



Tavola Rotonda Terapia della microangiopatia: oltre il controllo glicemico



XVIII
CONGRESSO
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RENE

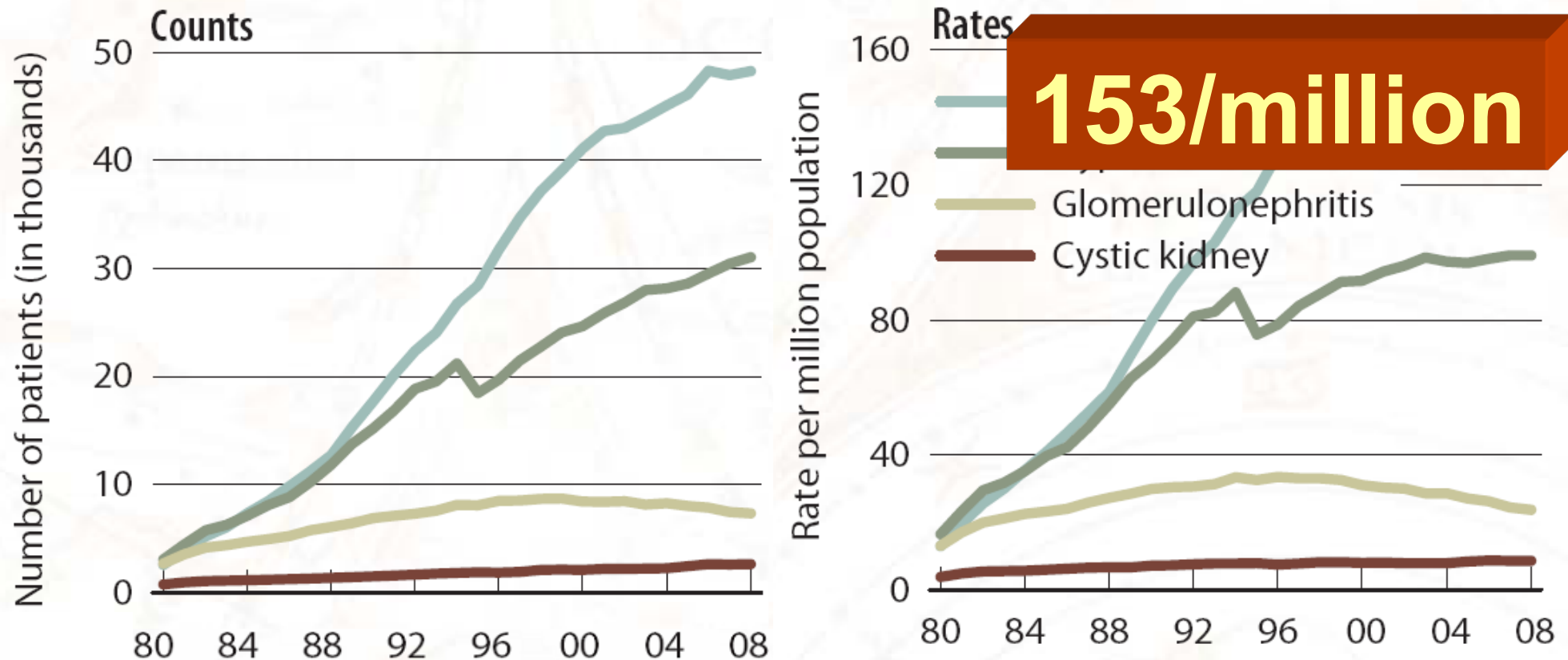


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Istituto Scientifico "CSS", San Giovanni Rotondo*



Incident counts & adjusted rates, by primary diagnosis



Incident ESRD patients; rates adjusted for age, gender, & race.

USRDS, 2010

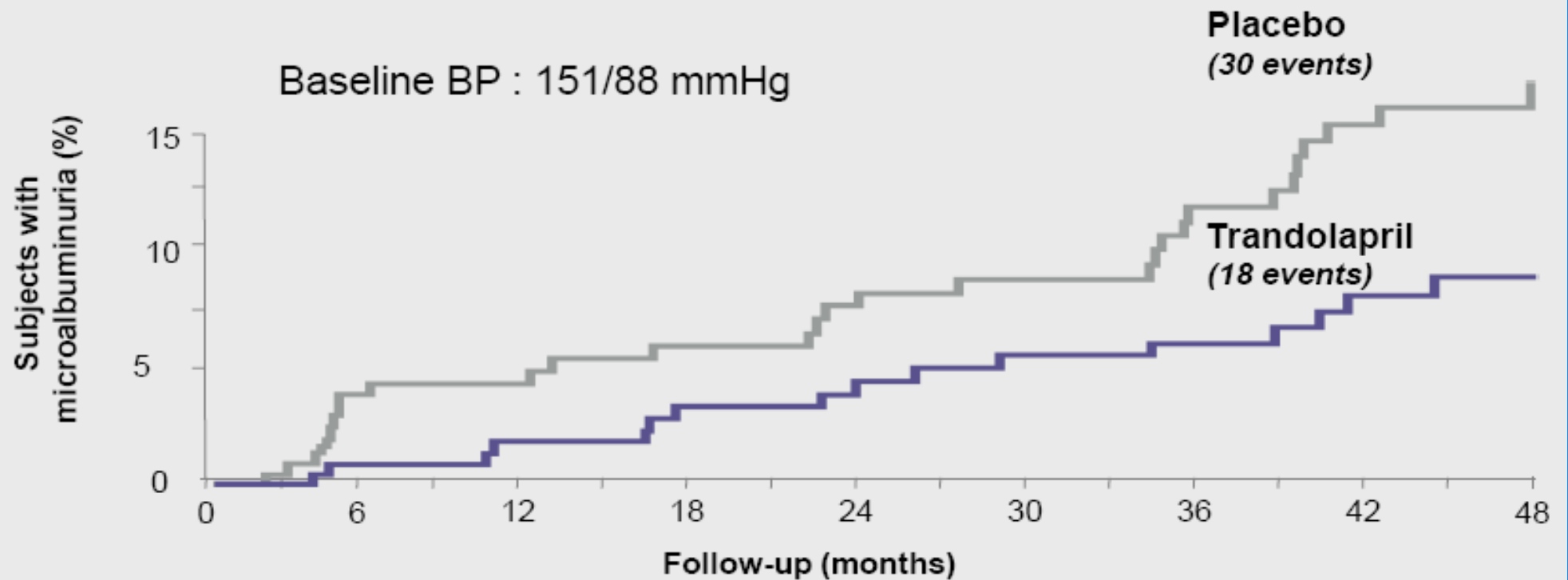
Nefropatia: oltre il controllo glicemico

- Blocco del RAS
 - *Prevenzione primaria*
 - *Doppio blocco del RAS*
 - *Inibizione diretta della renina*
- Terapie che agiscono su altri sistemi

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BENEDICT study: Prevention of microalbuminuria



No. at Risk

Trandolapril	301	254	237	224	207	198	188	149	104
Placebo	300	229	214	203	187	176	164	136	89

ADVANCE BP-Renal

Incidence of renal end-points

End Point	Perindopril- Indapamide (No. of Events/Patient [%])	Placebo	HR (95% CI)	P
Progression of nephropathy				
all renal events	1243/5569 (22.3)	1500/5571 (26.9)	0.79 (0.73 to 0.85)	0.0001
progression of ≥ 1 albuminuria stage	1179/5436 (21.7)	1442/5412 (26.6)	0.78 (0.72 to 0.84)	0.0001
new-onset microalbuminuria	1094/3995 (27.4)	1317/3991 (33.0)	0.79 (0.73 to 0.86)	0.0001
new-onset macroalbuminuria	114/5436 (2.1)	163/5412 (3.0)	0.69 (0.54 to 0.88)	0.0027
patients with normoalbuminuria	25/3995 (0.6)	35/3991 (0.9)	0.71 (0.42 to 1.18)	0.1841
patients with microalbuminuria	89/1441 (6.2)	128/1421 (9.0)	0.69 (0.52 to 0.91)	0.0074
doubling of serum creatinine 200 $\mu\text{mol/L}$	55/5569 (1.0)	45/5571 (0.8)	1.21 (0.81 to 1.79)	0.3483
end-stage kidney disease ^b	25/5569 (0.4)	21/5571 (0.4)	1.18 (0.66 to 2.11)	0.5736
Regression of nephropathy				
regression of ≥ 1 albuminuria stage	908/1638 (55.4)	816/1625 (50.2)	1.16 (1.06 to 1.28)	0.0017
regression to normoalbuminuria	848/1638 (51.8)	745/1625 (45.8)	1.15 (1.04 to 1.27)	0.0059
patients with microalbuminuria	797/1441 (55.3)	698/1421 (49.1)	1.15 (1.04 to 1.27)	0.0067
patients with macroalbuminuria	51/197 (25.9)	47/204 (23.0)	1.08 (0.72 to 1.60)	0.7146

