Istituto Superiore di Sanità
III Convegno

PREVENIRE LE COMPLICANZE DEL DIABETE DALLA RICERCA DI BASE ALL'ASSISTENZA

Roma, 16 febbraio 2009

Applicazioni cliniche della ricerca in retinopatia diabetica

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FROM BENCH TO BEDSIDE

Ovvero …

la storia di quattro storie finite in modo inatteso e di una che non si sa ancora come finirà …

Storia n° 1 - Somatostatina

GH/IGF-I Axis and DR

1952: Sheehan syndrome (post-partum pituitary apoplexy) observed to revert PDR

1950-70: Pituitary ablation effective in arresting progression of PDR

1960-70: Growth hormone levels increased in diabetes

1980-90: Insulin-like growth factor-I (IGF-1) increased in vitreous of eyes with PDR

1980-90: Somatostatin may slow florid PDR

1990- : Role of GH and IGF-1 in angiogenesis

Diabetes Vol. 2, No. 1, January-February, 1953

THE HOUSSAY PHENOMENON IN MAN

Recovery from Retinopathy in a Case of Diabetes With Simmonds' Disease

Jacob E. Poulsen, M.D. *GENTOFTE, DENMARK*

In a rare but instructive combination of endocrine disorders, nature has made the Houssay experiment in the human being. This has been observed in a small number of cases of diabetes, when damage to the pituitary gland by disease has caused loss of pituitary function with resultant modification of thediabetes. The changes in the ocular complications of diabetes observed in the following case are of special interests.

CASE REPORT

A female patient, born in 1915, had diabetes which began in 1924. During childhood and early youth it was very difficult to keep her diabetes under control; she was careless and uncooperative in regard to treatment. She had coma at least 20 times and was admitted to almost all the hospitals in Copenhagen. From 1936 to 1939, she was asmitted II times to Steno Memorial Hospital, on each occasion with ketosis and often with infectious complications.

IGFs in DR

- Elevated vitreous levels of IGF-I and -II found in patients with diabetic retinopathy[1,2]
- IGF-I actions in the retina
  - Induce leakage across blood retinal barrier[3]
  - Stimulate neovascularization[4]
  - Stimulate contraction of Müller cells[5]
  - Upregulate VEGF expression in retinal pigment epithelial cells
- Inhibition of IGF-I receptor function inhibits neovascularization[6]

1. Grant et al. Diabetes. 1986;35:416.; 2. Burgos et al. *Diabetes Care.* 2000;23:80.
3. Hussain et al. Diabetes. 1995;44:1209. ; 4. Castellon et al. *Exp Eye Res.* 2002;74;523.
5. Guidry et al. *Diabetes.* 2004;53:2428.; 6. Smith et al. *Nat Med.* 1999;5:1390.

IGF-I concentrations in Vitreous (Grant et al., 1986)

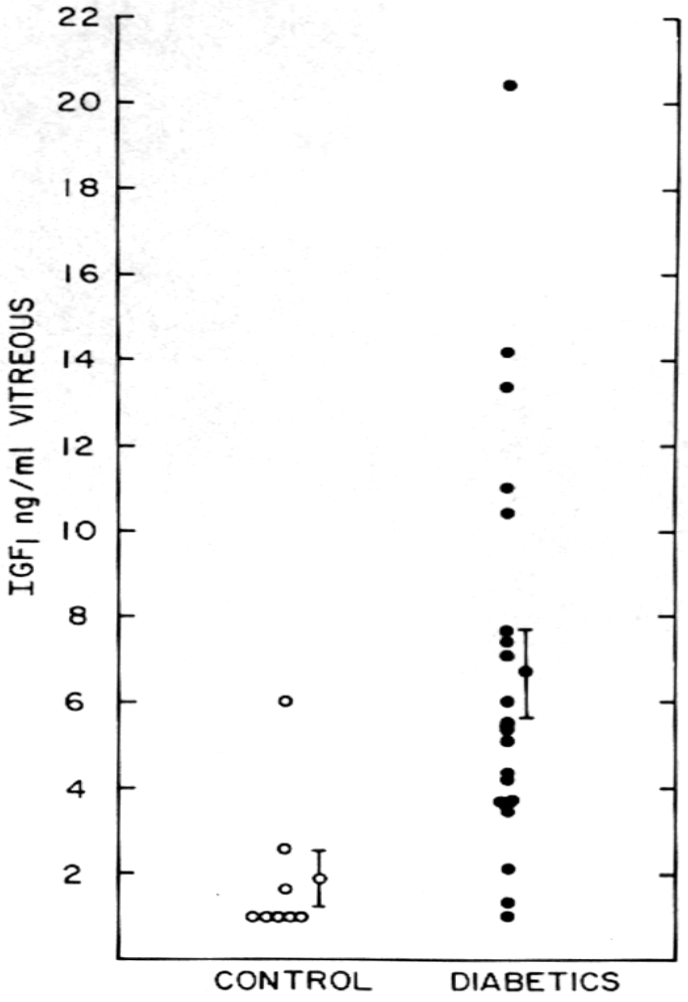
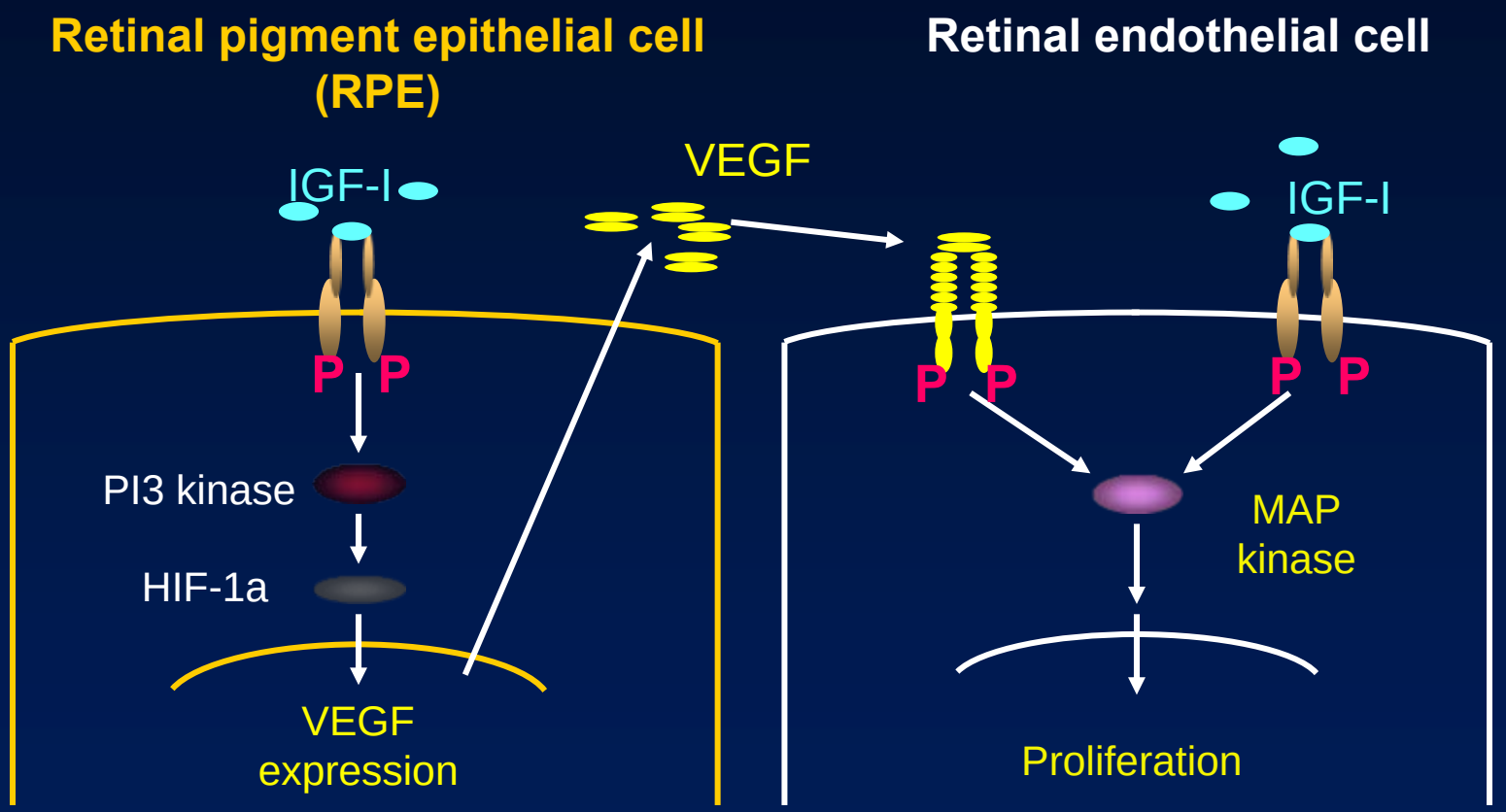


FIGURE 1. IGF-I concentrations in vitreous are shown for control and diabetic subjects. The mean concentration of IGF-I in vitreous from controls is 2.7 ± 0.96 versus 6.3 ± 0.13 ng/ml in diabetic subjects with neovascularization.

GH and IGF-I involvement in PDR: *in vitro* data

- Receptors for IGF-I on mammalian retinal microvascular cells
- IGF-I induces release of plasminogen activator and increases DNA synthesis in retinal endothelium
- GH can stimulate proliferation of human retinal endothelial cells (HREC)
- Somatostatin receptors present on HREC
- Octreotide inhibits endothelial cell proliferation stimulated by IGF-I or b-FGF

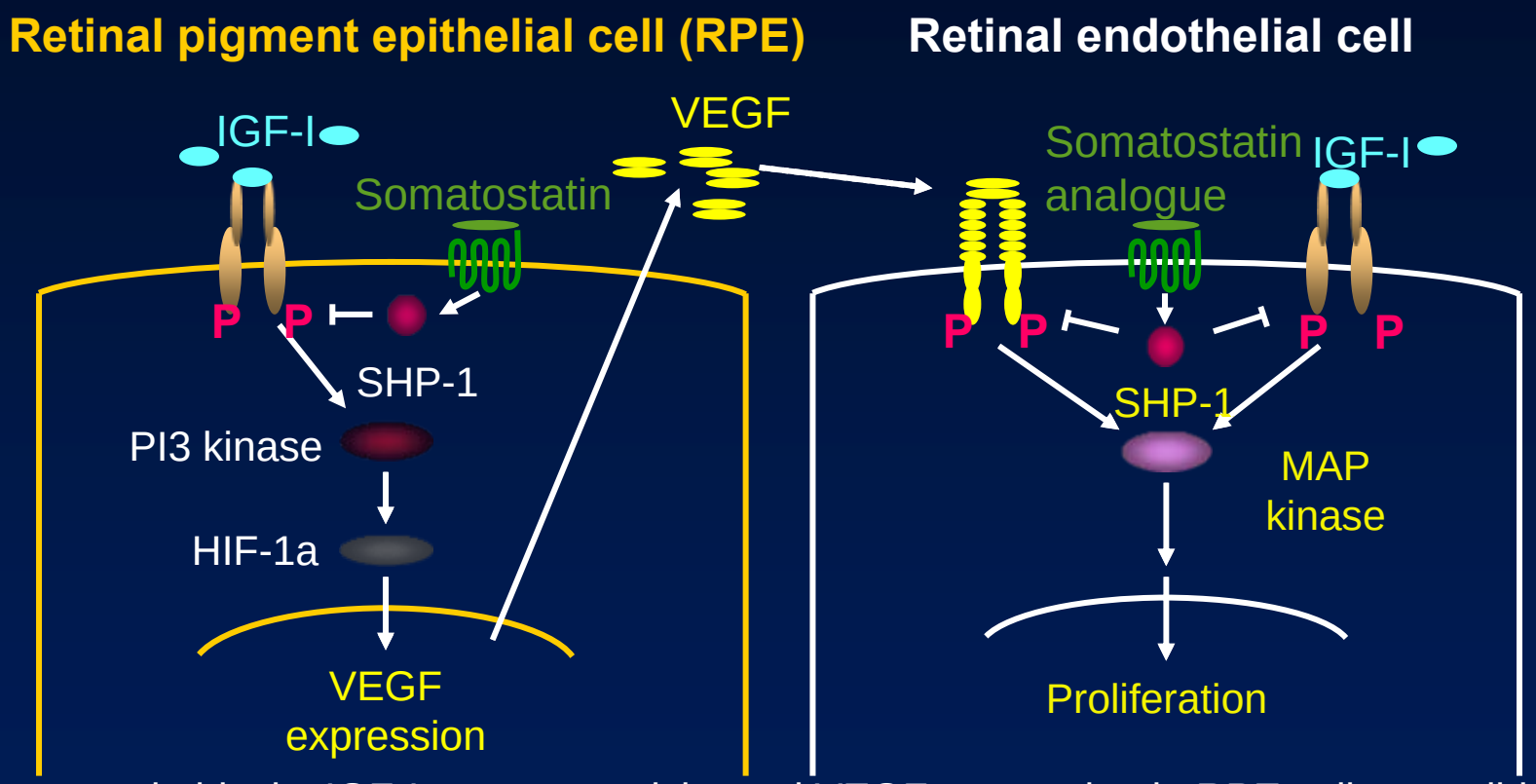
Stimulation of Endothelial Proliferation by IGF and VEGF



- IGF-I stimulates VEGF production by RPE cells
- IGF-I and VEGF promote neovascularization by endothelial cell proliferation

Treins et al. *Mol Endocrinol*. Epub before print. Smith et al. *Nat Med*. 1999;5:1390-1395.

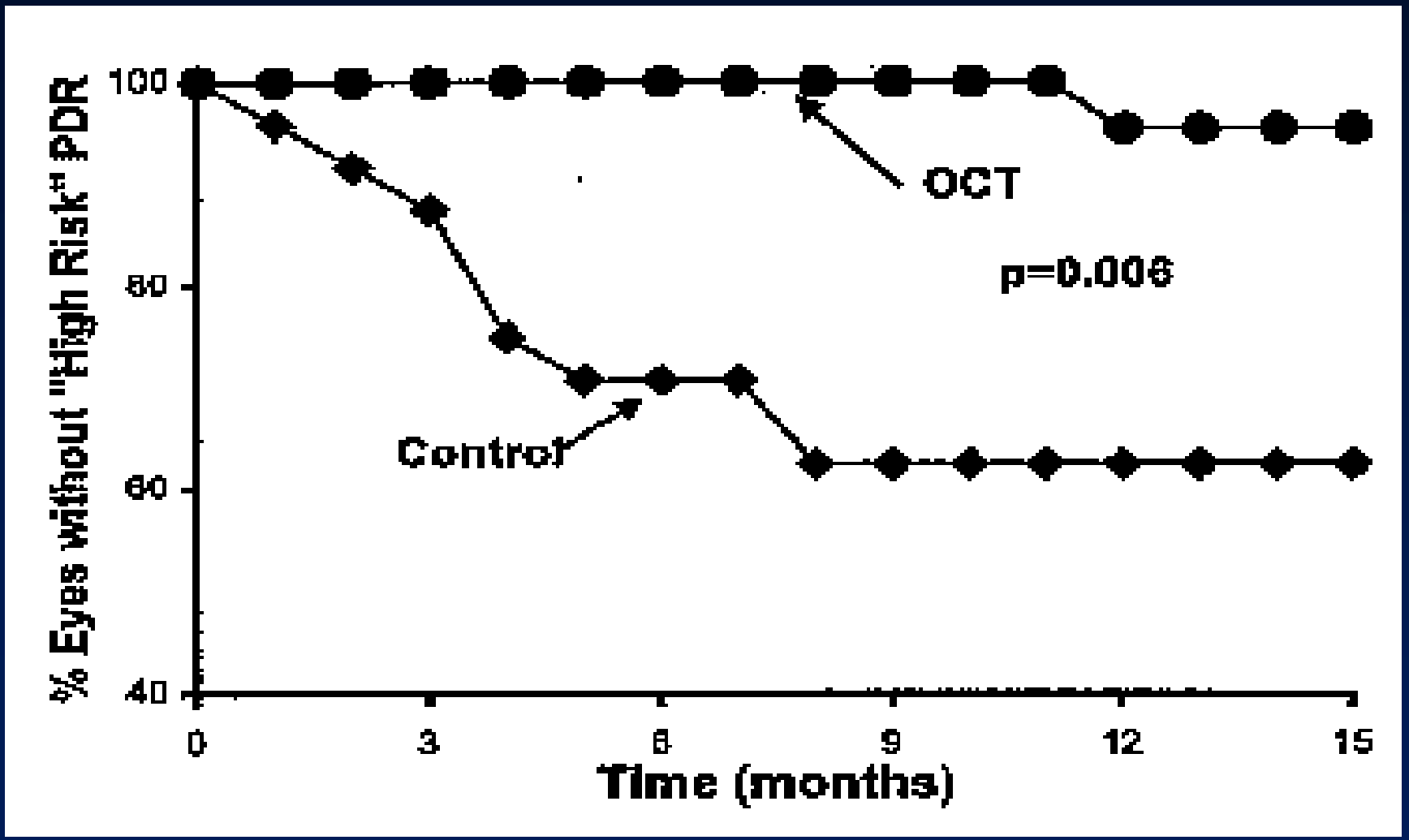
Proposed Model for Local Inhibition of Neovascularization by Somatostatin/ Somatostatin Analogues



- Somatostatin blocks IGF-I receptor activity and VEGF expression in RPE cells, possibly by activation of SHP-1 tyrosine phosphatase
- Somatostatin blocks IGF-I and VEGF stimulation of endothelial proliferation, possibly by activation of SHP-1

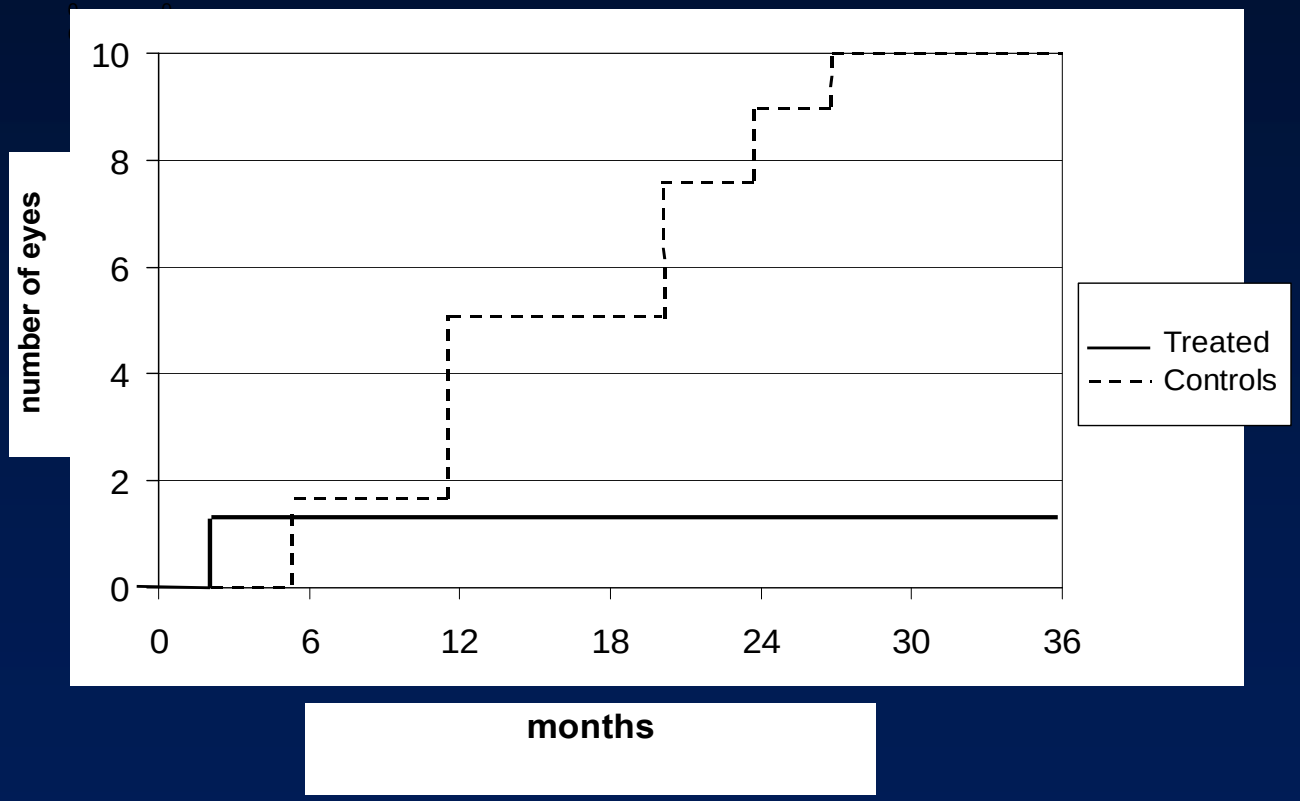
Treins et al. *Mol Endocrinol*. Epub before print. Smith et al. *Nat Med*. 1999;5:1390-1395.
Sall et al. *Exp Eye Res*. 2004;79:465-476. Baldysiak-Figiel et al. *J Endocrinol* 2004;180:417-24.

Octreotide Reduces Progression to High-Risk PDR



Grant et al. *Diabetes Care*. 2000;23:504.

Octreotide Reduces Risk of Vitreous Hemorrhage in Patients with Prior Laser Photocoagulation



Boehm et al. *Horm Metab Res*. 2001;33:300.

