mailed to participants
- **Contact:** only two face-to-face visits, then six monthly telephone contact and linkage to National Health Service (including Diabetic Eye Screening for referable eye disease and OCT-detected macular edema)

LENS Collaborative Group, Diabet Med 2024: e15310

2024: The LENS Study

- **Primary outcome: time to first occurrence of (i) referable diabetic retinopathy or maculopathy; or (ii) treatment for diabetic retinopathy or maculopathy**
- **Secondary outcomes:**
  - Six pre-specified subgroups
  - Components of the primary outcome
  - Any progression of retinopathy or maculopathy
  - Referable maculopathy (hard exudate or blot hemorrhage within 1 disc diameter of the fovea)
  - Macular edema (adverse event report or Diabetic Eye Screening OCT)
  - Visual acuity
  - Visual function
  - Quality of life

Baseline characteristics of 1151 participants (1)

Characteristic		Fenofibrate (n=576)	Placebo (n=575)
Age (years)		61	61
Sex	Female	27%	27%
	Male	73%	73%
Type of diabetes	T1DM	27%	26%
	T2DM	73%	74%
Diabetes duration (years)		18	18
R grade – worse eye	R0	1%	1%
	R1	**98%**	**98%**
	R2	2%	1%
M grade – worse eye	M0	90%	90%
	M1	**10%**	**10%**
Laser, injection, vitrectomy		9%	10%

Data shown as % or mean unless otherwise specified

Preiss et al, NEJM Evid 2023; 2024;3(8)

Baseline characteristics of 1151 participants (2)

Characteristic		Fenofibrate (n=576)	Placebo (n=575)
BMI (kg/m^2)		31	31
HbA1c (mmol/mol) (%)		66 (8.2%)	66 (8.2%)
Total cholesterol (mg/dL)		156	157
HDL cholesterol (mg/dL)		51	50
Triglycerides (mg/dL)*		137	138
eGFR (mL/min/1.73m^2), Screening	<60	10%	7%
	≥60	90%	93%
eGFR (mL/min/1.73m^2), Randomization	<60	23%	23%
	≥60	77%	77%
Non-insulin glucose lowering medication		69%	68%
Insulin		44%	43%
Statin		74%	75%

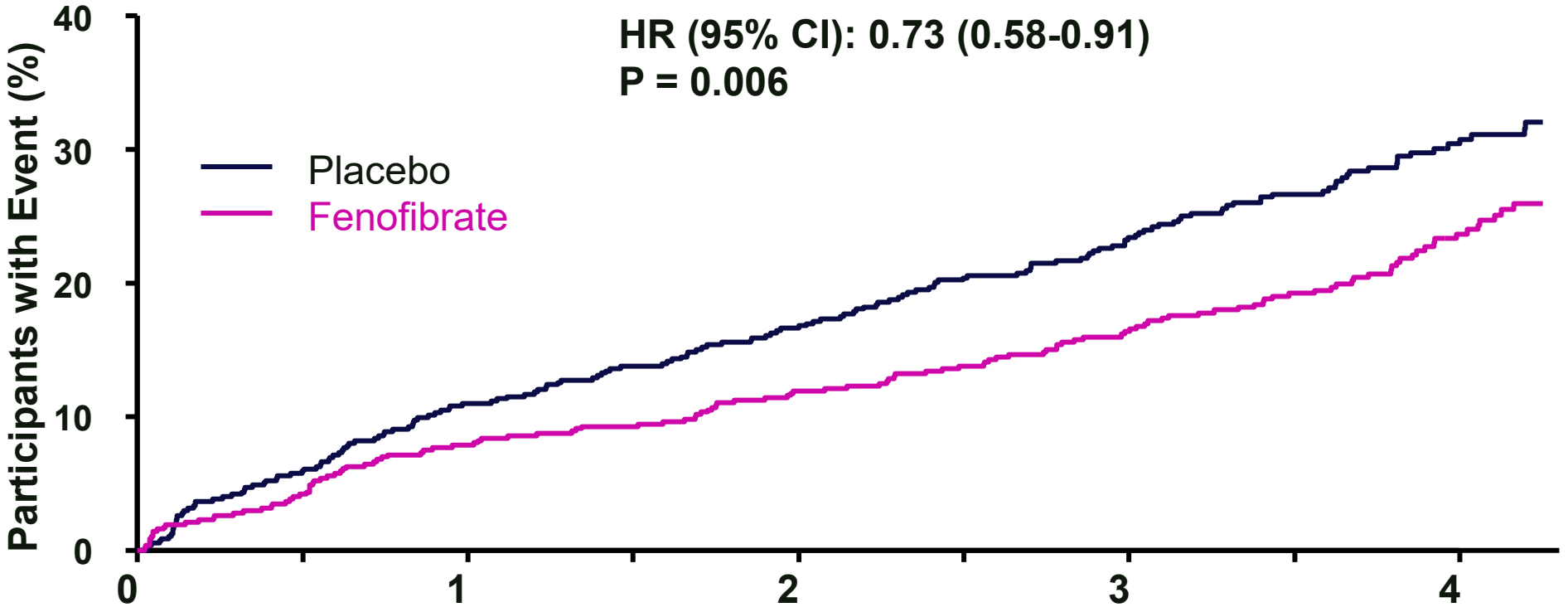
Preiss et al, NEJM Evid 2023; 2024;3(8)

LENS: Details of post-randomization follow-up

	Fenofibrate (n=576)	Placebo (n=575)
Median duration of follow-up	4.0 years	
Complete follow-up data	576 (100%)	573 (99.7%)
Average adherence to study treatment	88%	89%
Count of retinal screening episodes	1485	1469
Average (SE) retinal screening episodes per participant	2.58 (0.04)	2.55 (0.04)

Preiss et al, NEJM Evid 2023; 2024;3(8)

LENS: Primary outcome: referable disease or treatment



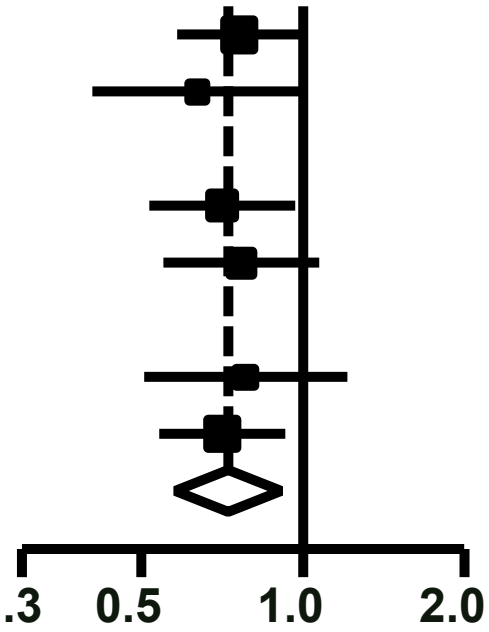
No. at Risk

Fenofibrate	576	525	492	421	228
Placebo	575	509	469	392	203

Preiss et al, NEJM Evid 2023; 2024;3(8)

