Cuneo 25 gennaio 2014

Il blocco del sistema renina angiotensina nel diabete

Federico Marazzi
Nefrologia Dialisi ASL CN 1
Savigliano - Saluzzo

Renin-angiotensin system revisited

F. Fyhrquist & O. Saijonmaa

From the Minerva Institute for Medical Research and Department of Internal Medicine, Helsinki University Central Hospital, Helsinki, Finland

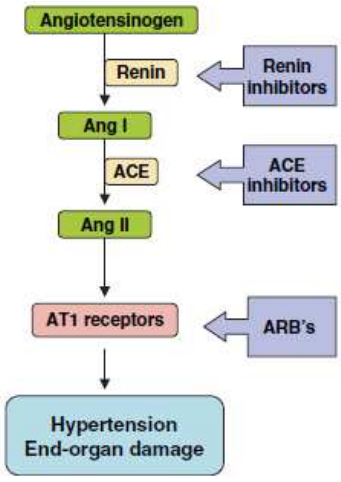


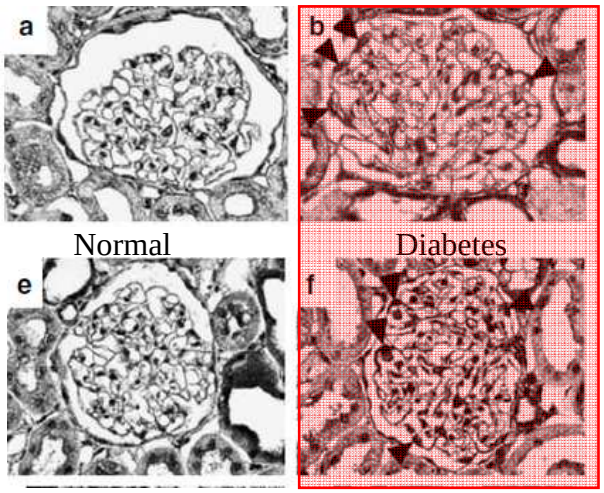
Fig. 5 Scheme of presently available renin-angiotensin system inhibitors.

Specificità del RAAS nel diabete.

IPERSTIMOLATO A LIVELLO TISSUTALE DA HG

Activation of the renin–angiotensin system within podocytes in diabetes

T-H Yoo[1,4], J-J Li[1,2,4], J-J Kim[1,4], D-S Jung[1], S-J Kwak[1], D-R Ryu[3], HY Choi[1], JS Kim[1], HJ Kim[1], SH Han[1], JE Lee[1], DS Han[1] and S-W Kang[1]



Angiotensina

AT1R

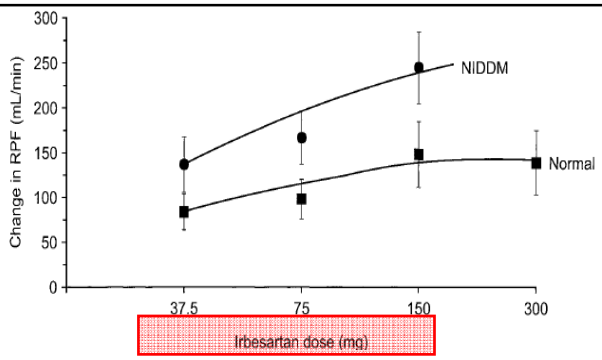
J Am Soc Nephrol 10: 2382–2391, 1999

The Paradox of the Low-Renin State in Diabetic Nephropathy

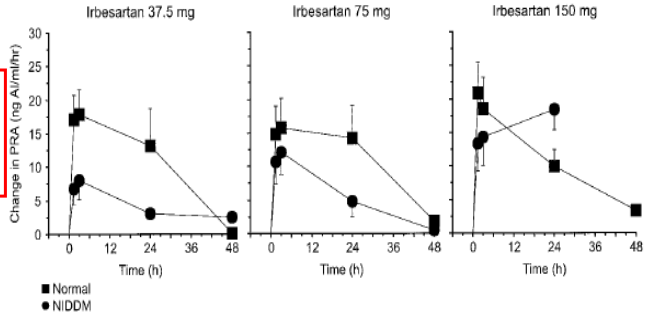
DEBORAH A. PRICE, LISA E. PORTER, MICHAEL GORDON, NAOMI D. L. FISHER, JOSE MARIO F. DE'OLIVEIRA, LORI M. B. LAFFEL, DIANE R. PASSAN, GORDON H. WILLIAMS, and NORMAN K. HOLLENBERG
Departments of Medicine and Radiology, Harvard Medical School and Brigham and Women's Hospital, Boston, Massachusetts.

Iperattivo nel rene e depresso a livello sistemico.

INCREMENTO DI RPF DOPO IRBESARTAN



PRA DEPRESSA COSTANTEMENTE IN DM II

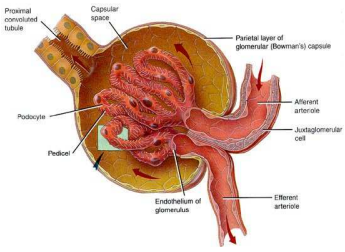


EDITORIAL

Renal hyperfiltration related to diabetes mellitus and obesity in human disease

Alexa N Sasson, David ZI Cherney

HEMODYNAMIC HYPOTHESIS FOR HYPERFILTRATION IN TYPE 1 DM



1. Nitric oxide (NO) system.
2. Cyclooxygenase 2 (COX2)- derived prostanoids.
3. The renin angiotensin system (RAS).
4. Protein kinase C (PKC).
5. Endothelin (ET).