Octreotide - Phase III Studies

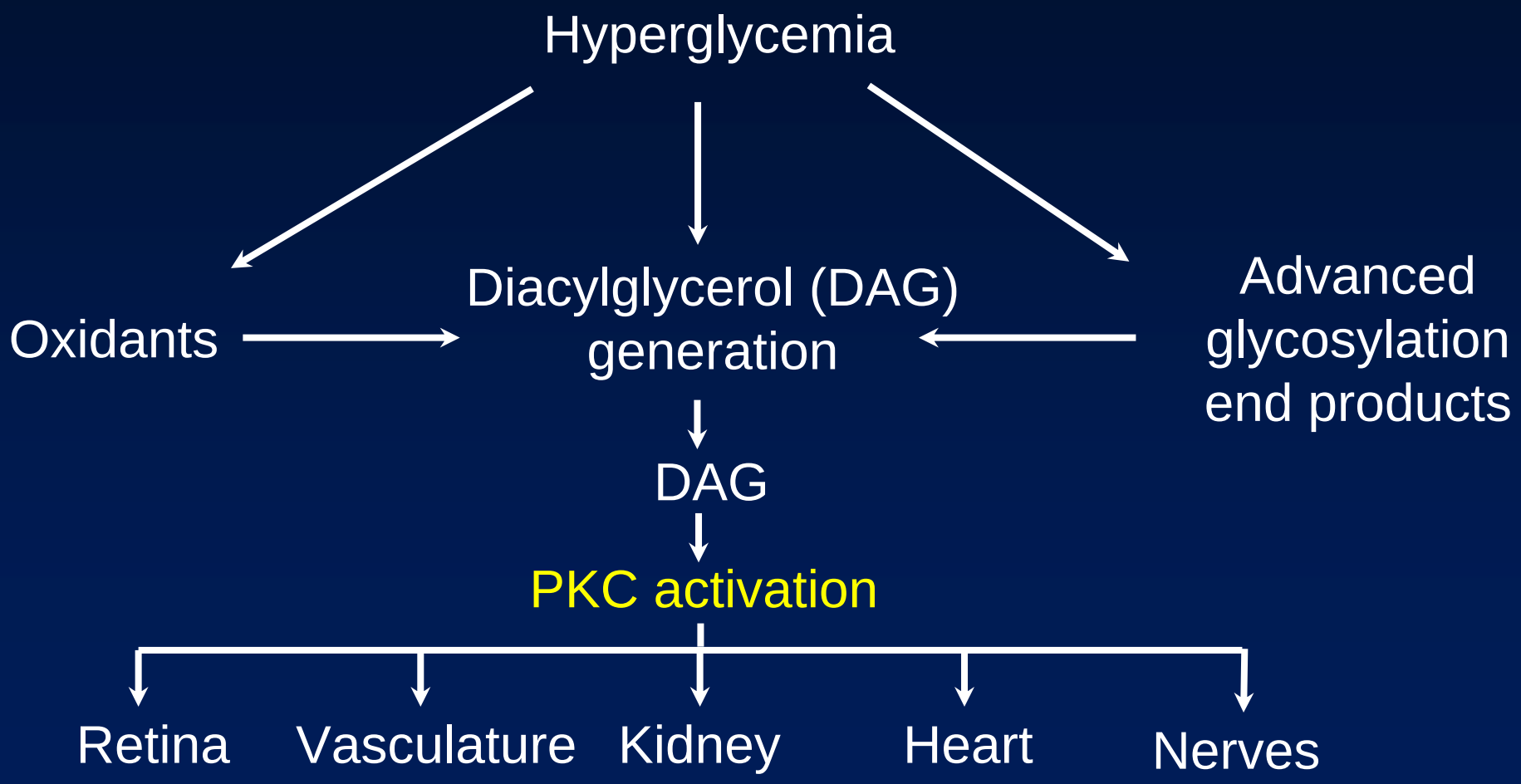
- Study 802
  European; 3 arms
  Sandostatin LAR 20 and 30 mg, Placebo

- Study 804
  American; 2 arms
  Sandostatin LAR 30 mg, Placebo

Status: completed

Storia n° 2 - Ruboxistaurina

Diabetes-Induced Activation of PKC



PKC Activation in the Vasculature

Increases:

- Basement matrix protein synthesis
- Activation of leukocytes
- Endothelial cell activation and proliferation
- Endothelial permeability
- Smooth muscle cell contraction
- Cytokine activation, TGF-β and VEGF, endothelin
- Angiogenesis

PKC-β in Diabetic Retinopathy

Hyperglycemia

PKC-β activation

Retinal vascular injury and dysfunction

Vascular leakage

Macular edema

PKC-β activation

Capillary nonperfusion

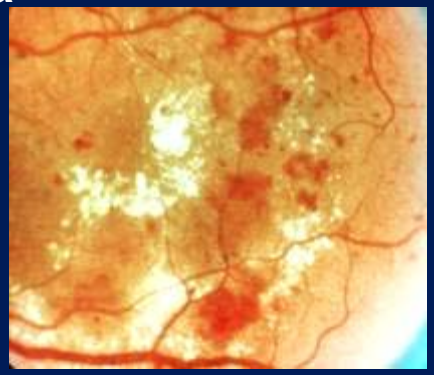
PKC-β activation

VEGF/VPF production

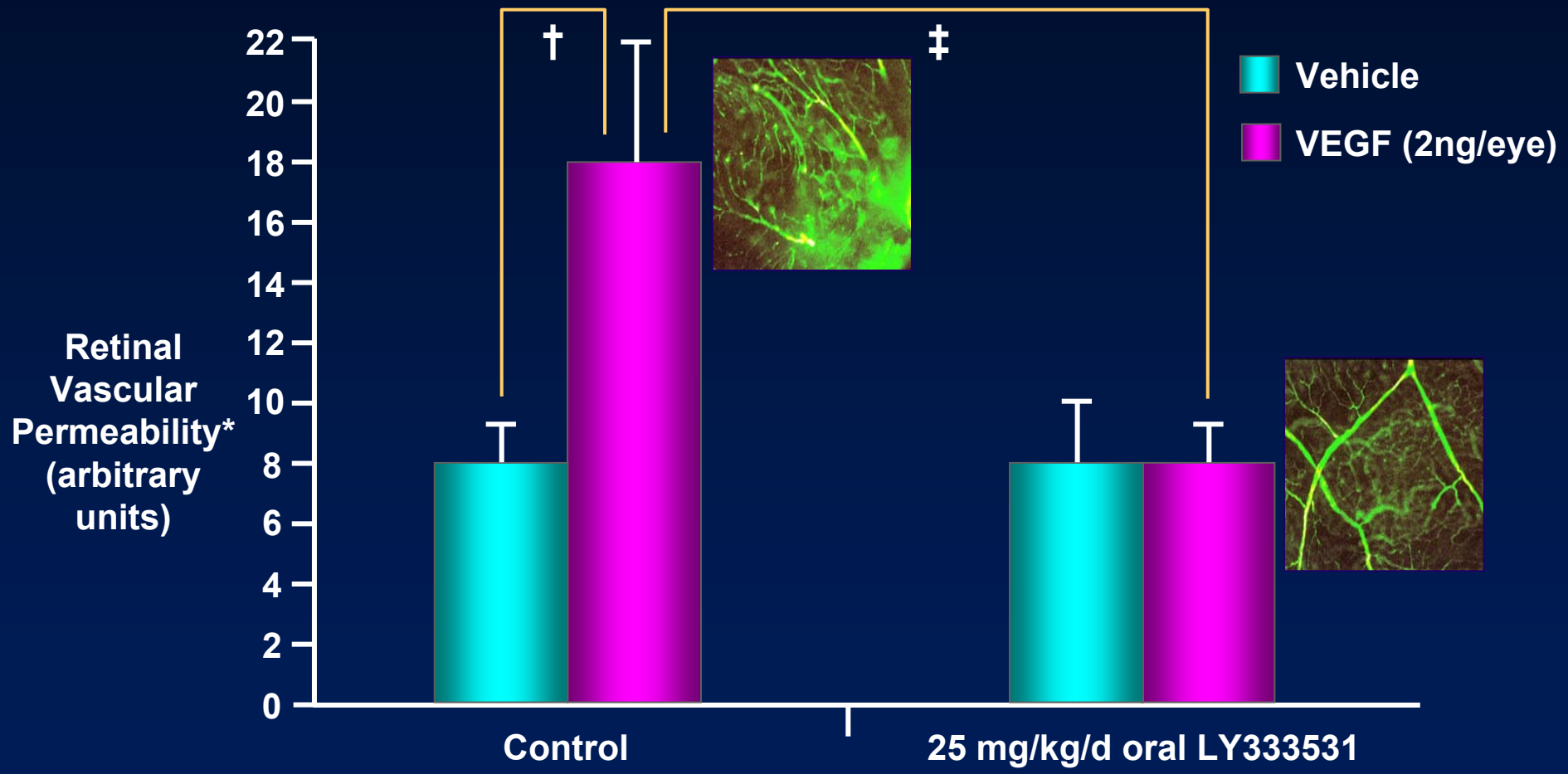
PKC-β activation

Neovascularization

Proliferative retinopathy



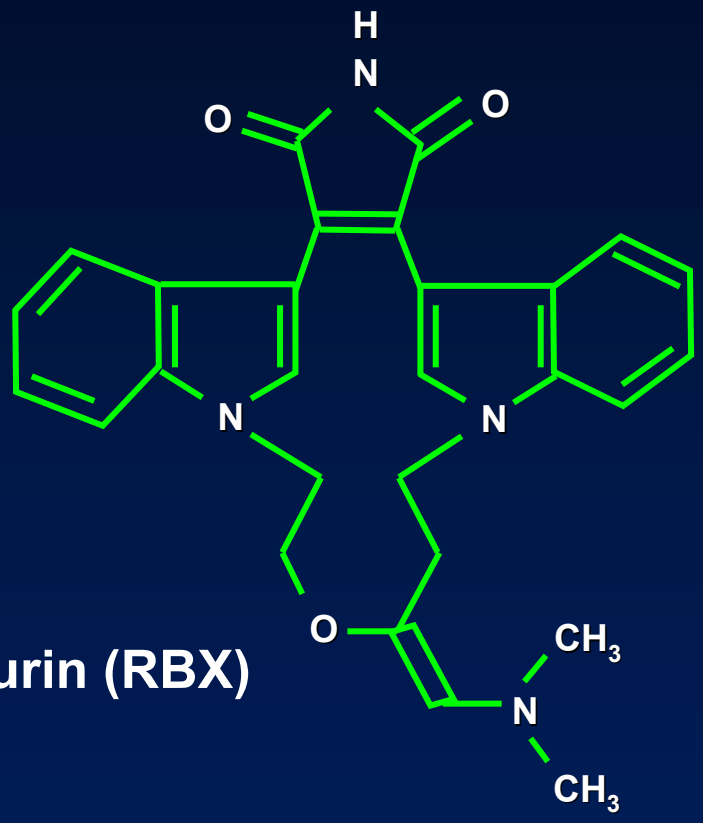
PKC-β Inhibition and Retinal Permeability



*Measured by vitreous fluorescein leakage. †P = .015. ‡P = .043.

Reproduced with permission from Aiello LP et al. *Diabetes*. 1997;46:1473-1480.

PKC-β Inhibitor



Ruboxistaurin (RBX)

- Highly PKC selective
- Highly β isoform selective
- Orally bioavailable

- Reduces retinal NV
- Reduces DM-induced perm
- Normalizes retinal blood flow

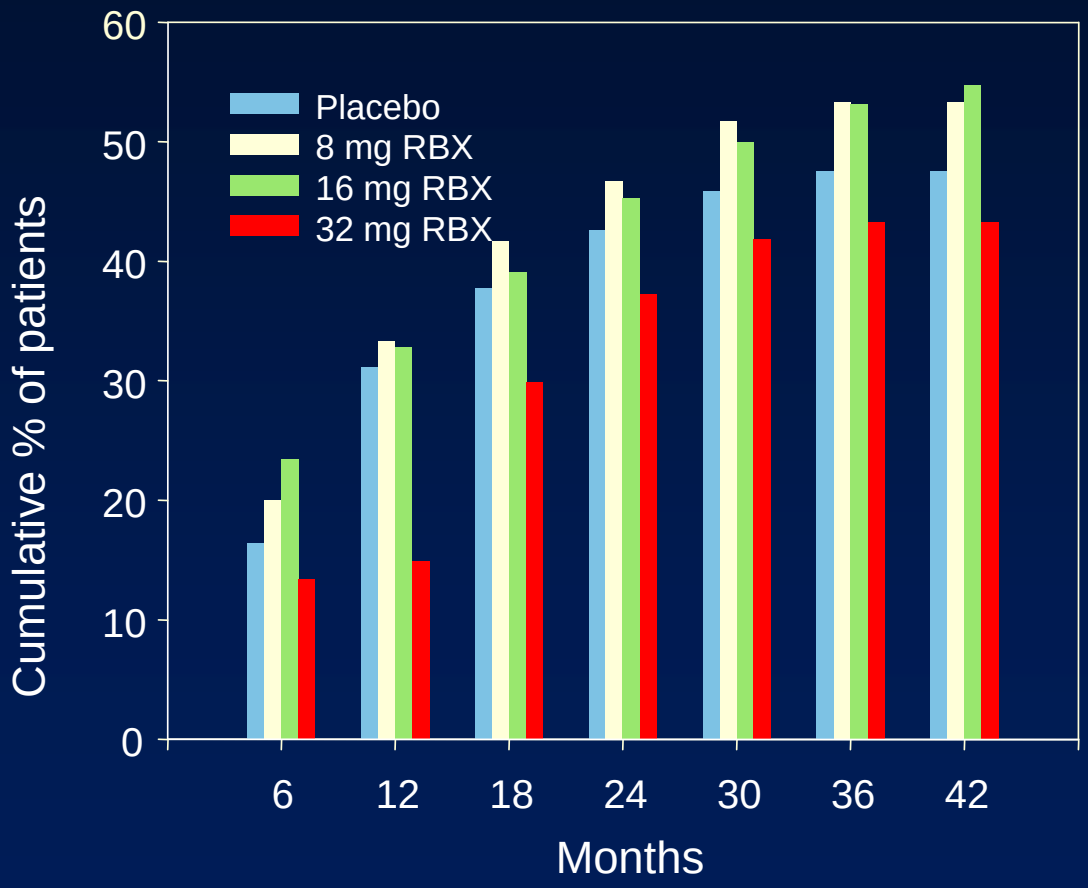
PKC–β Inhibition and DR trials

TRIAL	ACTION	INDICATION	STATUS
PKC-β inhibition	*Oral*	RBF & MCT	Phase Ib
DRS n=252	*8, 16, 32 mg Once*	NPDR Progression & Laser (CSMO)	Phase II/III
DME n=686	*Daily*	Diabetic ME Progression & Laser (CSMO)	Phase II/III
MBCM n=680	*32 mg v placebo*	DM ME NPDR	Phase III

PKC–β Inhibition and DR trials

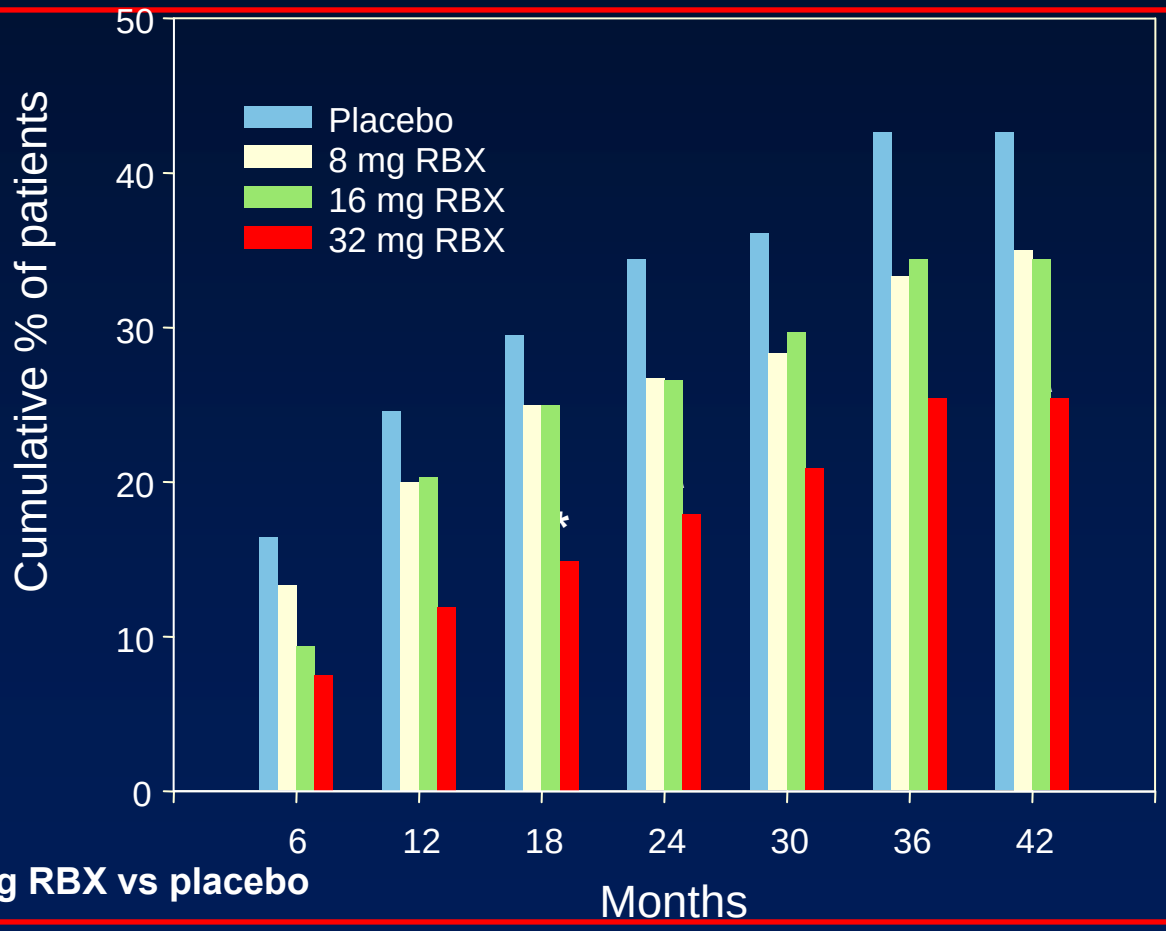
TRIAL	ACTION	INDICATION	STATUS
PKC-β inhibition	*Oral*	RBF & MCT	Phase Ib Completed
DRS n=252	***8, 16, 32 mg Once***	**NPDR Progression & Laser (CSMO)**	**Phase II/III Completed April 2002**
DME n=686	***Daily***	**Diabetic ME Progression & Laser (CSMO)**	**Phase II/III Completed Sept 2002**
MBCM n=680	*32 mg v placebo*	DM ME NPDR	Phase III

Progression of Diabetic Retinopathy or Photocoagulation



Aiello LP, et al. *Diabetologia*. 2003;46(suppl 2):A42.

Moderate Visual Loss (decrease of ≥15 letters)



*** *P* < 0.05 32 mg RBX vs placebo**

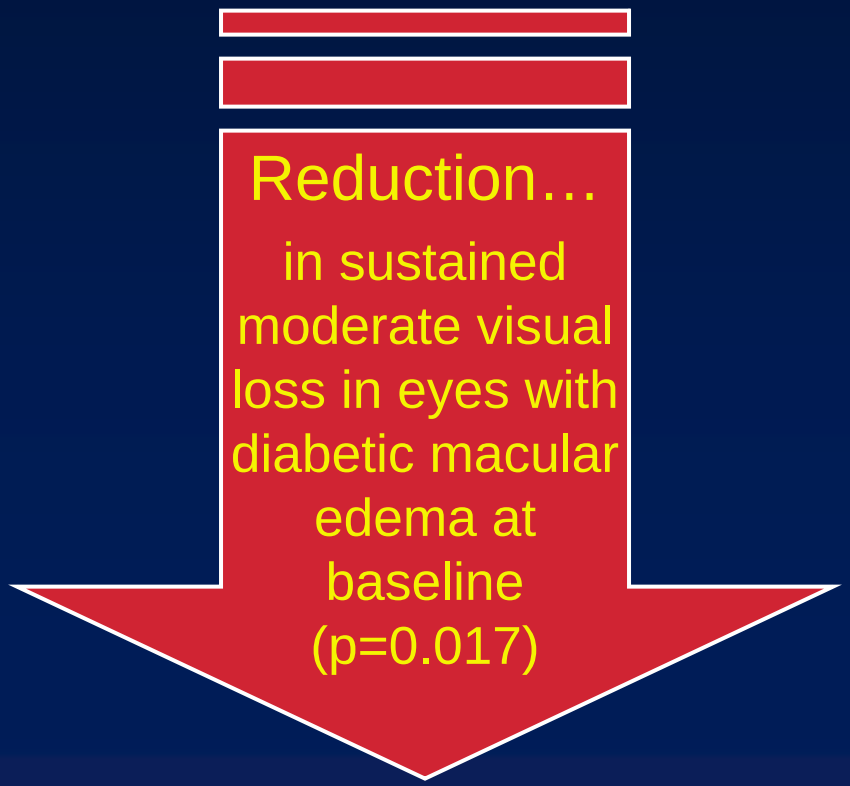
Aiello LP, et al. *Diabetologia*. 2003;46(suppl 2):A42.

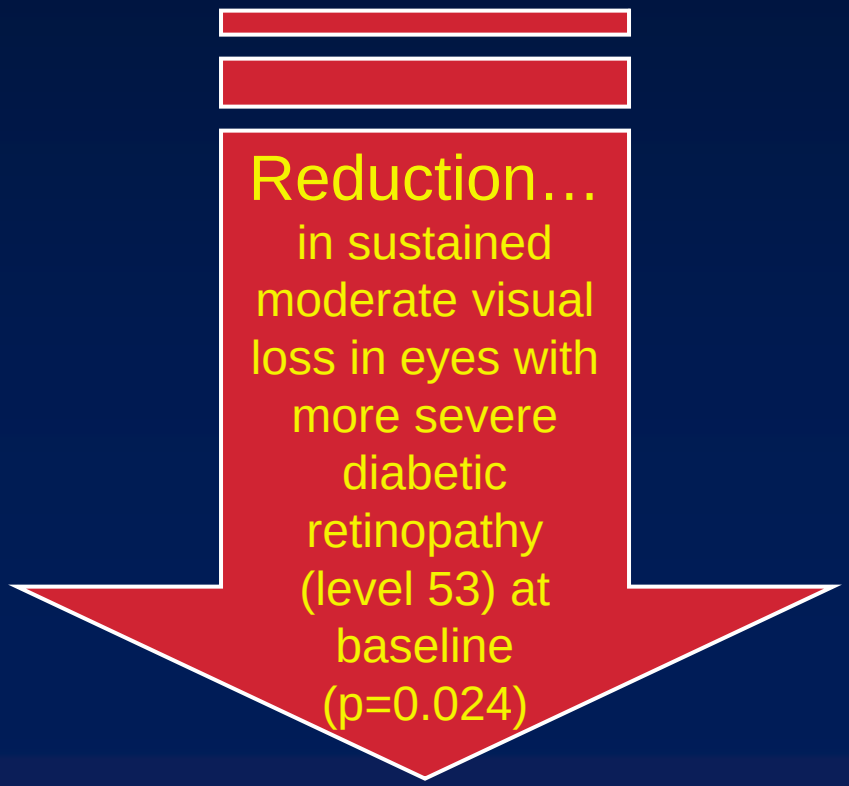
PKC–β Inhibition and DR trials

TRIAL	ACTION	INDICATION	STATUS
PKC-β inhibition	*Oral*	RBF & MCT	Phase Ib Completed
DRS n=252	*8, 16, 32 mg Once*	NPDR Progression & Laser (CSMO)	Phase II/III Completed April 2002
DME n=686	*Daily*	Diabetic ME Progression & Laser (CSMO)	Phase II/III Completed Sept 2002
MBCM n=680	***32 mg v placebo***	**DM ME NPDR**	**Phase III Completed 2005**

Phase 3 DR Study
Trial Results

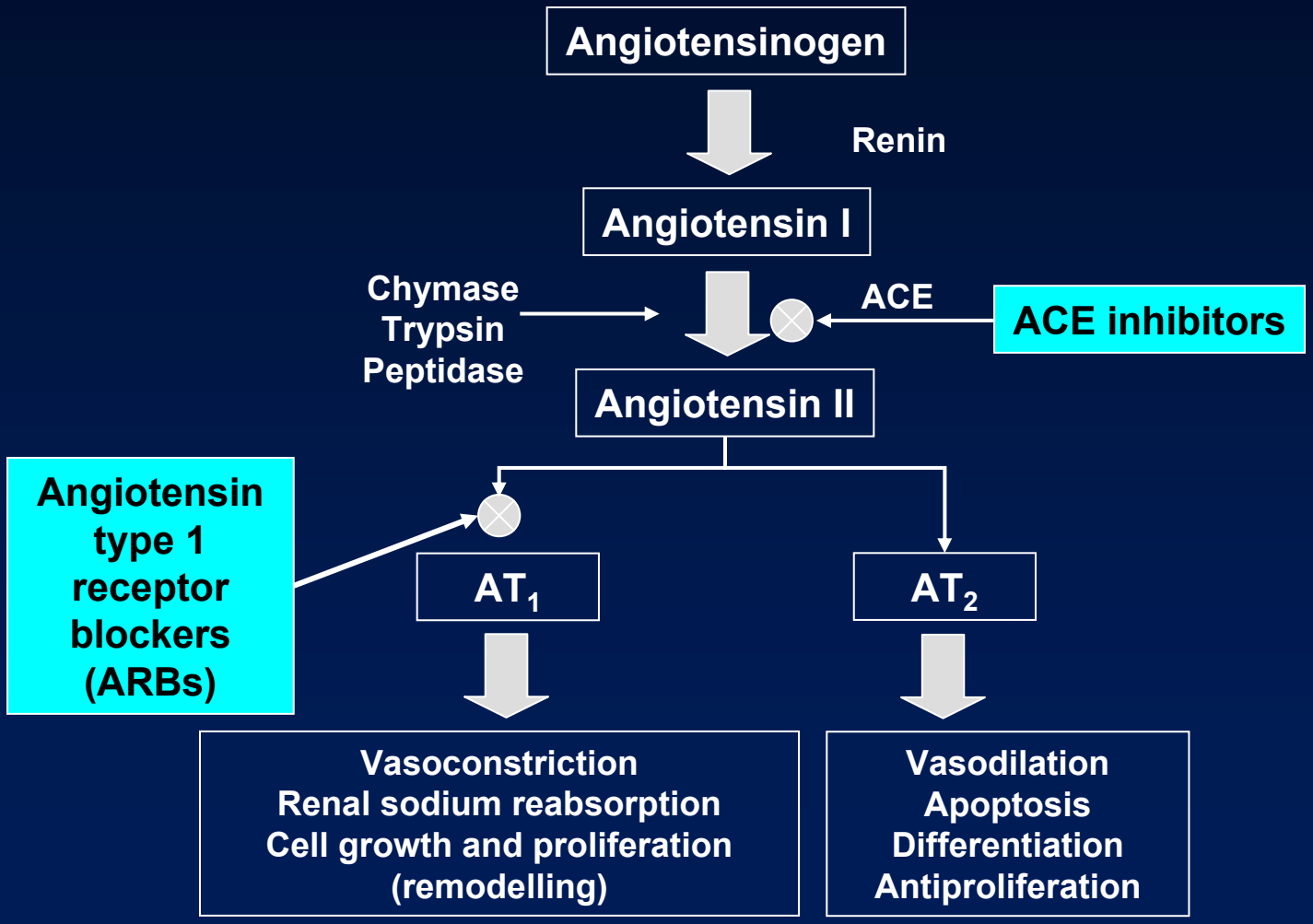
- Treatment with ruboxistaurin:
  - Demonstrated an effect (p = 0.038) on the study outcome of moderate visual loss