LENS: Primary outcome by sex, age, type of diabetes

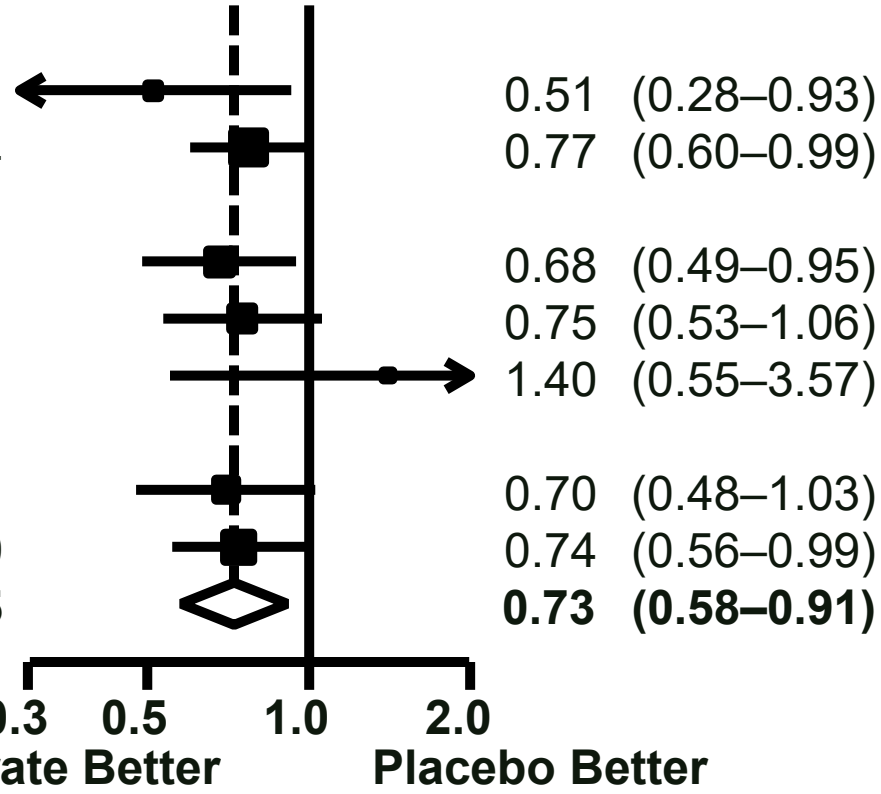
Subgroup	Fenofibrate (N=576) Number of participants with event / N	Placebo (N=575) Number of participants with event / N	Hazard Ratio (95% CI)	P(het/trend)
Sex				
Male	99/420	121/419	0.76 (0.58–0.99)	0.5
Female	32/156	47/156	0.64 (0.40–1.00)	
Age				
<60 years	68/249	93/264	0.71 (0.52–0.97)	0.73
≥60 years	63/327	75/311	0.77 (0.55–1.07)	
Type of diabetes				
Type 1	38/154	45/151	0.78 (0.51–1.21)	0.7
Type 2 and other	93/422	123/424	0.71 (0.54–0.93)	
All participants	**131/576**	**168/575**	**0.73 (0.58–0.91)**	



Preiss et al, NEJM Evid 2023; 2024;3(8)

LENS: Primary outcome by eGFR, HbA1c, timing of event

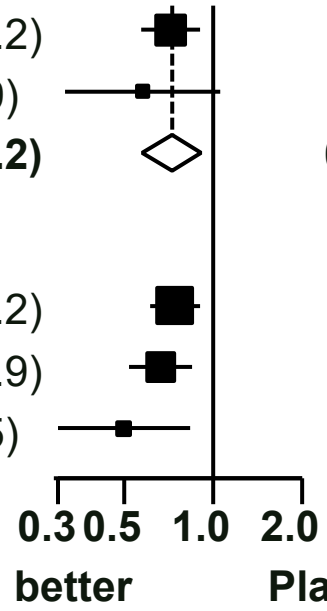
Subgroup	Fenofibrate (N=576)	Placebo (N=575)	Hazard Ratio (95% CI)
	Number of participants with event / N		
eGFR at randomization			
<60 mL/min/1.73m^2	17/130	32/131	0.51 (0.28–0.93)
≥60 mL/min/1.73m^2	114/446	136/444	0.77 (0.60–0.99)
HbA1c			
<70 mmol/mol	63/361	81/346	0.68 (0.49–0.95)
≥70 mmol/mol	57/177	79/193	0.75 (0.53–1.06)
Unknown	11/38	8/36	1.40 (0.55–3.57)
Timing of primary outcome			
Within first year	45/576	63/575	0.70 (0.48–1.03)
After first year	86/525	105/509	0.74 (0.56–0.99)
All participants	**131/576**	**168/575**	**0.73 (0.58–0.91)**



Preiss et al, NEJM Evid 2023; 2024;3(8)

LENS: Primary and secondary retinopathy outcomes

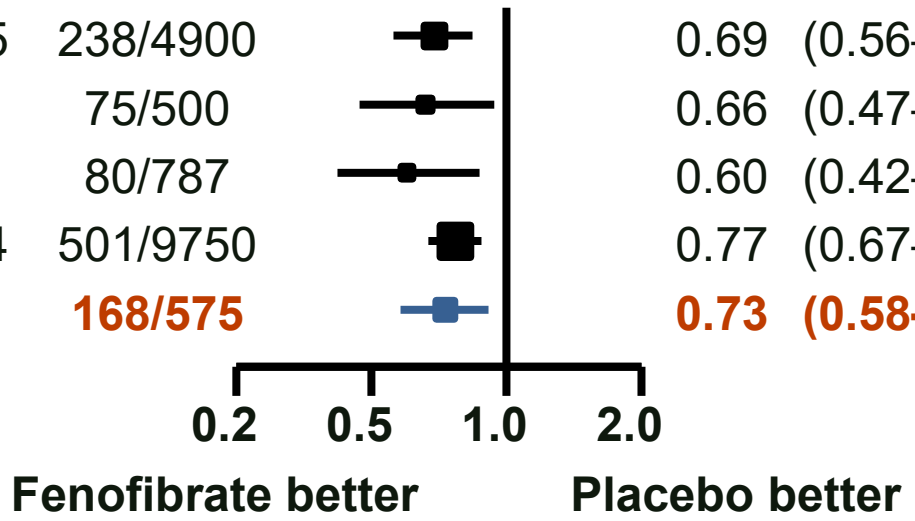
Type of Event	Fenofibrate (N=576) Number of participants with event (%)	Placebo (N=575) Number of participants with event (%)	Hazard ratio (95% CI)	P Value
Referable retinopathy or maculopathy	130 (22.6)	168 (29.2)	0.72 (0.57–0.91)	0.005
Treatment for retinopathy or maculopathy	17 (3.0)	28 (4.9)	0.58 (0.31–1.06)	0.08
Primary outcome: referable disease or treatment	**131 (22.7)**	**168 (29.2)**	**0.73 (0.58–0.91)**	**0.006**
Any progression of retinopathy or maculopathy	185 (32.1)	231 (40.2)	0.74 (0.61–0.90)	0.003
Referable maculopathy	107 (18.6)	149 (25.9)	0.66 (0.52–0.85)	0.001
Macular edema	22 (3.8)	43 (7.5)	0.50 (0.30–0.84)	0.008



Preiss et al, NEJM Evid 2023; 2024;3(8)

LENS in the context of hypothesis-generating trials

Trial	Year	Fenofibrate (Event/N)	Placebo (Event/N)	Result (95% CI)
FIELD (retinal laser)	2007	164/4895	238/4900	0.69 (0.56–0.84)
FIELD sub-study (post hoc composite)	2007	53/512	75/500	0.66 (0.47–0.94)
ACCORD Eye (composite)	2010	52/806	80/787	0.60 (0.42–0.87)
Trial meta-analysis (retinal laser)	2022	391/9754	501/9750	0.77 (0.67–0.88)
LENS (composite)	**2024**	**131/576**	**168/575**	**0.73 (0.58–0.91)**



Keech et al, Lancet 2007; 370: 1687-97
ACCORD Study Group, NEJM, 2010;363:233-44
Preiss et al, Diabetes Care 2022;45:e1-e2
Preiss et al, NEJM Evid 2023; 2024;3(8)

Summary of LENS trial results

- In participants with early diabetic retinopathy or maculopathy, treatment with fenofibrate reduced progression to referable eye disease, or treatment thereof
- Benefits of treatment appeared similar in various pre-specified groups of participants
- Fenofibrate reduced “any progression of retinopathy” and macular edema
- Benefits quantitatively similar to hypothesis-generating results from cardiovascular trials
- Methodology demonstrates how large retinal screening programs can be harnessed to conduct randomized trials

How does Fenofibrate work in the retina?

Considerations:

In FIELD, ACCORD, and LENS, retinal effects of fenofibrate are:

- Independent of glycemia
- Independent of effects on plasma lipids
- Maximal in early preclinical disease (NPDR)