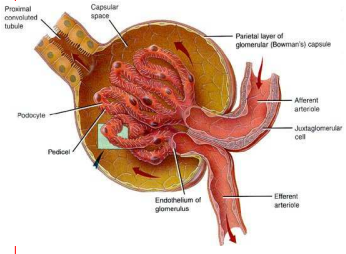
EDITORIAL

Renal hyperfiltration related to diabetes mellitus and obesity in human disease

Alexa N Sasson, David ZI Cherney

TUBULAR HYPOTHESIS FOR HYPERFILTRATION IN TYPE 1 DM

HG → Increased sodium reabsorption in the proximal tubule,mediated by the sodium-glucose cotransporter-2 (SGLT2).



↑ [NaCl] macula densa

↑ Resistenza Arteriolare Afferente

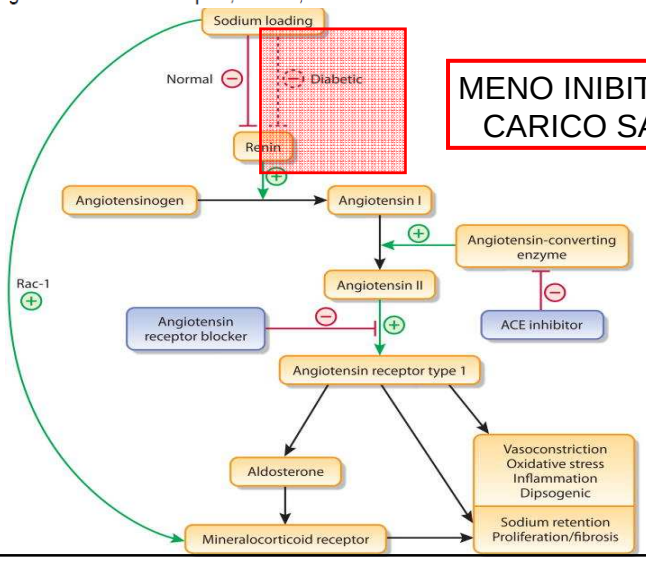
↓ SNGFR

VIA FEED BACK TUBULO GLOMERULARE

HYPERFILTRATION.

You are what you Eat: Dietary Salt Intake and Renin Angiotensin Blockade in Diabetic Nephropathy

David M. Charytan, MD MSc and **John P. Forman, MD MSc**
Renal Division, Brigham & Women's Hospital, Boston, MA
Kidney Int. 2012 August ; 82(3): 257–259.



MENO INIBITO DAL CARICO SALINO

Obes Facts 2012;5:611–624

AGISCE NEGATIVAMENTE SUL TROFISMO DELLE BETA CELLULE E SULLA SENSIBILITA' ALL'INSULINA

The Renin-Angiotensin System in the Pathophysiology of Type 2 Diabetes

Gijs H. Goossens

Department of Human Biology, NUTRIM School for Nutrition, Toxicology & Metabolism, Maastricht University Medical Center, Maastricht, the Netherlands

Several in vitro, animal, and clinical studies have demonstrated that the RAS may contribute to impaired insulin secretion and insulin resistance, thereby increasing the risk for type 2 diabetes.

The Renin-Angiotensin System and Beta-Cell Function
The Renin-Angiotensin System and Insulin Sensitivity
The Renin-Angiotensin System and Skeletal Muscle Function
The Renin-Angiotensin System and Adipose Tissue Function

The renin–angiotensin system and diabetes: An update

Antônio Ribeiro-Oliveira Jr[1] Vascular Health and Risk Management 2008:4(4) 787–803

FA «PENDERE LA BILANCIA» A FAVORE DEI FATTORI ENDOTELIO LESIVI

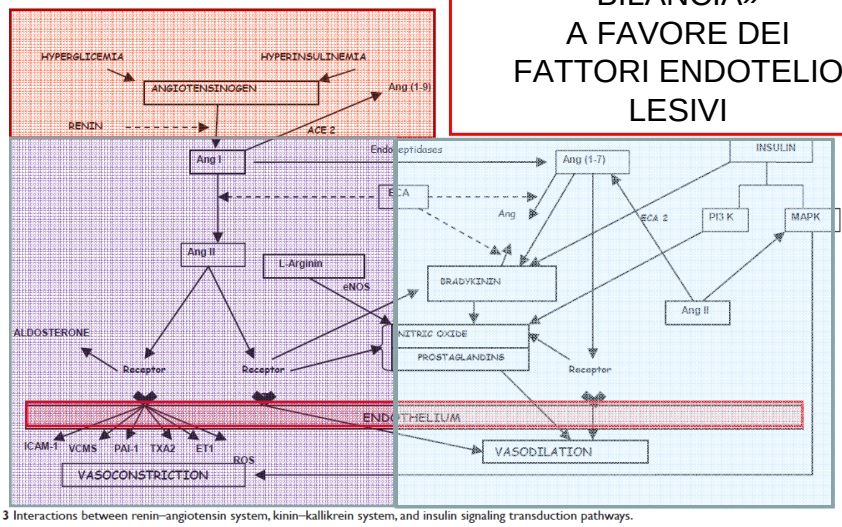
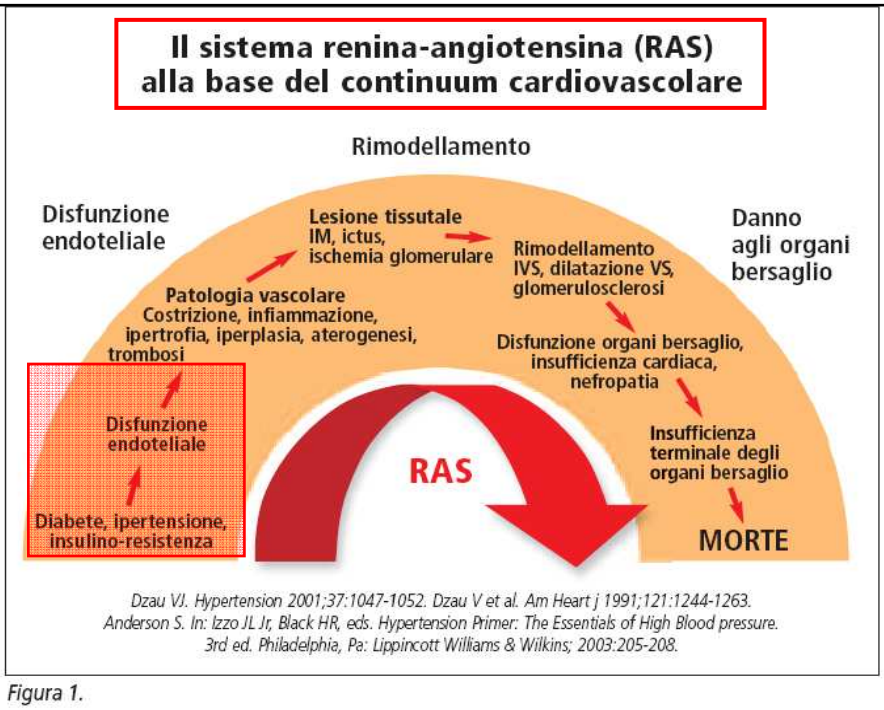