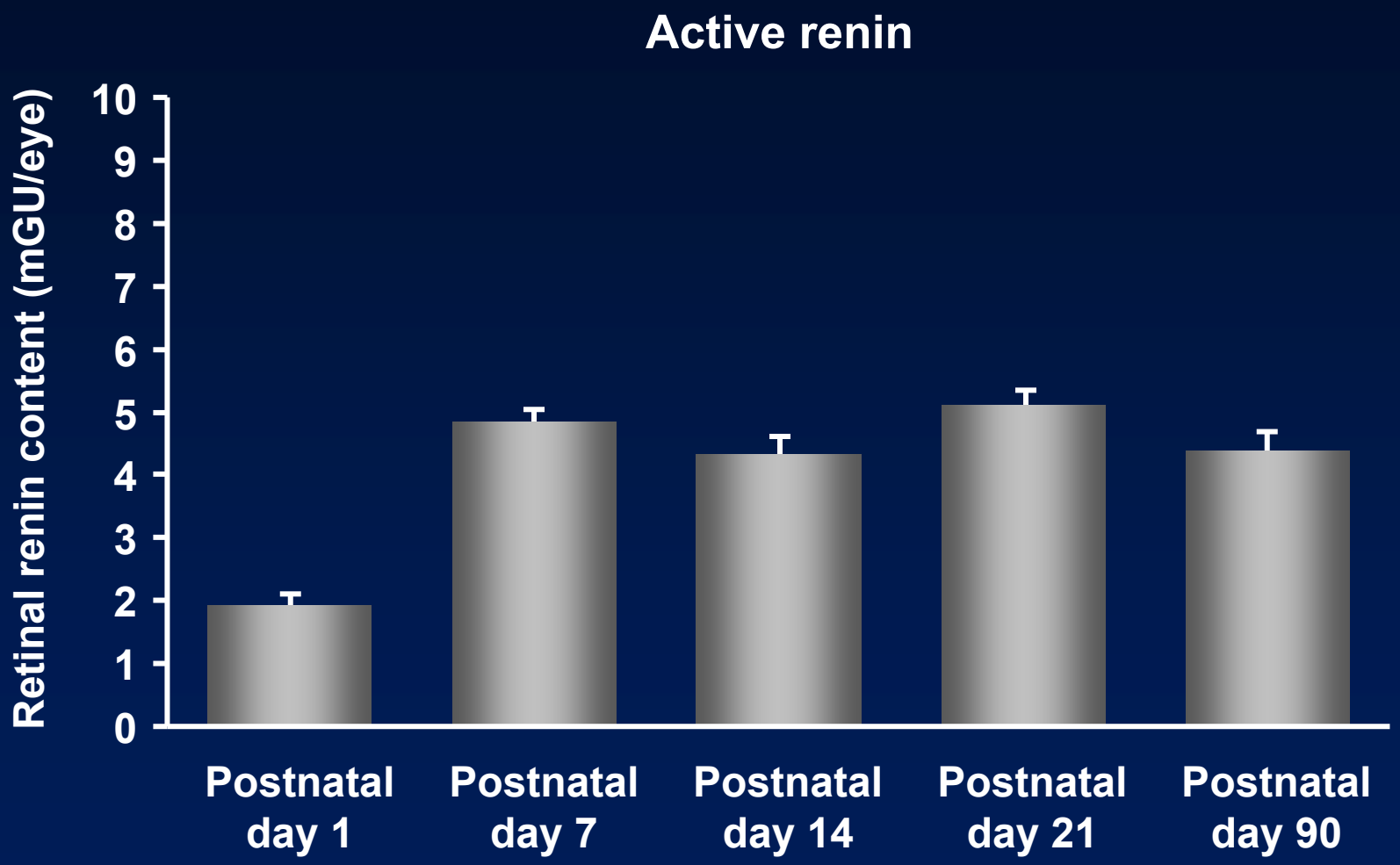
Storia n° 3 – Il sistema renina-angiotensina

The renin–angiotensin system (RAS)



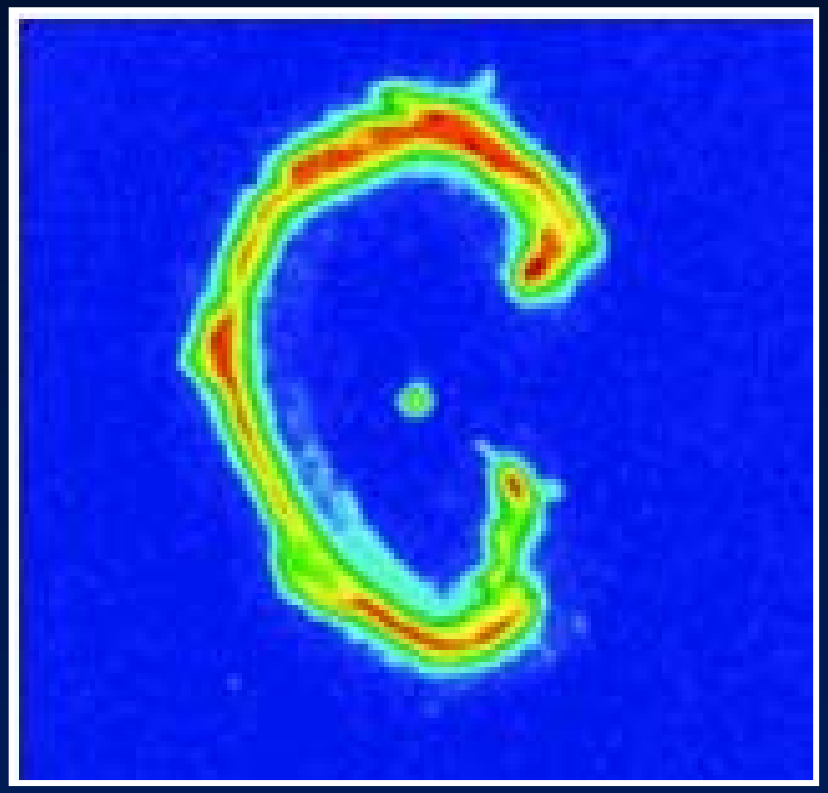
Easthope SE, Jarvis B. *Drugs* 2002; **62**:1253–1287.

The retinal RAS: renin levels in rat retina



Sarlos S, *et al. Invest Ophth Vis Sci* 2005; **46**: 1069–1077.

The retinal RAS: ACE levels in rat retina

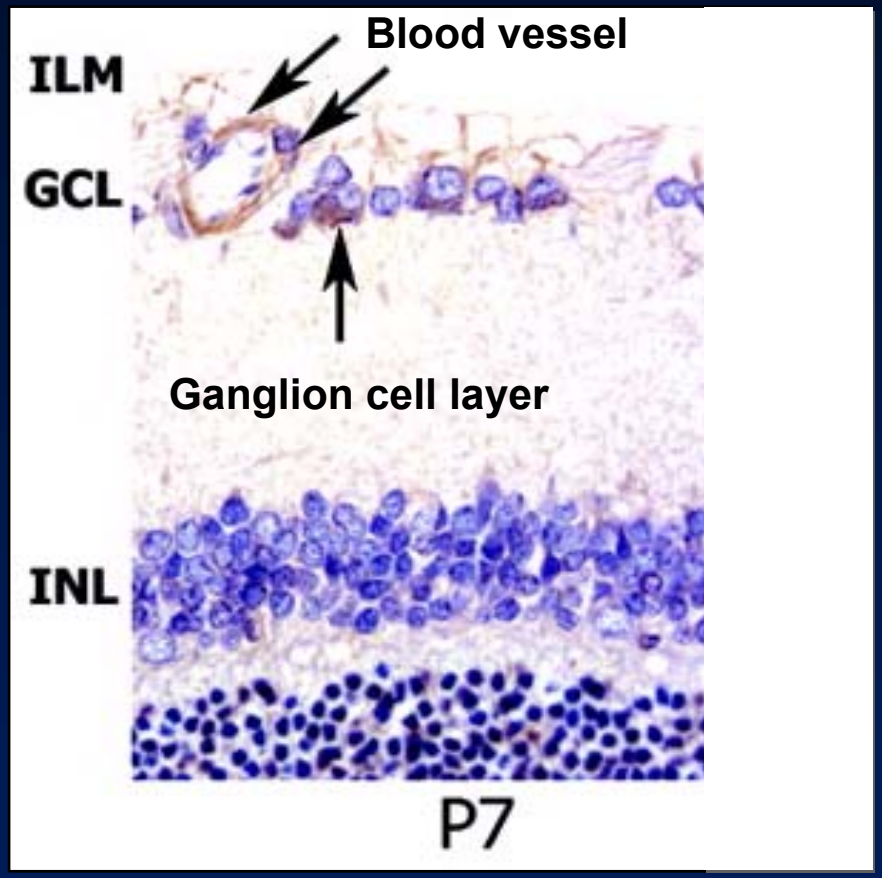


Representative computer-generated colour autoradiograph of specific ACE radioligand binding in retina of Sprague-Dawley rat

Shown is high (red), moderate (yellow and green) and low (blue) ACE binding

Sarlos S, *et al. Invest Ophth Vis Sci* 2005; **46**: 1069–1077.

The retinal RAS: AT_1-receptor distribution in rat retina

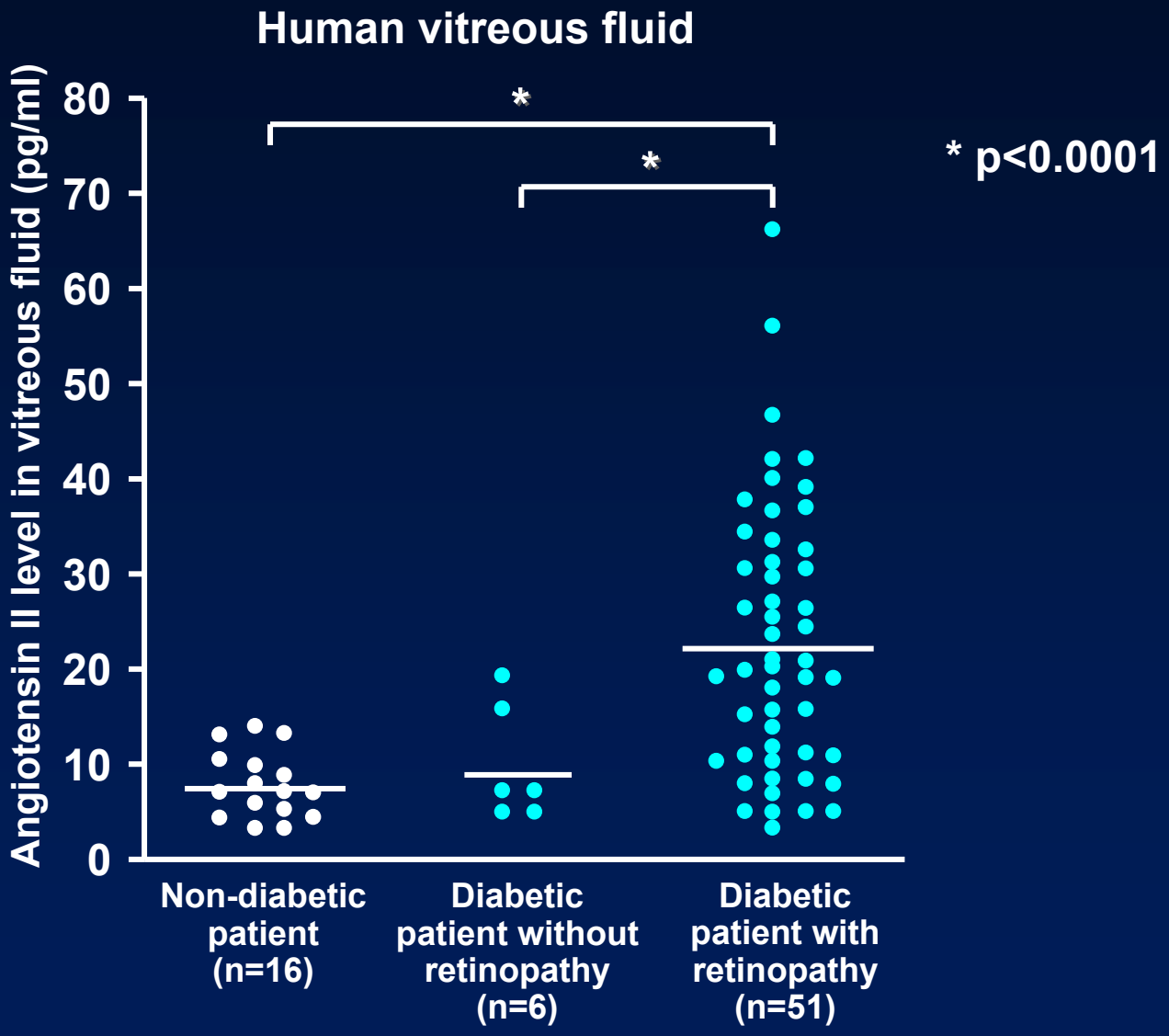


AT_1 receptor immunolabelling in Sprague-Dawley rat retinas at postnatal day (P) 7

Immunolabelling was observed in hyaloid vessels (double arrows), blood vessels in the inner limiting membrane and ganglion cell layer, and cells in the ganglion cell layer (single arrows)

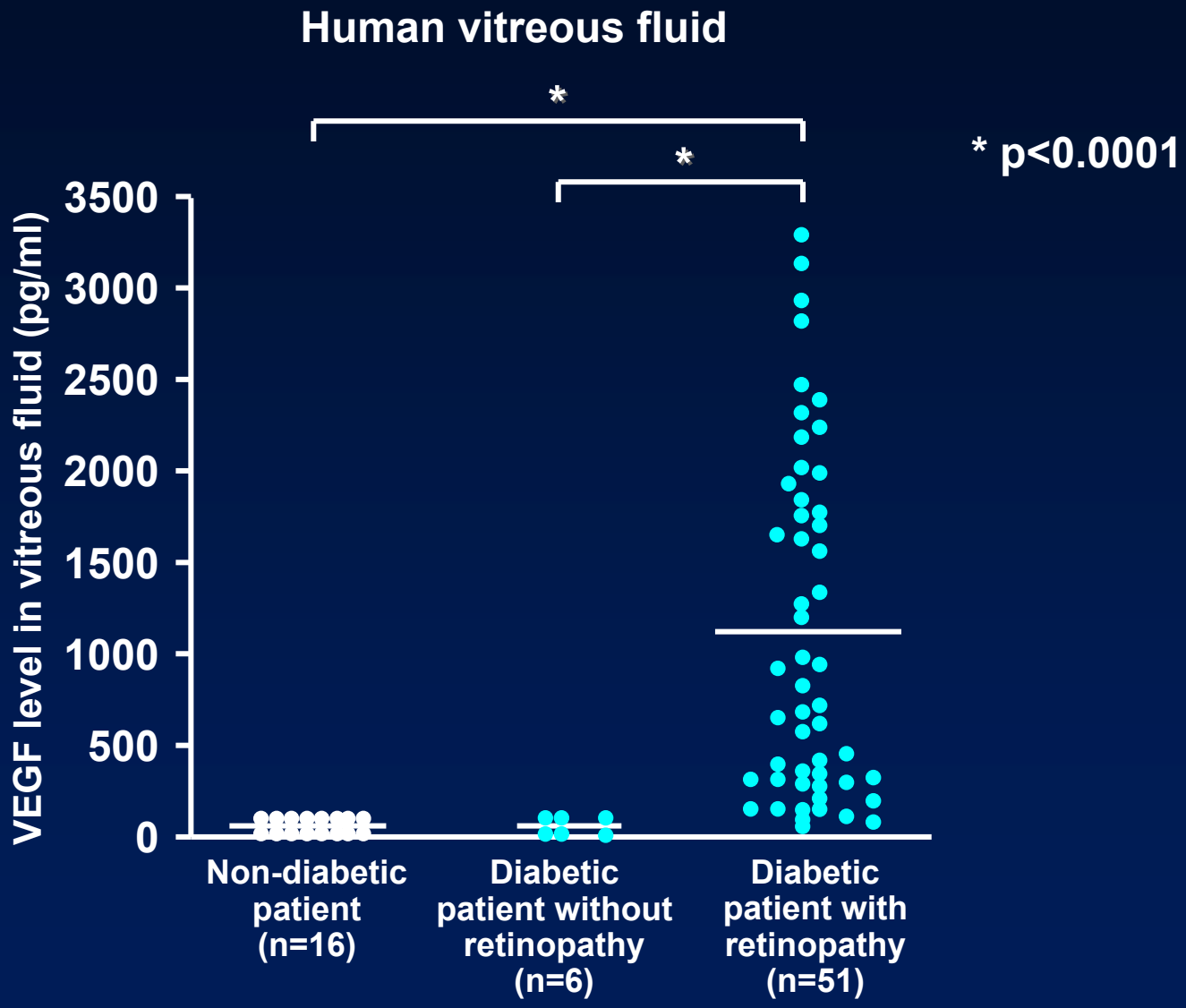
Sarlos S, *et al. Invest Ophth Vis Sci* 2005; **46**: 1069–1077.

The retinal RAS is activated in diabetes: vitreous angiotensin II levels



Funatsu H, *et al. Br J Ophthalmol* 2002; **86**: 311–315.

The retinal RAS is activated in diabetic retinopathy: vitreous VEGF levels

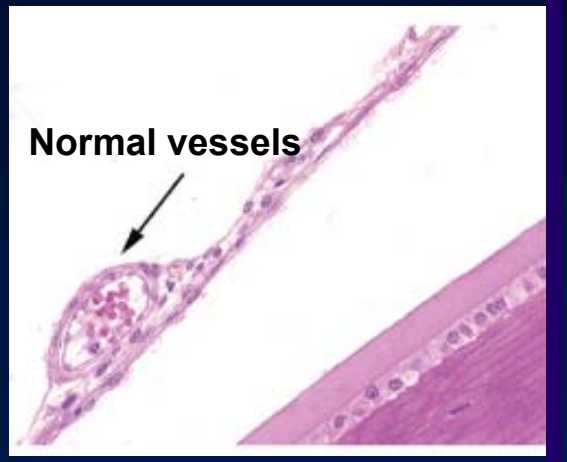


Funatsu H, *et al. Br J Ophthalmol* 2002; **86**: 311–315.

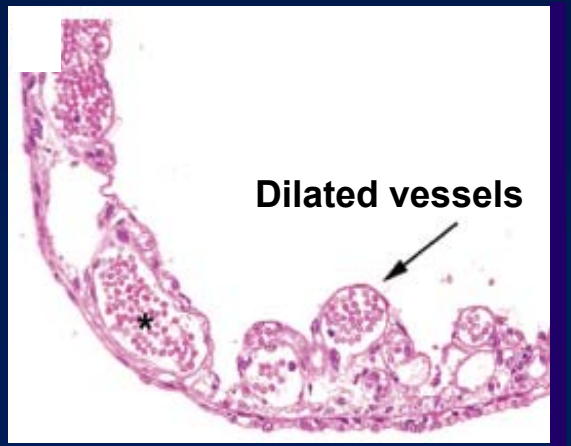
The RAS influences ocular endothelial cell proliferation in diabetes

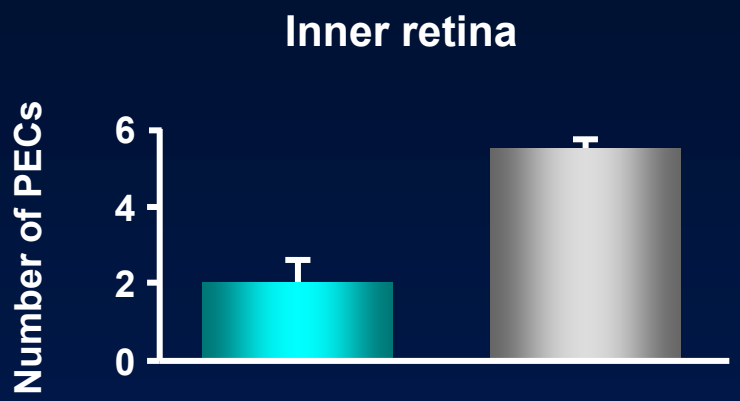
Rat iris

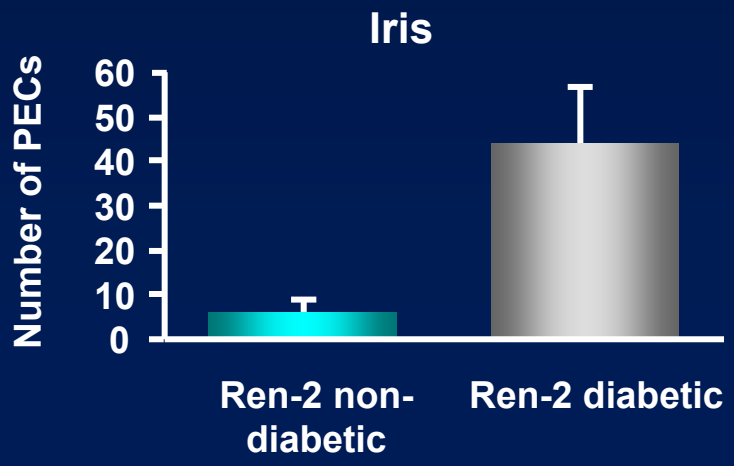
Non-diabetic



Diabetic

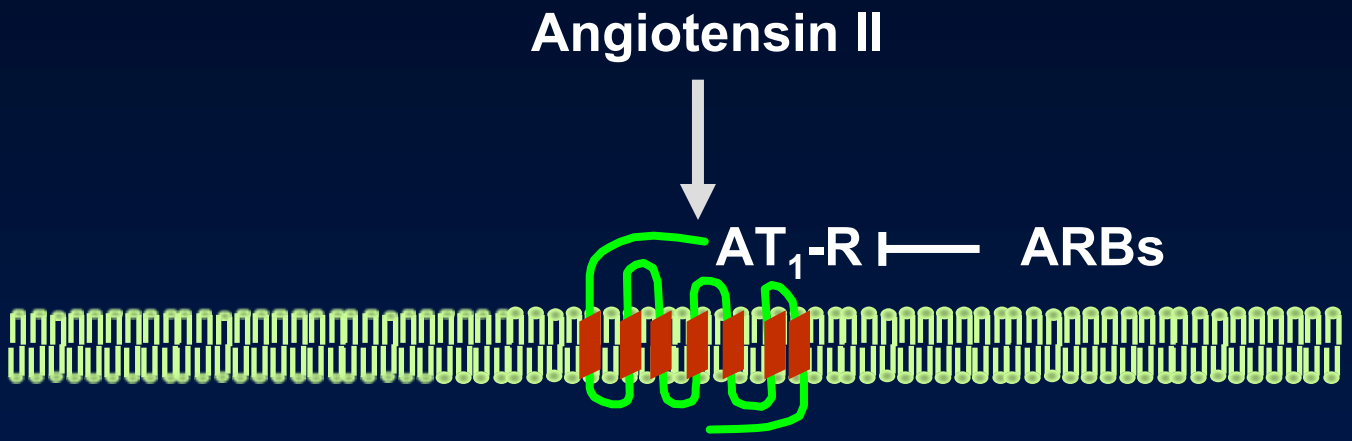






Moravski CJ, *et al. Am J Pathol* 2003; **162**: 151–160.

Molecular effects of angiotensin receptor blockers on retinal vascular cells and tissue



	Effect of ARBs
Retinal endothelial cells:	VEGF-R2 ↓
Retinal pericytes:	VEGF ↓ RAGE and ROS ↓
Retina *in vivo*:	VEGF ↓ VEGF-R2 ↓ DAG ↓

Clermont A, *et al*. *J Hypertens* 2006; **24**: S73–S80.