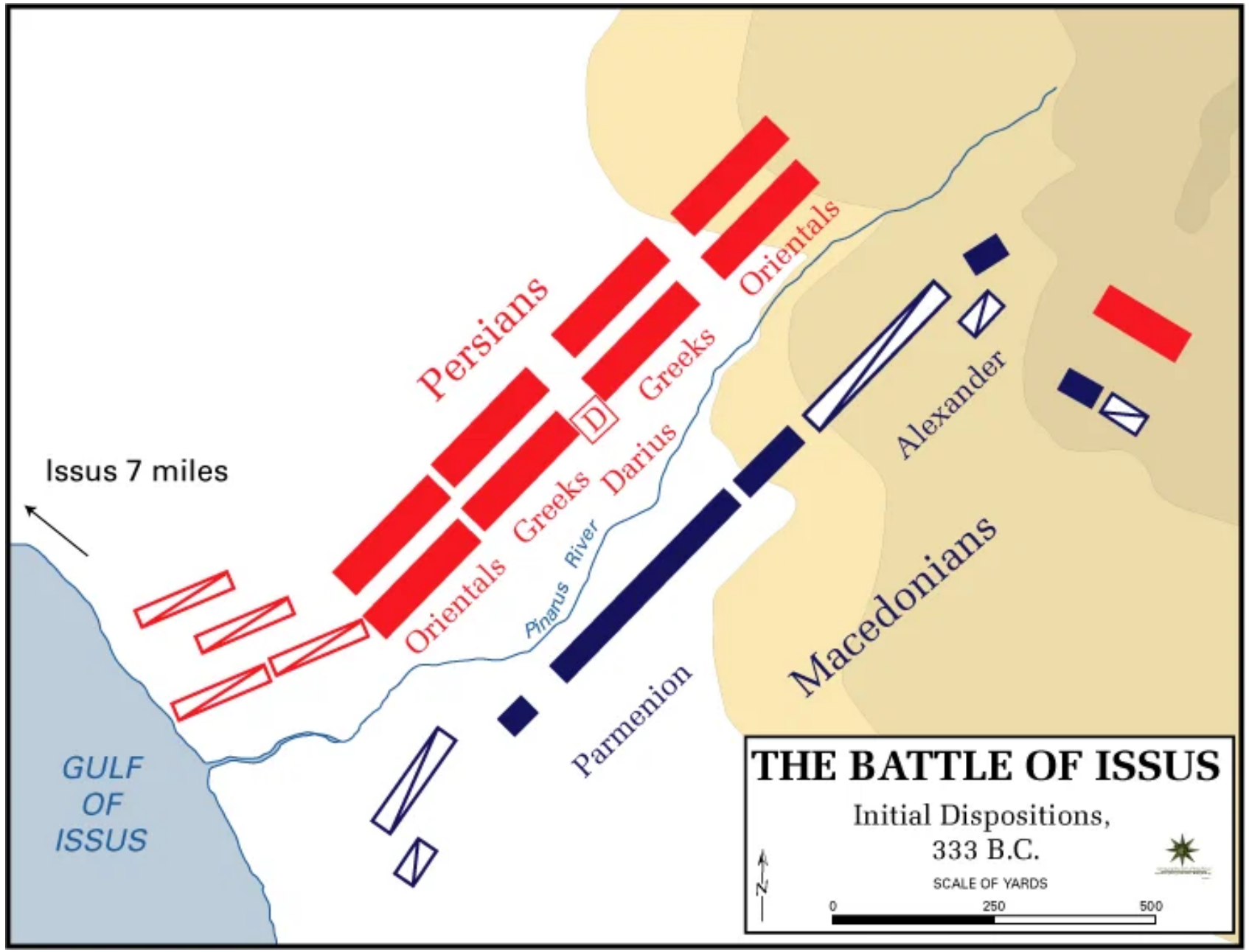
These suggest a specific action in the retina

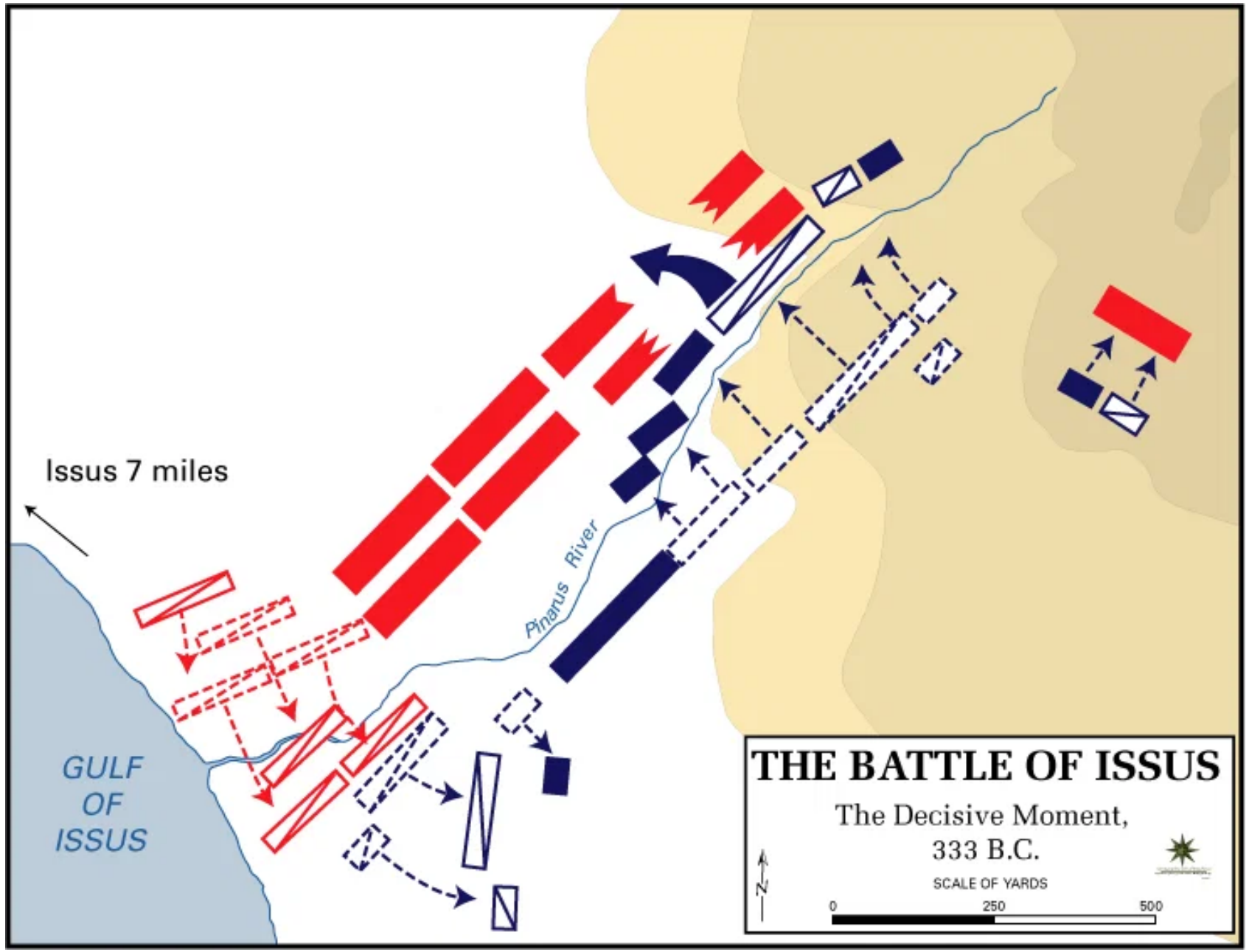
Hypothesis

Diabetic retinopathy is a two-stage disease defined by the presence or absence of blood retinal barrier failure:

- Initiation: Plasma factors that stress barriers
- Propagation: Consequences of barrier leakage

Risk factors may differ between them.


Persians
Orientals
Greeks
D
Darius
Greeks
Orientals
Issus 7 miles
Pinarus River
Alexander
Macedonians
Parmenion
GULF OF ISSUS
THE BATTLE OF ISSUS
Initial Dispositions,
333 B.C.
SCALE OF YARDS
0
250
500
N


Issus 7 miles
Pinarus River
GULF OF ISSUS
THE BATTLE OF ISSUS
The Decisive Moment,
333 B.C.
SCALE OF YARDS
0
250
500
N