Figure 3 Interactions between renin–angiotensin system, kinin–kallikrein system, and insulin signaling transduction pathways.
Abbreviations: MAPK, mitogen-activated protein kinase; PI3K, inositol 3 phosphatidil kinase; Ang, Angiotensin; ACE, angiotensin-converting enzyme; ACE2, angiotensin-converting enzyme 2; AT_1, AT_2, angiotensinergic receptors types 1 and 2; Mas, Mas receptor of angiotensin-(1-7); NO, nitric oxide; eNOS, endothelial nitric oxide synthase; ROS, reactive oxygen species; ET1, endothelin 1; TXA_2, thromboxane A_2; PAI 1, plasminogen activator inhibitor; VCMS, vascular smooth muscle cell; ICAM1, intracellular adhesion molecule 1.



Dzau VJ. Hypertension 2001;37:1047-1052. Dzau V et al. Am Heart j 1991;121:1244-1263. Anderson S. In: Izzo JL Jr, Black HR, eds. Hypertension Primer: The Essentials of High Blood pressure. 3rd ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2003:205-208.

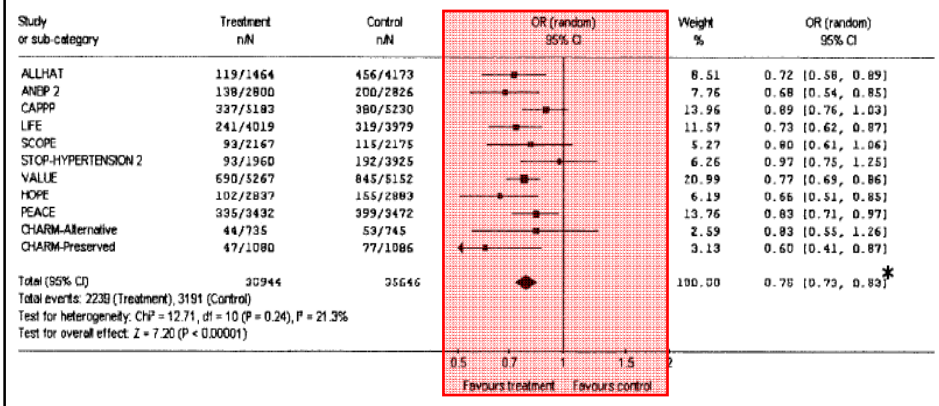
Figura 1.

PREVENZIONE DELL'INSORGENZA
DI NUOVI CASI DI DM II

The Impact of ACE Inhibitors or Angiotensin II Type 1 Receptor Blockers on the Development of New-Onset Type 2 Diabetes

Effie L. Gillespie, pharmd[1,2]
C. Michael White, pharmd[1,2]
Michael Kardas, pharmd[1]
Michael Lindberg, md[3,4]
Craig I. Coleman, pharmd[1,2]

Diabetes Care 28:2261–2266, 2005



PROTEZIONE CARDIOVASCOLARE

J Am Soc Nephrol 15: S6–S11, 2004

Optimizing Therapy in the Diabetic Patient with Renal Disease: Antihypertensive Treatment

GIACOMO DEFERRARI,* MAURA RAVERA,* VALERIA BERRUTI,* GIOVANNA LEONCINI,* and LUCA DEFERRARI†

*Department of Internal Medicine, *Sections of Nephrology and Dialysis and †Cardiology, University of Genoa, Genoa, Italy*

Table 1. The effect of various drugs on cardiovascular events in diabetes[a]

Trial	Number of Patients	Follow-Up (yr)	BP (mmHg)		Risk Reduction (%)
			New Drugs	Old Drugs	
ACEI *versus* CT					
UKPDS, 1998 (41)	758	8.4	144/83	143/81	+37
CAPPP, 1999, 2001 (48)	572	6.1	156/89	154/88	39[b]
HOPE, 2000 (17)	3527	4.5	140/77	143/77	25[b]
STOP-2, 2000 (51)	488	4.5	161/80	161/81	15
ACEI *versus* CCB					
FACET, 1998 (49)	380	2.5	157/88	153/86	51[b]
STOP-2, 2000 (51)	466	4.5	161/80	162/79	6
ABCD-HT, 1998, 2000 (46,20)	470	5.3	136/88	135/88	40[b]
ABCD-NT, 2002 (42)	480	5.3	132/78	132/78	19
CCB *versus* CT					
STOP-2, 2000 (51)	484	4.5	162/89	161/81	9
NORDIL, 2000 (53)	727	4.5	154/88	151/88	+12
INSIGHT, 2000 (54)	1302	4.0	138/82	138/82	1
ARB *versus* CT					
LIFE, 2002 (3)	1195	4.7	146/79	148/79	31[b]
IDNT, 2001 (34)	1148	2.6	141/77	144/80	9
RENAAL 2001 (35)	1513	3.4	140/74	142/74	7

[a] ACEI, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; ARB, Angiotensin II receptor blocker; CT, conventional therapy.