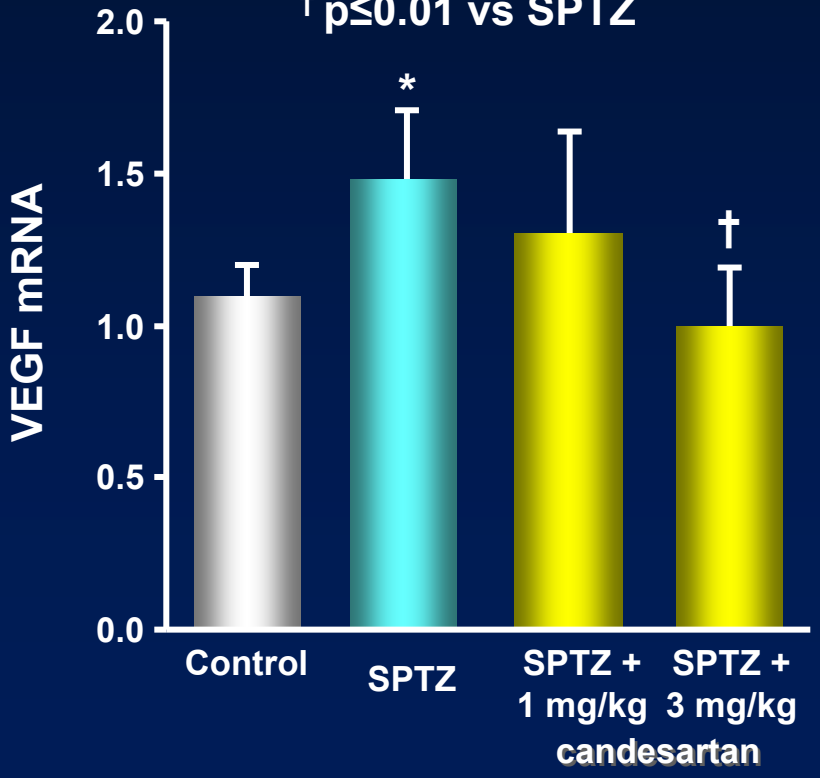
Impact of RAS blockade

Effect of candersartan on VEGF expression

Diabetic stroke-prone spontaneously hypertensive rats (SHRSP) with streptozocin-induced diabetes[1]

* p≤0.01 vs control

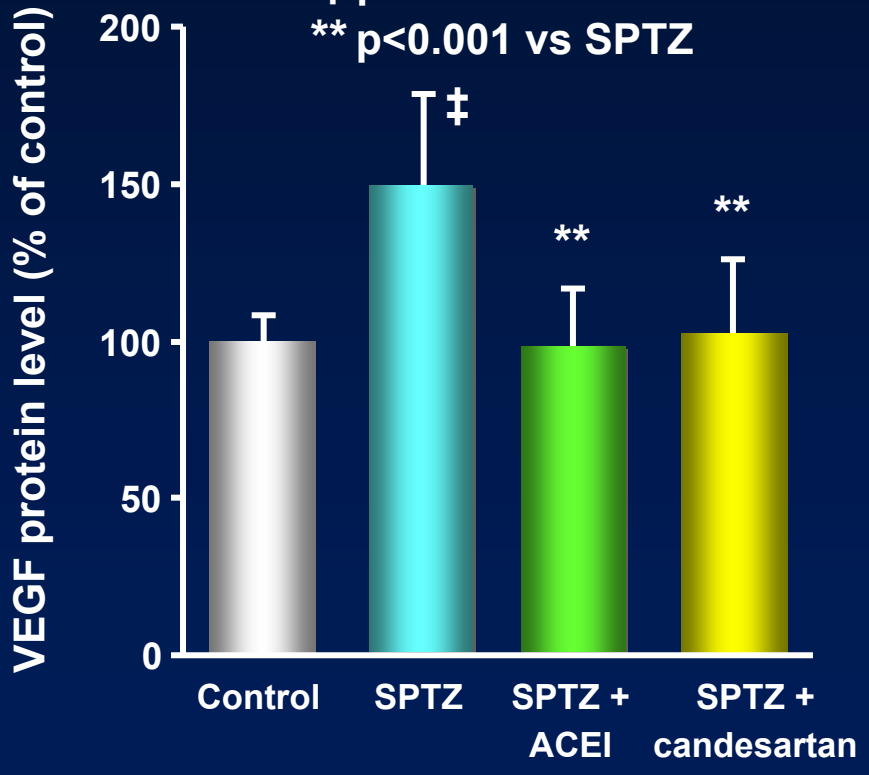
† p≤0.01 vs SPTZ



Streptozocin-treated (SPTZ) mice[2]

‡ p<0.05 vs control

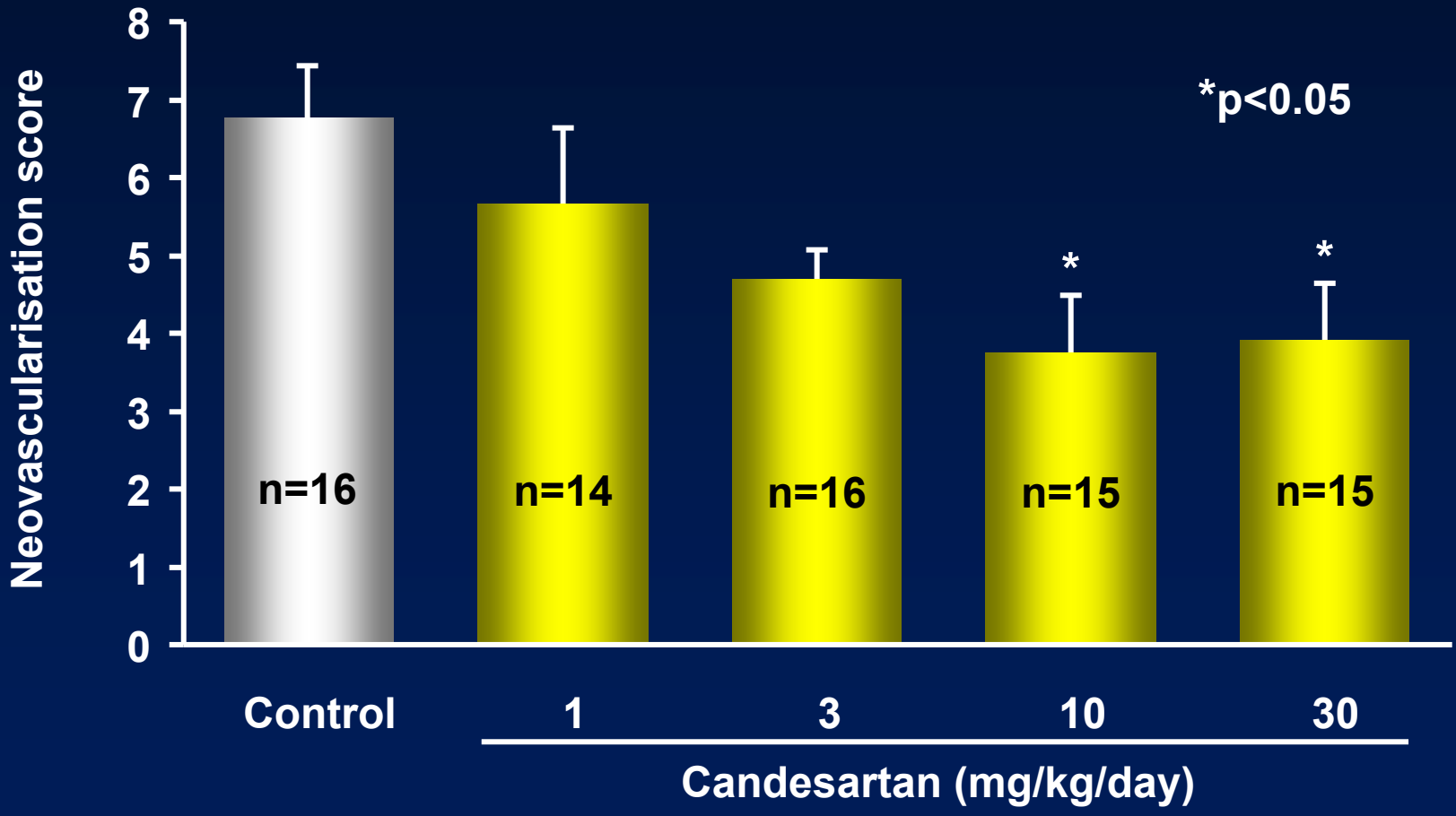
** p<0.001 vs SPTZ



1. Nagisa Y, *et al. Diabetologia* 2001; **43**: 883–888.
2. Ebrahimian TG, *et al. Arterioscler Thromb Vasc Biol* 2005; **25**: 65–70.

Impact of RAS blockade

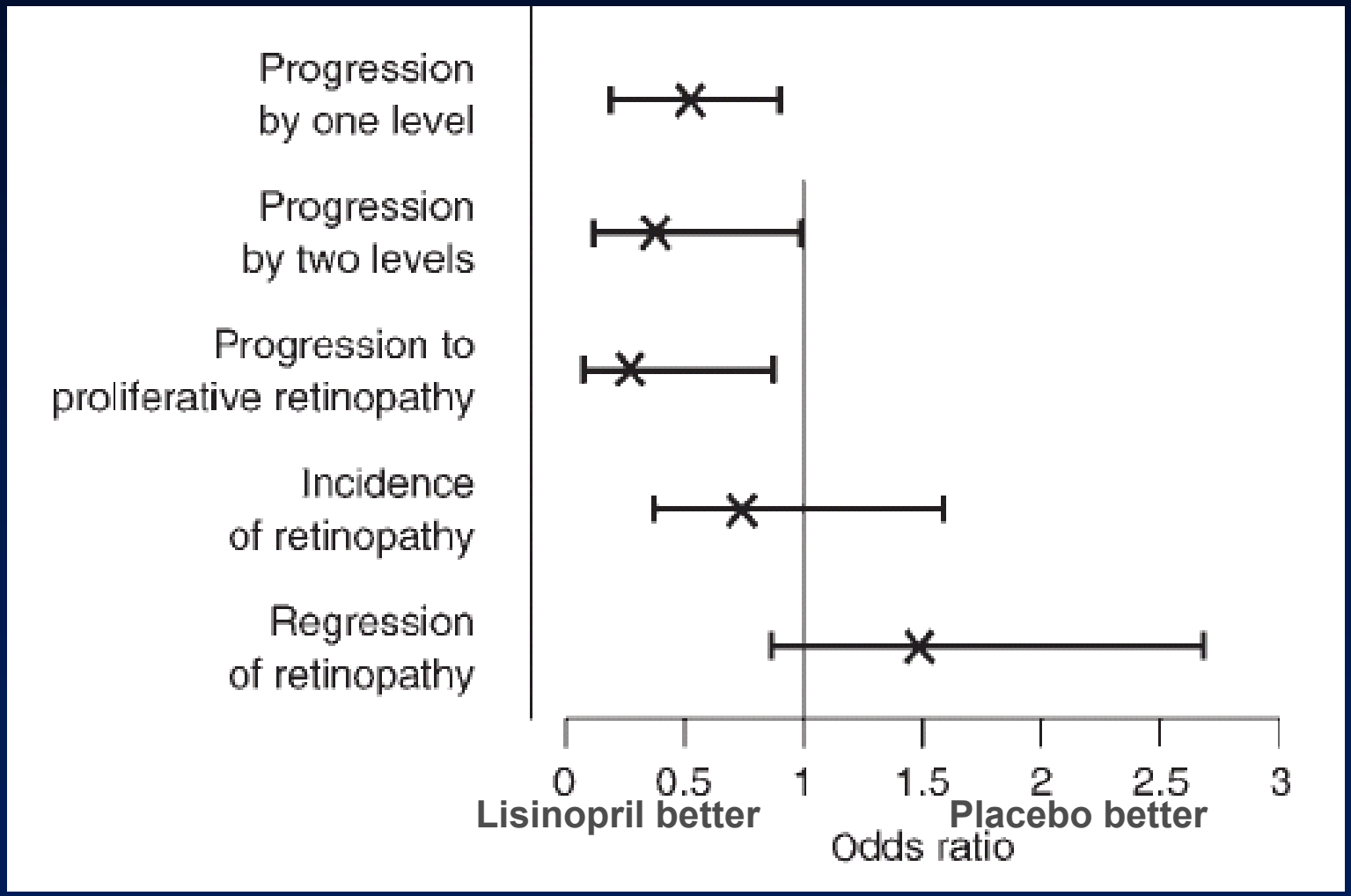
Effect of candesartan on hypoxia-induced neovascularisation in mice



Nakamura H, *et al. Eur J Pharmacol* 2005; **512**: 239–246.

EUCLID

Incidence, progression and regression of diabetic retinopathy in patients with type 1 diabetes



Chaturvedi et al. *Lancet* 351:28–31, 1998

Treatment by lisinopril:

(EUCLID, Lancet 351, 28-31, 1998)

- Reduces by 50% the risk of 1-step progression of DR on the EURODIAB scale (O.R. = 0.50; 95% CI = 0.28-0.89; p<0.02)
- Reduces by 80% the risk of progression to proliferative RD (O.R. = 0.20; 95% CI = 0.04-0.91; p<0.04)

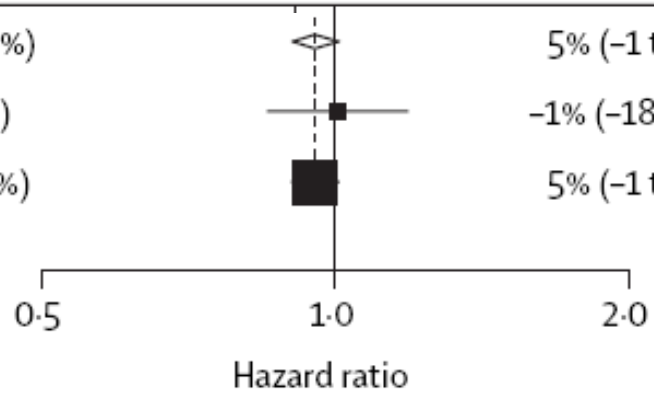
(for a decrease of 3 mmHg in systolic BP)

Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial

*ADVANCE Collaborative Group**

www.thelancet.com Published online September 2, 2007 DOI:10.1016/S0140-6736(07)61303-8

	Number (%) of patients with event		Favours perindopril–indapamide	Favours placebo	Relative risk reduction (95% CI)
	Perindopril–indapamide (n=5569)	Placebo (n=5571)			
Total eye events	2531 (45·4%)	2611 (46·9%)			5% (–1 to 10)
New or worsening retinopathy	289 (5·2%)	286 (5·1%)			–1% (–18 to 15)
Visual deterioration	2446 (43·9%)	2514 (45·1%)			5% (–1 to 10)



DIRECT

DI*abetic* ***RE****tinopathy* ***C****andesartan* ***T****rials*

DIRECT - Programme of investigator initiated and led studies

Three randomised placebo-controlled studies on the effects of the ARB candesartan on incidence and progression of diabetic retinopathy

- **DIRECT-Prevent 1**
  Type 1 diabetes without diabetic retinopathy
- **DIRECT-Protect 1**
  Type 1 diabetes with mild-to-moderate diabetic retinopathy
- **DIRECT-Protect 2**
  Type 2 diabetes with mild-to-moderate diabetic retinopathy

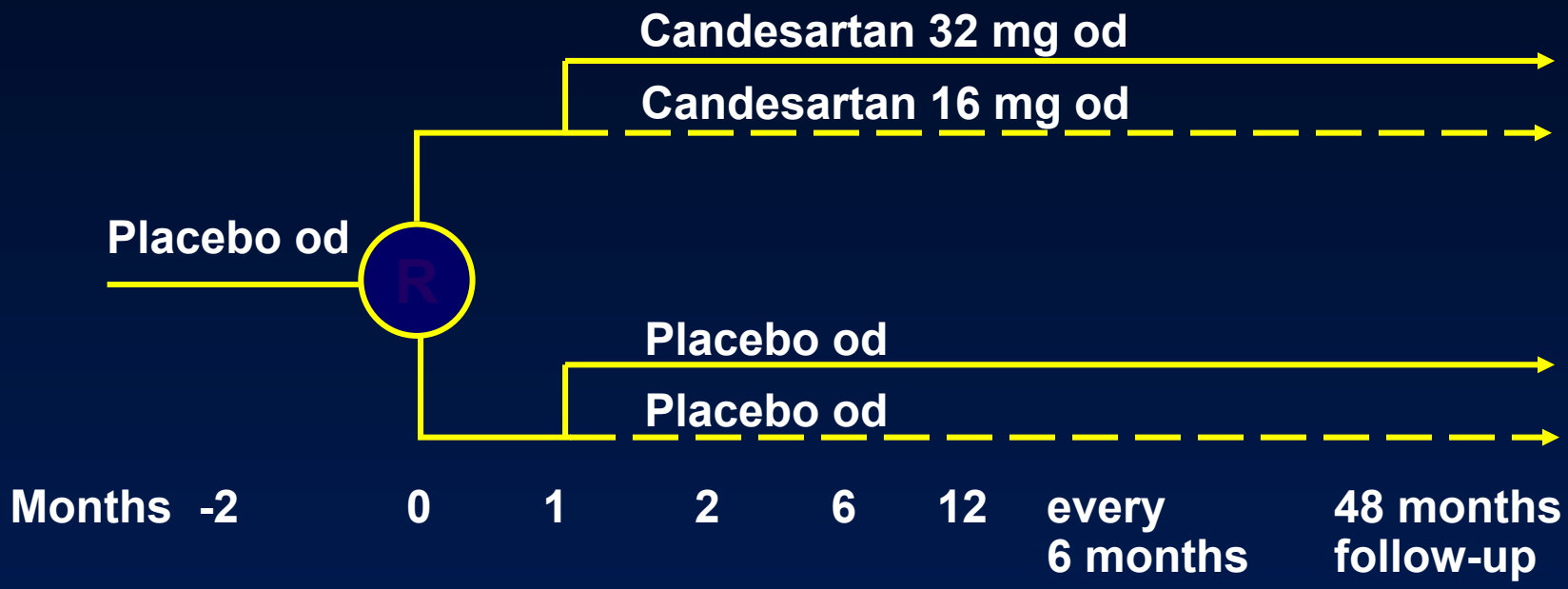
DIRECT Programme: Inclusion criteria

	DIRECT-Prevent 1	DIRECT-Protect 1	DIRECT-Protect 2
Number of patients	1421	1905	1905
Age (years)	18-50	18-55	37-75
Diabetes duration (years)	1-15	1-20	1-20
Microalbuminuria	No	No	No
Blood pressure (mmHg)	SBP ≤130 DBP ≤85	SBP ≤130 DBP ≤85	No HTN treatment SBP ≤130 DBP ≤85 HTN treatment SBP ≤160 DBP ≤90
Retinal grading level (ETDRS scale)	10/10	≥20/10 up to ≤47/47	≥20/10 up to ≤47/47

DIRECT Programme

309 centres in 30 countries

DIRECT Programme: Individual study designs



Investigations:

Retinal photographs	annually
Urinary albumin excretion rate	annually
Blood pressure	six monthly
Adverse events	six monthly

Effect of candesartan on prevention (DIRECT-Prevent 1) and progression (DIRECT-Protect 1) of retinopathy in type 1 diabetes: randomised, placebo-controlled trials

*Nish Chaturvedi, Massimo Porta, Ronald Klein, Trevor Orchard, John Fuller, Hans Henrik Parving, Rudy Bilous, Anne Katrin Sjølie, for the DIRECT Programme Study Group**

Summary

Background Results of previous studies suggest that renin-angiotensin system blockers might reduce the burden of diabetic retinopathy. We therefore designed the DIabetic REtinopathy Candesartan Trials (DIRECT) Programme to assess whether candesartan could reduce the incidence and progression of retinopathy in type 1 diabetes.

Published Online September 26, 2008
DOI:10.1016/S0140-6736(08)61412-9

Effect of candesartan on progression and regression of retinopathy in type 2 diabetes (DIRECT-Protect 2): a randomised placebo-controlled trial

*Anne Katrin Sjølie, Ronald Klein, Massimo Porta, Trevor Orchard, John Fuller, Hans Henrik Parving, Rudy Bilous, Nish Chaturvedi, for the DIRECT Programme Study Group**

Summary

Background Diabetic retinopathy remains a leading cause of visual loss in people of working age. We examined whether candesartan treatment could slow the progression and, secondly, induce regression of retinopathy in people with type 2 diabetes.

Published Online September 26, 2008
DOI:10.1016/S0140-6736(08)61411-7

DIRECT Programme: Outcome measures

- The primary endpoint is
  - 2-step change in ETDRS level for incidence
  - 3-step change in ETDRS level for progression
- Secondary endpoints include
  - regression of retinopathy (3-step or 2-step sustained)
- Change in overall retinopathy severity

ETDRS retinopathy scale (based on 7-field stereo photographs)

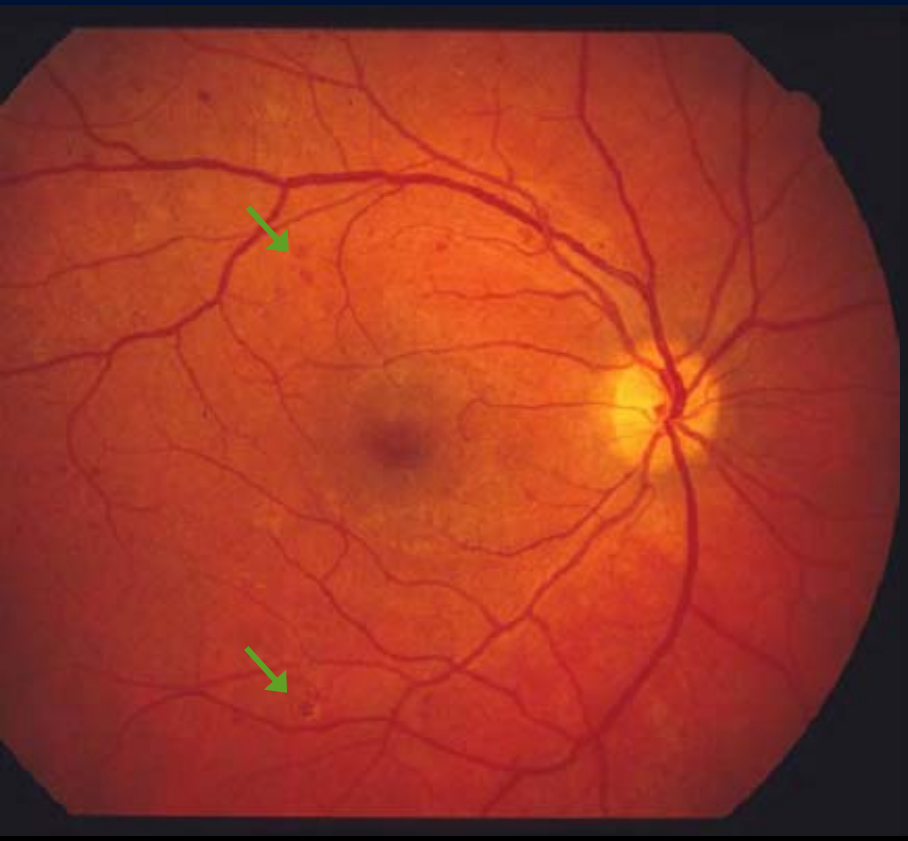
Levels and severity on the Early Treatment of Diabetic Retinopathy Study scale used for the DIRECT Programme

Level	Severity
10	DR absent
20	MA only
35	Mild NPDR
43	Moderate NPDR
47	Moderately severe NPDR
53	Severe NPDR
61, 65, 71, 75, 81	Proliferative DR

DR Diabetic retinopathy
MA Microaneurysms
NPDR Non-proliferative diabetic retinopathy