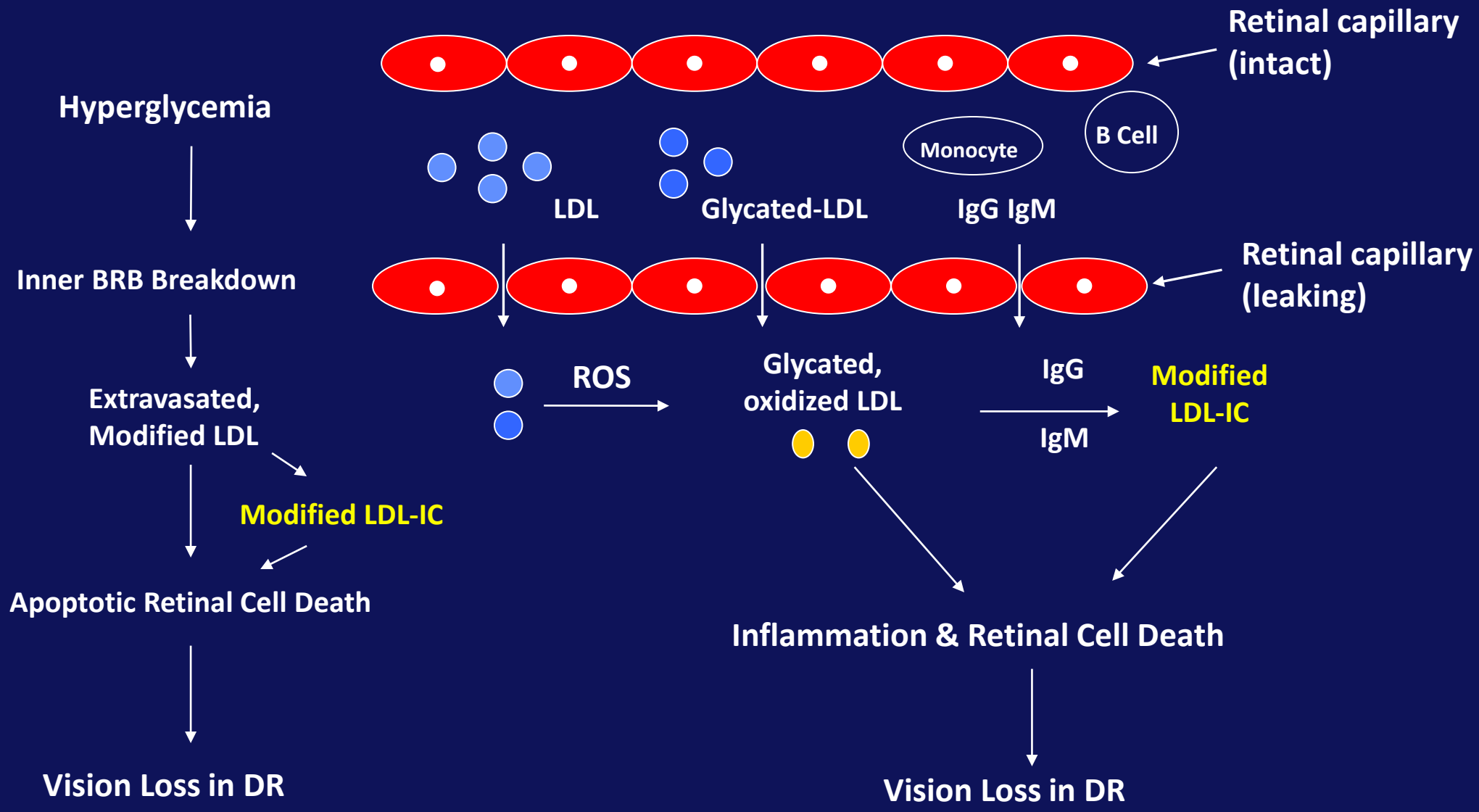
Theme/Hypothesis

A significant breach of a line of defense is disastrous:

- ‘Game’ is changed
- Risks are different and greater
- Rear-guard action: likelihood of success greatly diminished
- Strategy and tactics must be adjusted

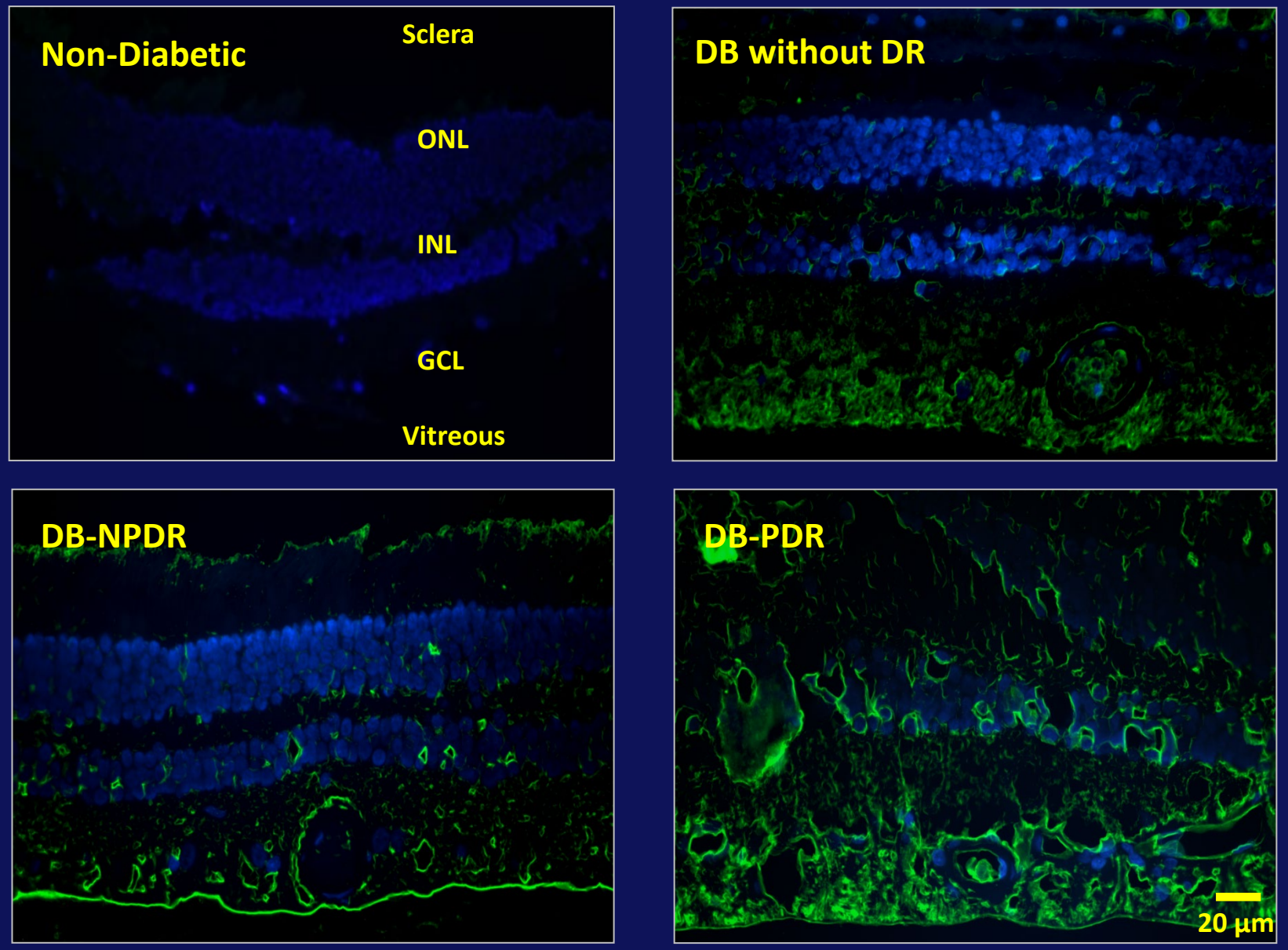
Important barriers must be defended!

Lipids in Diabetic Retinopathy.
Hypotheses: intra-vascular and extravasated lipoproteins in DR



Extravasated LDL in the retina!

