

V CONVEGNO Centro Studi e Ricerche – Fondazione AMD
Firenze, 17-20 Novembre 2010

Rene e Diabete

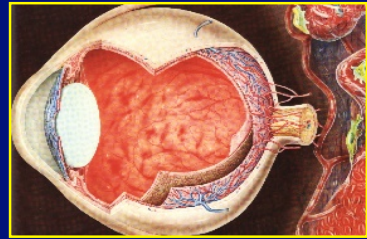
Aggiornamento e prospettive sul
tema: il contributo del diabetologo

Salvatore A. De Cosmo

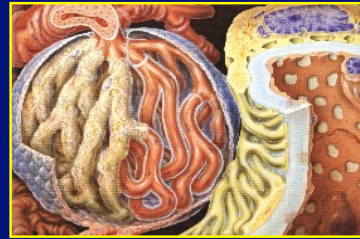
IRCCS “CSS” San Giovanni Rotondo



Effetti del miglioramento del controllo glicemico nel diabete tipo 2



Retinopatia



Nefropatia



Neuropatia



CVD

Kumamoto
VDCN

-28%
-25%*

-50%

-19%

-26%

-18%

UKPDS
-14%

* ns

Riduzione del rischio per riduzioni dell'1% della HbA1c

VDCN = velocità di conduzione nervosa

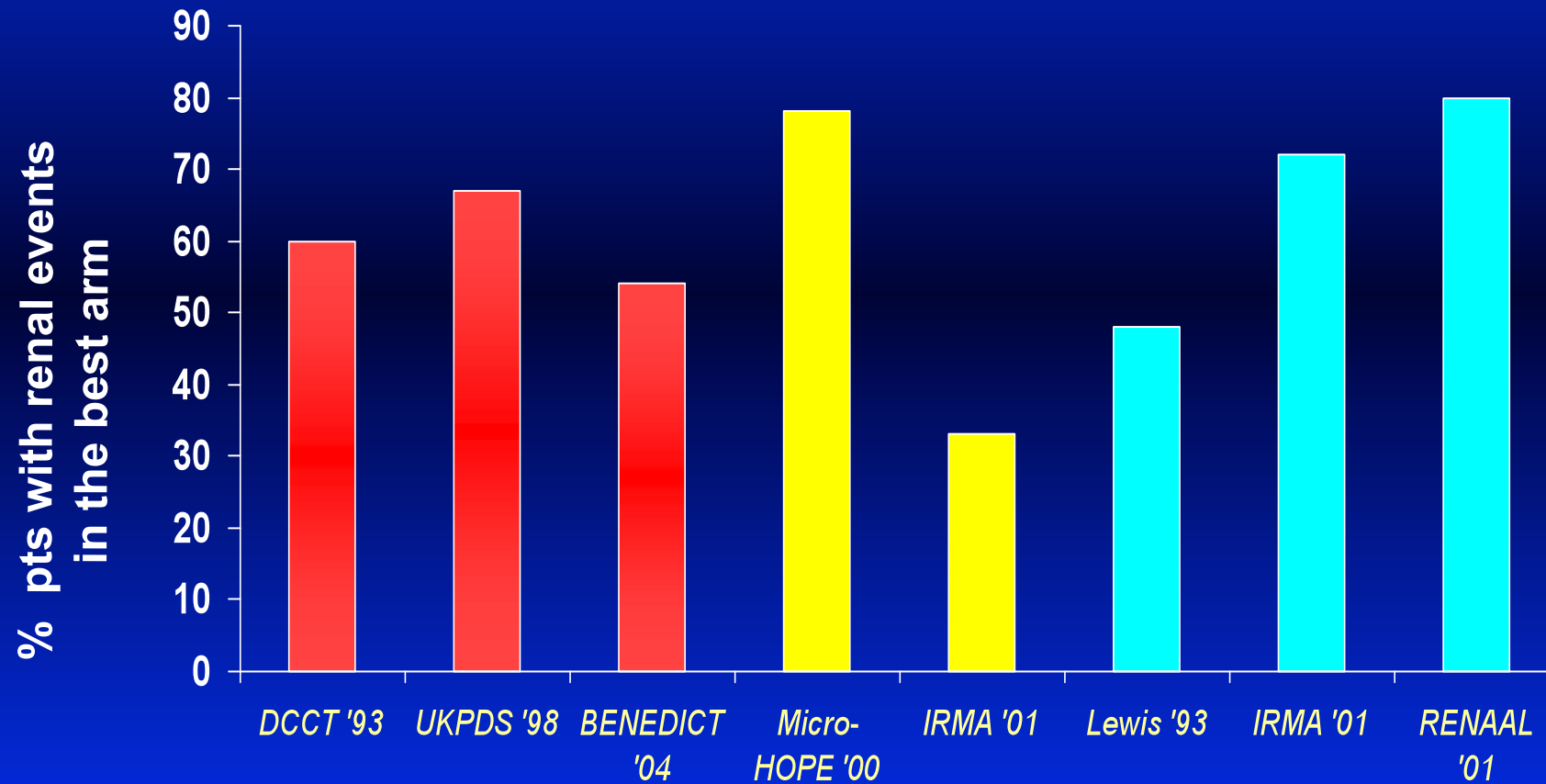
Ohkubo Y et al., Diabetes Res Clin Pract 28: 103-117, 1995

UK Prospective Diabetes Study Group, Lancet 352: 837-853, 1998

Established Therapy in Diabetic Kidney Disease (DKD)

- Excellent clinical trials demonstrating clear benefit of inhibition of renin-angiotensin system in DKD (Captopril Trial, 1993; IRMA2, IDNT, RENAAL, 2003)
- Intensive BP control recommended by current guidelines based on epidemiological studies, subgroup analysis of larger trial and clinical studies
- Despite above interventions risk of CKD Stage 5 in DKD is substantial