JASN, 2009

The NEW ENGLAND JOURNAL of MEDICINE

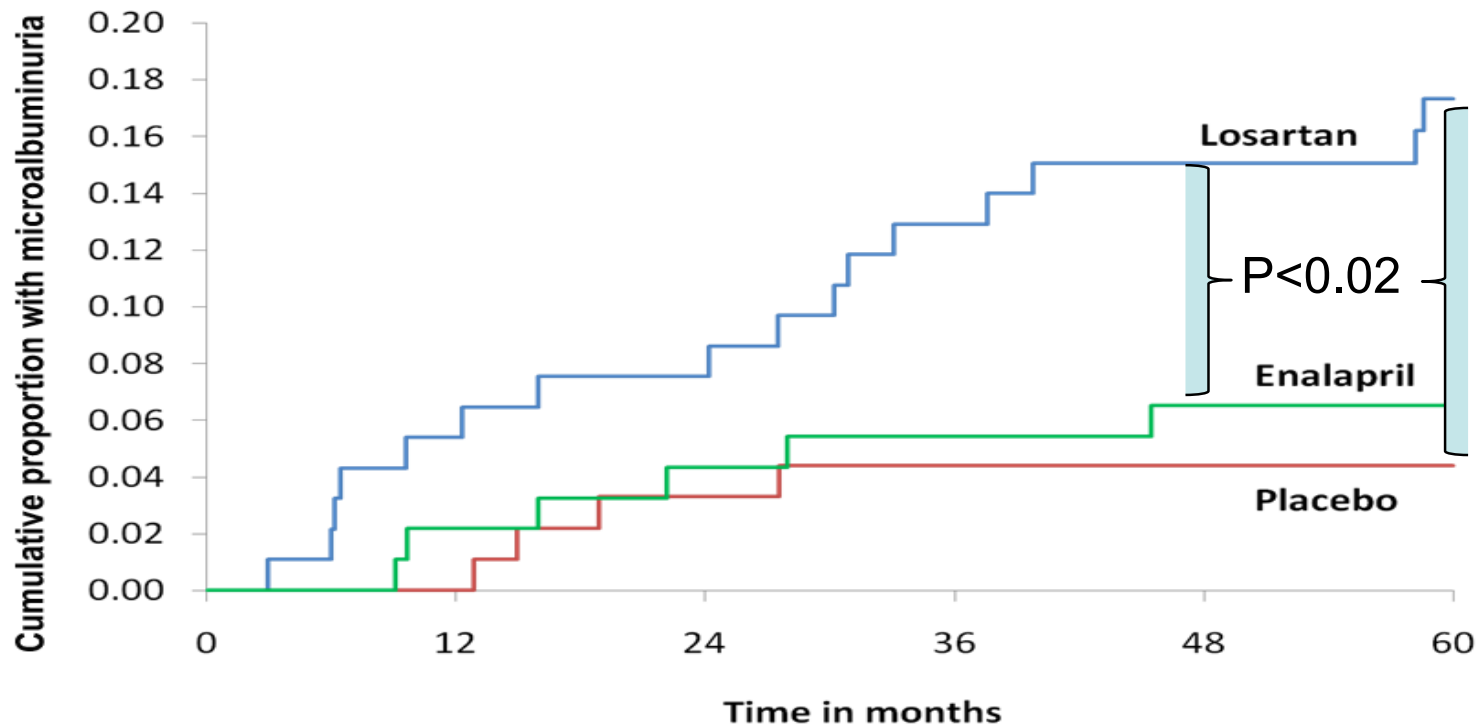
ORIGINAL ARTICLE

Renal and Retinal Effects of Enalapril and Losartan in Type 1 Diabetes

Michael Mauer, M.D., Bernard Zinman, M.D., Robert Gardiner, M.D.,
Samy Suissa, Ph.D., Alan Sinaiko, M.D., Trudy Strand, R.N.,
Keith Drummond, M.D., Sandra Donnelly, M.D., Paul Goodyer, M.D.,
Marie Claire Gubler, M.D., and Ronald Klein, M.D., M.P.H.

RASS: Renin Angiotensin System Study
NEJM , 361:40-51, 2009

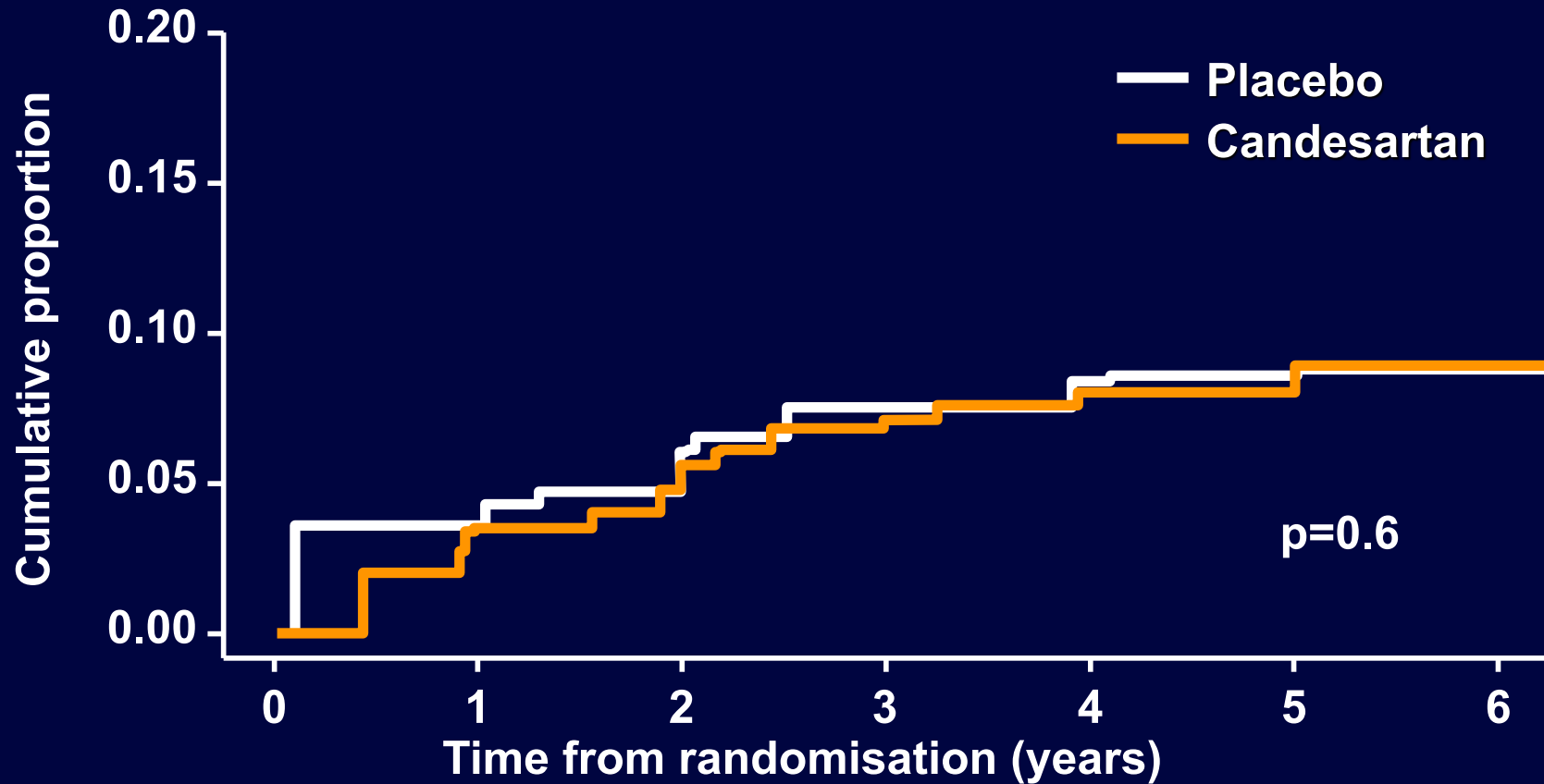
Cumulative Proportion of Subjects Developing Microalbuminuria