[b] Differences between old and new drugs, $P < 0.05$.

PREVENZIONE PRIMARIA DELLA NEFROPATIA DIABETICA

Annals of Internal Medicine | ARTICLE

Effect of Candesartan on Microalbuminuria and Albumin Excretion Rate in Diabetes

Three Randomized Trials

Rudy Bilous, MD; Nish Chaturvedi, MD; Anne Katrin Sjølie, MD; John Fuller, MD; Ronald Klein, MD; Trevor Orchard, MD; Massimo Porta, MD; and Hans-Henrik Parving, MD*

Conclusion: Candesartan, 32 mg/d, for 4.7 years did not prevent microalbuminuria in mainly normotensive patients with type 1 or type 2 diabetes.

Ann Intern Med. 2009;151:11-20.

N Engl J Med. 2009 July 2:

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

Michael Mauer[1,2], Bernard Zinman[3], Robert Gardiner[4], Samy Suissa[5], Alan Sinaiko[1], Trudy Strand[1], Keith Drummond[6], Sandra Donnelly[3], Paul Goodyer[6], Marie Claire Gubler[7], and Ronald Klein[8]

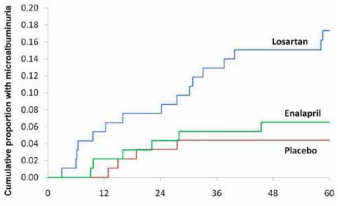
a. Effects of Enalapril and Losartan Relative to Placebo on Mesangial Fractional Volume Change from the Baseline to the 5-Year Biopsy

	Placebo (N=85)	Enalapril (N=86)	Losartan (N=85)
Mean mesangial fractional volume at baseline	0.187	0.201	0.189
Mean change in mesangial fractional volume from baseline	0.016	0.005	0.026
Difference in change *vs.* placebo			
Mean difference	0 (reference)	−0.011	0.010
p-value		0.16	0.17
Adjusted* difference in change *vs.* placebo			
Mean difference	0 (reference)	−0.006	0.008
p-value		0.38	0.26

b. Effects of Enalapril and Losartan Relative to Placebo on Albumin Excretion Rate and Glomerular Filtration Rate During the Five-year Follow-up and at the Five-year Biopsy

Normoalbuminuric, normotensive T1DM participants randomized to RAS blockade with an ACEI or an ARB.

	Placebo (N=85)	Enalapril (N=86)	Losartan (N=85)
Albumin Excretion Rate (µg/min)			
Mean at baseline	6.4±6	6.3±5	6.5±7
Mean over 5 yrs of follow-up	6.5±6	7.7±16	10.6±18
Mean difference *vs.* placebo*	0 (reference)	1.3	4.0
p-value*		0.47	0.033
Mean at the five-year biopsy visit	5.3±4	6.9±8	14.0±36
Mean difference *vs.* placebo*	0 (reference)	1.0	8.0
p-value*		0.74	0.007
Glomerular Filtration Rate (ml/min/1.73m²)			
Mean at baseline	126±22	129±20	131±18
Mean over 5 yrs of follow-up	125±18	124±18	125±17
Mean difference *vs.* placebo†	0 (reference)	−2.6	−2.4
p-value†		0.11	0.14
Mean at the five-year biopsy visit	120±22	123±20	121±21
Mean difference *vs.* placebo†	0 (reference)	0.4	1.5
p-value†		0.88	0.54



DR

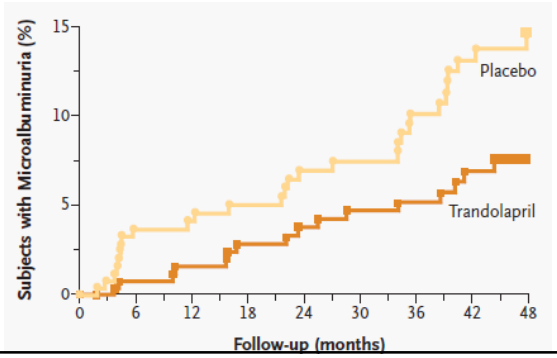
	N	Events (%)	Adjusted*	95% CI	p-value
2-Step or more progression					
Placebo	74	28 (38)	Reference	Reference	Reference
Enalapril	77	19 (25)	0.35	0.14–0.85	0.02
Losartan	72	15 (21)	0.30	0.12–0.73	0.008
3-Step or more Progression					
Placebo	74	21 (28)	Reference	Reference	Reference
Enalapril	77	15 (19)	0.39	0.15–0.98	0.045
Losartan	72	9 (13)	0.21	0.07–0.61	0.004

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 4, 2004 VOL. 351 NO. 19

Preventing Microalbuminuria in Type 2 Diabetes

Piero Ruggenenti, M.D., Anna Fassi, M.D., Anelja Parvanova Ilieva, M.D., Simona Bruno, M.D., Ilian Petrov Iliev, M.D., Varusca Brusegan, M.D., Nadia Rubis, R.N., Giulia Gherardi, R.N., Federica Arnoldi, R.N., Maria Ganeva, Stat.Sci.D., Bogdan Ene-Iordache, Eng.D., Flavio Gaspari, Ph.D., Annalisa Perna, Stat.Sci.D., Antonio Bossi, M.D., Roberto Trevisan, M.D., Alessandro R. Dodesini, M.D., and Giuseppe Remuzzi, M.D., for the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) Investigators