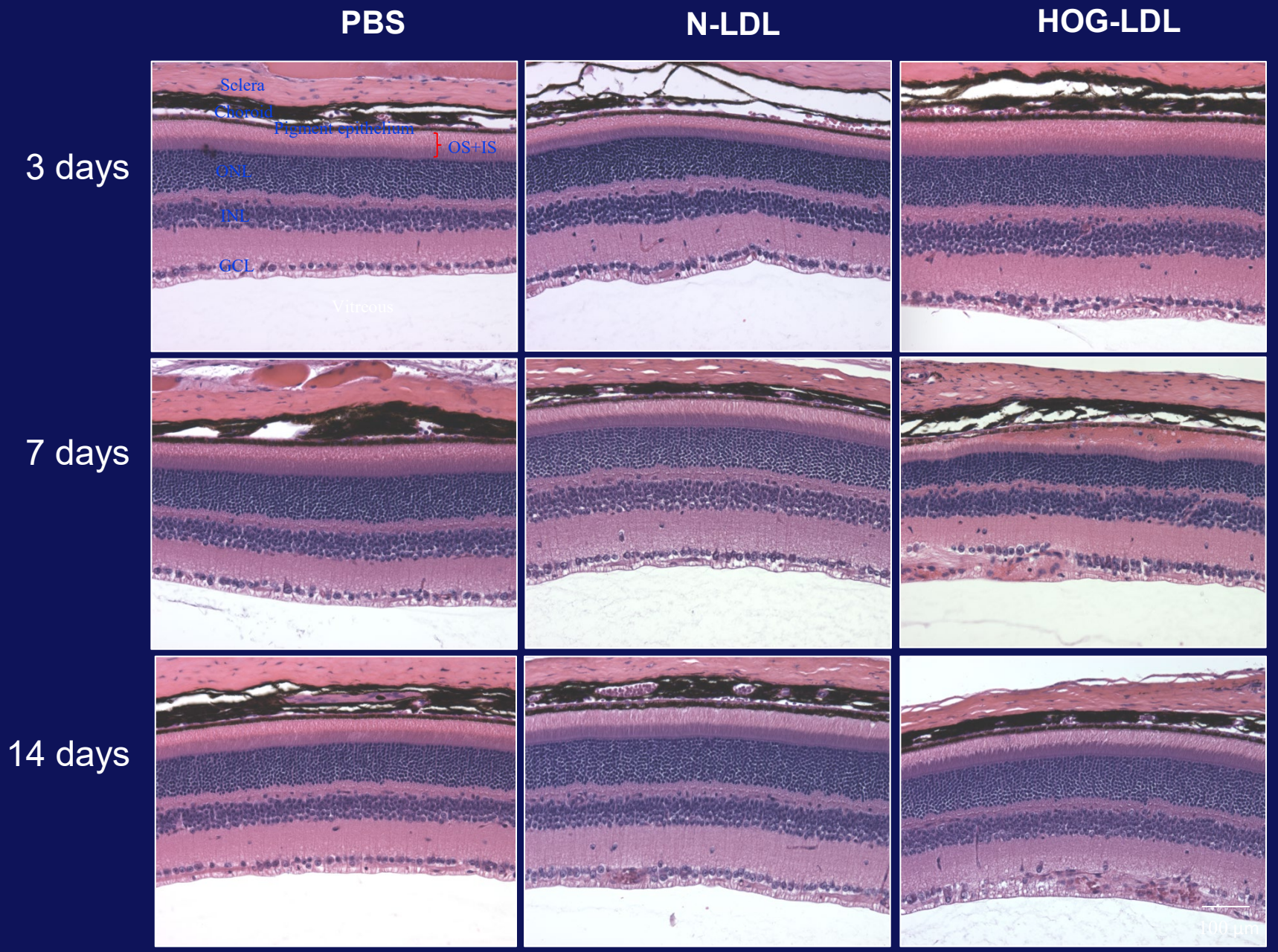
Ox-LDL is present in human diabetic retina



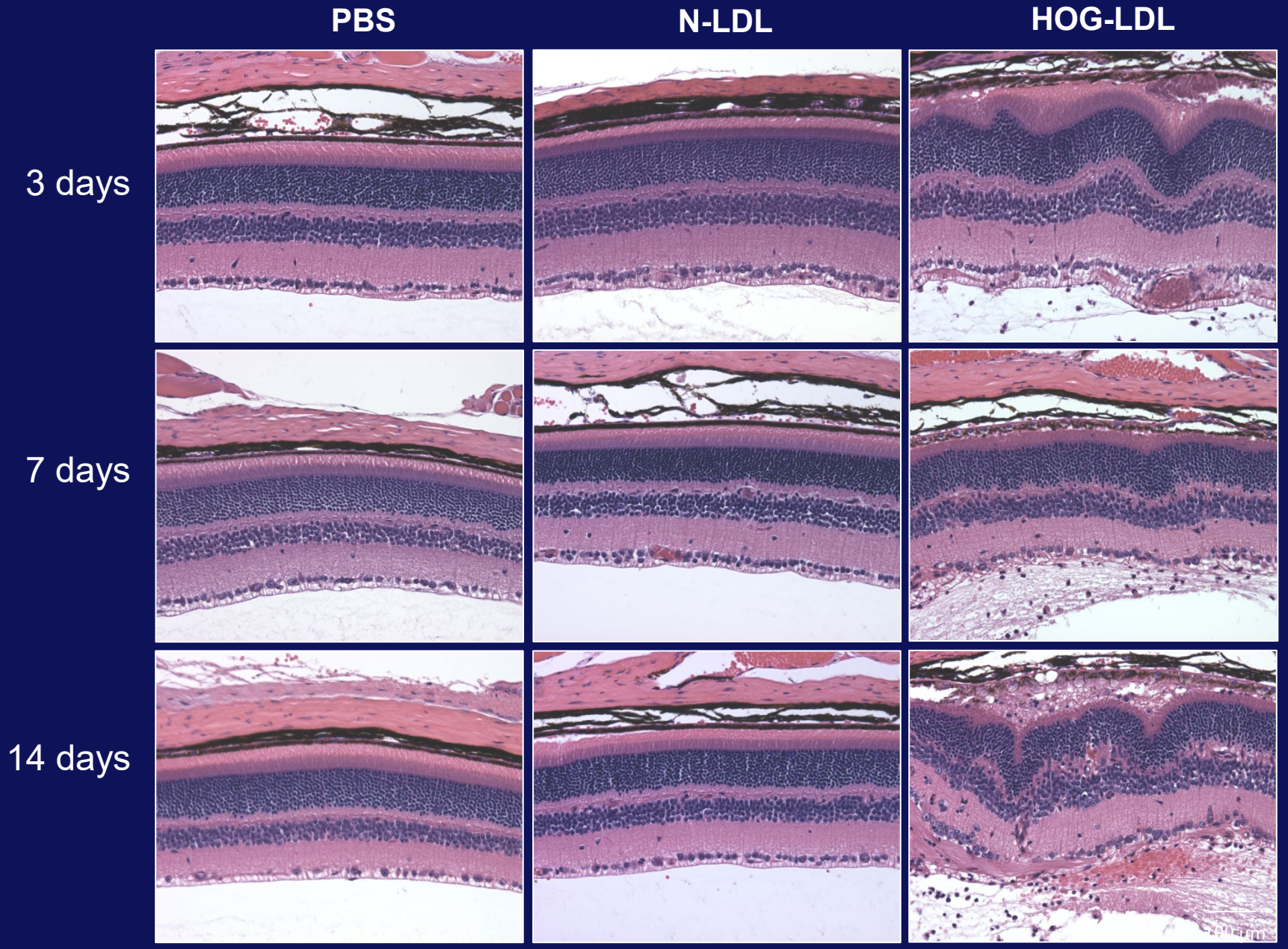
ONL: outer nuclear layer; **INL:** inner nucleolus layer; **GCL:** ganglion cell layer

Wu, Lyons et al., 2008 IOVS

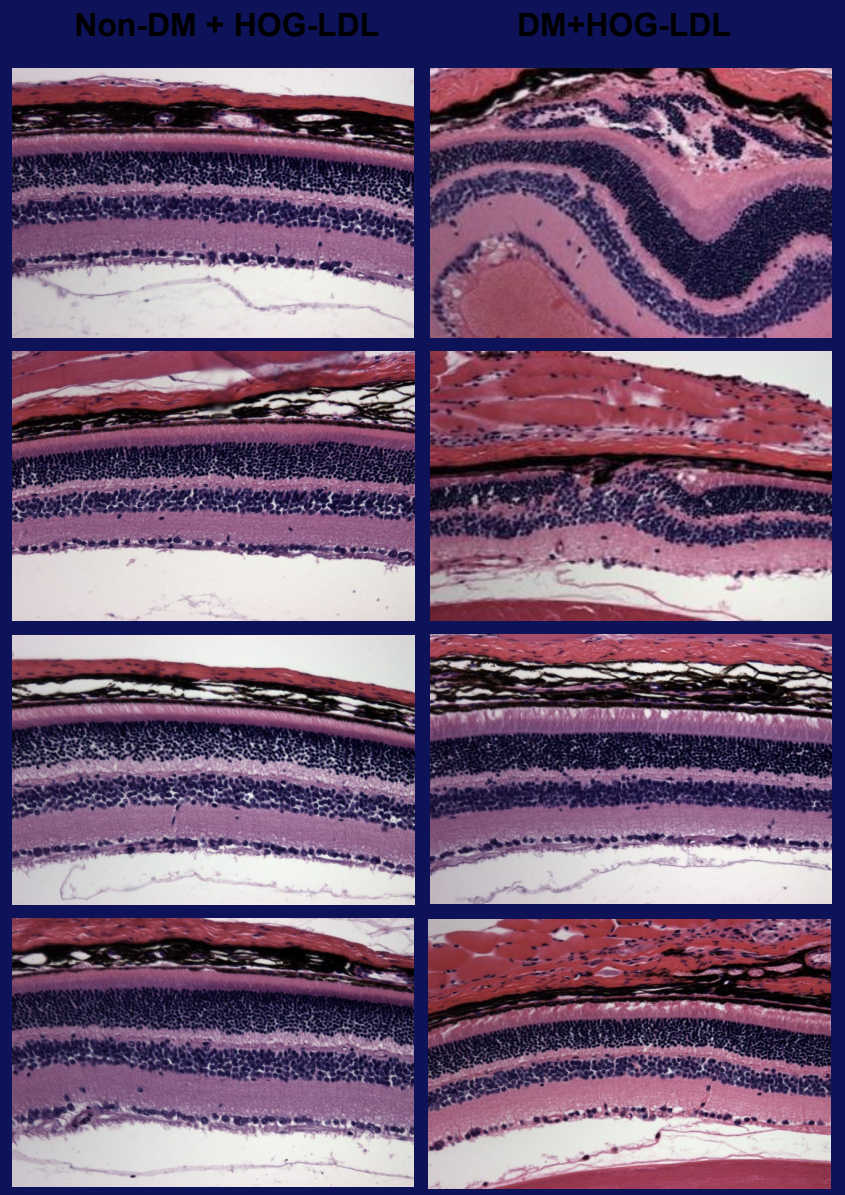
H&E staining of non-diabetic mouse retinas after PBS, N-LDL, and HOG-LDL injection (Yu, Lyons et al. Diabetologia 2016)