RASS Group

Mauer M, NEJM, 2009

DIRECT-Renal: Microalbuminuria incidence



Number at risk

Placebo	2618	2410	2247	2092	1754	526	15
Candesartan	2613	2426	2278	2150	1793	540	13

Fig. 9

ROADMAP: Study design

Hypothesis: Early intervention with an ARB prevents or delays the time to first onset of microalbuminuria

(in patients without pretreatment with ACEi or ARB in the last 6 months)

**4447 patients with type-2 diabetes
and ≥ 1 add. CV risk factor and normoalbuminuria**

R

Olmesartan 40 mg

(+ non-RAS blood pressure medication)

n = 2232

Placebo

(+ non-RAS blood pressure medication)

n = 2215

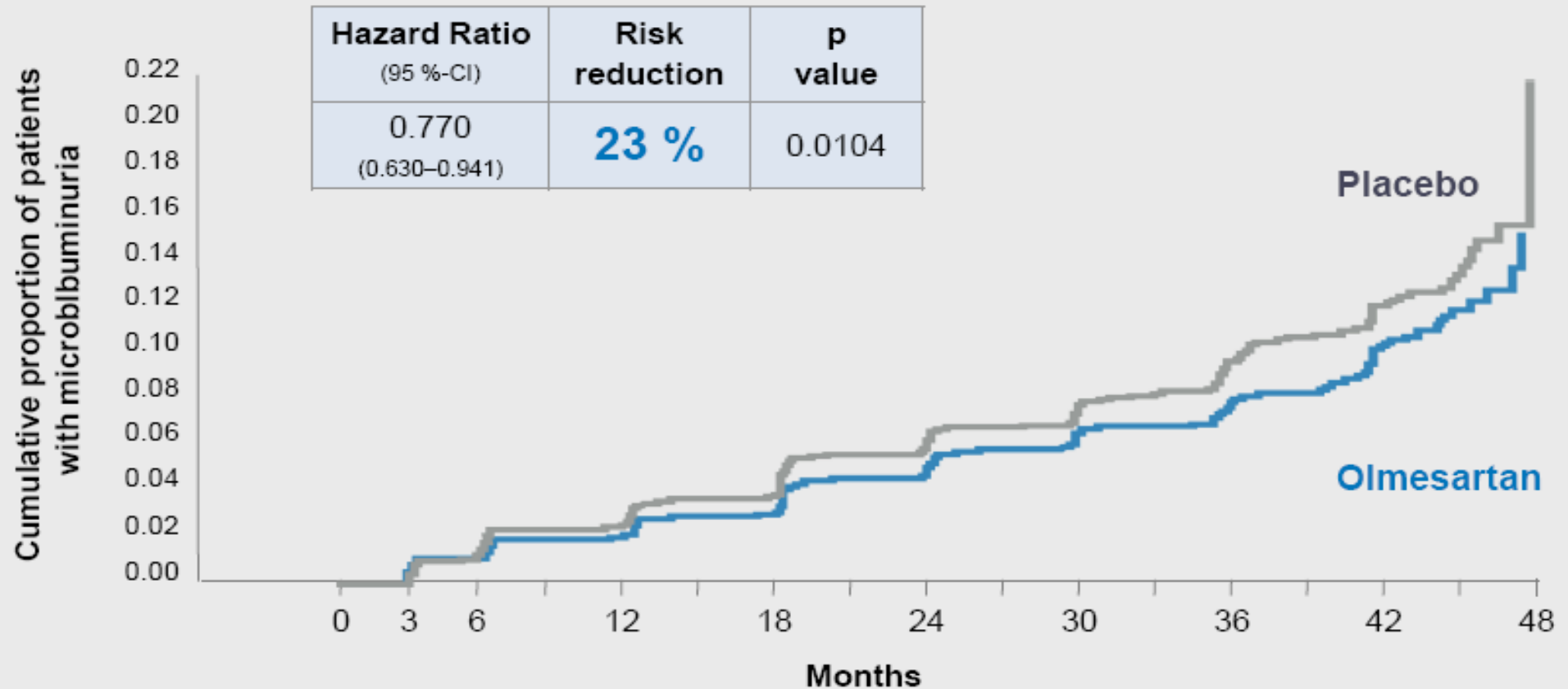
Primary endpoint: Time to onset of microalbuminuria

Secondary endpoint: Renal and cardiovascular events

ROADMAP: Primary endpoint

N Engl J Med 2011;364:907-17

Time to first occurrence of MAU



Patients at risk

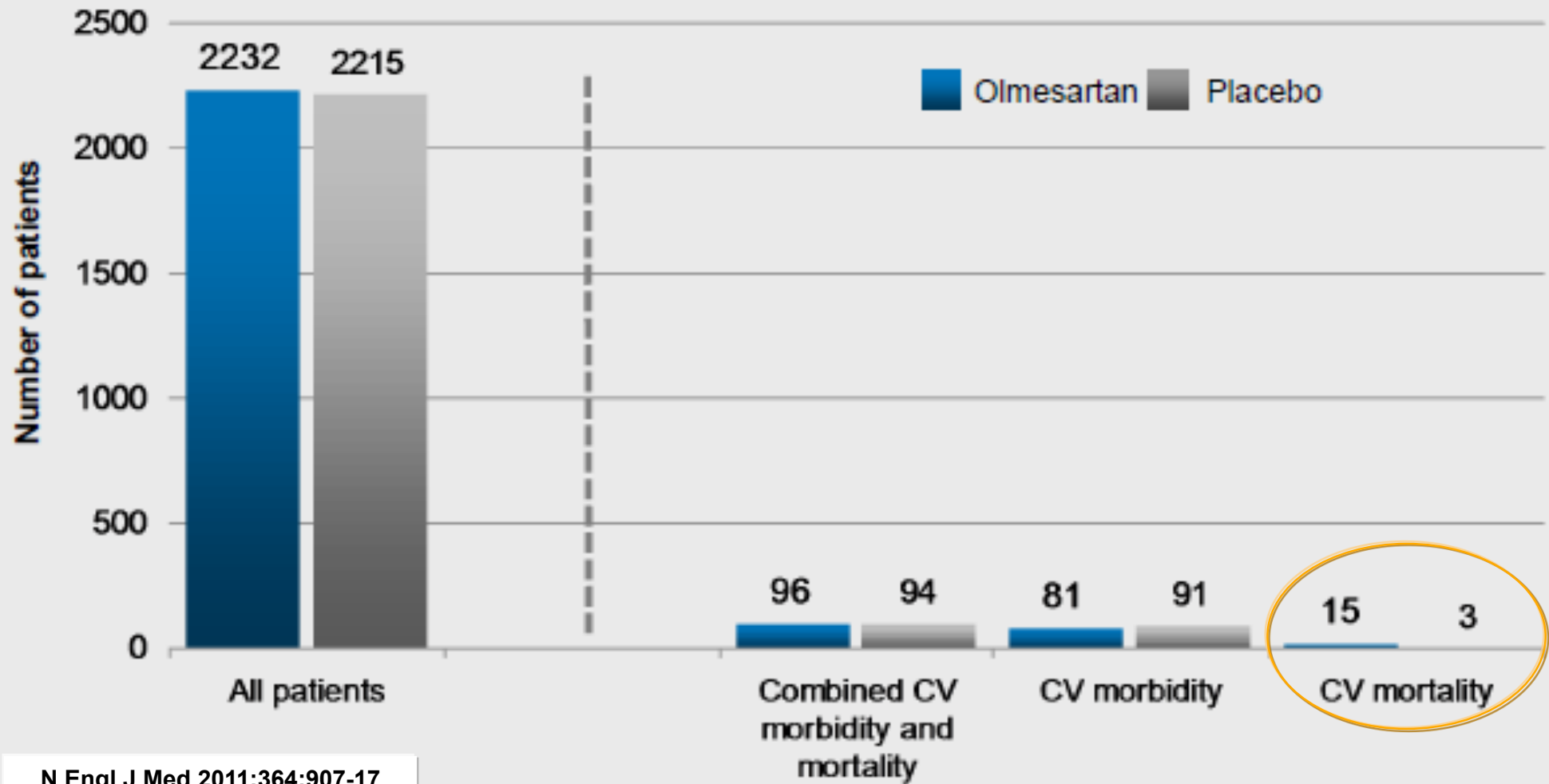
OM 40 mg

2160	2097	2025	1923	1833	1727	1629	1325	754	67
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Placebo

2139	2076	2004	1887	1787	1685	1592	1308	699	49
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ROADMAP: Cardiovascular events