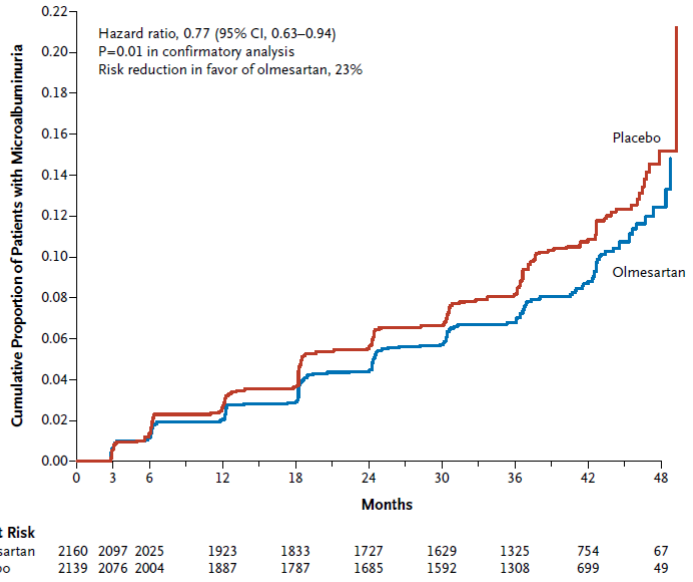


N 1204

Olmesartan for the Delay or Prevention of Microalbuminuria in Type 2 Diabetes

the ROADMAP Trial Investigators

N Engl J Med 2011;364:907-17.



No. at Risk										
Olmesartan	2160	2097	2025	1923	1833	1727	1629	1325	754	67
Placebo	2139	2076	2004	1887	1787	1685	1592	1308	699	49

PREVENZIONE SECONDARIA DELLA NEFROPATIA DIABETICA

Randomised controlled trial of long term efficacy of captopril on preservation of kidney function in normotensive patients with insulin dependent diabetes and microalbuminuria

BMJ VOLUME 319 3 JULY 1999

Elisabeth R Mathiesen, Eva Hommel, Henrik P Hansen, Ulla M Smidt, Hans-Henrik Parving

After 8 years :

Progressed to diabetic nephropathy:

Control Group 40% (9/23) .

Captopril Group 10% (2/21)

P = 0.019.

Decline in mean glomerular filtration rate (ml/min):

Control Group 11.8 (P = 0.03)

Captopril Group 1.4 (P = 0.65)

P = 0.09 .

LONG-TERM STABILIZING EFFECT OF ANGIOTENSIN-CONVERTING ENZYME-INHIBITION ON PLASMA CREATININE AND ON PROTEINURIA IN NORMOTENSIVE TYPE-II DIABETIC-PATIENTS

RAVID, M (RAVID, M); SAVIN, H (SAVIN, H); JUTRIN, I (JUTRIN, I); BENTAL, T (BENTAL, T); KATZ, B (KATZ, B); LISHNER, M (LISHNER, M)

ANNALS OF INTERNAL MEDICINE APR 15 1993

RCT 94 pts. Enalapril, 10 mg per day or placebo, 5 years.

Kidney Function Decline

Enalapril Group -1%

Placebo Group 13% in the placebo group and

P < 0.05.

Albuminuria

Enalapril Group :

143 +/- 64 mg/24 h to 140 +/- 134 mg/24.

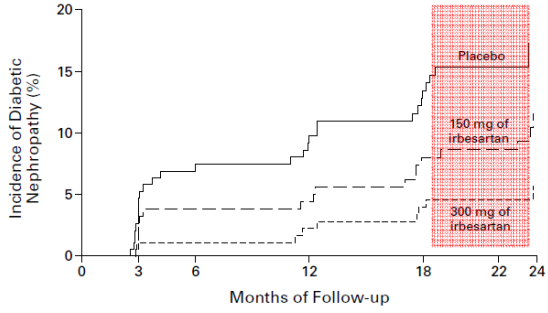
Placebo Group:

123 +/- 58 mg/24 h to 310 +/- 167 mg/24 .

P < 0.05.

THE EFFECT OF IRBESARTAN ON THE DEVELOPMENT OF DIABETIC NEPHROPATHY IN PATIENTS WITH TYPE 2 DIABETES

HANS-HENRIK PARVING, M.D., D.M.SC., HENDRIK LEHNERT, M.D., JENS BRÖCHNER-MORTENSEN, M.D., D.M.SC., RAMON GOMIS, M.D., STEEN ANDERSEN, M.D., AND PETER ARNER, M.D., D.M.SC., FOR THE IRBESARTAN IN PATIENTS WITH TYPE 2 DIABETES AND MICROALBUMINURIA STUDY GROUP*

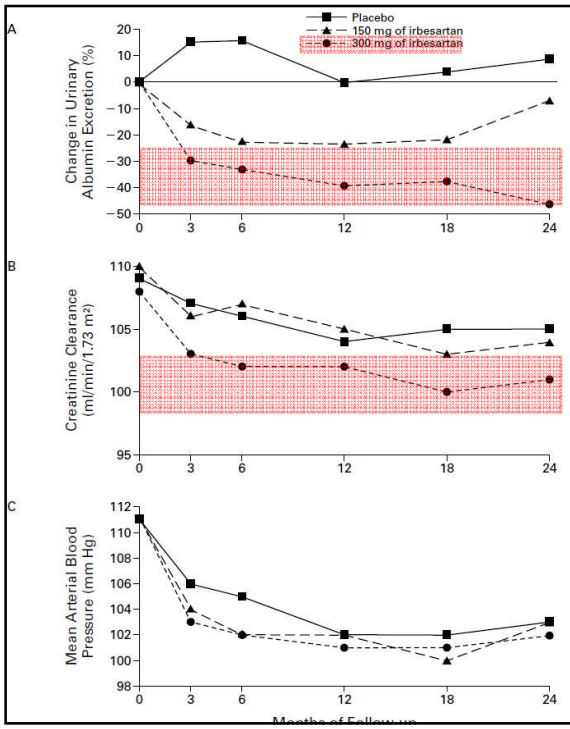


NO. AT RISK

Placebo	201	201	164	154	139	129	36
150 mg of irbesartan	195	195	167	161	148	142	45
300 mg of irbesartan	194	194	180	172	159	150	49

Figure 2. Incidence of Progression to Diabetic Nephropathy during Treatment with 150 mg of Irbesartan Daily, 300 mg of Irbesartan Daily, or Placebo in Hypertensive Patients with Type 2 Diabetes and Persistent Microalbuminuria.