Diabetic retinopathy
Microaneurysms only

Level 20



Right eye

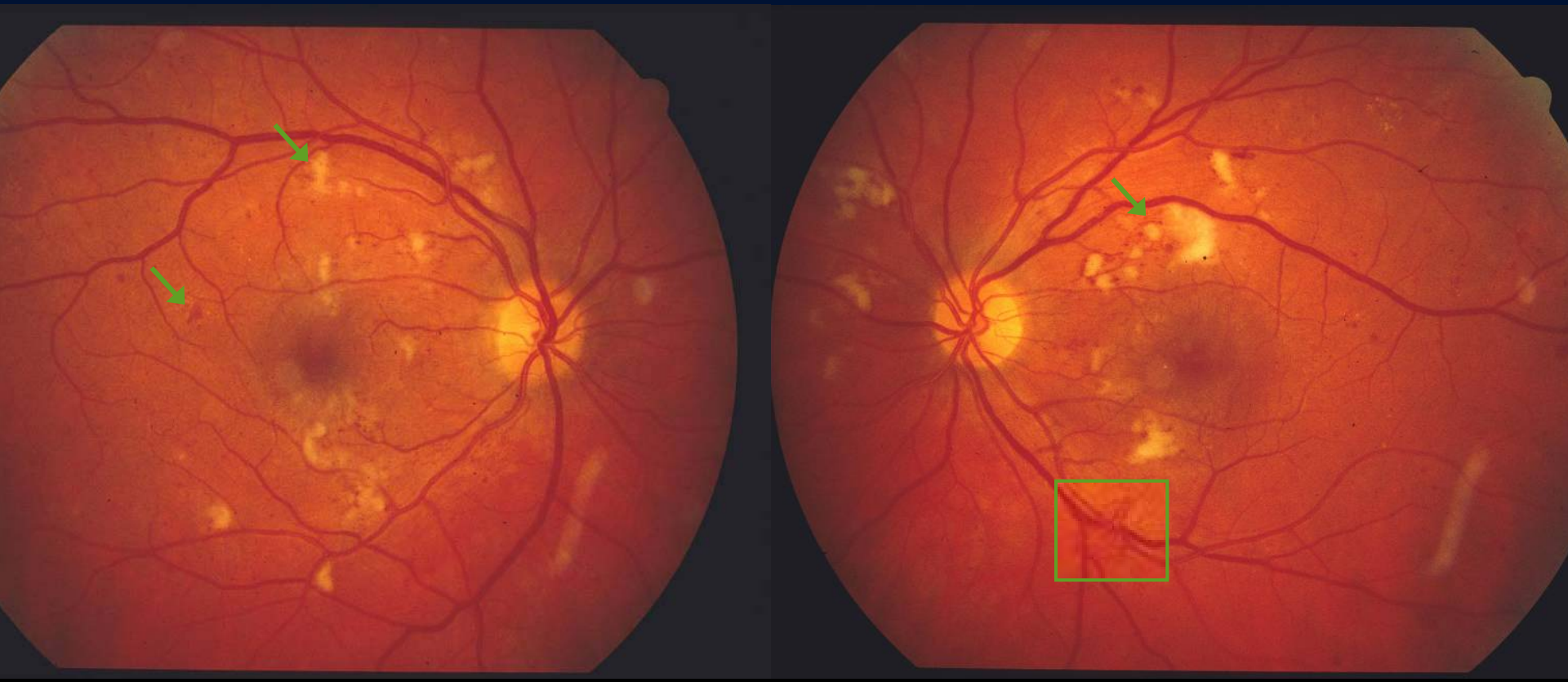
Level 20

Left eye

Diabetic retinopathy
3-step change

Level 35

Level 43



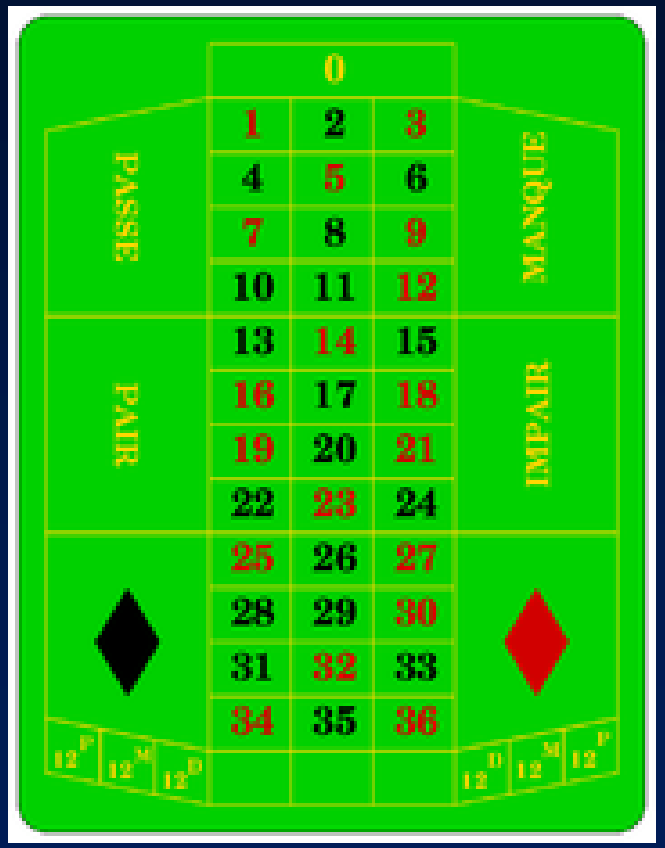
Right eye

Left eye

DIRECT-Prevent 1

Effect of candesartan on incidence of retinopathy in type 1 diabetic patients

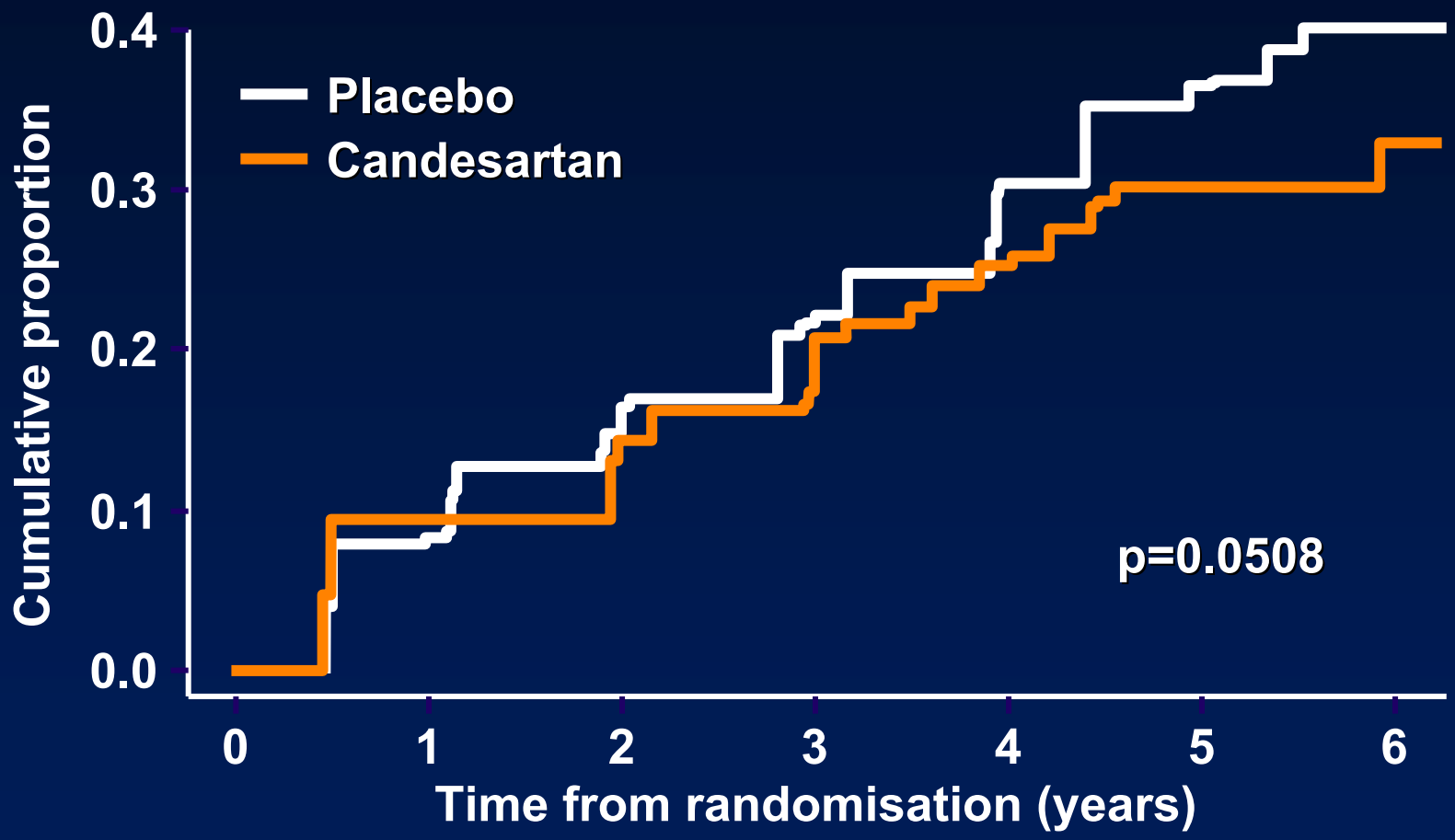
È vitale puntare sul numero giusto …
… 2-step o 3-step progression?



DIRECT Programme: Outcome measures

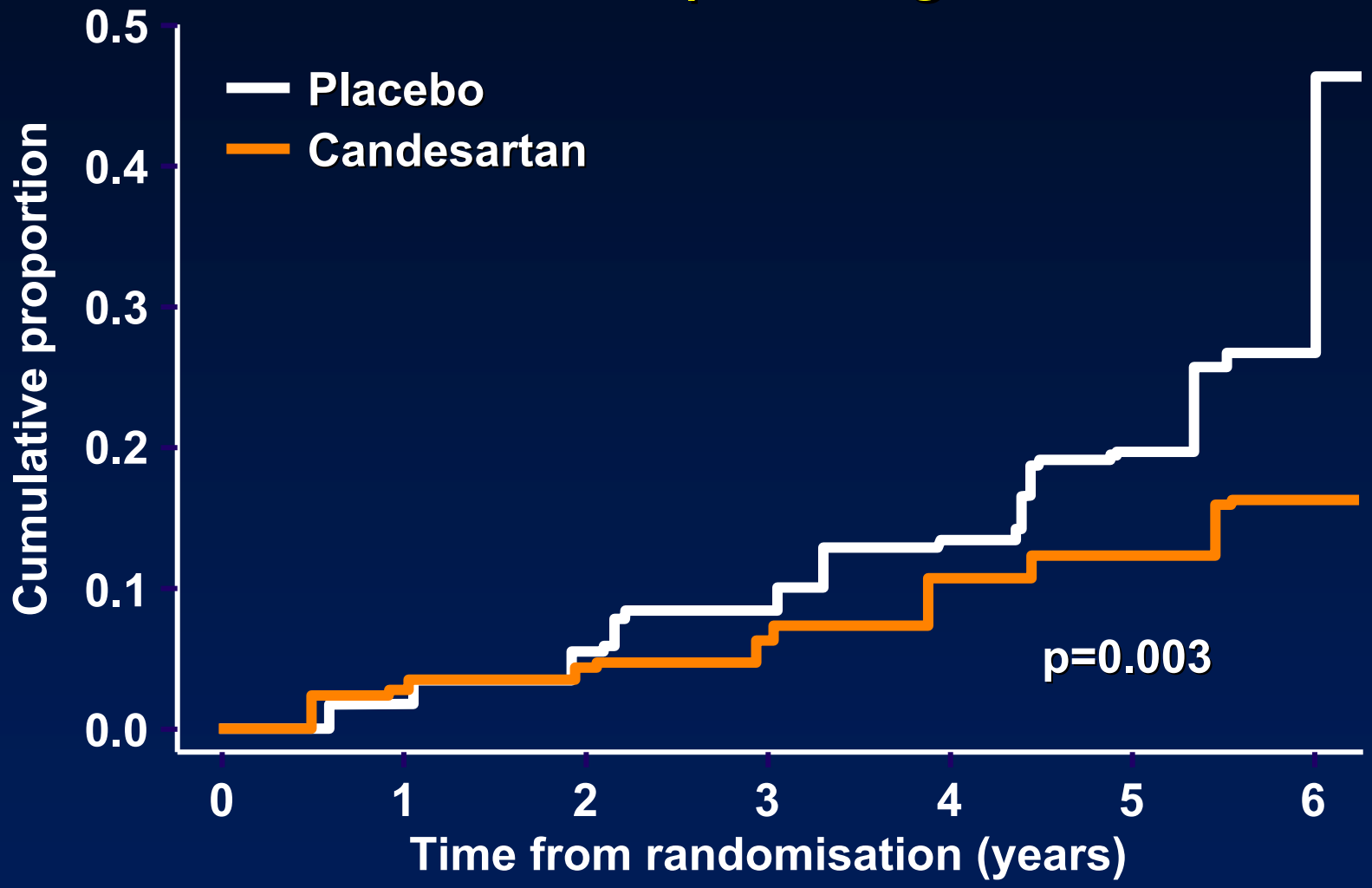
- The primary endpoint is
  - **2-step change** in ETDRS level for incidence
  - 3-step change in ETDRS level for progression
- Secondary endpoints include
  - regression of retinopathy (3-step or 2-step sustained)
- Change in overall retinopathy severity

DIRECT-Prevent 1: Retinopathy incidence 2-step change



No at risk							
Placebo	710	644	585	518	347	87	0
Candesartan	711	633	573	524	356	92	1

DIRECT-Prevent 1: Retinopathy incidence 3-step change



No at risk							
Placebo	710	663	630	587	419	109	1
Candesartan	711	651	615	587	422	108	1

DIRECT-Prevent 1: Hazard ratios for retinopathy incidence (candesartan vs placebo)

2-step change

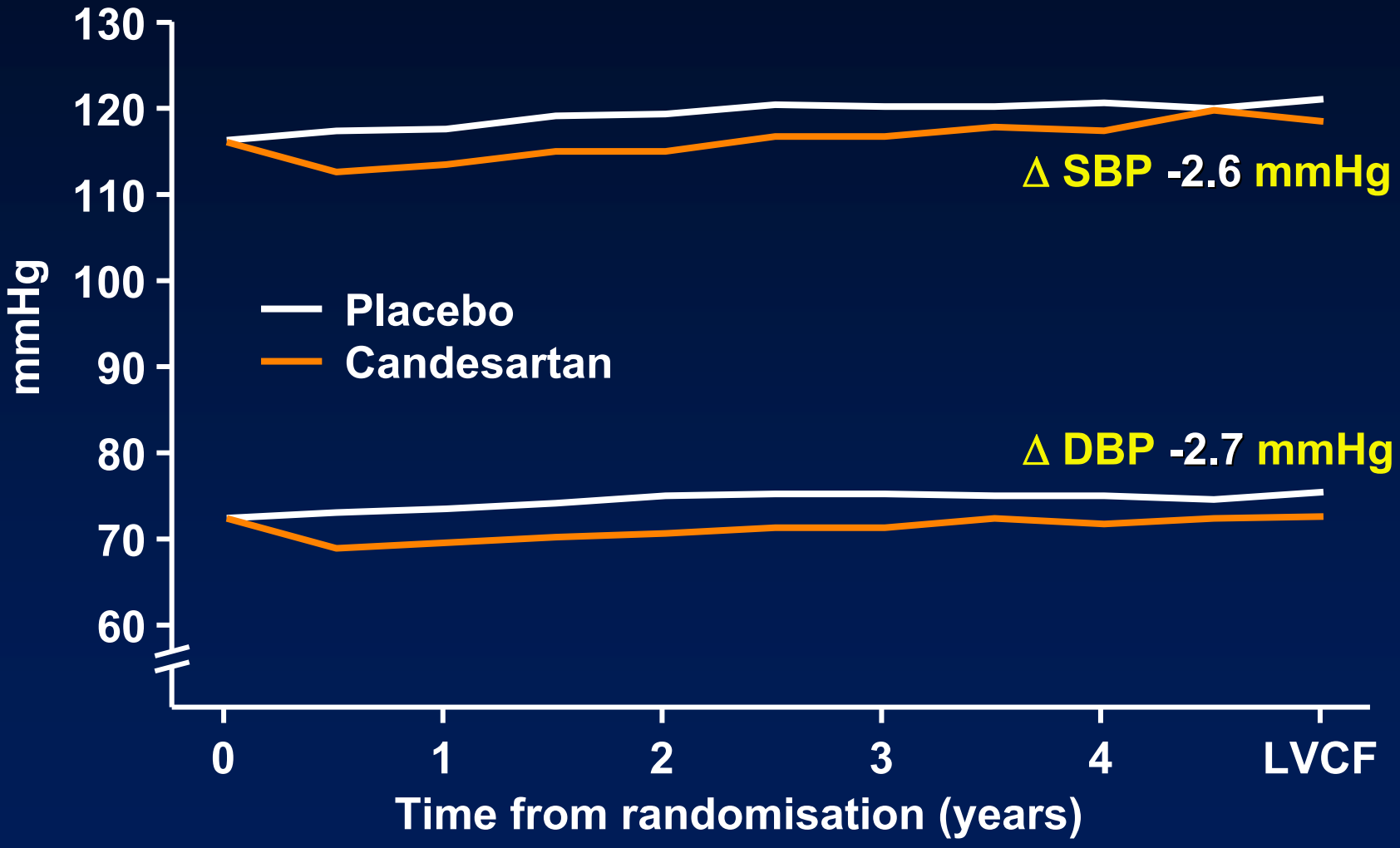
	HR	95% CI	
		Lower	Upper
Unadjusted	0.82	0.67	1.00
Adjusted*	0.88	0.72	1.07

3-step change

	HR	95% CI	
		Lower	Upper
Unadjusted	0.65	0.48	0.87
Adjusted*	0.71	0.53	0.95

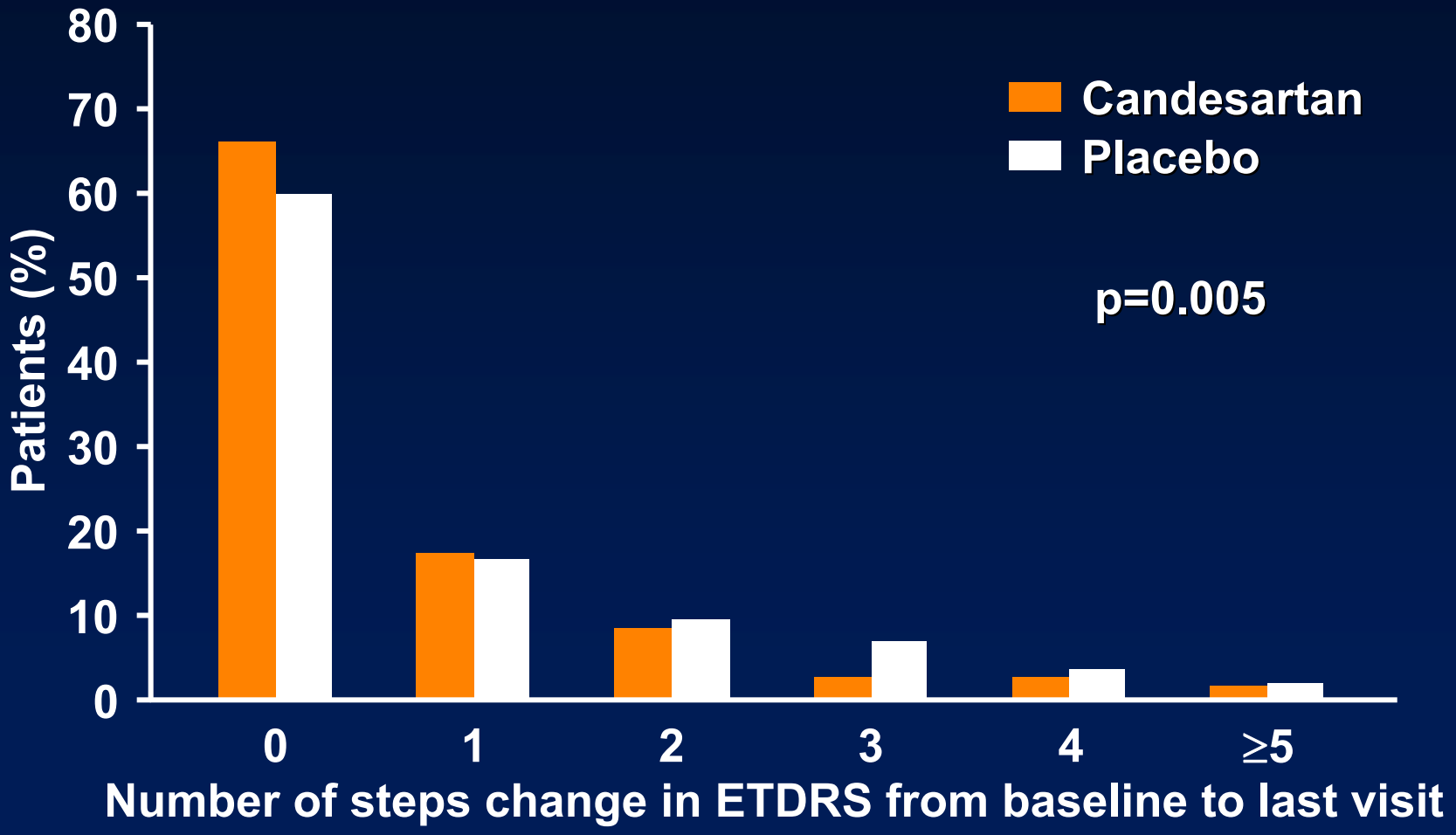
* Pre-specified adjustment for baseline diabetes duration, HbA_{1c} and SBP

DIRECT-Prevent 1: Systolic and diastolic blood pressure



LVCF = Last Value Carried Forward

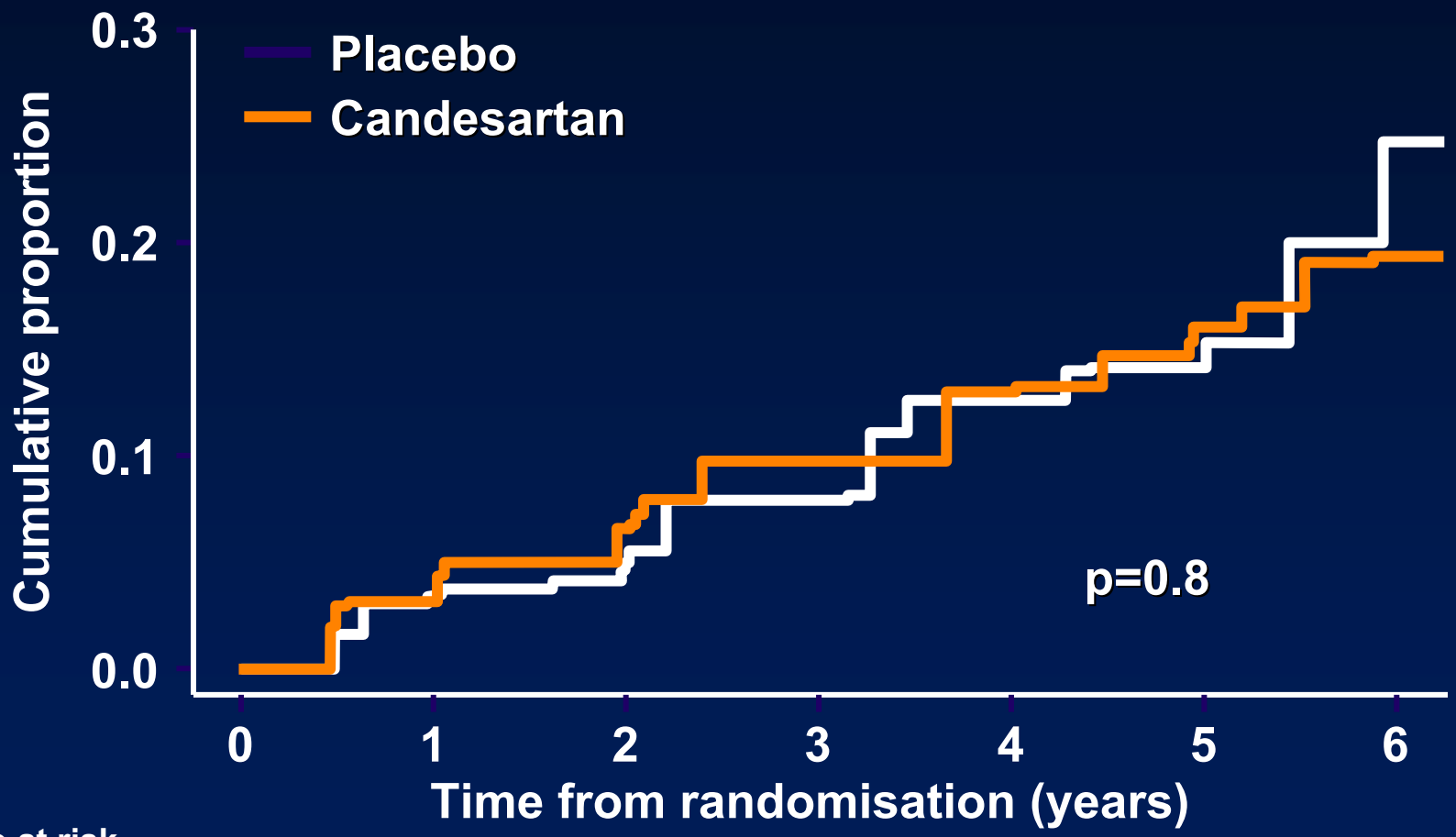
DIRECT-Prevent 1: Change in ETDRS level



DIRECT-Protect 1

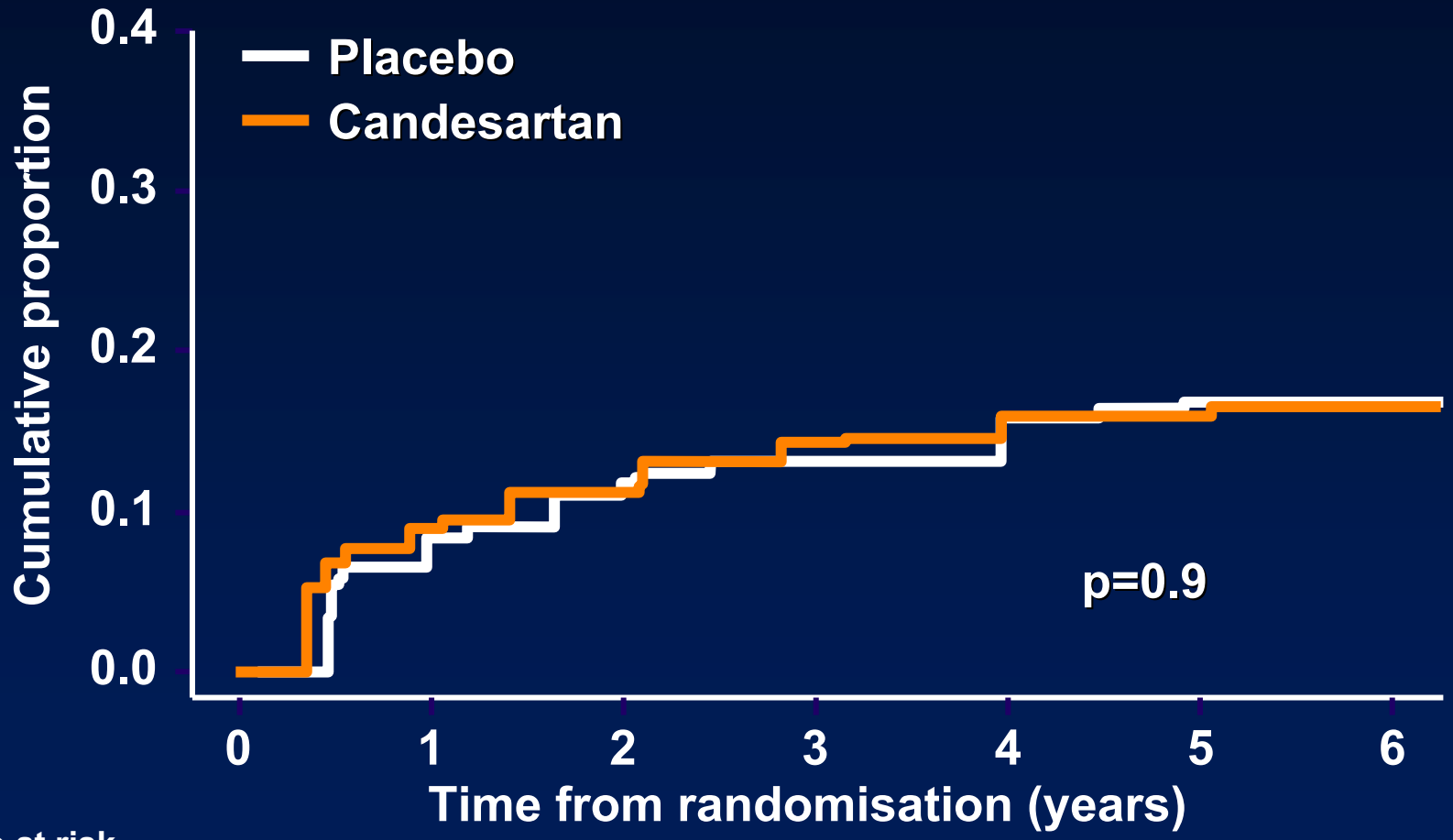
Effect of candesartan on progression of retinopathy in type 1 diabetic patients