Nefropatia: oltre il controllo glicemico

- Blocco del RAS

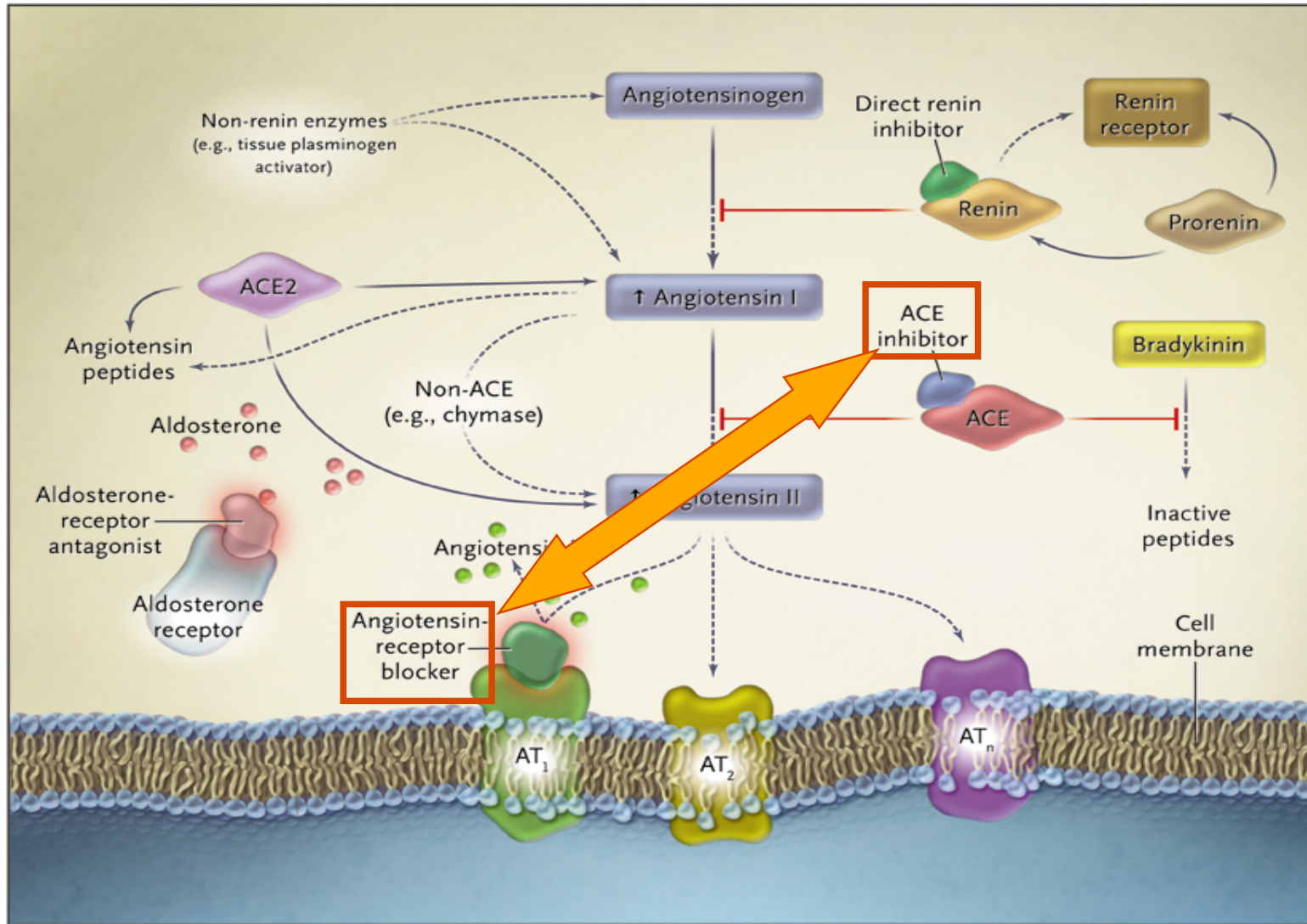
- *Prevenzione primaria*

- *Doppio blocco del RAS*

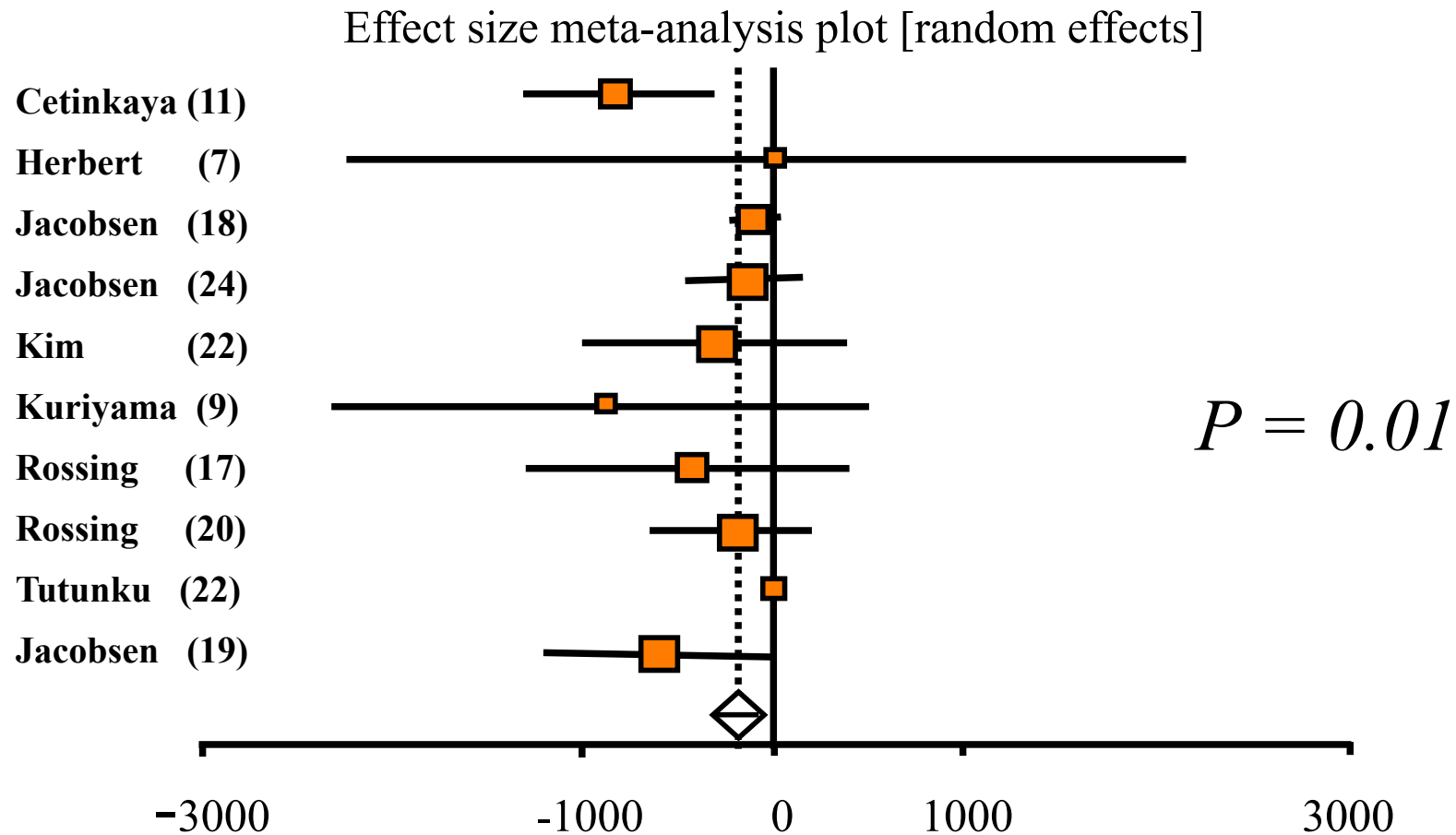
- *Inibizione diretta della renina*

- Terapie che agiscono su altri sistemi

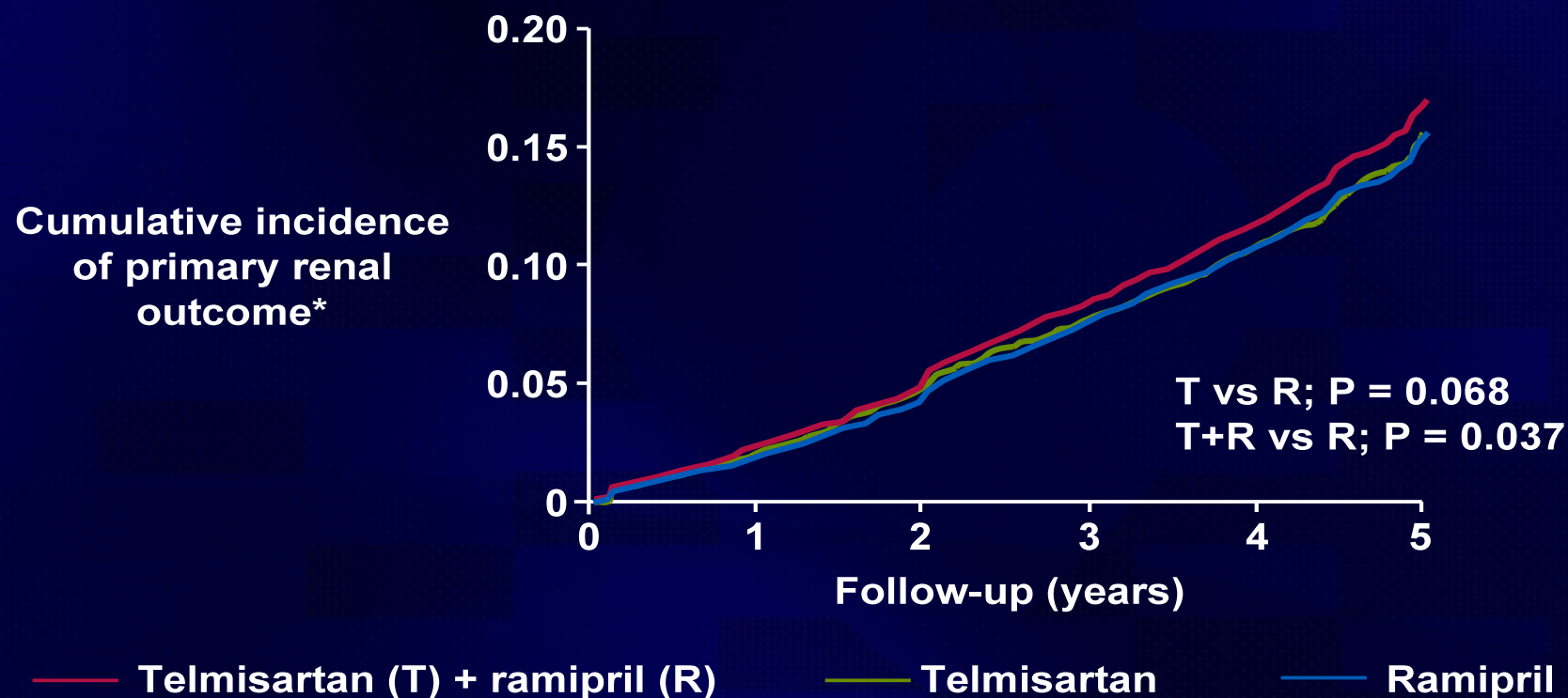
Il doppio blocco del RAS



RAAS Dual Blockade and *short term* proteinuria reduction: **a meta-analysis**



ONTARGET: Effects of telmisartan, ramipril, and combination on primary renal outcome



*Dialysis, doubling of serum creatinine, death

Mann JFE et al. *Lancet*.
2008;372:547-53.

ONTARGET renal data

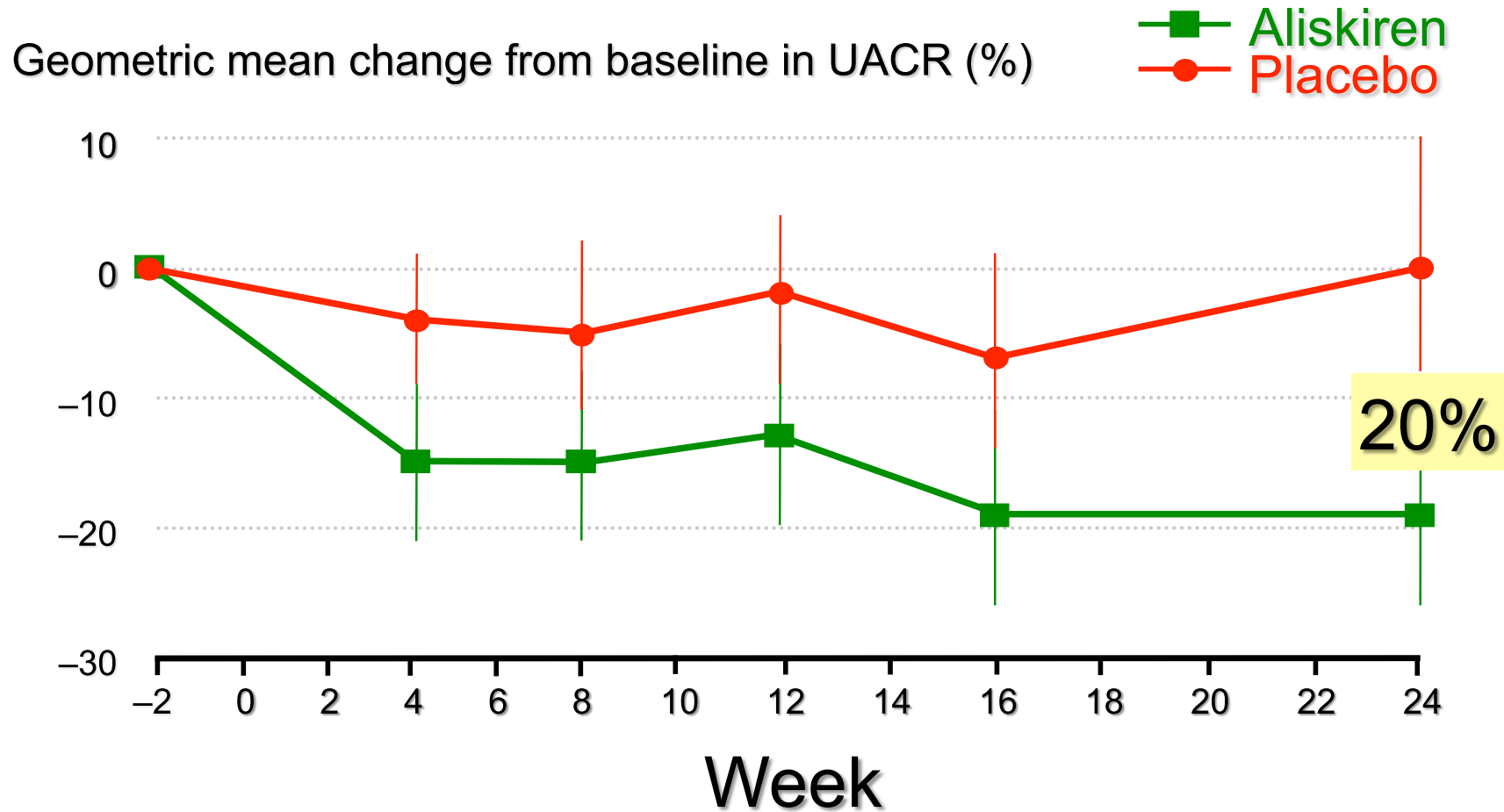
	Ramipril n (%)	Telmisartan n (%)	Ramipril+ telmisartan n (%)	Telmisartan vs ramipril HR (95% CI)	p	Ramipril+ telmisartan vs ramipril HR (95% CI)	p
All dialysis, doubling, death	1150 (13.4)	1147 (13.4)	1233 (14.5)	1.00 (0.92-1.09)	0.968	1.09 (1.01-1.18)	0.037
All dialysis and doubling	174 (2.03)	189 (2.21)	212 (2.49)	1.09 (0.89-1.34)	0.420	1.24 (1.01-1.51)	0.038
All dialysis	48 (0.56)	51 (0.60)	63 (0.74)	1.07 (0.72-1.58)	0.747	1.33 (0.92-1.94)	0.133
All death	1014 (11.8)	989 (11.6)	1065 (12.5)	0.98 (0.90-1.07)	0.641	1.07 (0.98-1.16)	0.144
Doubling	140 (1.63)	155 (1.81)	166 (1.95)	1.11 (0.88-1.39)	0.378	1.20 (0.96-1.50)	0.110
Acute dialysis	13 (0.15)	20 (0.23)	28 (0.33)	1.55 (0.77-3.11)	0.221	2.19 (1.13-4.22)	0.020
Chronic dialysis	33 (0.39)	31 (0.36)	34 (0.40)	0.94 (0.58-1.54)	0.817	1.05 (0.65-1.69)	0.854