H&E staining of STZ-diabetic mouse retinas after PBS, N-LDL, and HOG-LDL injection (Yu, Lyons et al. Diabetologia 2016)

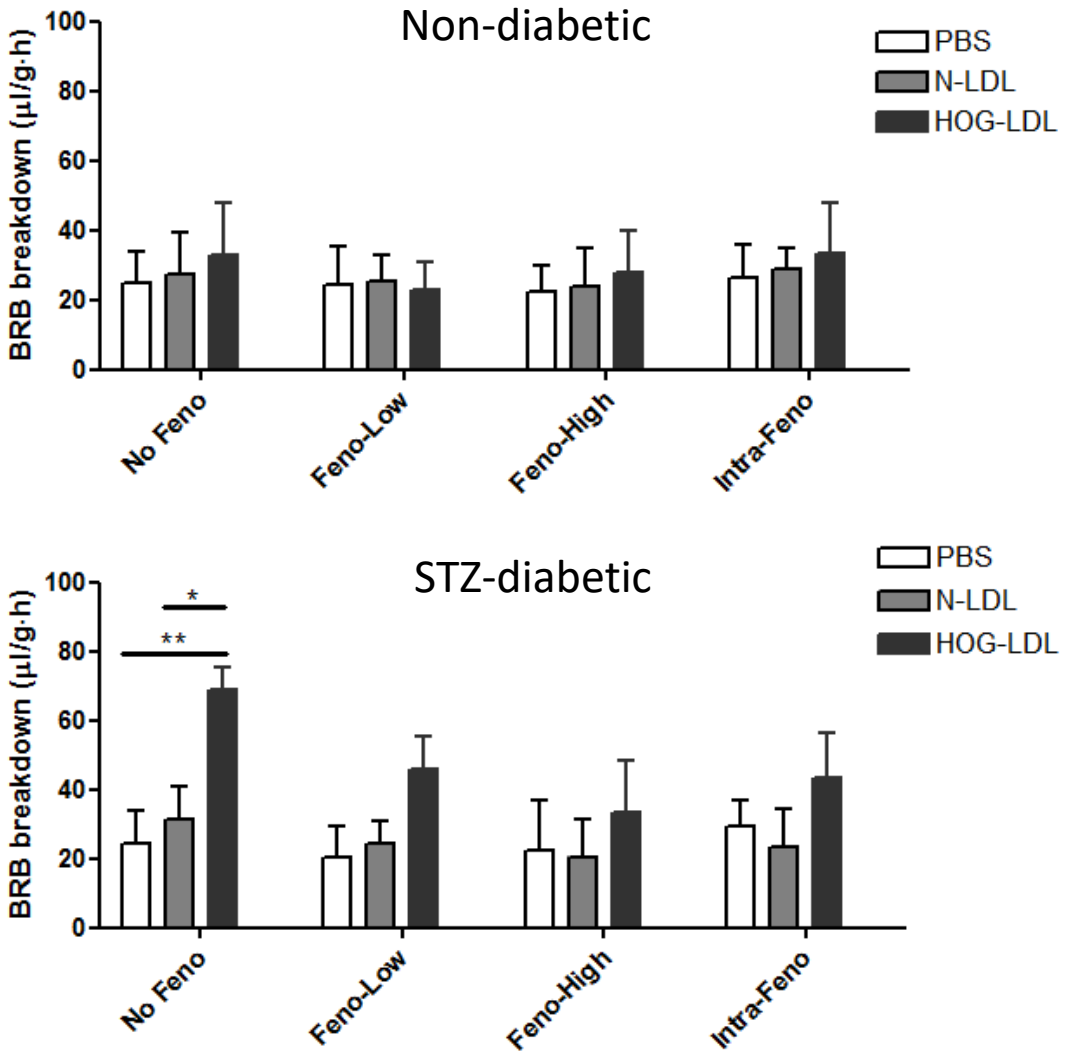


Fenofibrate improves retinal structure changes following ‘highly oxidized, glycated (HOG-) LDL intra-vitreal injection in diabetic mouse retina



Yu, Lyons et al.
(unpublished)

Fenofibrate prevents Blood Retinal Barrier breakdown in diabetes



Lyons et al.
(unpublished)

FIELD: Amputation rates

Published, Lancet, May 23, 2009

Effect of fenofibrate on amputation events in people with type 2 diabetes mellitus (FIELD study): a prespecified analysis of a randomised controlled trial

Kushwin Rajamani, Peter G Colman, Li Ping Li, James D Best, Merryn Voysey, Michael C D'Emden, Markku Laakso, John R Baker, Anthony C Keech, on behalf of the FIELD study investigators

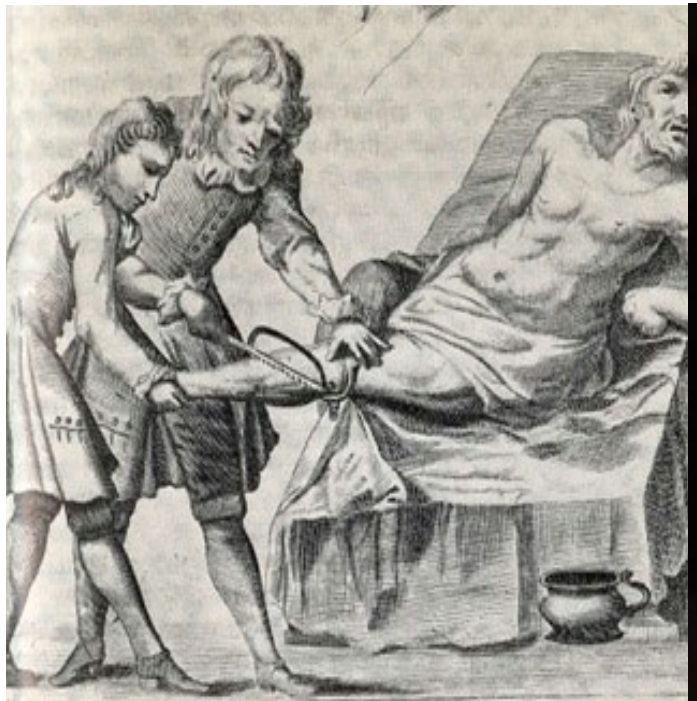
Lancet 2009; 373: 1780–88

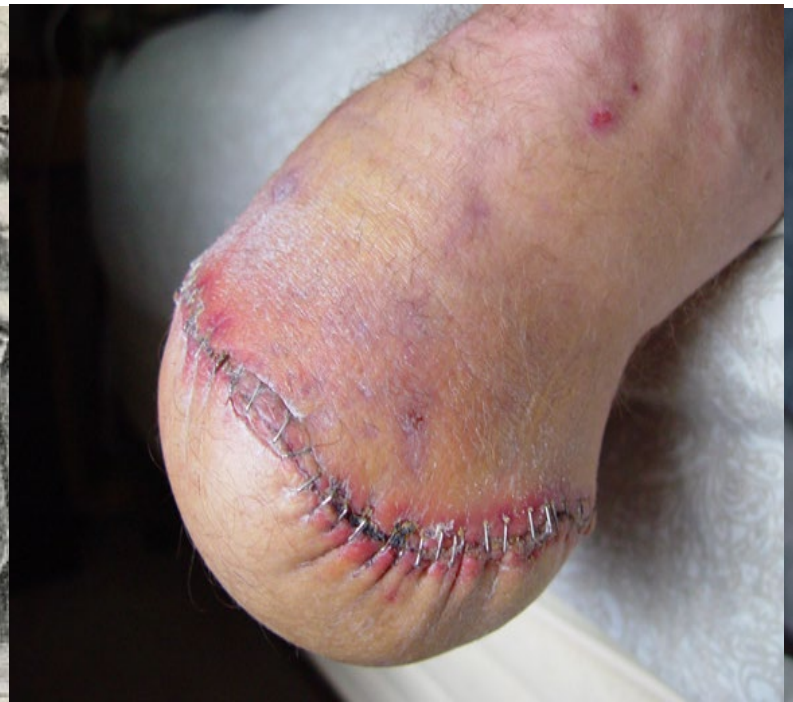
National Health and Medical Research Council Clinical Trials Centre, University of Sydney, Sydney, NSW, Australia (K Rajamani MBBCh, L P Li BMed, M Voysey MBiostat, Prof A C Keech FRACP); Department of Diabetes and