The difference between the placebo group and the 150-mg group was not significant (P=0.08 by the log-rank test), but the difference between the placebo group and the 300-mg group was significant (P<0.001 by the log-rank test).



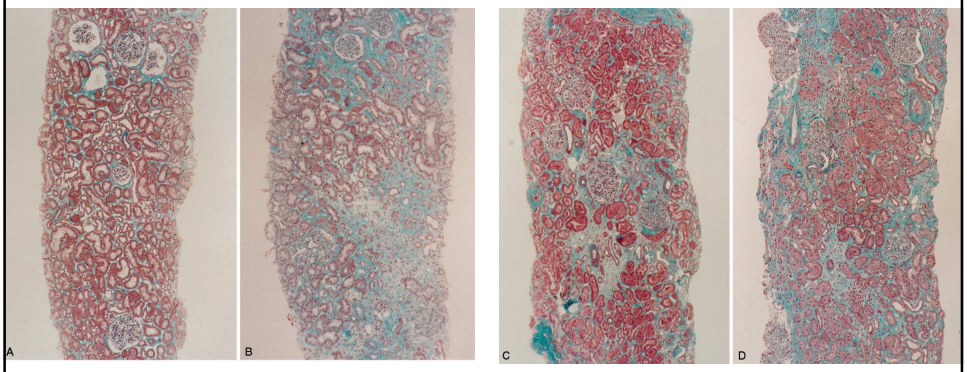
Conclusions
Irbesartan is renoprotective independently of its blood-pressure–lowering effect in patients with type 2 diabetes and microalbuminuria

PREVENZIONE TERZIARIA DELLA PROGRESSIONE DELLA NEFROPATIA DIABETICA

Expansion of Cortical Interstitium Is Limited by Converting Enzyme Inhibition in Type 2 Diabetic Patients with Glomerulosclerosis

2 years

DANIEL J. CORDONNIER,* NICOLE PINEL,§ CLAIRE BARRO,‖ CLAIRE MAYNARD,* PHILIPPE ZAOUI,*‖ SERGE HALIMI,*‖ BRUNO HURAULT DE LIGNY,† YVES REZNIC,† DOMINIQUE SIMON,‡ and RUDOLF W. BILOUS,# FOR THE DIABIOPSIES GROUP*



Placebo

Perindopril

J Am Soc Nephrol

THE EFFECT OF ANGIOTENSIN-CONVERTING–ENZYME INHIBITION ON DIABETIC (DM I) NEPHROPATHY

EDMUND J. LEWIS, M.D., LAWRENCE G. HUNSICKER, M.D., RAYMOND P. BAIN, PH.D., AND RICHARD D. ROHDE, B.S., FOR THE COLLABORATIVE STUDY GROUP*

Table 2. Outcome Events in Patients with Diabetic Nephropathy in the Captopril and Placebo Groups.

EVENT	CAPTOPRIL (N = 207)	PLACEBO (N = 202)
	number of patients	
Death*	8	14
Dialysis or transplantation	20	31
Death, dialysis, or transplantation	23	42
Stopping points†		
Doubling of serum creatinine‡	25	43
Neutropenia	1	1
Captopril-specific side effect	2	1
Nonspecific side effect	3	3
Hyperkalemia	3	0
Failed blood-pressure control	1	3
Intercurrent illness or condition	11	7
Pregnancy	1	1
Study medication discontinued for other reasons	19	11
Scheduled follow-up visits discontinued*	27	31

*Includes patients who had previously reached other stopping points.

†Includes patients reaching stopping points who stopped taking their coded medication but continued their scheduled visits.

‡The primary end point was a doubling of the base-line serum creatinine concentration to at least 2.0 mg per deciliter.

N Engl J Med 1993

RENOPROTECTIVE EFFECT OF THE ANGIOTENSIN-RECEPTOR ANTAGONIST IRBESARTAN IN PATIENTS WITH NEPHROPATHY DUE TO TYPE 2 DIABETES

EDMUND J. LEWIS, M.D., LAWRENCE G. HUNSICKER, M.D., WILLIAM R. CLARKE, PH.D., TOMAS BERL, M.D., MARC A. POHL, M.D., JULIA B. LEWIS, M.D., EBERHARD RITZ, M.D., ROBERT C. ATKINS, M.D., RICHARD ROHDE, B.S., AND ITAMAR RAZ, M.D., FOR THE COLLABORATIVE STUDY GROUP*

N Engl J Med, Vol. 345, No. 12 · September 20, 2001

EFFECTS OF LOSARTAN ON RENAL AND CARDIOVASCULAR OUTCOMES IN PATIENTS WITH TYPE 2 DIABETES AND NEPHROPATHY

BARRY M. BRENNER, M.D., MARK E. COOPER, M.D., PH.D., DICK DE ZEEUW, M.D., PH.D., WILLIAM F. KEANE, M.D., WILLIAM E. MITCH, M.D., HANS-HENRIK PARVING, M.D., GIUSEPPE REMUZZI, M.D., STEVEN M. SNAPINN, PH.D., ZHONXIN ZHANG, PH.D., AND SHAHNAZ SHAHINFAR, M.D., FOR THE RENAAL STUDY INVESTIGATORS*