Mann JFE et al. *Lancet* 2008; 372:547-553

Nefropatia: oltre il controllo glicemico

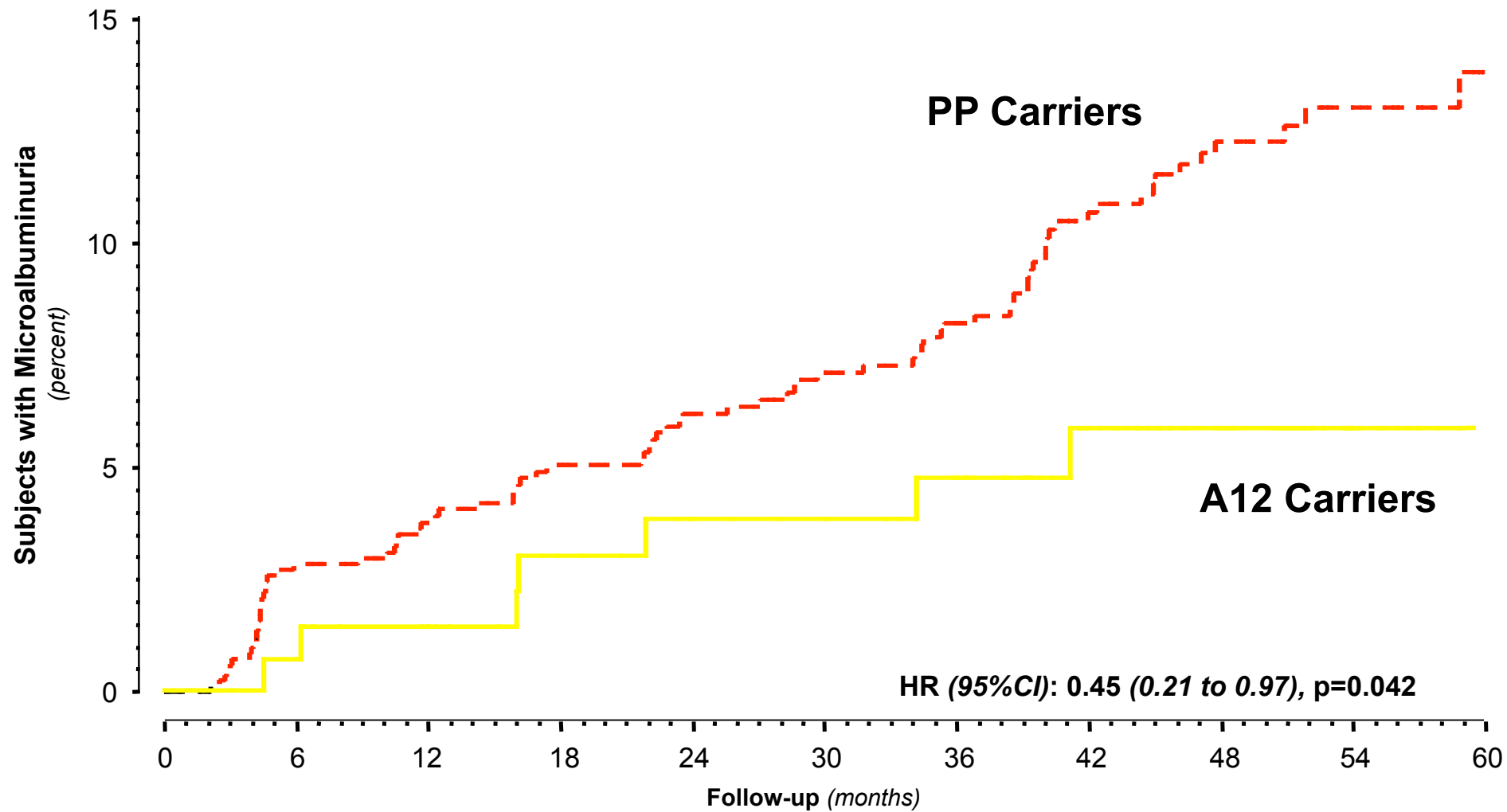
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AVOID: changes in UACR throughout the study



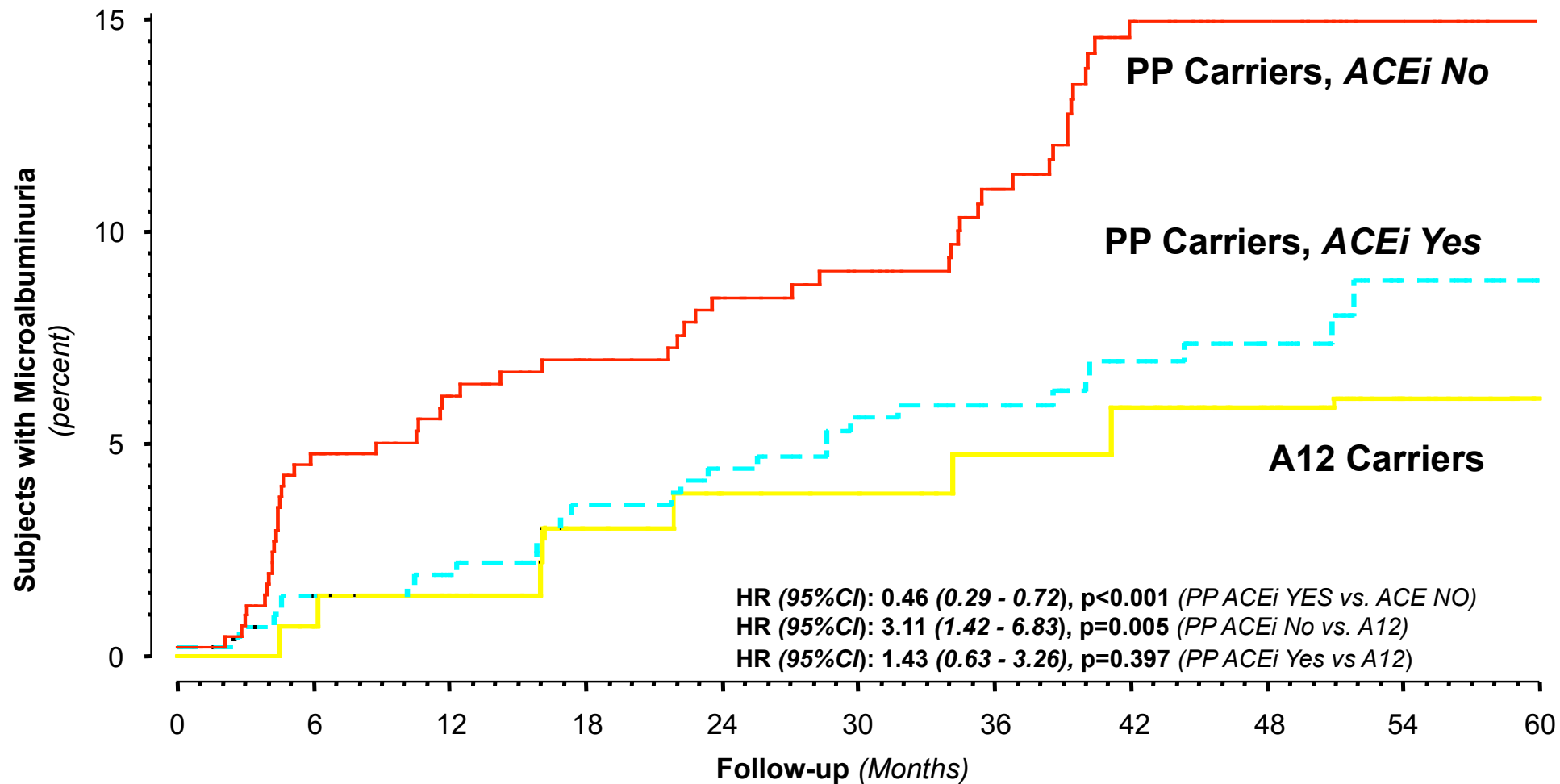
Nefropatia: oltre il controllo glicemico

- Il blocco del RAS non previene lo sviluppo di nefropatia nel diabete di tipo 1, mentre nel diabete di tipo 2 i dati sono contrastanti
- L'impiego del doppio blocco e degli inibitori della renina riduce la proteinuria, ma non ci sono studi a lungo termine sull'efficacia e sicurezza.