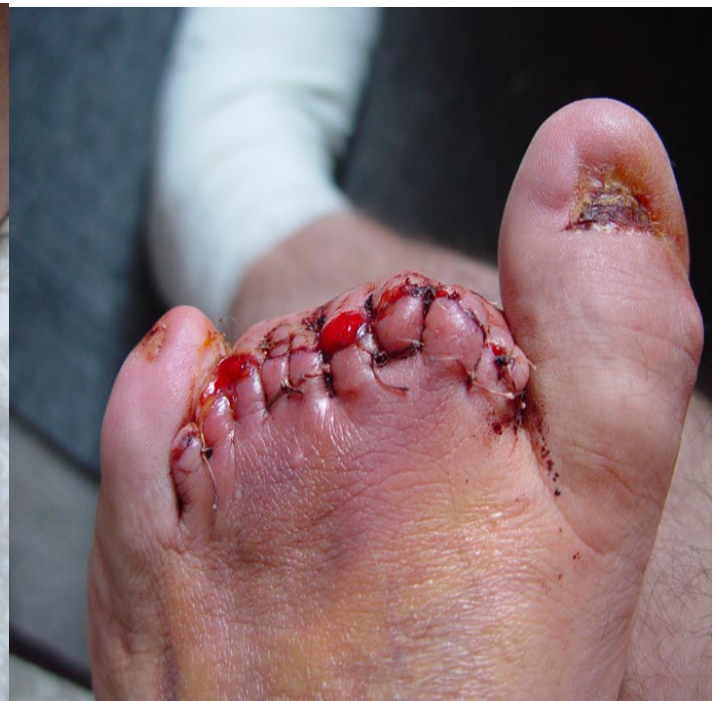
Summary

Background Amputations in people with type 2 diabetes mellitus substantially impair their quality of life and impose high costs on health-care systems. Our aim was to assess the effect of fenofibrate on amputation events in a large cohort of patients with type 2 diabetes.

Methods In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, 9795 patients aged 50–75 years with type 2 diabetes were randomly assigned by computer-generated randomisation sequence to receive fenofibrate 200 mg per day (n=4895) or matching placebo (n=4900) for 5 years' duration. Information about non-traumatic amputation—a prespecified tertiary endpoint of the study—was routinely gathered. Clinicians who