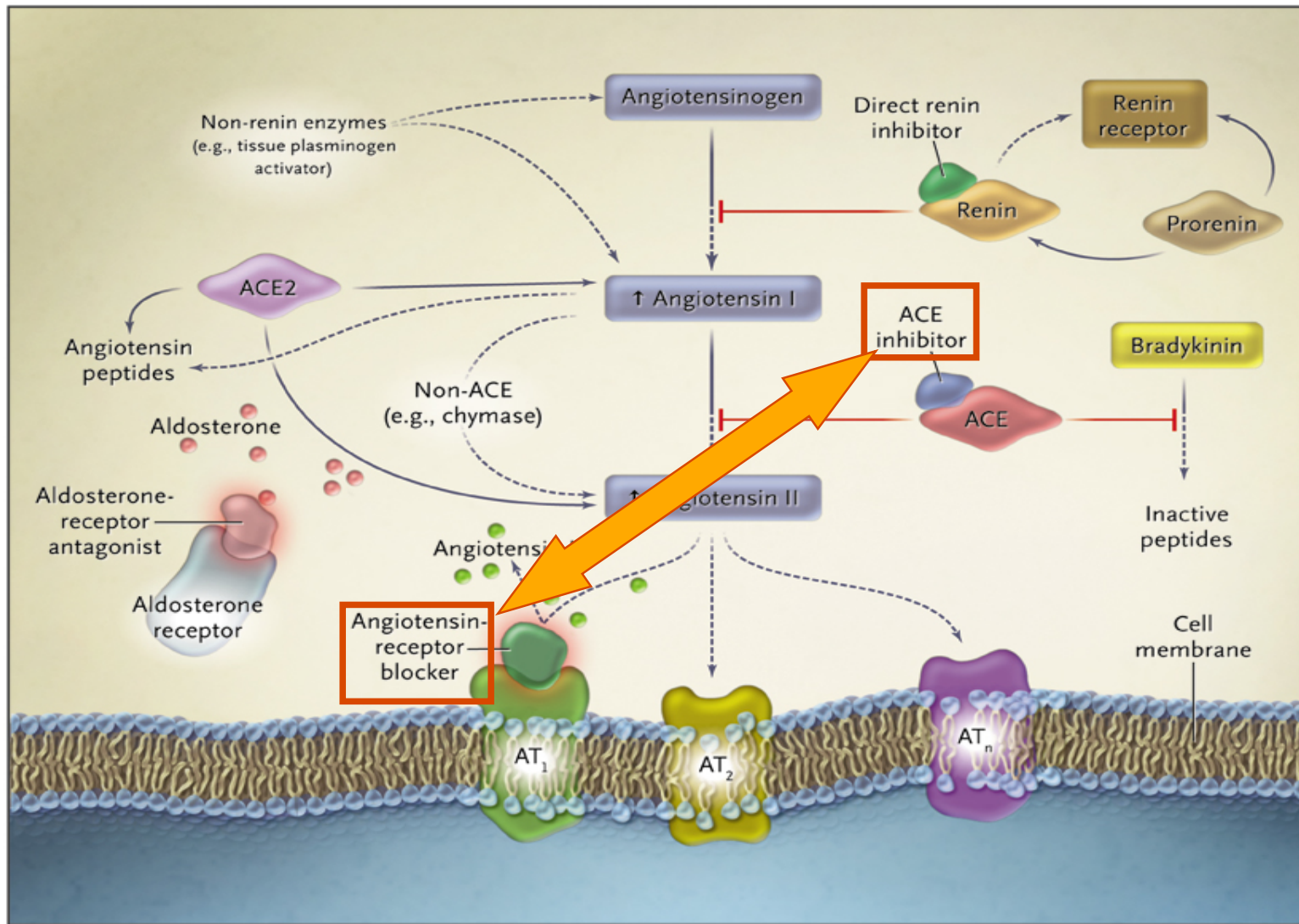
The “forgotten majority” in the leading intervention trials on diabetic nephropathy