DIRECT-Protect 1: Retinopathy progression 3-step change



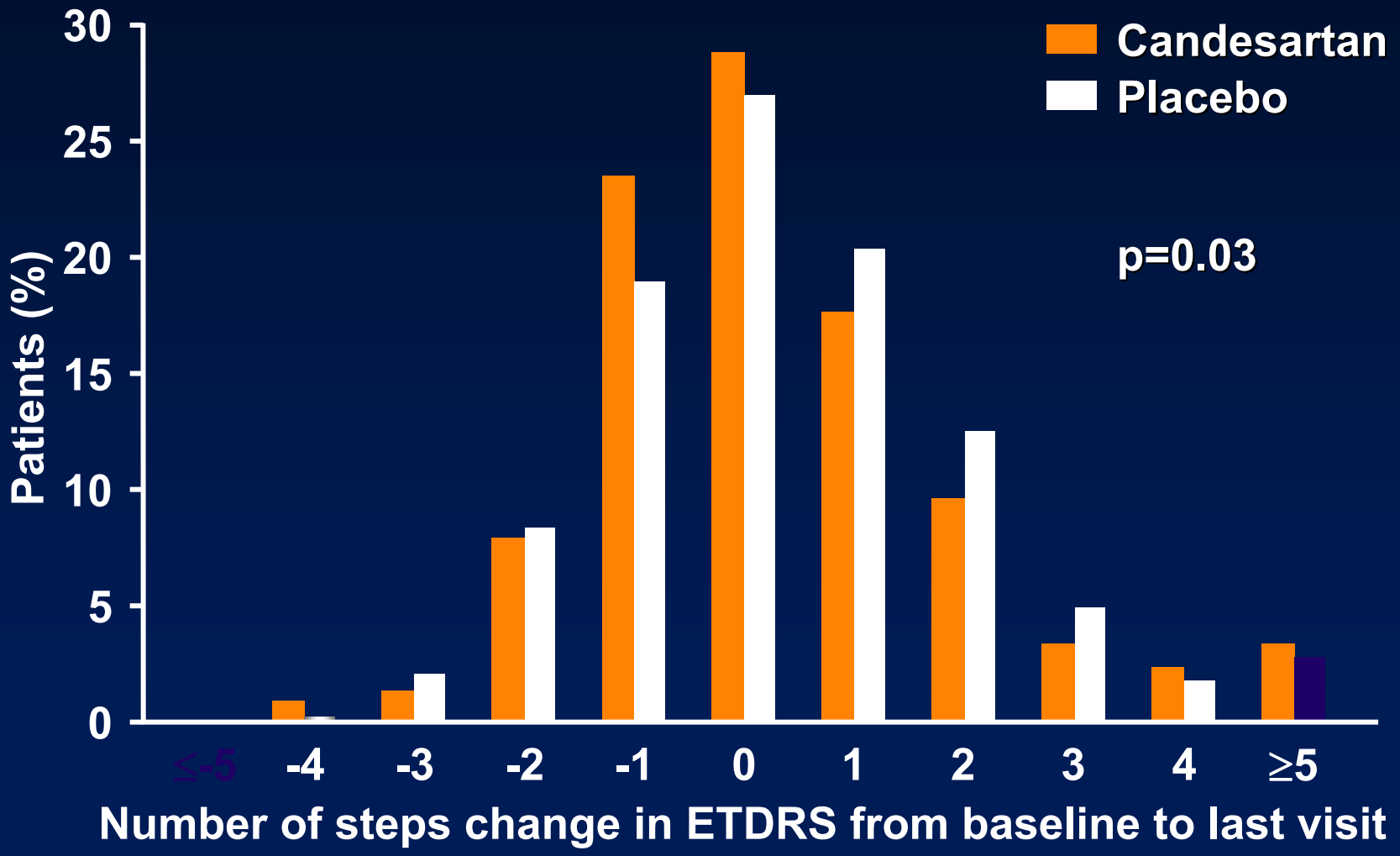
No at risk							
Placebo	954	875	820	770	612	188	4
Candesartan	951	863	814	767	626	195	5

DIRECT-Protect 1: Retinopathy regression



No at risk							
Placebo	954	840	772	713	559	167	5
Candesartan	951	820	773	728	591	187	5

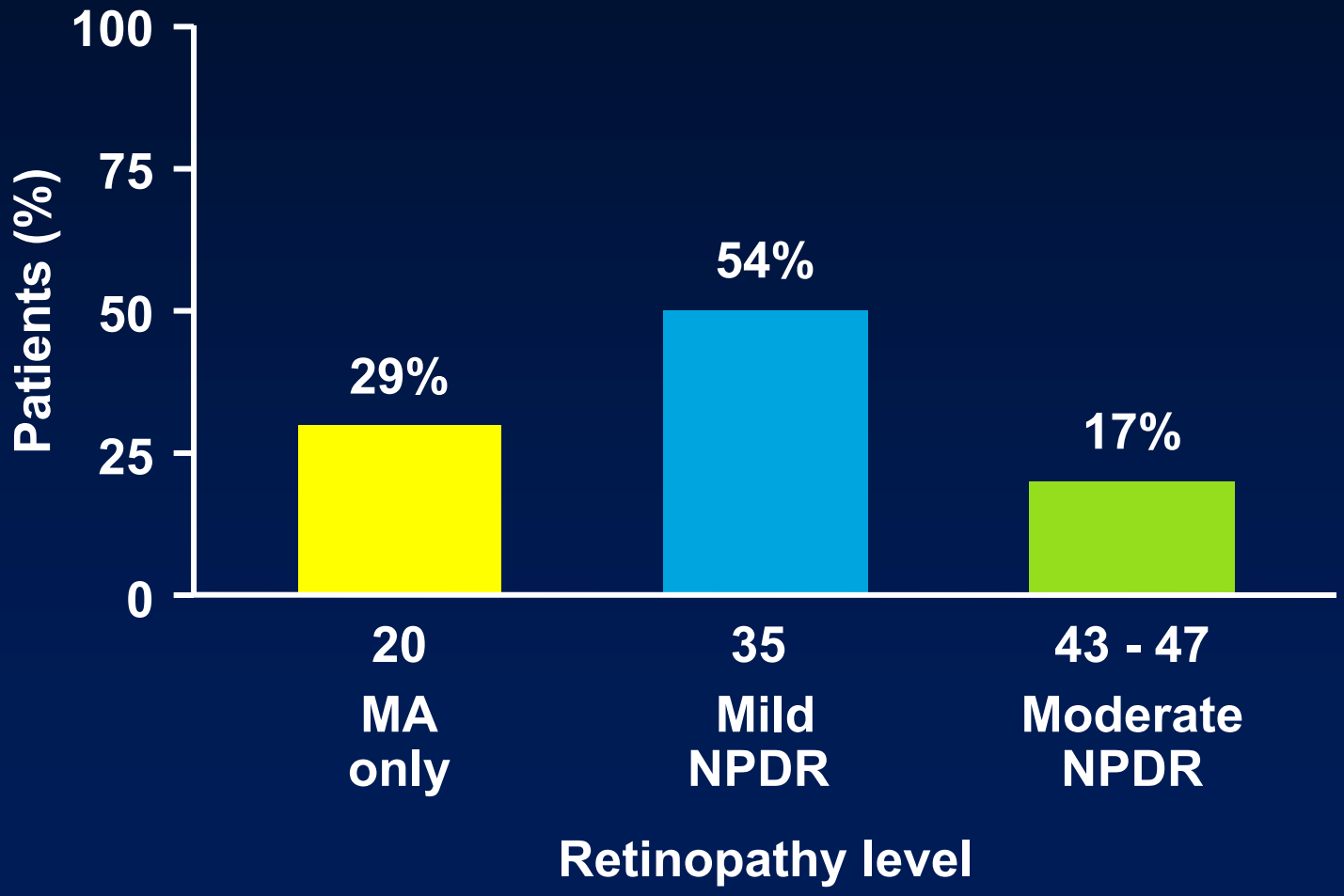
DIRECT-Protect 1: Change in ETDRS level



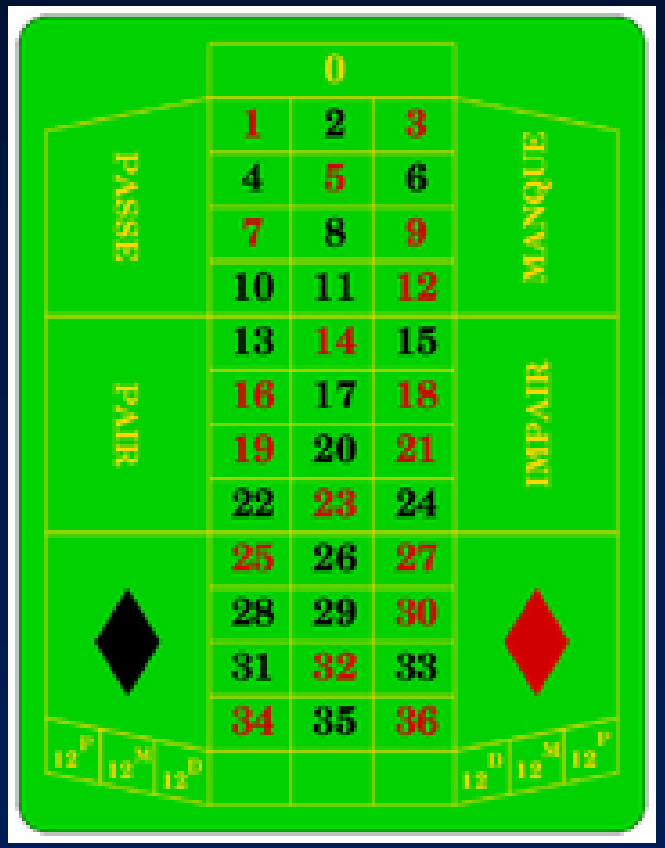
DIRECT-Protect 2

Effect of candesartan on progression of retinopathy in type 2 diabetic patients

DIRECT-Protect 2: Retinopathy levels at baseline (worst eye)



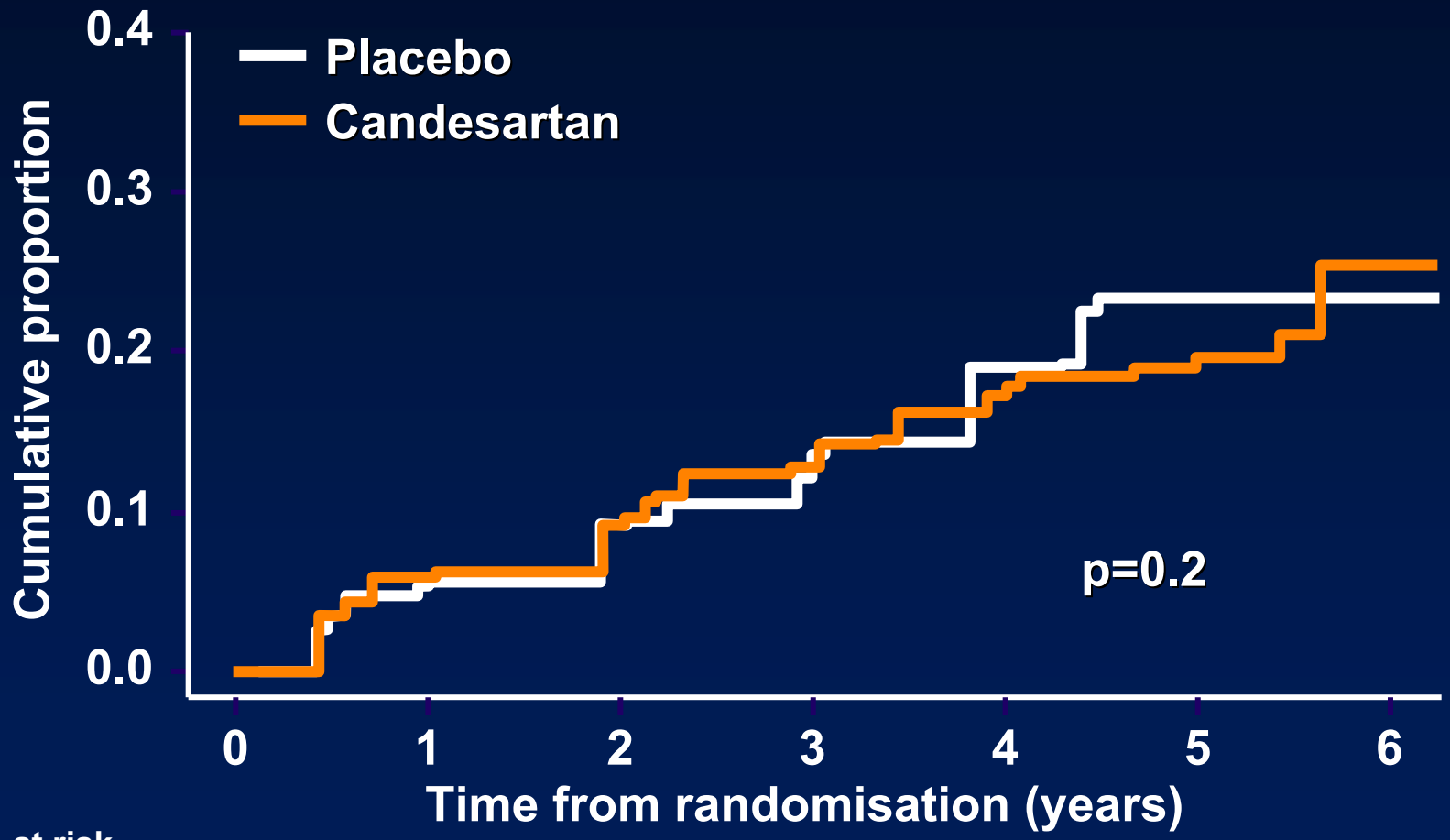
È vitale puntare sul numero giusto …
… DR progression o regression?



DIRECT Programme: Outcome measures

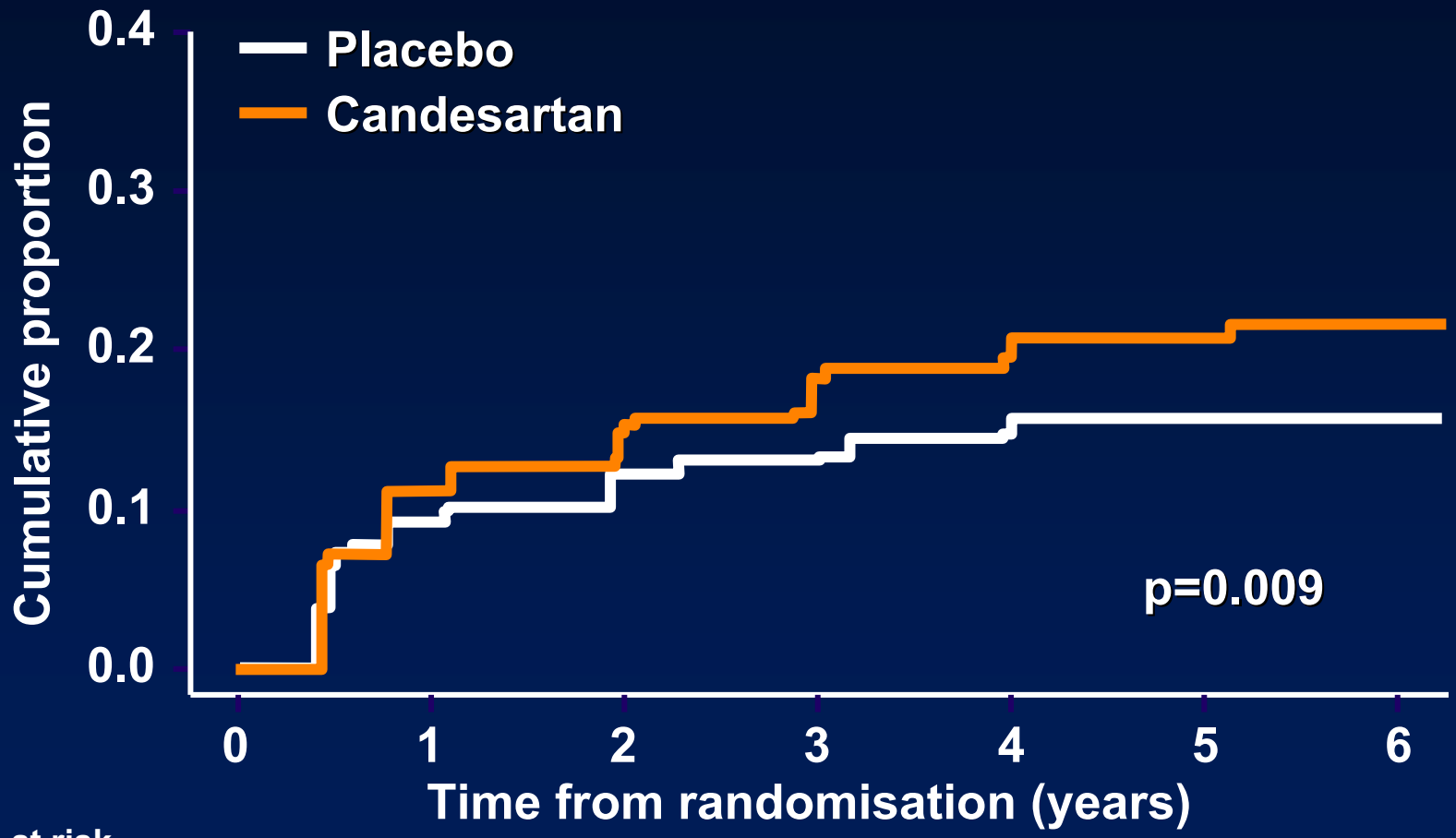
- The primary endpoint is
  - 2-step change in ETDRS level for incidence
  - 3-step change in ETDRS level for **progression**
- Secondary endpoints include
  - **regression** of retinopathy (3-step or 2-step sustained)
- Change in overall retinopathy severity

DIRECT-Protect 2: Retinopathy progression 3-step change



No at risk							
Placebo	954	845	794	737	513	112	3
Candesartan	951	848	807	737	540	123	0

DIRECT-Protect 2: Retinopathy regression



No at risk							
Placebo	954	812	760	713	510	93	1
Candesartan	951	811	755	692	492	100	0

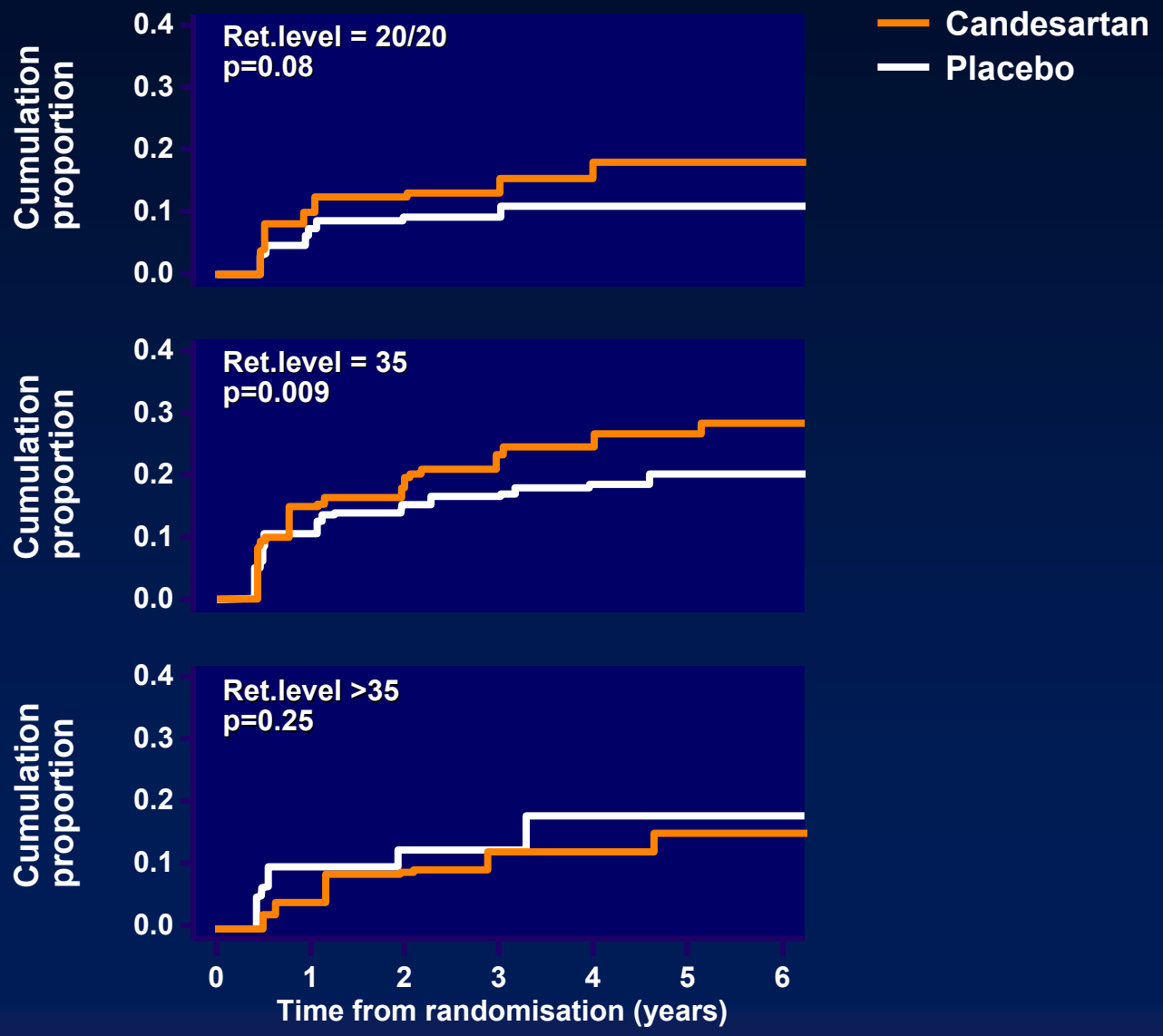
DIRECT-Protect 2: Hazard ratios for retinopathy regression (candesartan vs placebo)