Patients at Risk

A12	177	137	128	120	112	108	102	80	55	33	23
PP	942	764	709	671	633	605	569	459	308	160	93



Patients at Risk

A12	177	137	128	120	112	108	102	80	55	33	23
PP ACEi Yes	464	395	370	347	330	315	301	244	168	88	53
PP ACEi No	478	368	339	324	302	289	268	215	139	72	40

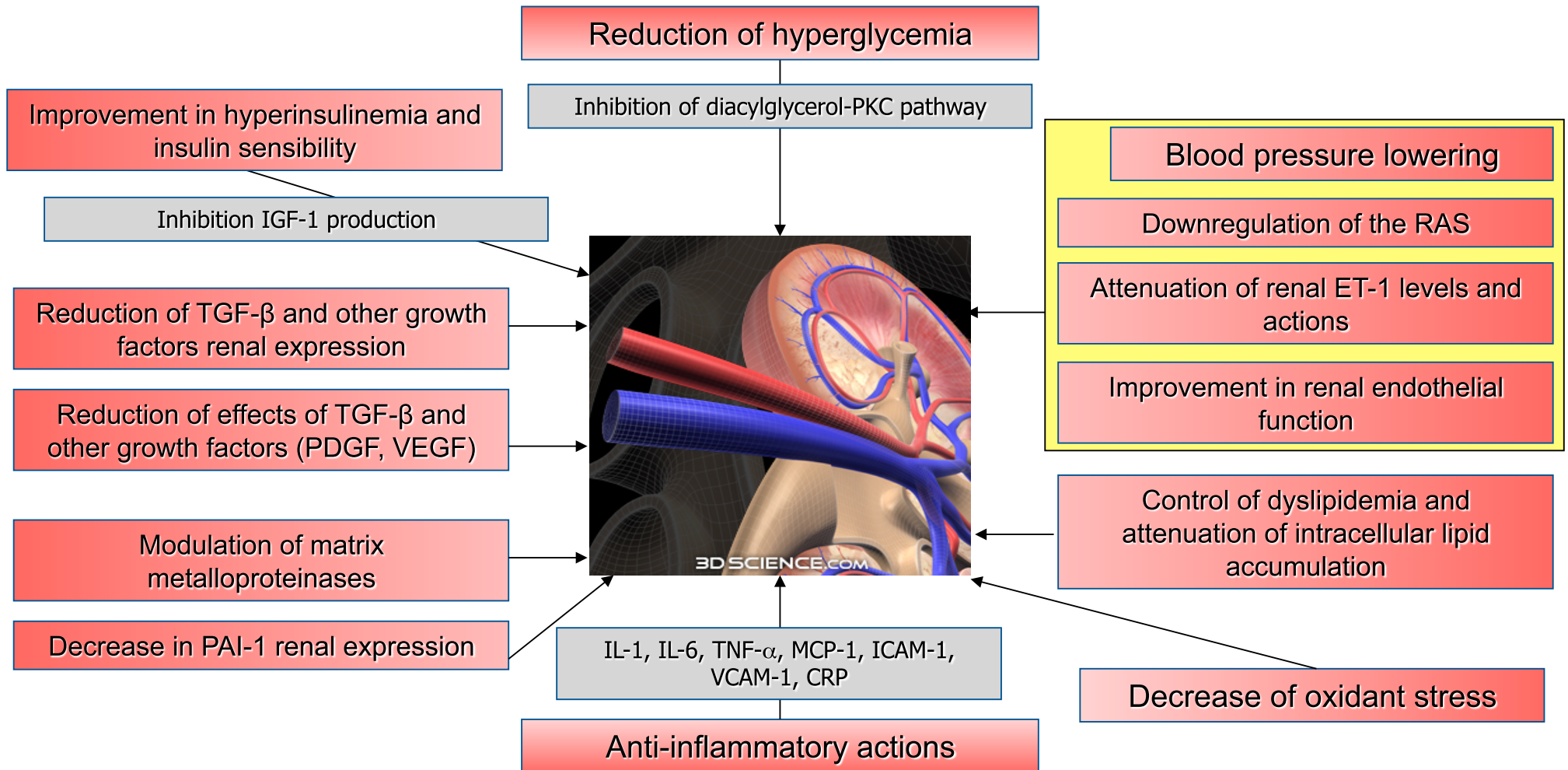
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Emerging new approaches in DN

- Tiazolidinedioni
- Ipolipemizzanti
- Ruboxistaurin
- Sulodexide
- Pentoxifillina
- Anti-fibrotici
- Anti-AGE
- Analoghi vit. D

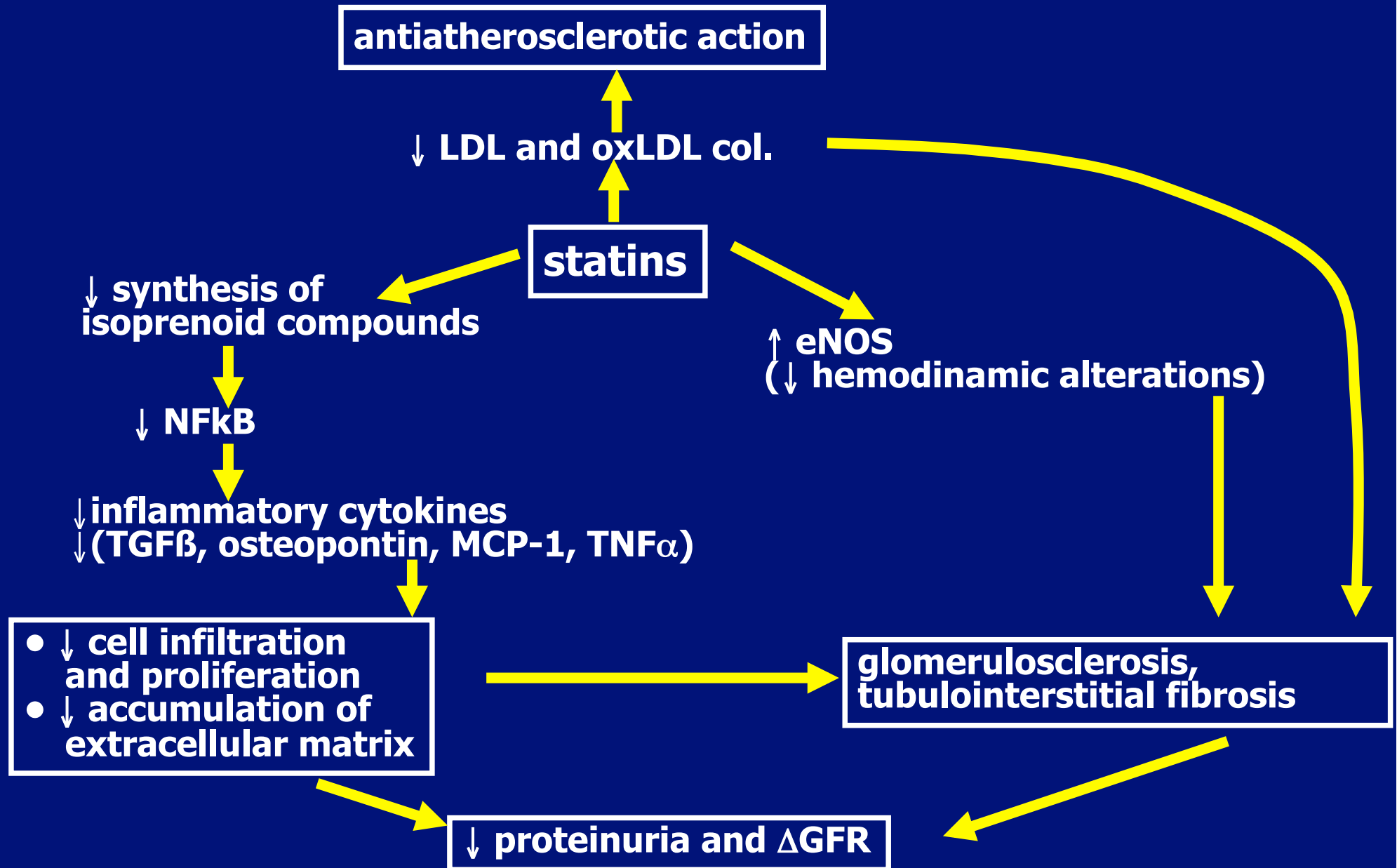
Actions of TZDs possibly contributing to a **renoprotective** effect



Effect of TZDs on Albuminuria in Diabetes: A Meta-analysis

- 2860 pts with type 2 diabetes enrolled in RCTs.
- TZD treatment was associated with a significant decrease of 24.8% in albumin excretion in patients with normo- or micro-albuminuria at baseline.
- No differences between the effect of Rosi and Pio

Rationale for the use of statins in DN



Effects of statins in patients with chronic kidney disease: meta-analysis and meta-regression of randomised controlled trials