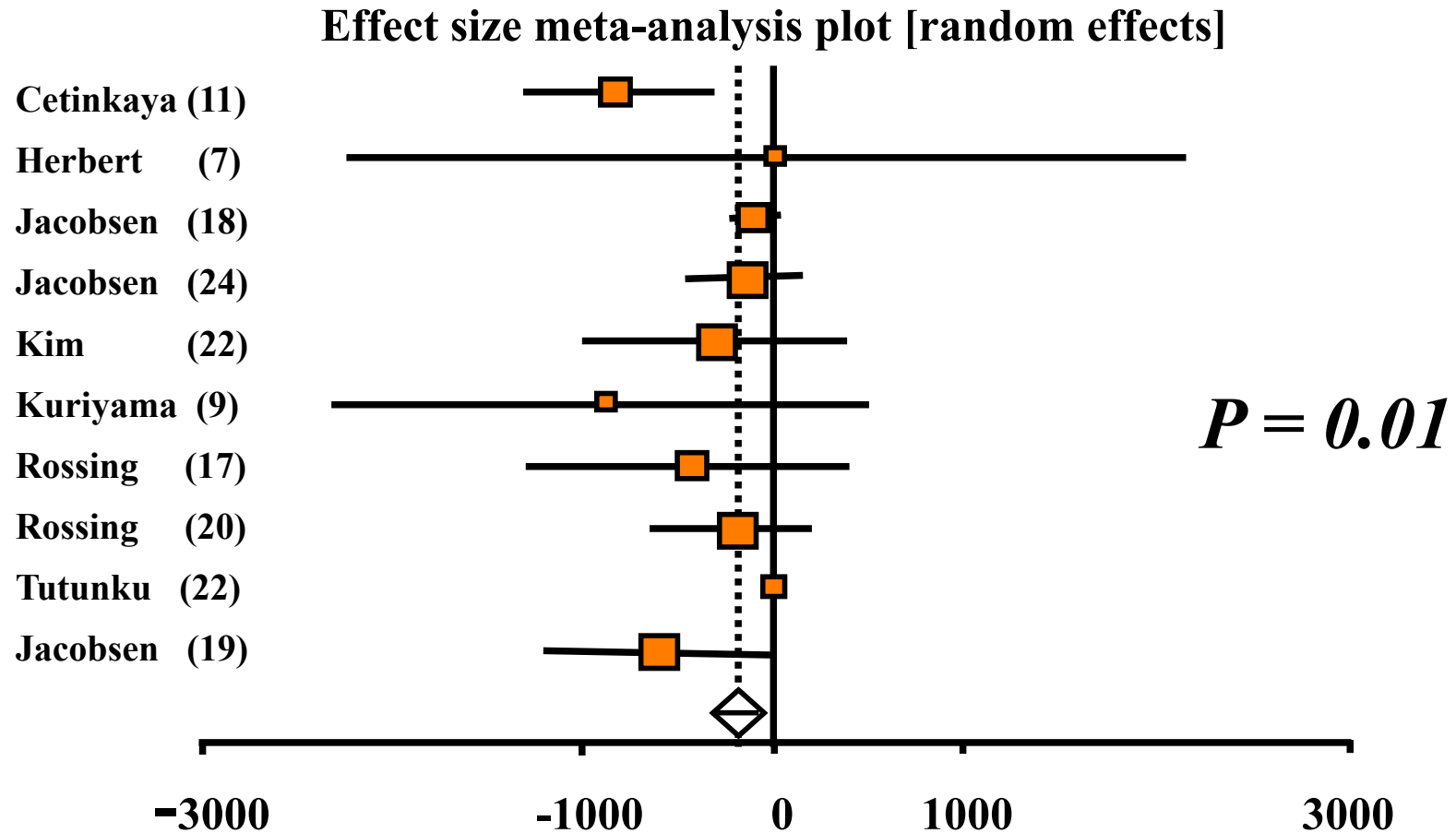
Emerging new approaches in DN

- Dual block
- Anti-renin (Aliskiren)
- Mineralcorticoid antagonist
- Tiazolidinediones
- Statins
- Ruboxistaurin
- Sulodexide
- Pentoxifillina
- Anti-fibrotici
- Anti-AGE
- Analoghi vit. D