N Engl J Med, Vol. 345, No. 12 · September 20, 2001

LA RICERCA DI UN'ULTERIORE RIDUZIONE DEL RISCHIO

J Am Soc Nephrol 18: 1540–1546, 2007

Albuminuria Is a Target for Renoprotective Therapy Independent from Blood Pressure in Patients with Type 2 Diabetic Nephropathy: *Post Hoc* Analysis from the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) Trial

Wouter B.A. Eijkelkamp,* Zhongxin Zhang,† Giuseppe Remuzzi,‡ Hans-Henrik Parving,§ Mark E. Cooper,‖ William F. Keane,† Shahnaz Shahinfar,† Gilbert W. Gleim,† Matthew R. Weir,¶ Barry M. Brenner,** and Dick de Zeeuw*

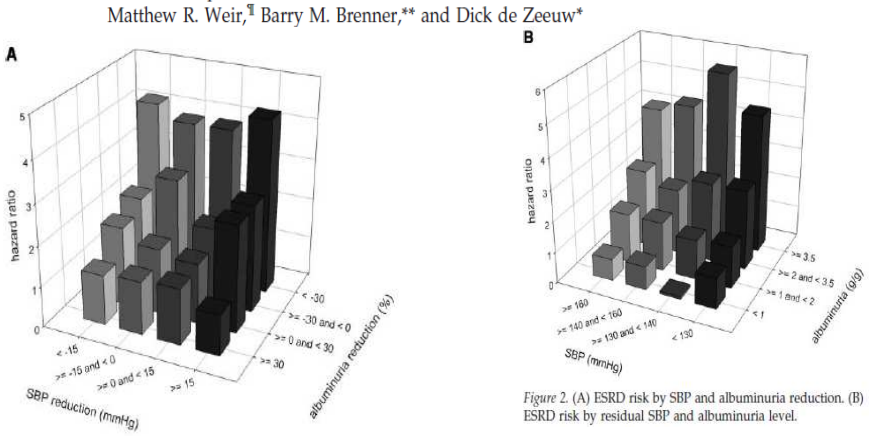
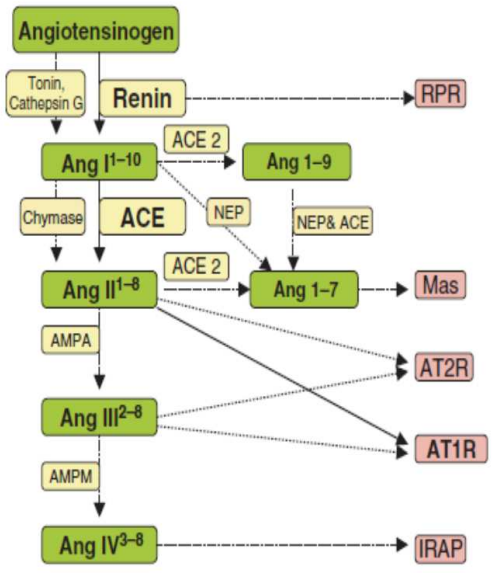


Figure 2. (A) ESRD risk by SBP and albuminuria reduction. (B) ESRD risk by residual SBP and albuminuria level.



Time course of the antiproteinuric and antihypertensive effects of direct renin inhibition in type 2 diabetes

F Persson[1], P Rossing[1], KJ Schjoedt[1], T Juhl[1], L Tarnow[1], CDA Stehouwer[2], C Schalkwijk[2], F Boomsma[3], E Frandsen[4] and H-H Parving[5,6]

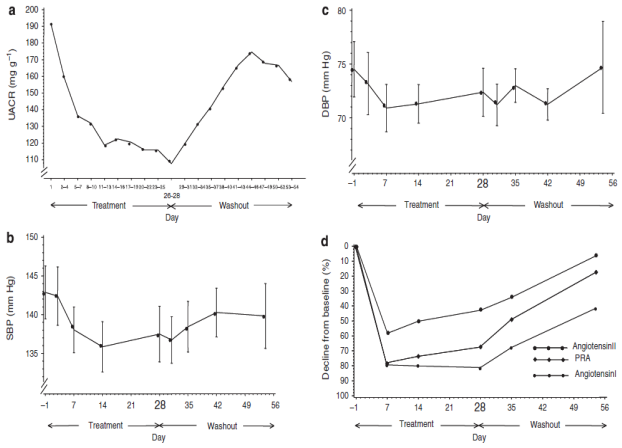


Table 1. Overview of dual RAAS blockade by treatment and medical indication. Some relevant trial support is mentioned.

	ACEI and ARB	DRI and ACEI or ARB	AA and ACEI or ARB
Hypertension	**Yes**, has modest incremental BP effect BUT **No**, without proven CVD benefit (ONTARGET) **Maybe**, untested in severely hypertensive BP ≥ 160/100 mm Hg excluded from ONTARGET. Any BP reduction would be expected to provide CVD benefit	**Yes**, modest incremental BP effect BUT **No** CVD benefit and increased adverse effects (early closure ALTITUDE)	**Yes**, significant BP reductions and recommended for resistant hypertension
Post acute MI with LV dysfunction	**No** (VALIANT)	**No** benefit on remodelling (ASPIRE)	**Yes** (EPHESUS), mortality benefit with eplerenone
Chronic systolic heart failure	**Yes**, recommended if heart failure symptoms persist in the presence of maximised ACEI and β-blocker and not immediately post-MI (CHARM added and Val-HeFT)	**Maybe**, awaiting the results of ATMOSPHERE trial	**Yes** (RALES), mortality benefit with spironolactone. Recommended for severe CHF along with the strategies to reduce hyperkalaemia
Diabetic microalbuminuria	**Yes**, improves albuminuria BUT **No**, despite small BP and albuminuria improvements, no benefit seen on composite CVD or renal outcomes. Concern over excess renal function decline in low renal risk group (ONTARGET)	**No** CVD benefit and increased adverse effects (early closure ALTITUDE)	
Diabetic nephropathy	**Yes**, improves proteinuria BUT **No** evidence yet on hard end points. Monitor for hyperkalaemia **Maybe**, awaiting NEPHRON D and VALID trial. Validated hard end points	**Yes**, improves proteinuria BUT **No** CVD benefit and increased adverse effects (early closure ALTITUDE)	**Maybe**, meta-analysis suggests benefits on proteinuria and BP, but no evidence on hard end points and hyperkalaemia may be limiting
Diabetes (without any of the above)	**No**, lack of evidence to support CVD events reduction (ONTARGET) Retinopathy effects to be explored		
Adverse effects of	Hyperkalaemia, hypotension, acute renal injury and GFR decline		