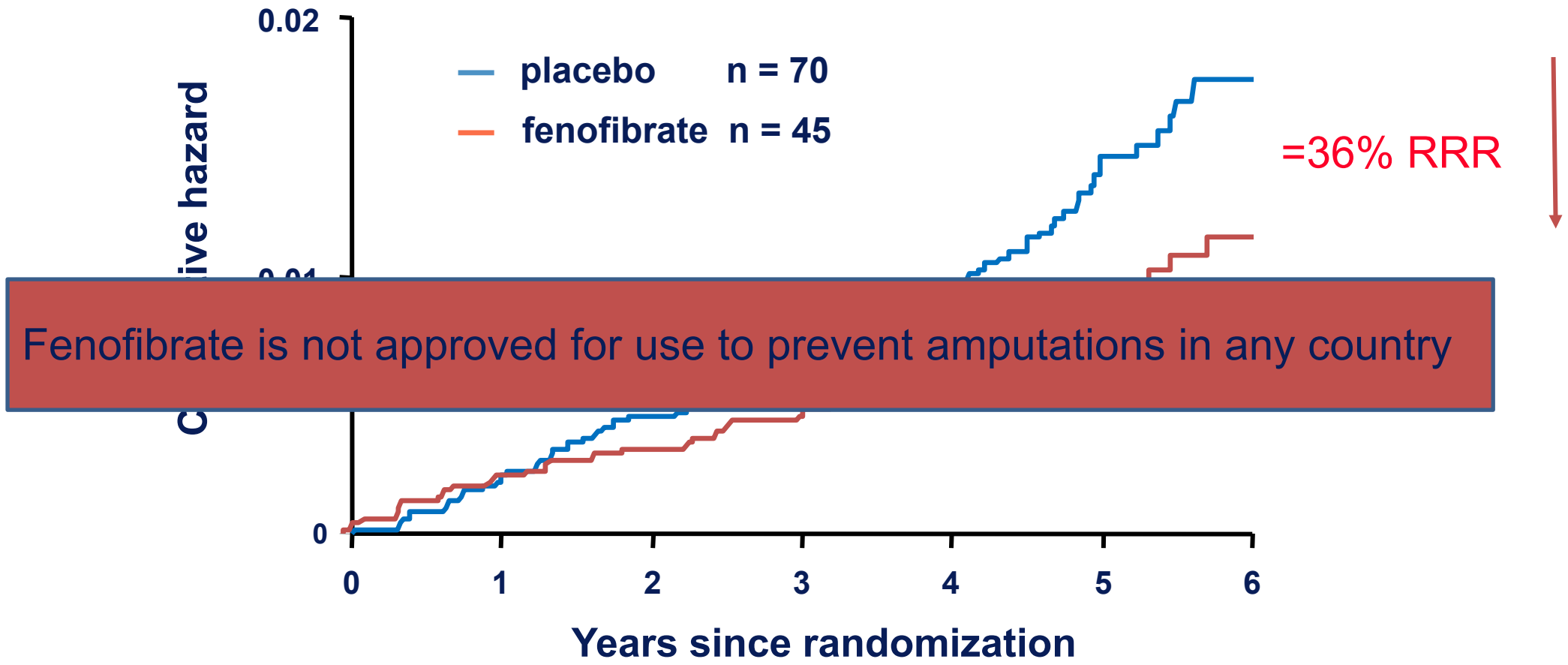






Fenofibrate associated with reduced amputations

First diabetes-related amputation **HR 0.64 (0.44–0.94), *P* = 0.020**

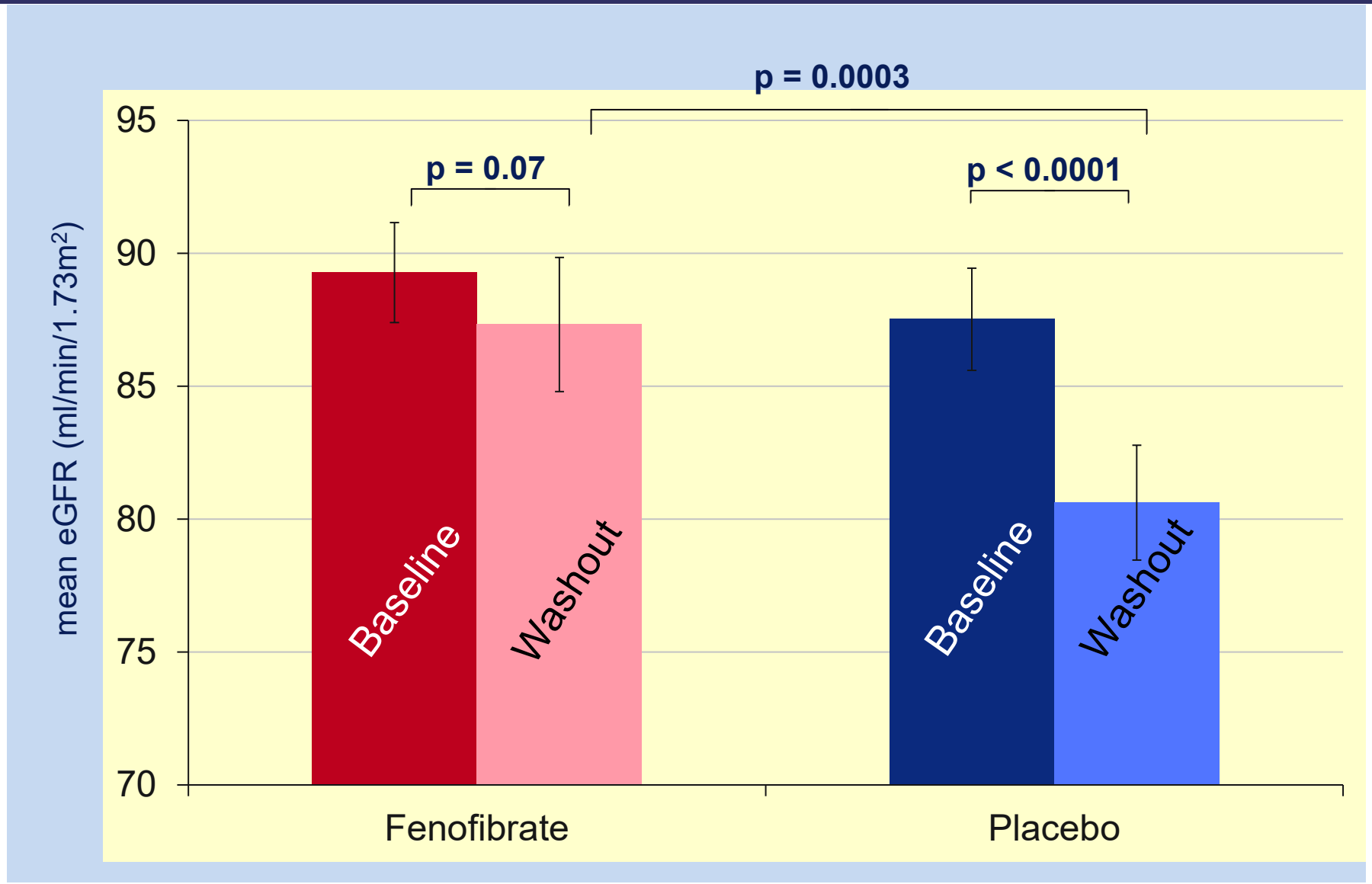


Fenofibrate is not approved for use to prevent amputations in any country

All diabetes-related amputations 37% RRR, p=0.04

Rajamani K, Keech AC et al; *Lancet* 2009; 373:1780-88

FIELD: Fall in eGFR from baseline to washout (n=661)



Learning Assessment Questions

Objective 1: Identify the pathogenesis and recognized risk factors for visual impairment and blindness caused by diabetes, with a focus on diabetic retinopathy

Question 1: Risk factors for diabetic retinopathy include all the following except:

- Poor blood sugar control?
- High blood pressure?
- Long duration of diabetes?
- Hyperlipidemia?
- Male sex?
- Smoking?
- Microalbuminuria?

Diabetes INITIATIVE of South Carolina

Learning Assessment Answers

Objective 1: Identify the pathogenesis and recognized risk factors for visual impairment and blindness caused by diabetes, with a focus on diabetic retinopathy

Question 1: Risk factors for diabetic retinopathy include all the following except:

- Poor blood sugar control? YES
- High blood pressure? YES
- Long duration of diabetes? YES
- Hyperlipidemia? yes
- Male sex? yes
- Smoking? NO
- Microalbuminuria? YES

Learning point: Surprisingly, there is no evidence that smoking increases risk for retinopathy. This again suggests DR has a pathogenesis distinct from cardiovascular disease.

Diabetes INITIATIVE of South Carolina

Learning Assessment Questions

Objective 2: Evaluate risks and benefits of currently accepted preventive measures and treatments for diabetic retinopathy.

Question 2: In people with diabetes:

(a) The onset and progression of DR can be delayed by which three of the following:

- Good blood sugar control?
- Good blood pressure control?
- Statin treatment?
- GLP-1 agonists?
- DPP4 inhibitors?
- Fenofibrate?

(b) (True or false?) For advanced, sight-threatening DR:

- Intraocular anti-angiogenic injections are low-cost and convenient
- Laser photocoagulation causes loss of retinal tissue and potential night blindness
- Vitrectomy is a last resort for some

Diabetes INITIATIVE of South Carolina

Learning Assessment Answers

Objective 2: Evaluate risks and benefits of currently accepted preventive measures and treatments for diabetic retinopathy.

Questions 2: In people with diabetes:

(a) The onset and progression of DR can be delayed by which three of the following:

- Good blood sugar control? YES
- Good blood pressure control? YES
- Statin treatment? NO
- GLP-1 agonists? NO
- DPP4 inhibitors? NO
- Fenofibrate? YES

(b) (True or false?) For advanced, sight-threatening DR:

- Intraocular anti-angiogenic injections are low-cost and convenient NO
- Laser photocoagulation causes loss of retinal tissue and potential night blindness YES
- Vitrectomy is a last resort for some YES

Learning points: Measures that protect the blood retinal barriers delay retinopathy. Some that cause a rapid improvement in glycemia may accelerate it, at least transiently.

Learning Assessment Questions

Objective 3: Assess the newly recognized role of an old drug, fenofibrate, in preserving vision in people with diabetes

Question 3 (true or false?): In diabetic patients, fenofibrate:

- Slows progression of early retinopathy by ~30% independent of A1C, plasma lipids, or type of diabetes
- Reduces cardiovascular risk in some patient categories
- May be combined safely with statin treatment
- May reduce progression of other microvascular complications of diabetes
- Is safe to use during pregnancy
- May protect blood-retinal barriers

Diabetes INITIATIVE of South Carolina

Learning Assessment Answers

Objective 3: Assess the newly recognized role of an old drug, fenofibrate, in preserving vision in people with diabetes

Question 3 (true or false?): In diabetic patients, fenofibrate:

- Slows progression of early retinopathy by ~30% independent of A1C, plasma lipids, or type of diabetes — TRUE
- Reduces cardiovascular risk in some categories — TRUE
- May be combined safely with statin treatment — TRUE
- May reduce progression of other microvascular complications of diabetes — TRUE
- Is safe to use during pregnancy — Category C
- May protect blood-retinal barriers — TRUE

Learning point: A new use for an old drug. Indication for DR is now approved in over a dozen countries.

Clinical Scenarios, Quiz

Which of the following patients would be the best candidate for fenofibrate?

1. Jennifer, a 20-year-old woman with a five-year history of Type 1 diabetes, A1C 6.8%, normotensive, no evidence of retinopathy or other complications of diabetes. Planning to become pregnant.

2. James, a 35-year-old man diagnosed with Type 2 diabetes 10 years ago. A1C 7.9%. BP 137/89. Early non-proliferative retinopathy, microalbuminuria. Mild hypertension. On metformin, statin, HCTZ and ACEI.

3. Frederick, a 29-year-old man with Type 1 diabetes for 17 years. He has received laser treatment for diabetic retinopathy and has impaired vision. Microalbuminuria. A1c 9.1%. BP 142/92. On insulin, ACEI and statin.

Clinical Scenarios, Answer

Which of the following patients would be the best candidate for fenofibrate:

1. Jennifer, a 20-year-old woman with a five-year history of Type 1 diabetes, A1C 6.8%, normotensive, no evidence of retinopathy or other complications of diabetes who is planning to become pregnant.

2. James, a 35-year-old man diagnosed with Type 2 diabetes 10 years ago. A1C 7.9%. BP 137/89. Early non-proliferative retinopathy, microalbuminuria. Mild hypertension. On metformin, statin, HCTZ and ACEI.

3. Frederick, a 29-year-old man with Type 1 diabetes for 17 years. He has received laser treatment for diabetic retinopathy and has impaired vision. Microalbuminuria. A1c 9.1%. BP 142/92. On insulin, ACEI and statin.

Learning point: Existing evidence shows that fenofibrate is most effective in slowing retinopathy <u>in patients with early but evident retinal abnormalities</u>. It is effective regardless of type of diabetes, sex, or patient age.

Connections

1. Could the utility of fenofibrate in DR have been realized earlier?
2. Did ‘silos’ between disciplines prevent progress?
3. ‘Straight line’ vs lateral thinking: it’s a lipid drug, so that’s how it must work.
4. Will we implement this new knowledge at scale? How?

Conclusions

In both Type 1 and Type 2 diabetes:

While statins reduce cardiovascular risk, but are ineffective against microvascular complications,

- Fenofibrate reduces progression of early diabetic retinopathy
- Evidence from FIELD suggests it is also reno-protective and reduces amputations
- Fenofibrate is the only fibrate with a safe side-effect profile when combined with a statin
- Fenofibrate is pregnancy category C