Il doppio blocco

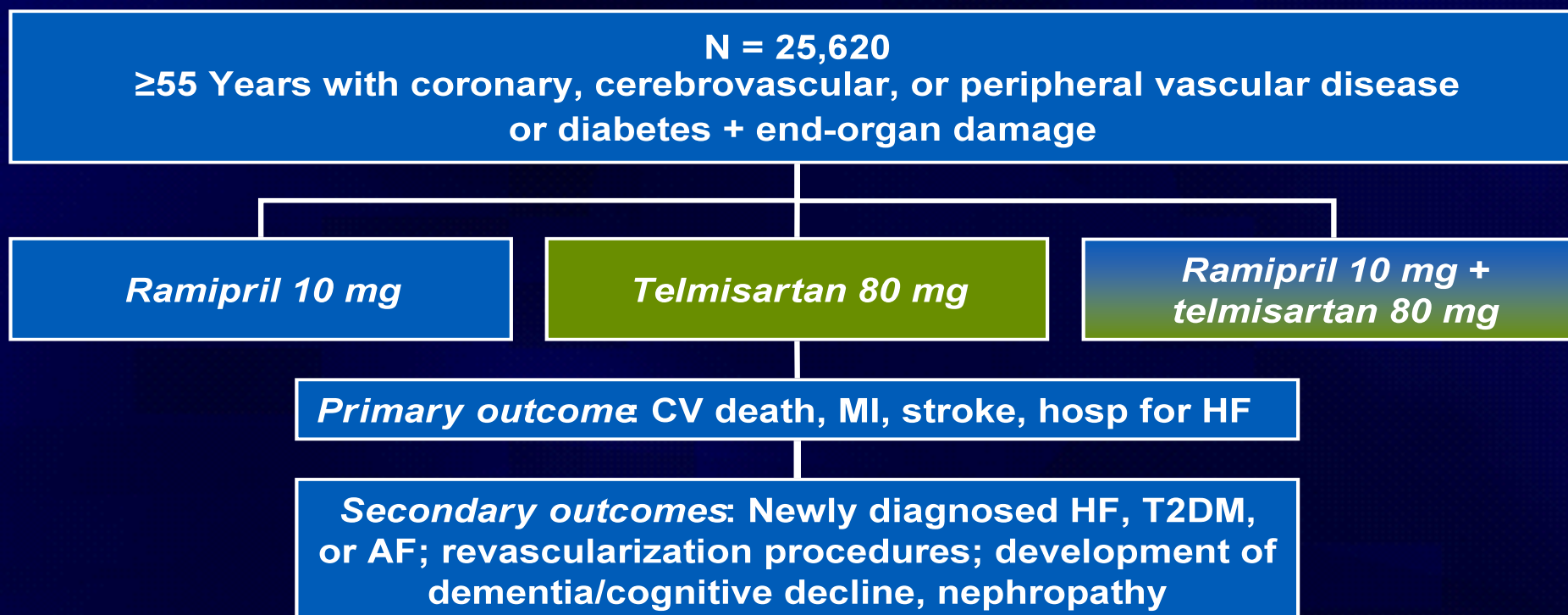


RAAS Dual Blockade and *short term* proteinuria reduction: **a metanalysis**

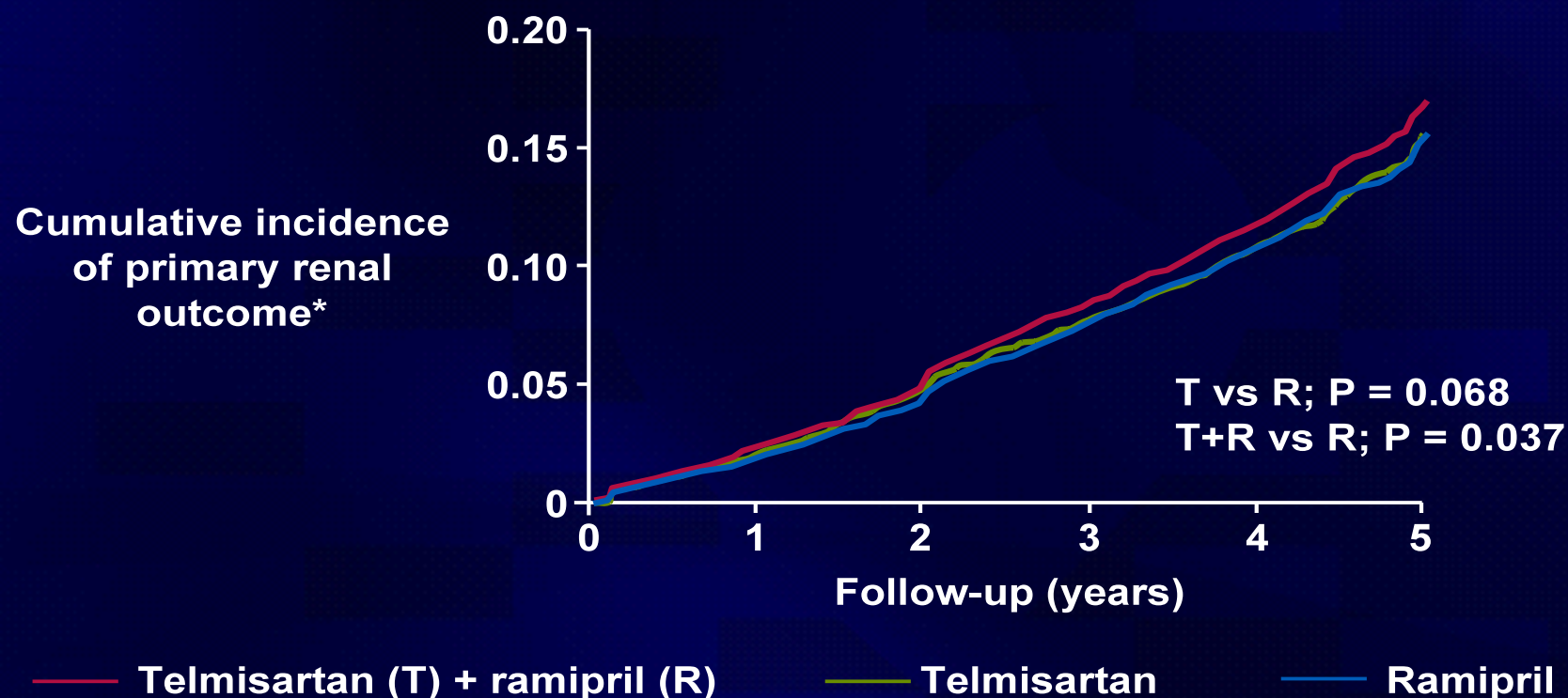


ONTARGET: Study design

Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial



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

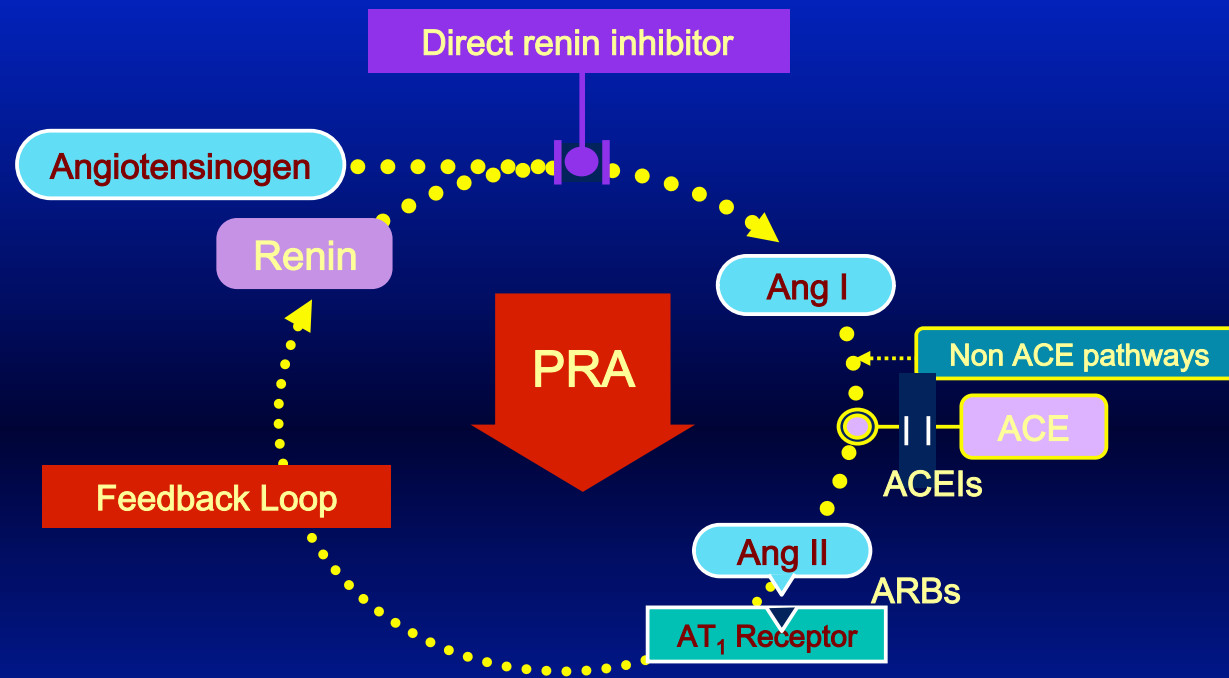
	Ramipril n (%)	Telmisartan n (%)	Ramipril+ telmisartan n (%)	Telmisartan vs ramipril HR (95% CI)	p	Ramipril+ telmisartan vs ramipril HR (95% CI)	p
All dialysis, doubling, death	1150 (13.4)	1147 (13.4)	1233 (14.5)	1.00 (0.92-1.09)	0.968	1.09 (1.01-1.18)	0.037
All dialysis and doubling	174 (2.03)	189 (2.21)	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