Parametro	N.	Differenza rispetto al placebo	P
Colesterolo totale (mg/dl)	6390	-42.3 (-47.3/-37.3)	< 0.05
Colesterolo HDL (mg/dl)	5621	0.41 (-0.78/1.60)	NS
Colesterolo LDL (mg/dl)	6216	-43.1 (-47.9/-38.4)	< 0.05
Trigliceridi (mg/dl)	5569	-23.7 (-33.5/-13.9)	< 0.05
Velocità di filtrazione Glomerulare (ml/min/1.73 m ²)	548	1.48 (-2.32/5.28)	NS
Proteinuria 24 h	311	-0.73 (-0.95/-0.52)	< 0.05

Selective vitamin D receptor activation with paricalcitol for



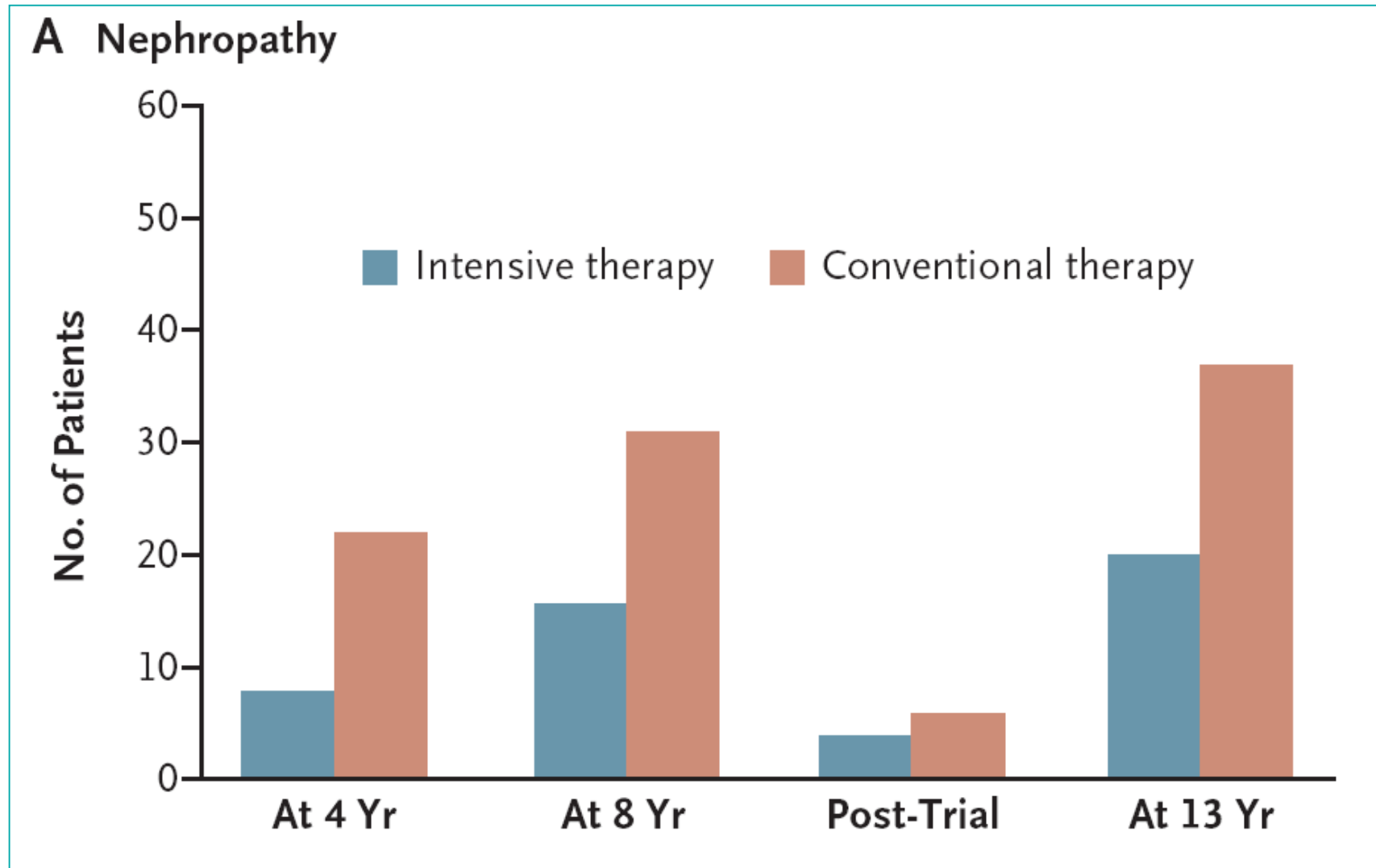
reduction of albuminuria in patients with type 2 diabetes

(VITA)

Dick de Zeeu
Giuseppe Re

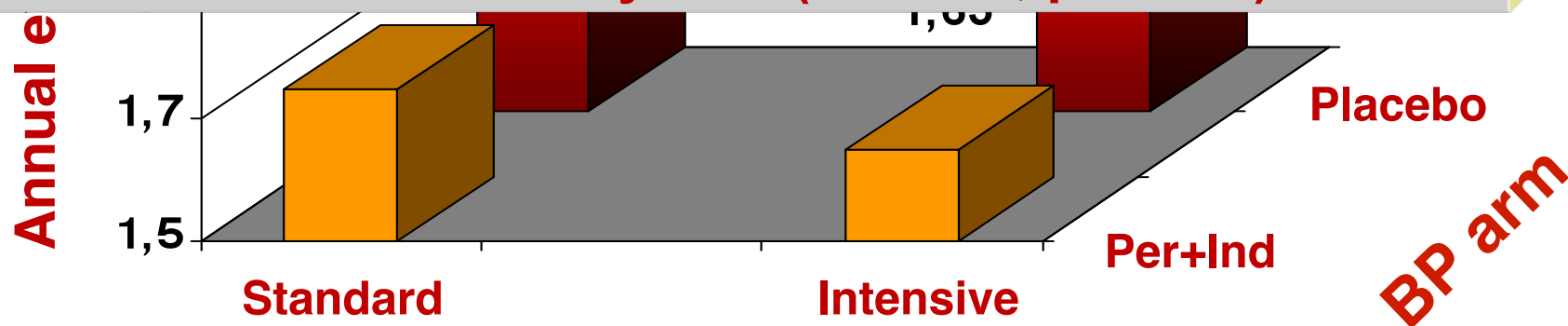
	Placebo	Combined paricalcitol	1 µg paricalcitol	2 µg paricalcitol
Geometric mean urinary albumin-to-creatinine ratio				
Baseline to last measurement during treatment				
Patients	88	184	92	92
Baseline (mg/mmol)	61	62	63	61
Last measurement during treatment (mg/mmol)	60	51	54	49
Percentage change (95% CI)	-3% (-16 to 13)	-16% (-24 to -9)	-14% (-24 to -1)	-20% (-30 to -8)
Last measurement during treatment to 60 days after treatment completion				
Patients	72	139	71	68
Last measurement during treatment (mg/mmol)	60	51	57	45
60 days after treatment completion (mg/mmol)	55	63	75	52
Percentage change (95% CI)	-7% (-20 to 8)	23% (11 to 36)	34% (15 to 55)	13% (-3 to 32)
Mean 24 h urinary albumin				
Baseline to last measurement during treatment				
Patients	78	146	74	72
Baseline (mg)	609	662	613	717
Last measurement during treatment (mg)	564	507	554	463
Percentage change (95% CI)	-9% (-23 to 8)	-23% (-32 to -13)	-10% (-25 to 6)	-34% (-45 to -21)
Last measurement during treatment to 60 days after treatment completion				
Patients	71	143	73	70
Last measurement during treatment (mg)	623	486	531	444
60 days after treatment completion (mg)	599	614	694	540
Percentage change (95% CI)	-1% (-16 to 16)	25% (12 to 39)	31% (12 to 54)	19% (1 to 39)

Efficacy of Multiple Risk Factor Intervention in High-Risk Subjects (Type 2 Diabetes with Microalbuminuria): *Steno-2*



ADVANCE: Combined Effects of Routine Blood Pressure–lowering and Intensive Glucose Control Strategy on The Incidence of Death from Any Cause.

Compared with neither intervention, combination treatment reduced the risk of new or worsening nephropathy by 33% (95% CI 12–50%, $P=0.005$), new onset of macroalbuminuria by 54% (35–68%, $P<0.0001$), and new onset of microalbuminuria by 24% (16–33%, $p<0.001$).



*RRR 18% (95% CI 1 to 32), $p=0.04$
versus the group of standard and placebo

Glucose arm

modified, *Diabetes Care*, 2009