	HR	95% CI	
		Lower	Upper
Unadjusted	1.34	1.08	1.68
Adjusted*	1.38	1.11	1.73
Adjusted**	1.33	1.06	1.67

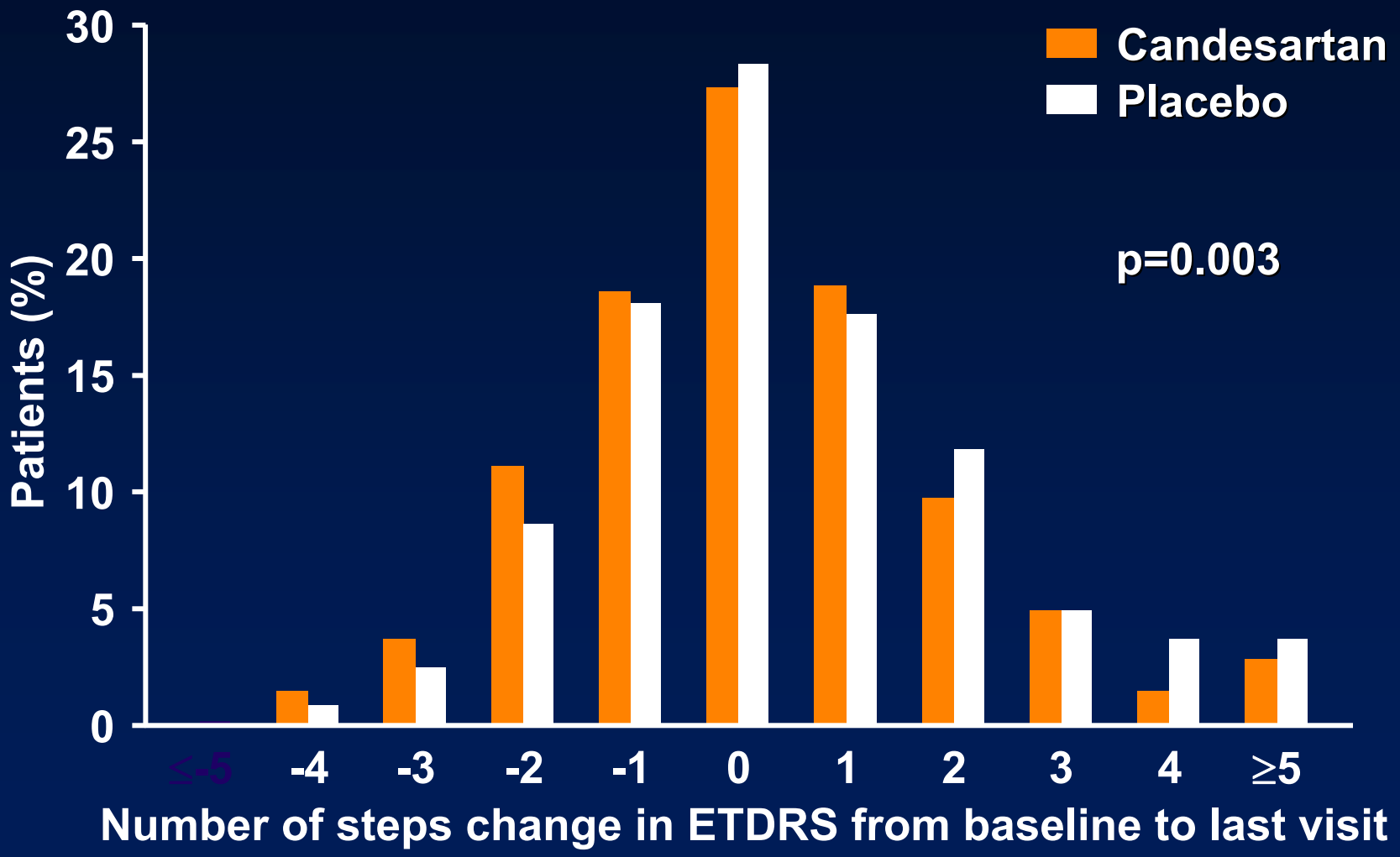
* Pre-specified adjustment for baseline level of retinopathy, diabetes duration, HbA_{1c}, UAER, SBP and antihypertensive treatment

** Pre-specified adjustment for baseline level of retinopathy, diabetes duration, HbA_{1c}, UAER, antihypertensive treatment and SBP during study

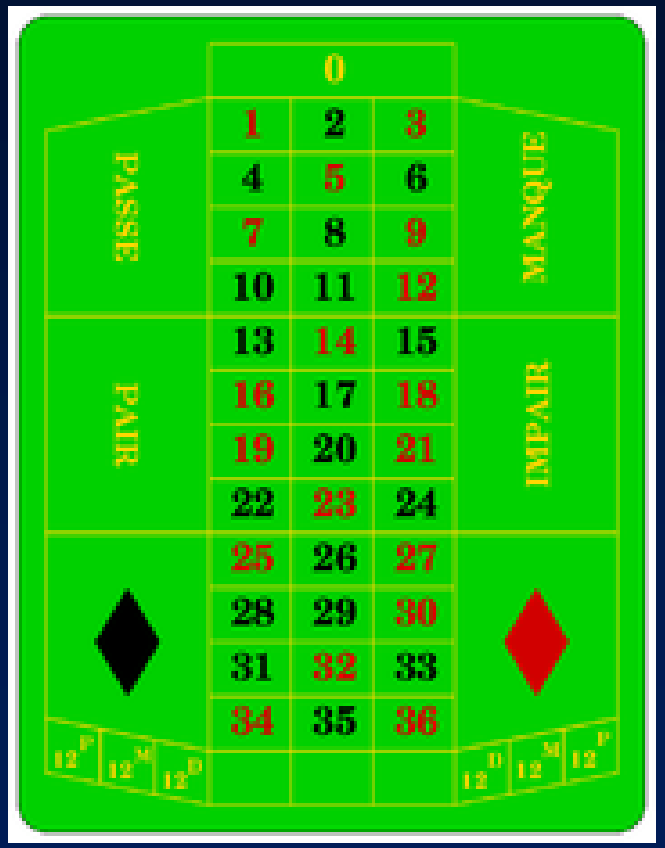
DIRECT-Protect 2: Regression of DR by baseline level



DIRECT-Protect 2: Change in ETDRS level



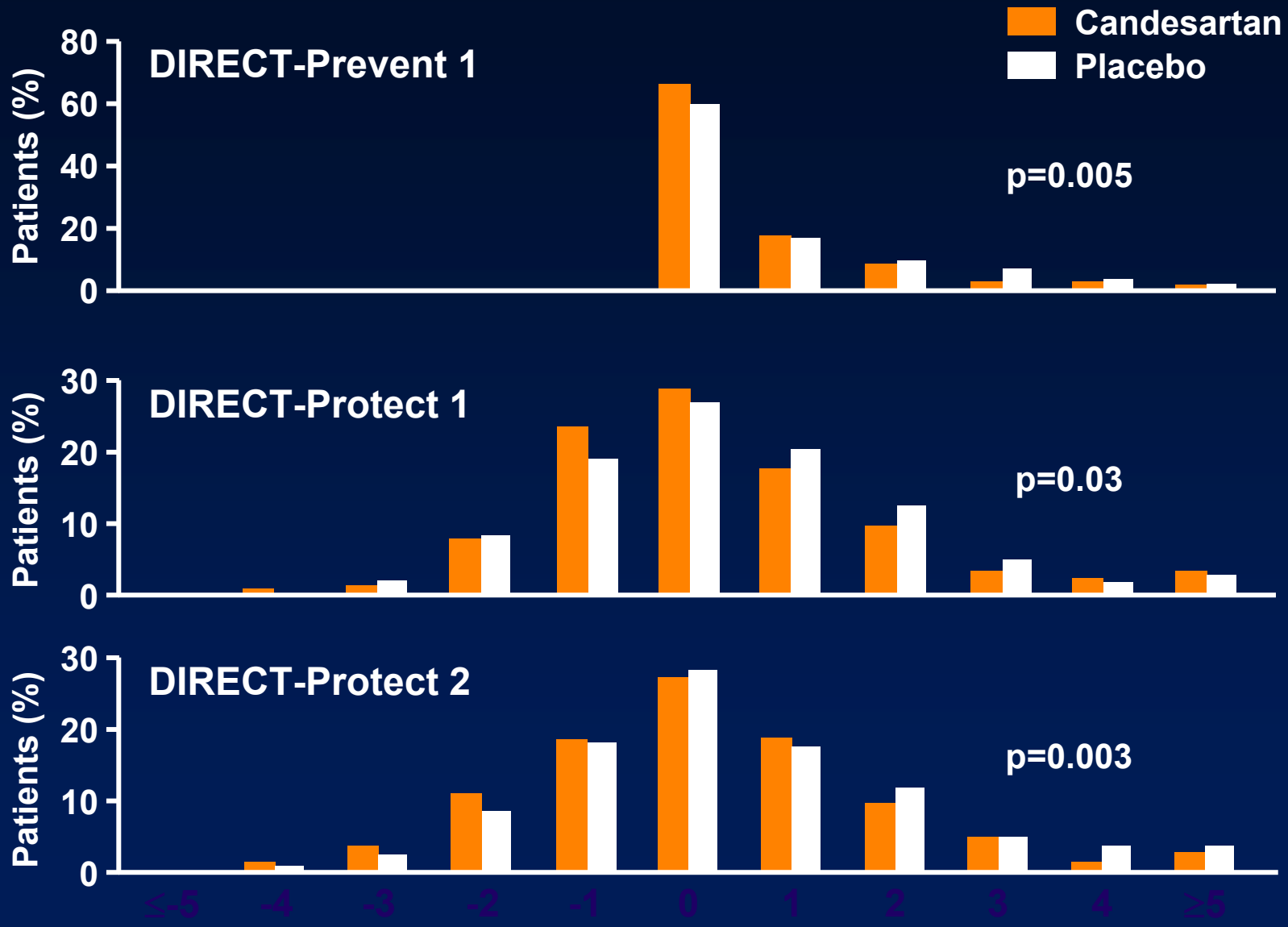
È vitale puntare sul numero giusto …
… change in overall DR severity?



DIRECT Programme: Outcome measures

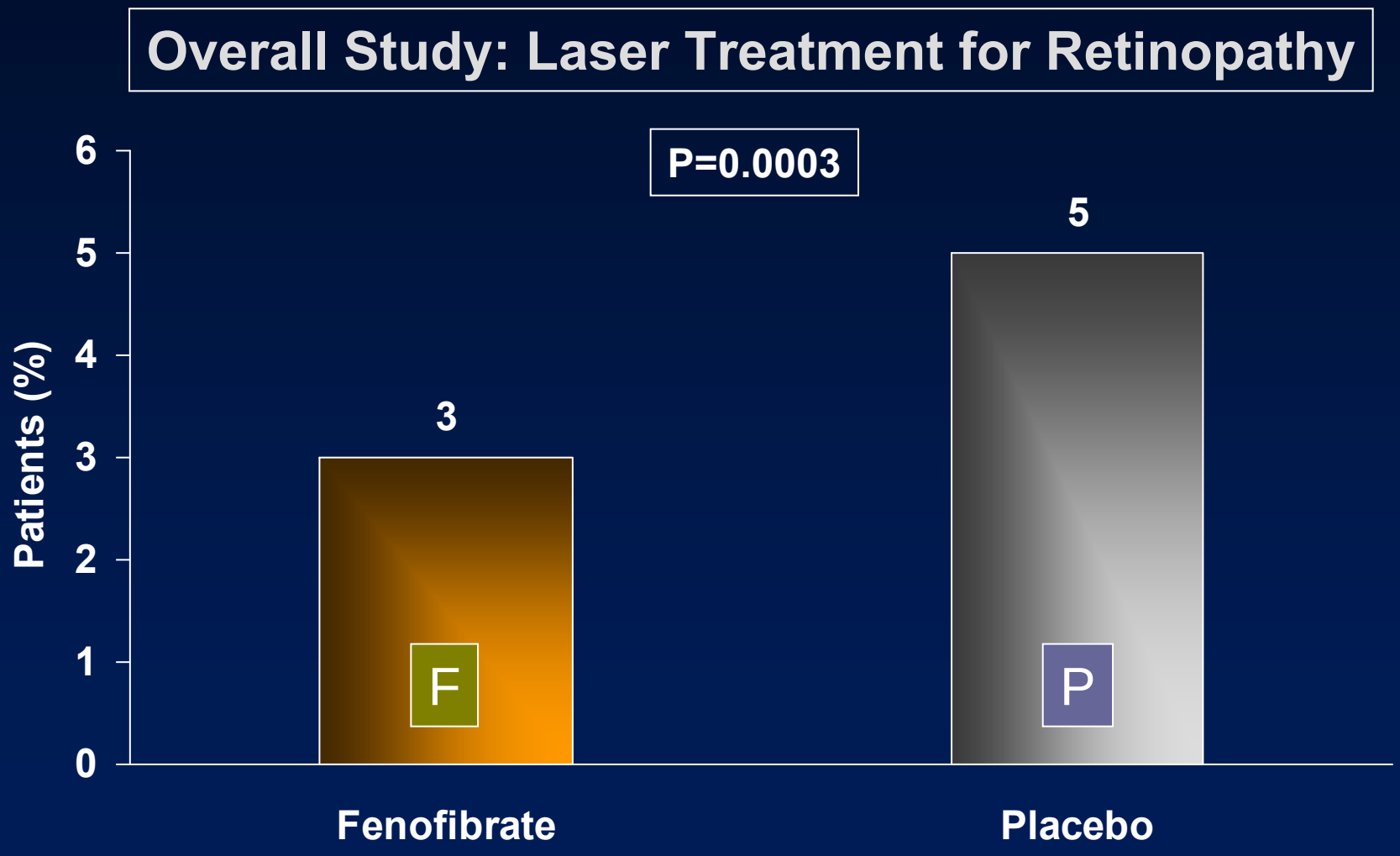
- The primary endpoint is
  - 2-step change in ETDRS level for incidence
  - 3-step change in ETDRS level for progression
- Secondary endpoints include
  - regression of retinopathy (3-step or 2-step sustained)
- **Change in overall retinopathy severity**

DIRECT: Change in ETDRS level



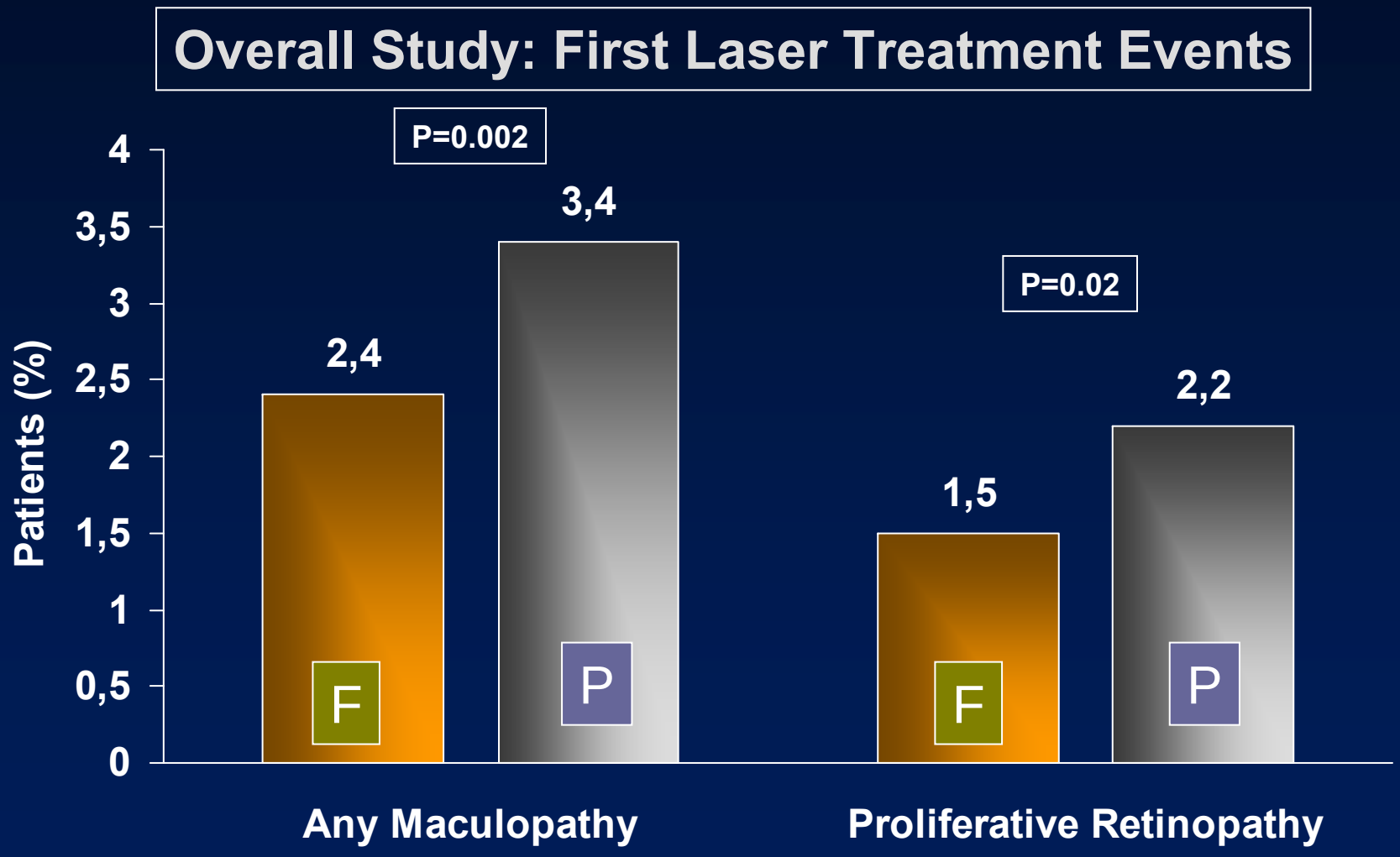
Storia n° 4 – Il fenofibrato

Retinopathy in the FIELD Trial



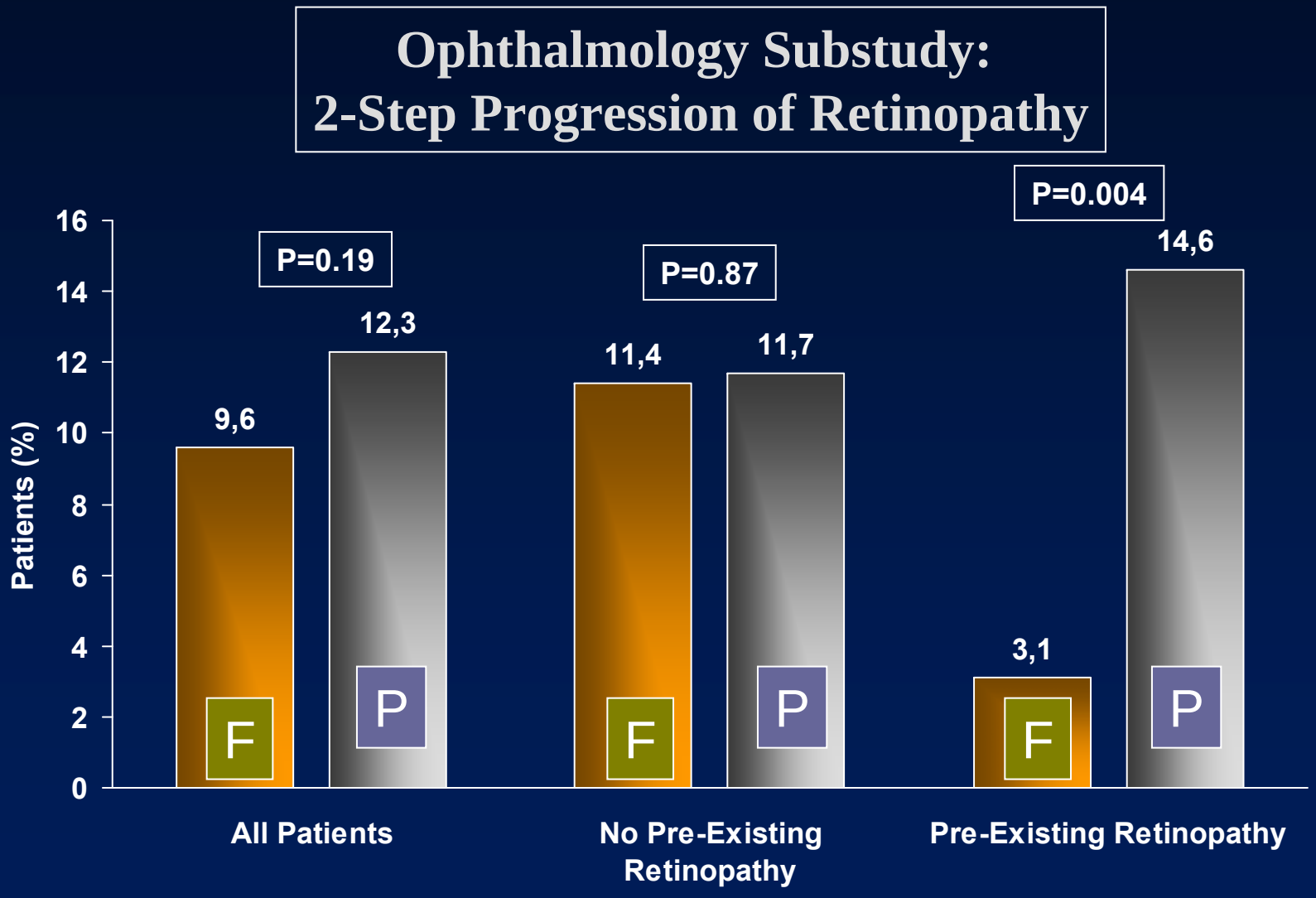
Keech et al. Lancet 2007; DOI:10.1016/S0140-6736(07)61607-9 Ref

Retinopathy in the FIELD Trial



Keech et al. Lancet 2007; DOI:10.1016/S0140-6736(07)61607-9

Retinopathy in the FIELD Trial



Keech et al. Lancet 2007; DOI:10.1016/S0140-6736(07)61607-9 Ref

Retinopathy in the FIELD Trial

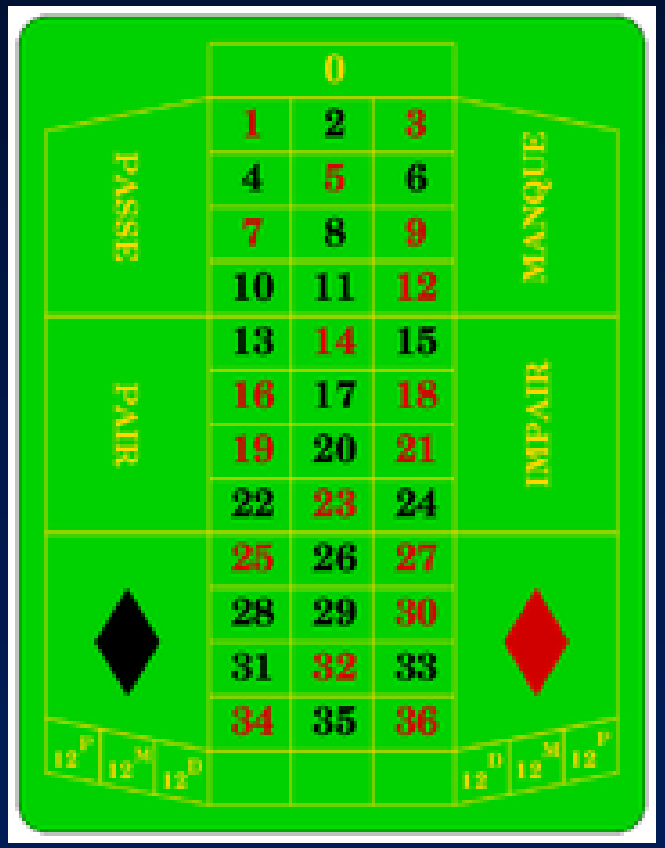
In diabetic patients, 5 years of treatment with fenofibrate:

- Reduced the need for laser treatment for diabetic retinopathy
- Reduced 2-step progression of retinopathy grade in patients with but not without pre-existing retinopathy
- Did not reduce fasting glucose, A1c or blood pressure2

Keech et al. Lancet 2007; DOI:10.1016/S0140-6736(07)61607-9

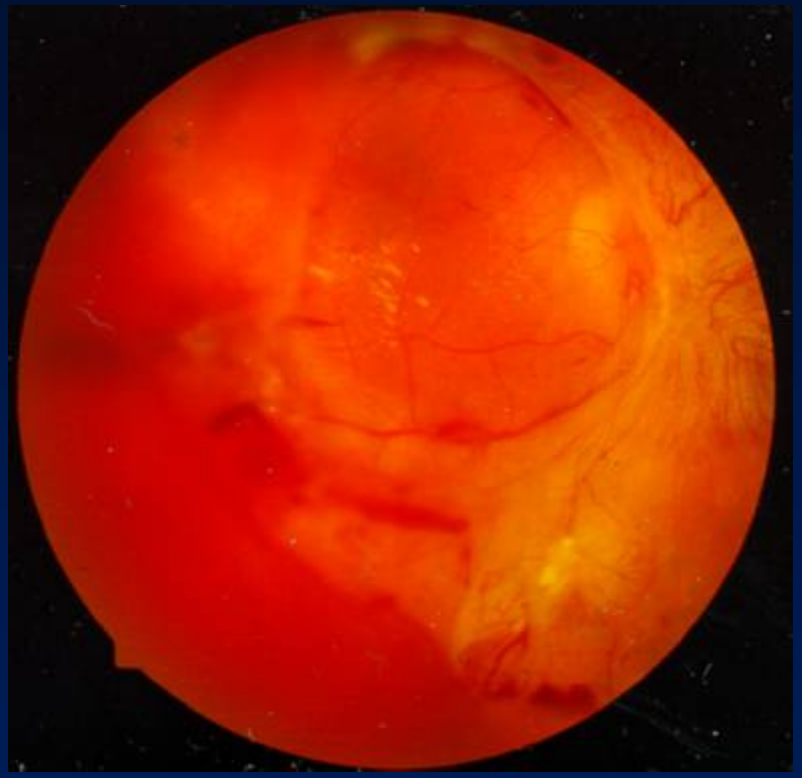
Ref

È vitale puntare sul numero giusto!