Emerging new approaches in DN

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Direct renin inhibition acts at the point of activation of the Renin System and neutralizes the PRA rise



	Ang I	Ang II	Renin	PRA
ACE-I	↑	↓	↑	↑
ARB	↑	↑	↑	↑
Aliskiren	↓	↓	↑	↓

AVOID Study

The NEW ENGLAND
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ESTABLISHED IN 1812

JUNE 5, 2008

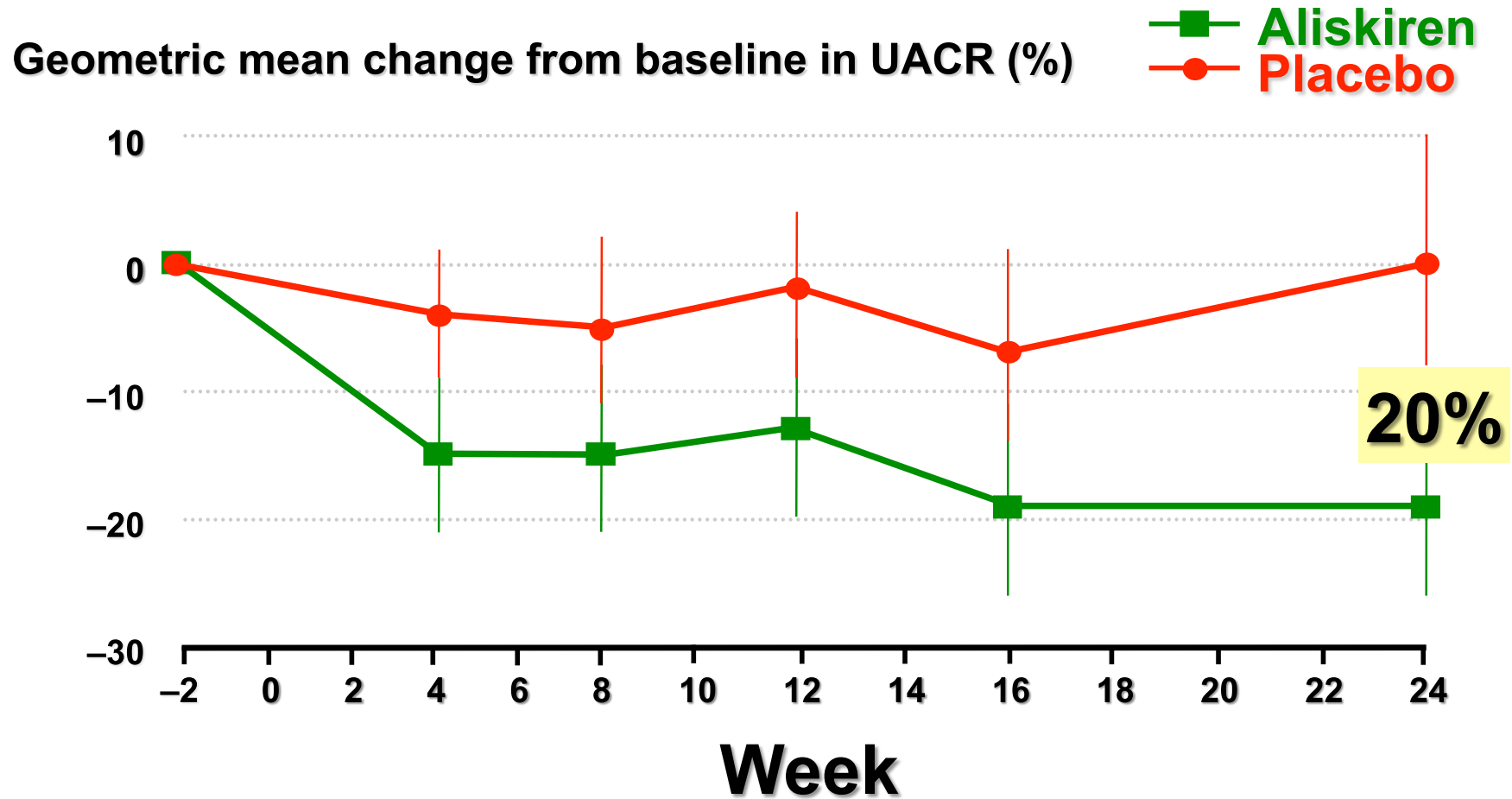
VOL. 358 NO. 23

Aliskiren Combined with Losartan in Type 2 Diabetes and Nephropathy

Hans-Henrik Parving, M.D., D.M.Sc., Frederik Persson, M.D., Julia B. Lewis, M.D., Edmund J. Lewis, M.D.,
and Norman K. Hollenberg, M.D., Ph.D., for the AVOID Study Investigators*

**Double blind, randomized, placebo-controlled study on
599 patients** Inclusion criteria: mild-to-moderate hypertension
type 2 diabetes, proteinuria

AVOID: changes in UACR throughout the study



Nephrol Dial Transplant (2009) 24: 1663–1671

doi: 10.1093/ndt/gfn721

Advance Access publication 14 January 2009

Trial Design



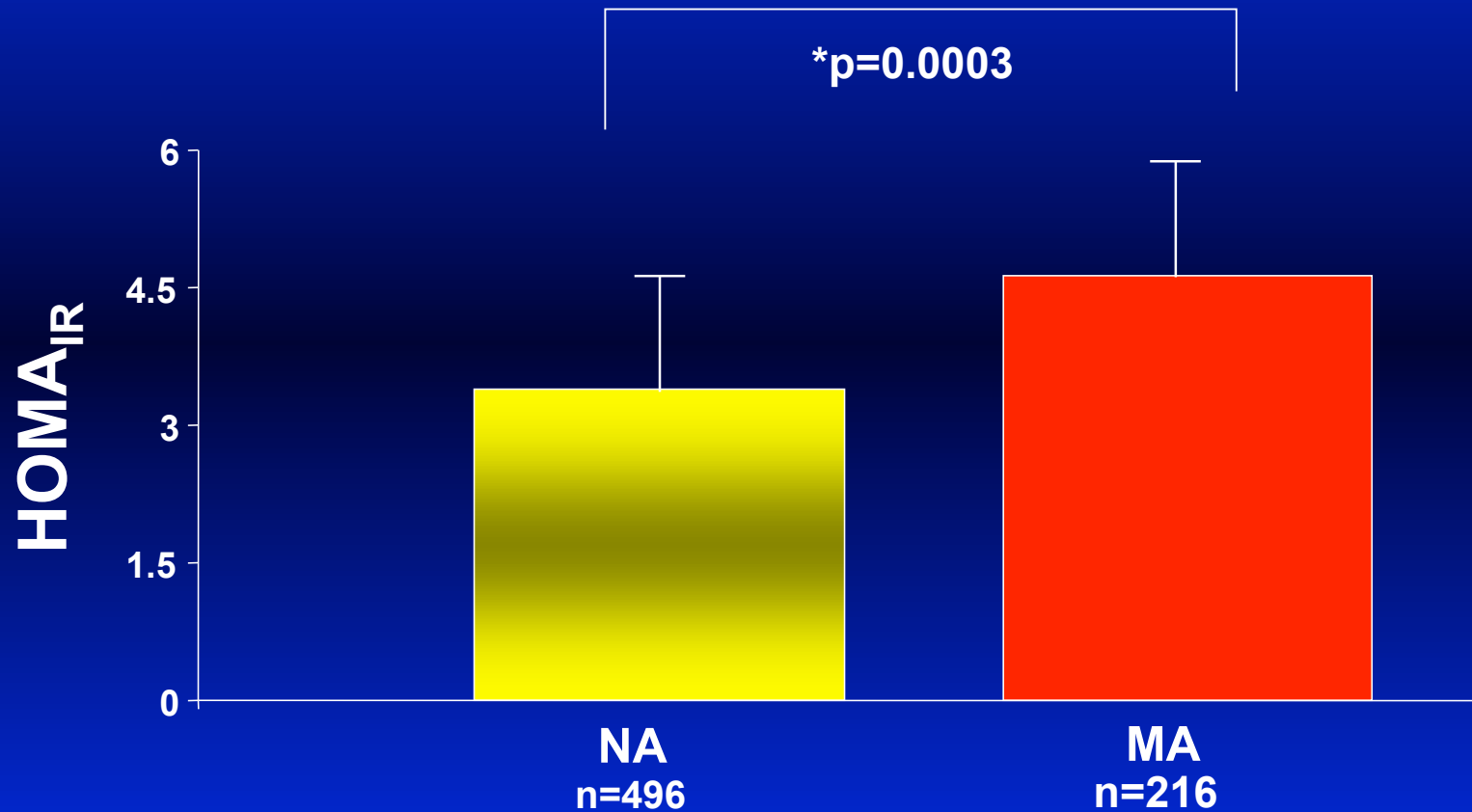
Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE): rationale and study design

Hans-Henrik Parving^{1,2}, Barry M. Brenner³, John. J. V. McMurray⁴, Dick de Zeeuw⁵,
Steven M. Haffner⁶, Scott D. Solomon³, Nish Chaturvedi⁷, Mathieu Ghadanfar⁸, Nicole Weissbach⁸,
Zhihua Xiang⁸, Juergen Armbrecht⁸ and Marc A. Pfeffer³

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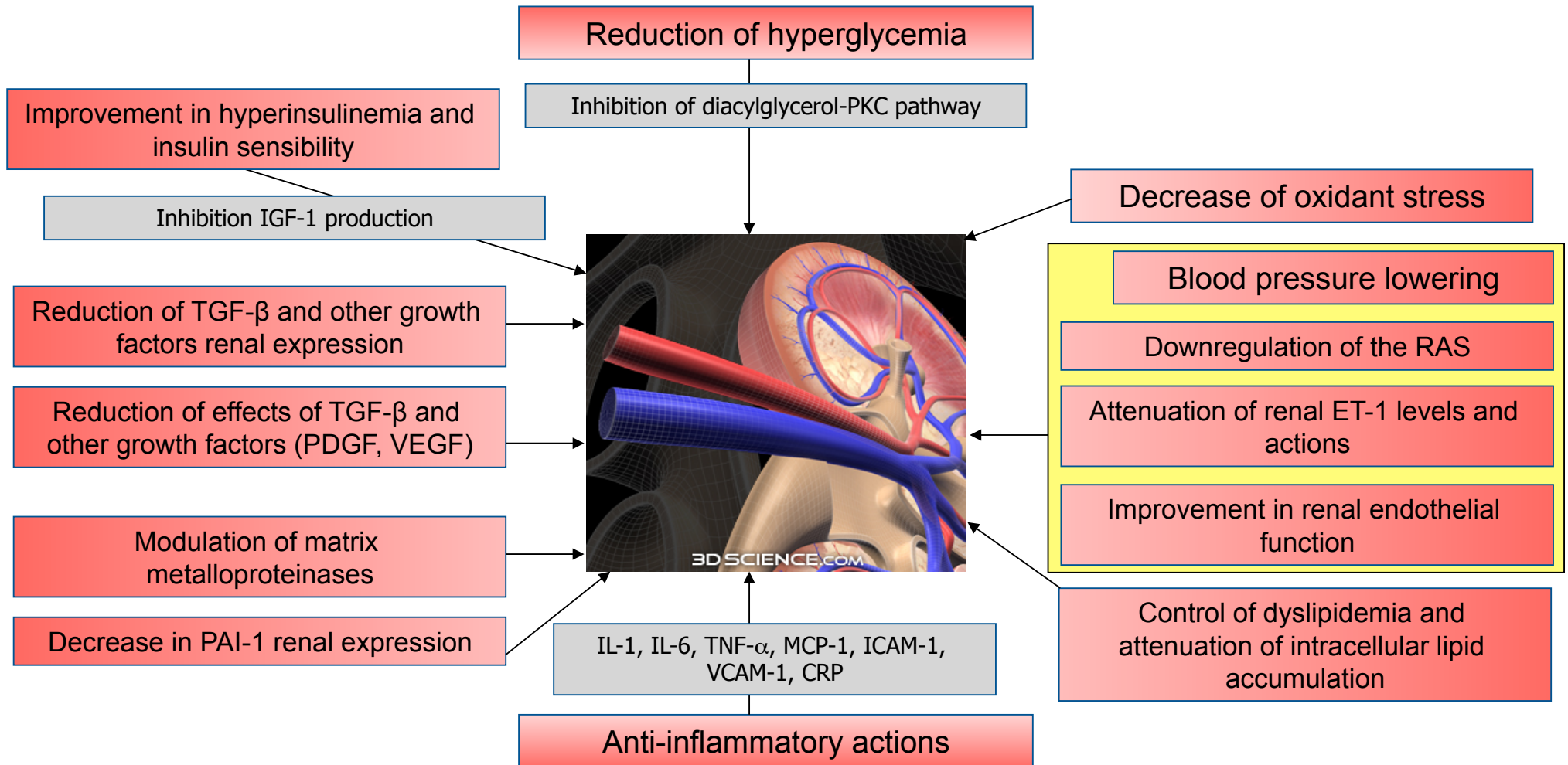
HOMA_{IR} of 712 T2D with Normoalbuminuria (NA) or Micro-macroalbuminuria (MA)