Epilogo …

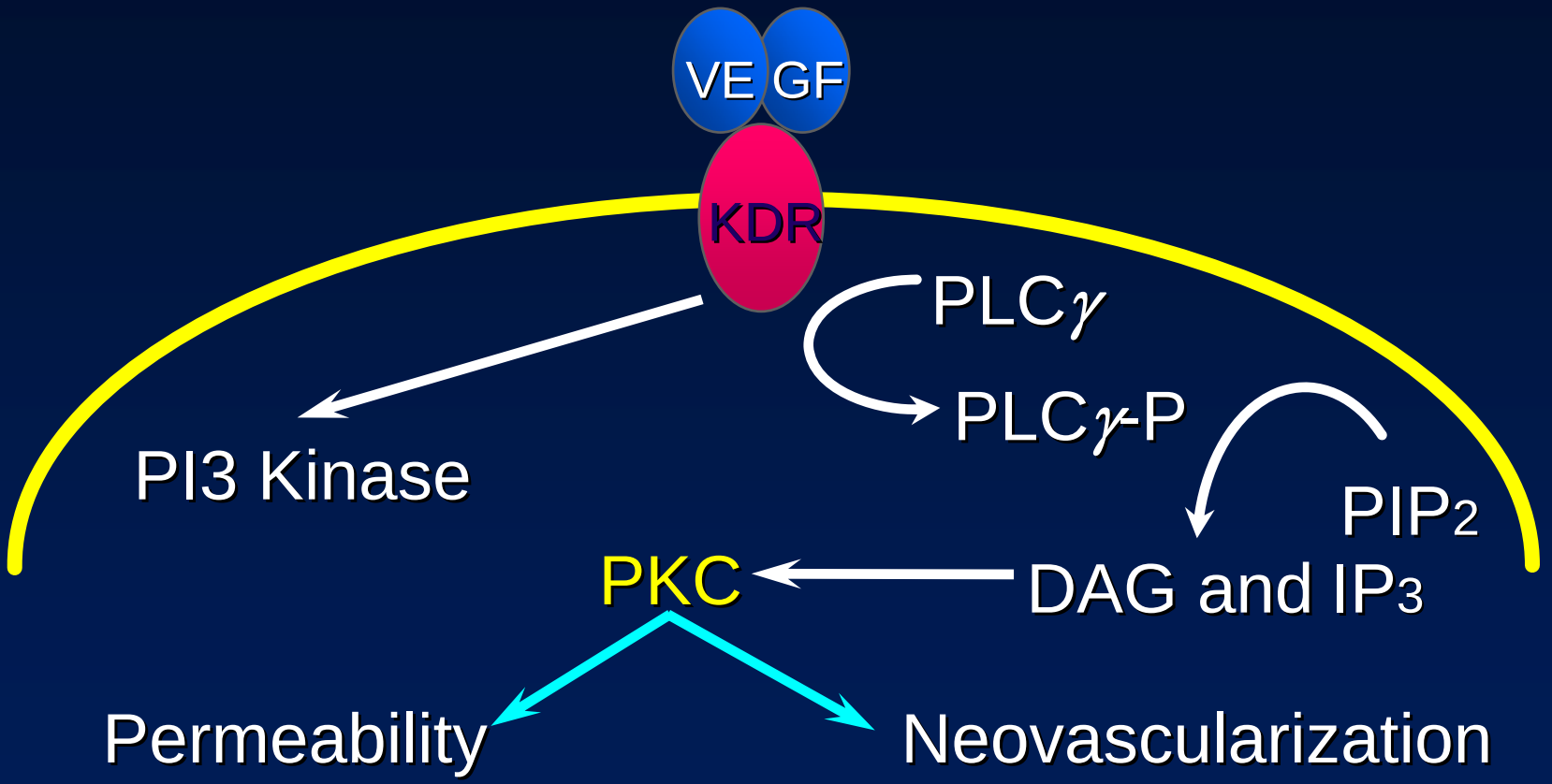
Growth Factor Mediation in Diabetic Retinopathy



VEGF, GH, IGF, FGF, HGF, PDGF, TGF, Ang, ATII, and many more…

Ang = angiopoietin; ATII = angiotensin II; FGF = fibroblast growth factor;
GH = growth hormone; HGF = hepatic growth factor; IGF = insulin-like growth factor;
PDGF = platelet-derived growth factor; TGF = transforming growth factor;
VEGF = vascular endothelial growth factor.

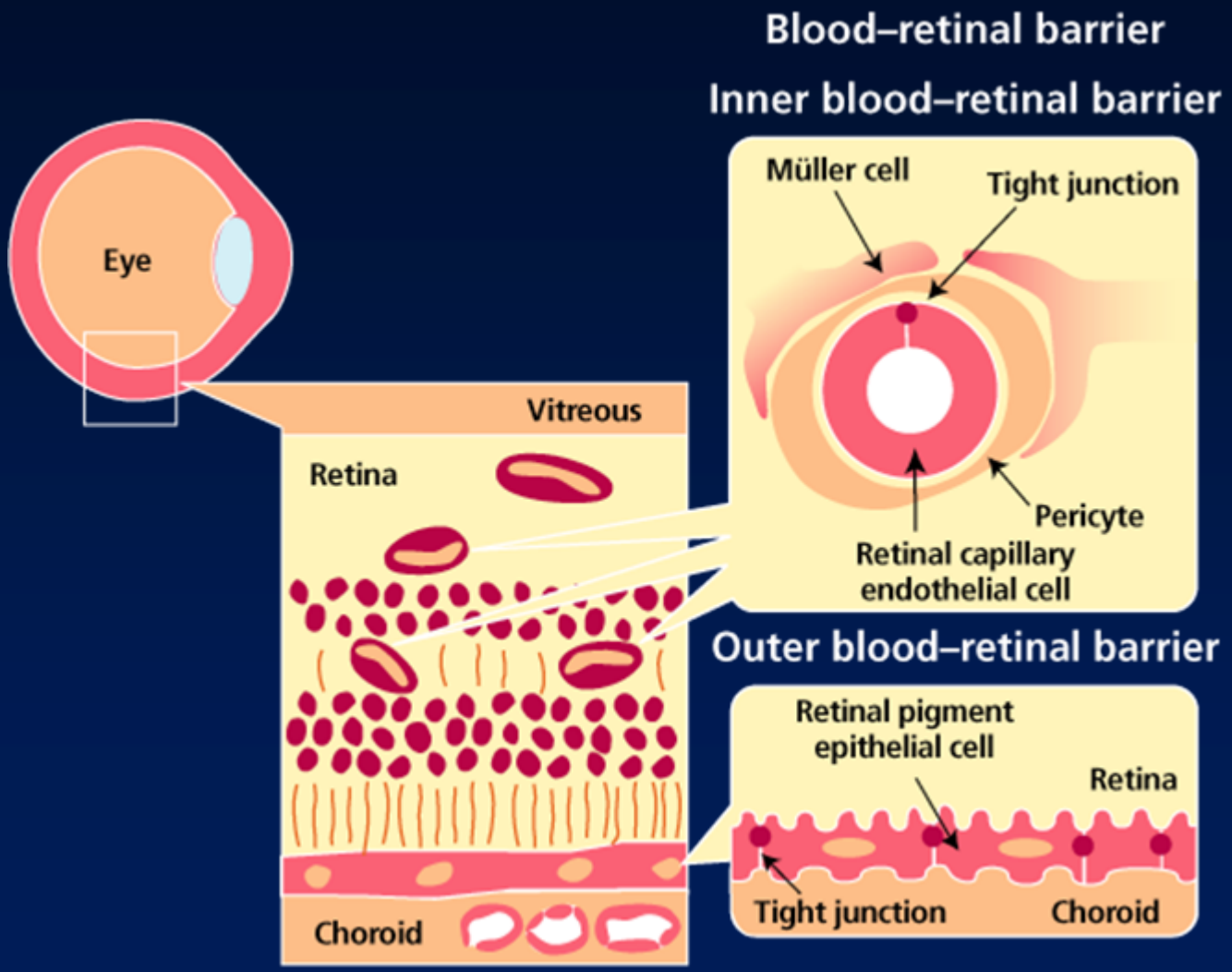
Mechanism of VEGF Action



DAG = diacylglycerol; IP3 = inositol 1,4,5-trisphosphate; KDR = kinase insert domain receptor; PI3 = phosphatidylinositol 3-kinase; PLCγ = phospholipase C-γ; PIP2 = phosphatidylinositol 4, 5 biphosphate.

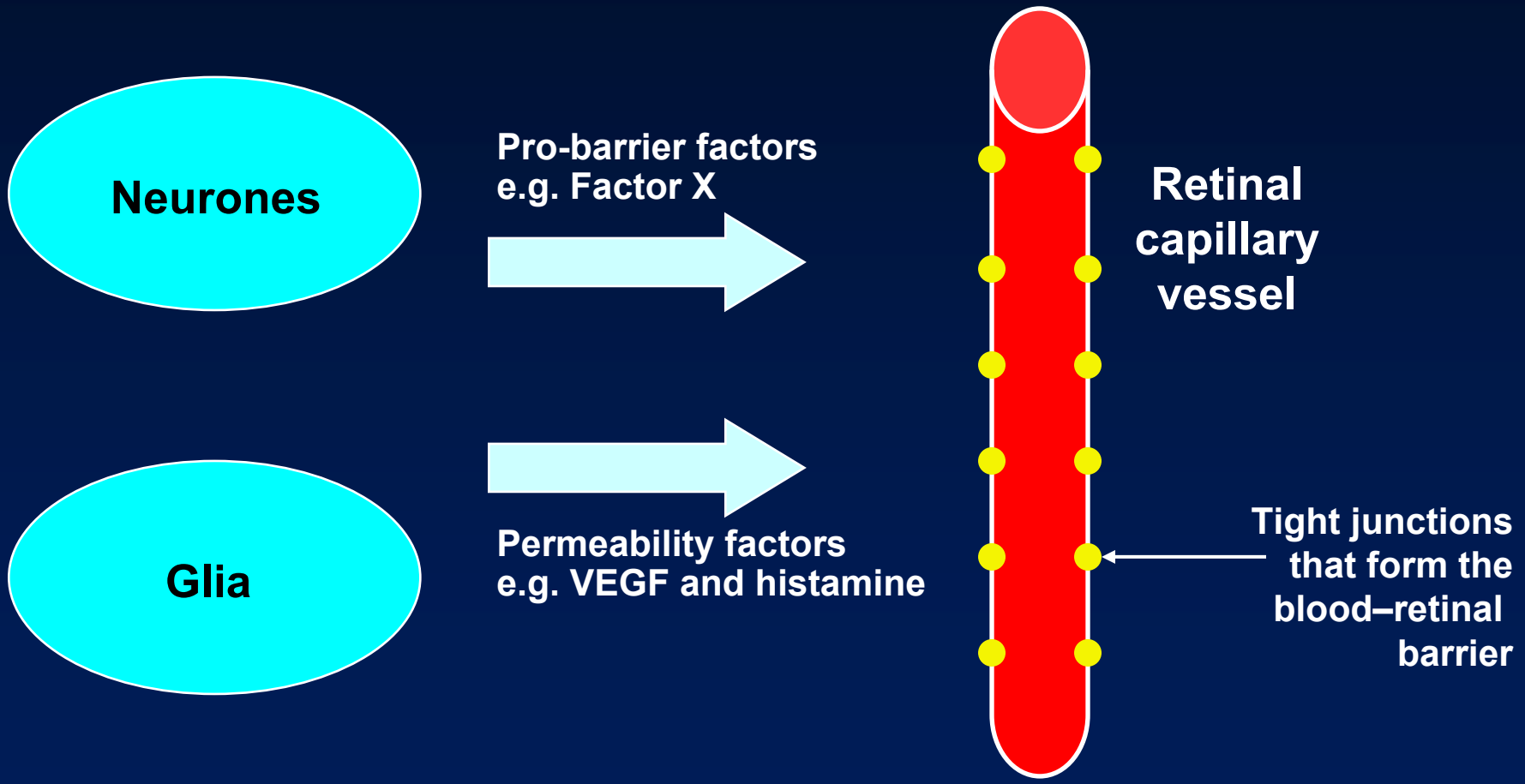
Xia P et al. *J Clin Invest.* 1996;98:2018-2026.

Blood–retinal barrier



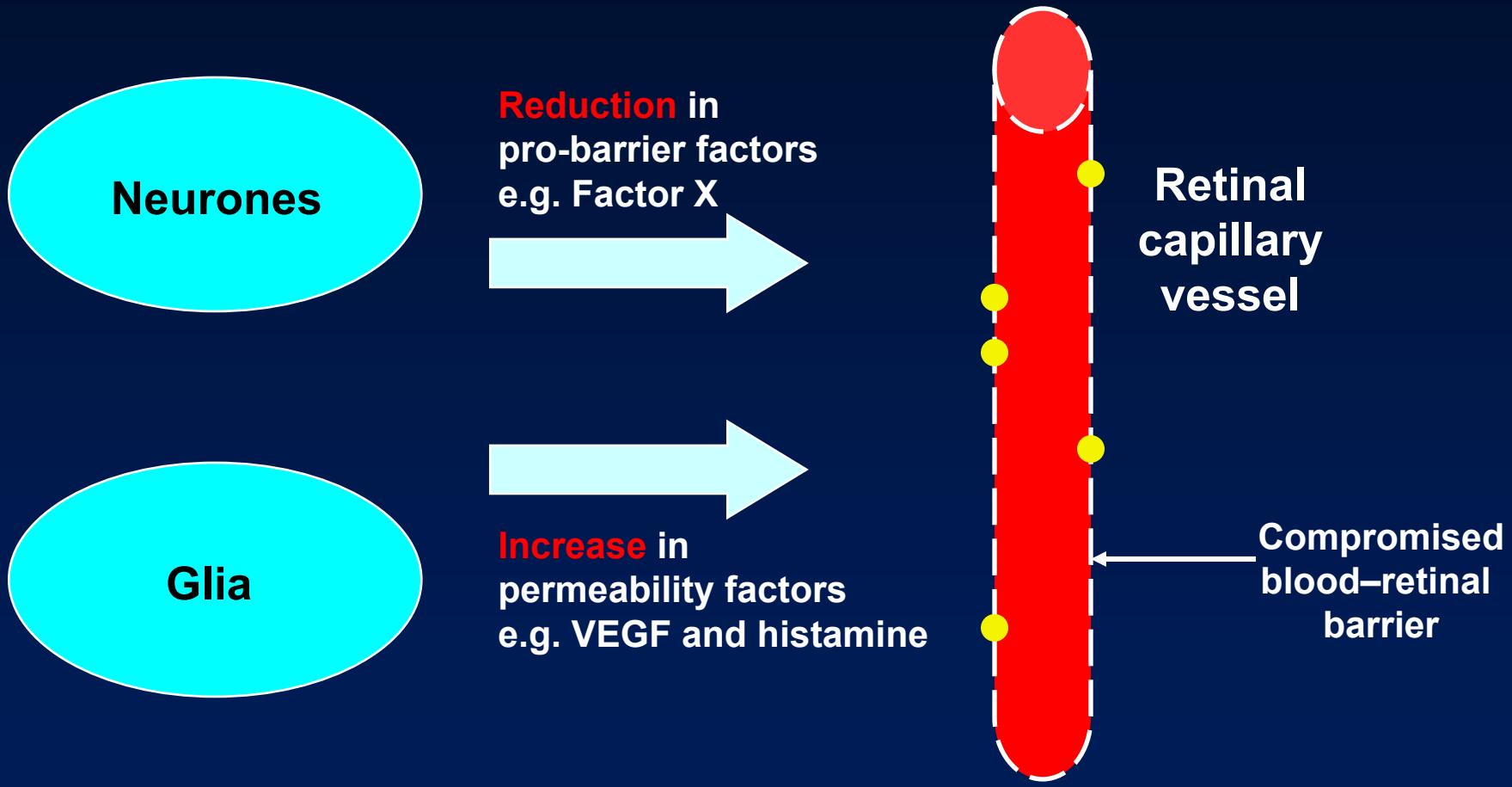
Hosoya KI, *et al*. *Biol Pharm Bull* 2005; **28**: 1–8.

Blood–retinal barrier



Gardner TW, *et al*. *Surv Ophthalmol* 2002; **47**: S253–S262.

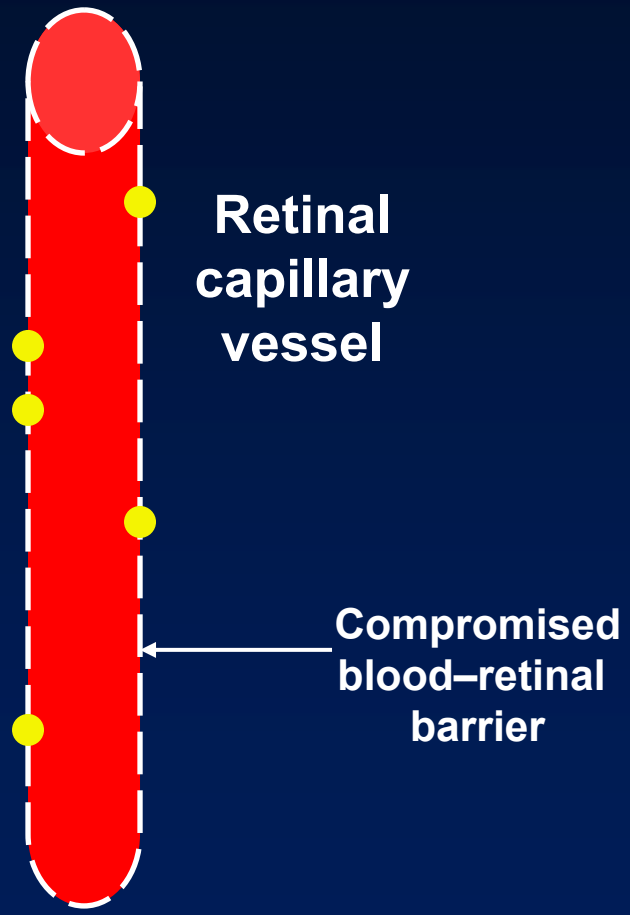
Blood–retinal barrier in diabetes



Gardner TW, *et al*. *Surv Ophthalmol* 2002; **47**: S253–S262.

VEGF: key player in diabetic retinopathy

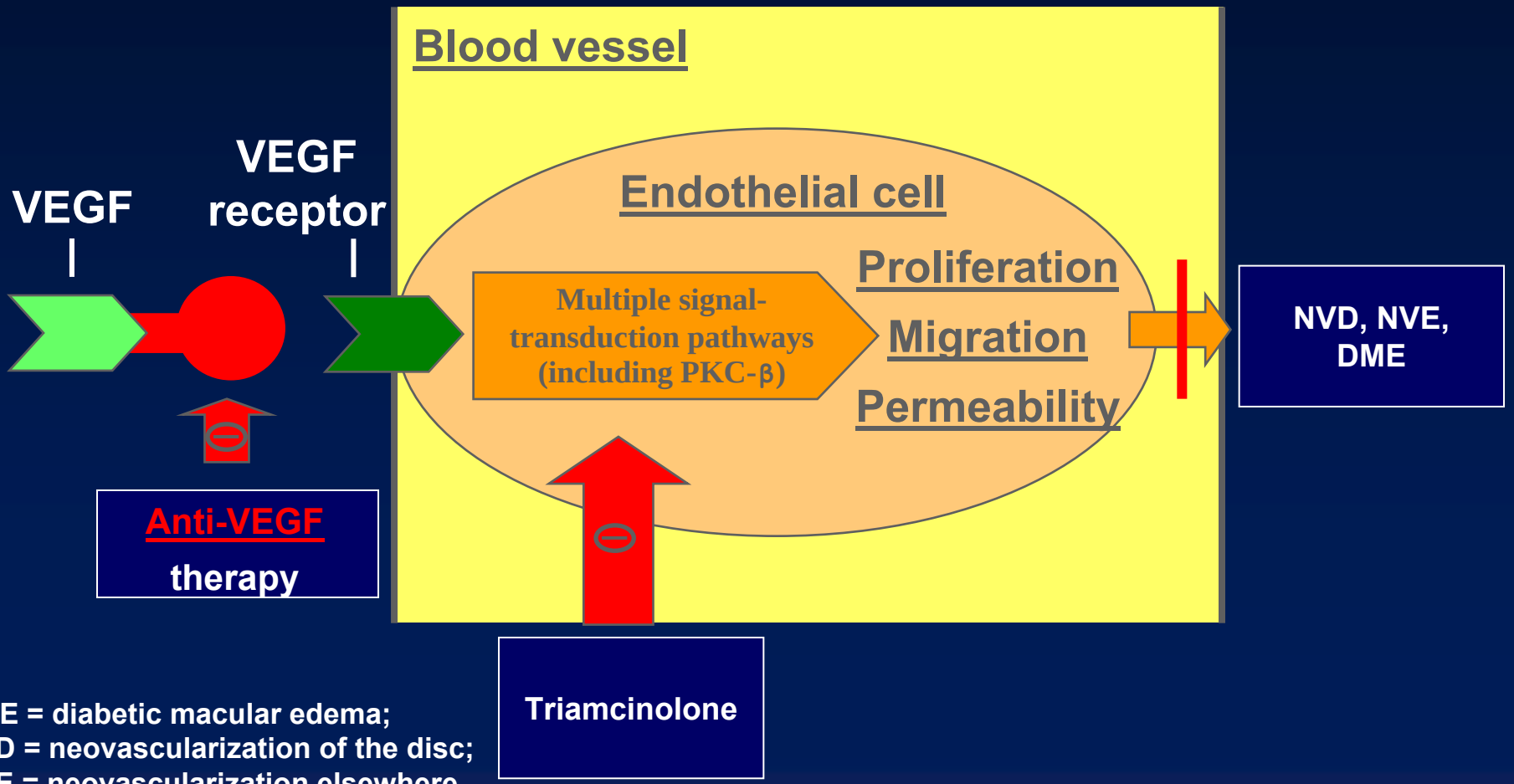
- VEGF also disrupts the expression of proteins maintaining the tight junctions of the blood–retinal barrier
- As a result, vascular permeability increases



Gardner TW, *et al*. *Surv Ophthalmol* 2002; **47**: S253–S262.

Inhibition of Angiogenesis/Permeability

Signal → Signal Transduction → Neovascularization/Edema



DME = diabetic macular edema;
NVD = neovascularization of the disc;
NVE = neovascularization elsewhere.

Agents for intra-vitreal use

Agent	Action	Indication
Pegaptanib sodium	Intravitreal aptamer VEGF inhibitor	DME
Ranibizumab	Intravitreal humanized anti-VEGF antibody fragment	DME
Bevacizumab	Anti-VEGF antibody	DME
Triamcinolone acetonide	Intravitreal steroid injection	DME

Grazie per l'attenzione e …
buona fortuna a tutti!