*adjusted for age, gender and BMI

De Cosmo S. Diabetes Care 28:910-15, 2005

Actions of TZDs possibly contributing to a renoprotective effect



modified from Sarafidis PA et al., *Kidney Int* 70: 1223-1233, 2006.

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

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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

AURORA: primary endpoint



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EDITORIAL

Sunset for Statins after AURORA?

Giovanni F.M. Strippoli, Ph.D., and Jonathan C. Craig, Ph.D.

N Engl J Med 2009; 360:1455-1457 | [April 2, 2009](#)

	0	1	2	3	4	5
No. at risk:						
Rosuvastatin	1390	1152	962	826	551	148
Placebo	1384	1163	952	809	534	153

N Engl J Med 2009;360:1395-407.

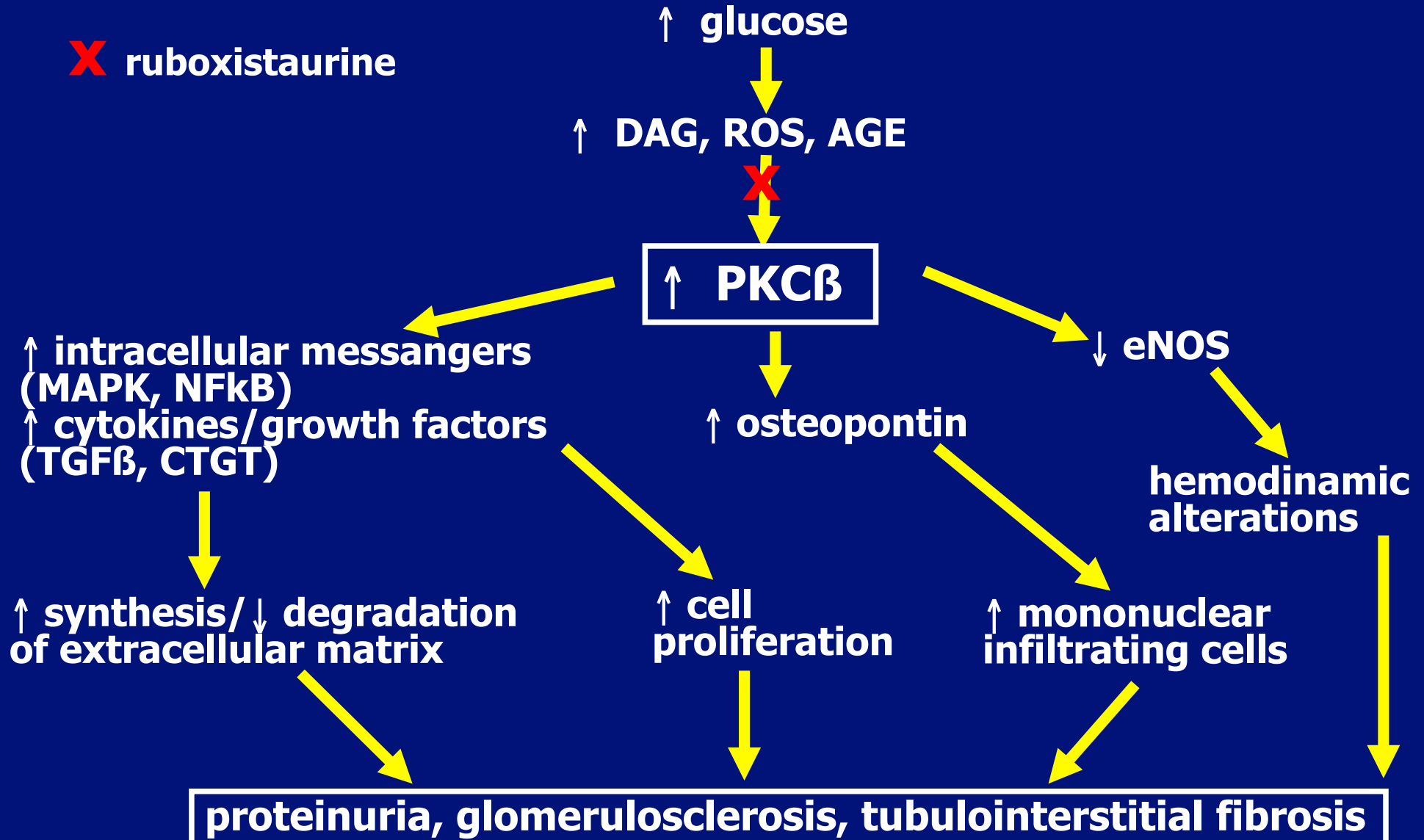
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Rationale for the use of ruboxistaurine in DN

X ruboxistaurine



Published ahead of print on May 30, 2007
Clin J Am Soc Nephrol 2: 631-636, 2007
© 2007 [American Society of Nephrology](#)
doi: 10.2215/CJN.00840207

Diabetes and the Kidney

Kidney Outcomes in Long-Term Studies of Ruboxistaurin for Diabetic Eye Disease

Katherine R. Tuttle^{*}, Janet B. McGill[†], Douglas J. Haney[‡], Toni E. Lin[‡], Pamela W. Anderson[‡]; for the PKC-DRS, PKC-DMES, and PKC-DRS 2 Study Groups

^{*} Providence Medical Research Center and University of Washington School of Medicine, Spokane, Washington; [†] Department of Medicine, Washington University, St. Louis, Missouri; and [‡] Lilly Research Laboratories, Eli Lilly and Company, Indianapolis,

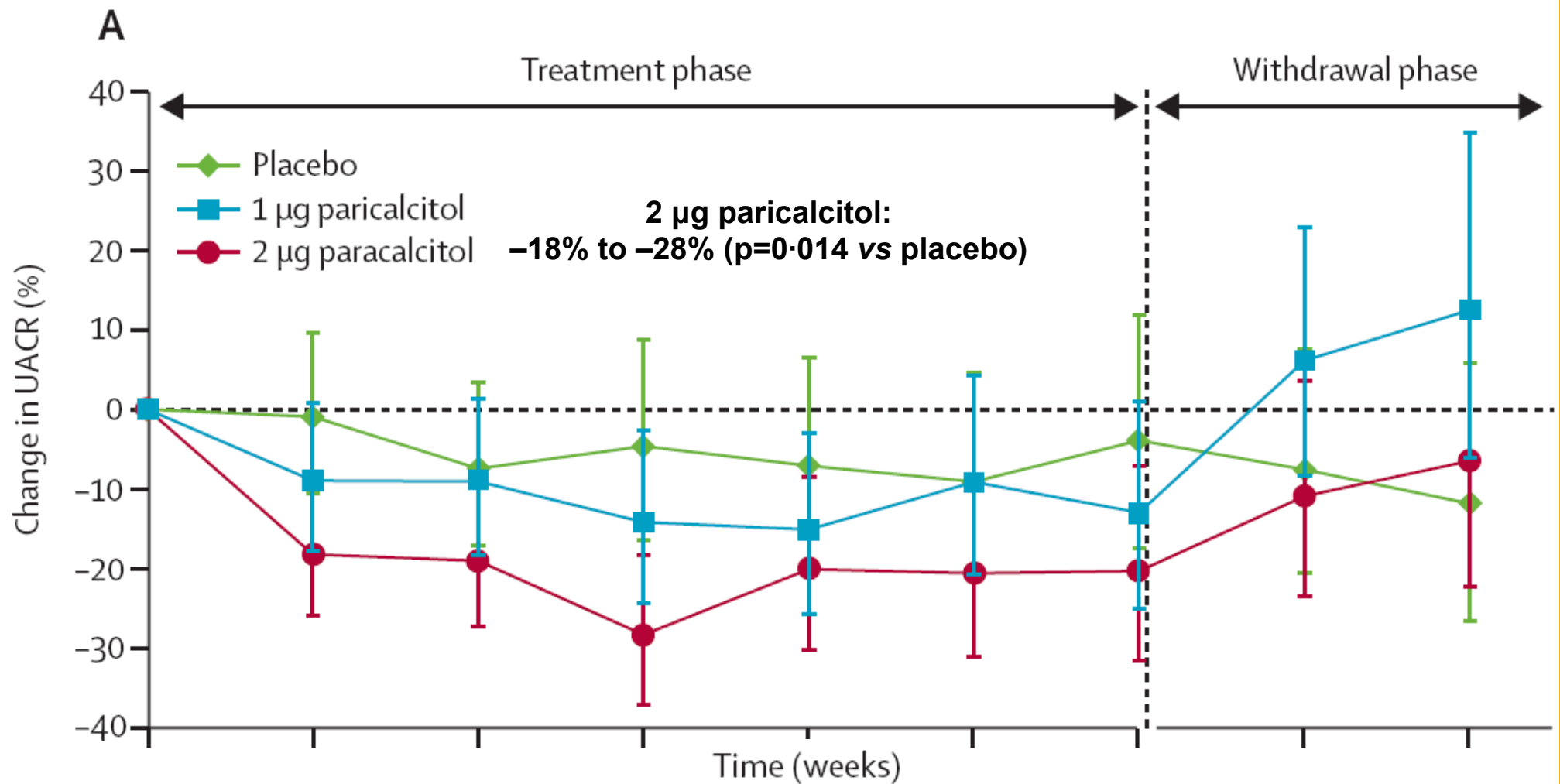
Conclusions: Long-term kidney outcomes in patients with diabetic eye disease were similar in placebo and RBX groups. In conclusion, large-scale, prospective trials in patients with diabetic nephropathy are needed to confirm safety and potential benefits of RBX on clinical outcomes.

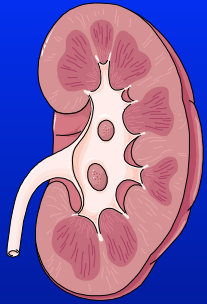
Related Article

Protein Kinase C- β Inhibition: A Promise Not Yet Fulfilled

George L. Bakris

Selective vitamin D receptor activation with paricalcitol for reduction of albuminuria in patients with type 2 diabetes





Standard Italiani per la Cura del Diabete Mellito 2009-2010

AMD-SID

Raccomandazioni

- **Ottimizzare il compenso glicemico per ridurre il rischio e/o rallentare la progressione della nefropatia.**
(Livello della prova I, Forza della raccomandazione A)
- **Ottimizzare il controllo pressorio per ridurre il rischio e/o rallentare la progressione della nefropatia.**
(Livello della prova I, Forza della raccomandazione A)