Is there benefit in dual renin–angiotensin–aldosterone system blockade? No, yes and maybe: A guide for the perplexed

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dvr.sagepub.com
SAGE

Jencia Wong[1,2]

- ACEI/ARB in combination: possible benefit in the very hypertensive or in those with untreated high residual CVD risk.
- ACEI/ARB in combination: most studies point to a further (20%) reduction in albuminuria but no evidence yet on hard end points in proteinuric renal disease.
- One should not extrapolate the lack of benefit of dual therapy seen in ONTARGET to patients with high-risk, proteinuric renal disease.
- DRI and ACEI or ARB combination: there is an additive effect on BP, an additional benefit on albuminuria but no benefit on hard outcomes, and there is additional associated risk.
- AA and ACEI or ARB combination: there is an additive effect on BP and there is probable additional benefit on proteinuria.

American Journal of Nephrology

Future Perspectives

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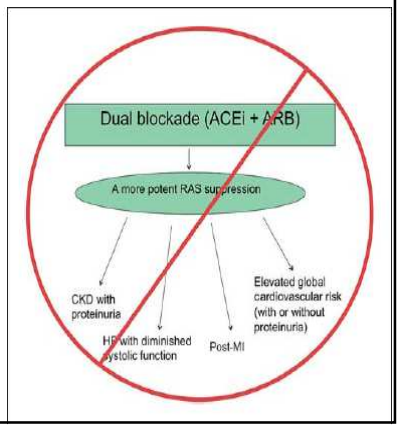
DOI: 10.1159/000357593

Perspective on Combination RAS Blocking Therapy: Off-TARGET, Dis-CORD, MAP-to-Nowhere, Low ALTITUDE, and NEPHRON-D

Friedrich C. Luft

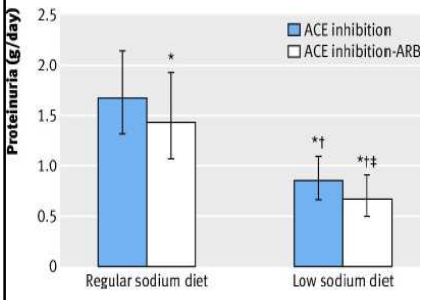


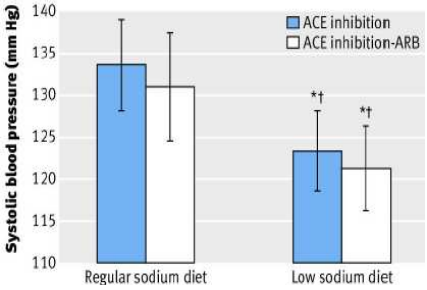
BMJ

BMJ 2011;343:d4366 doi: 10.1136/bmj.d4366

Moderate dietary sodium restriction added to angiotensin converting enzyme inhibition compared with dual blockade in lowering proteinuria and blood pressure: randomised controlled trial

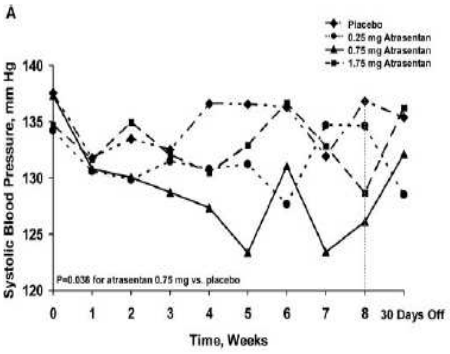
Maartje C J Slagman *internist in training*[1], Femke Waanders *internist in training*[1], Marc H Hemmelder *internist in training*[2], Arend-Jan Woittiez *internist-nephrologist*[3], Wilbert M T Janssen *internist-nephrologist*[4], Hiddo J Lambers Heerspink *pharmacist*[5], Gerjan Navis *internist-nephrologist*[1], Gozewijn D Laverman *internist-nephrologist, HONEST coordinator*[1 3], for the HONEST (HOlland NEphrology STudy) Group

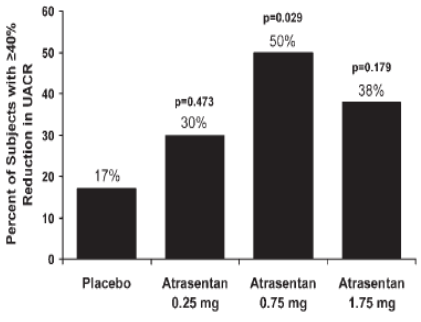




Addition of Atrasentan to Renin-Angiotensin System Blockade Reduces Albuminuria in Diabetic Nephropathy

Donald E. Kohan,* Yili Pritchett,† Mark Molitch,‡ Shihua Wen,† Tushar Garimella,† Paul Audhya,† and Dennis L. Andress†





Clin J Am Soc Nephrol 8: 1870–1876, 2013

25 (OH) Vitamin D Levels and Renal Disease Progression in Patients with Type 2 Diabetic Nephropathy and Blockade of the Renin-Angiotensin System

Gema Fernández-Juárez, José Luño,† Vicente Barrio,‡ Soledad García de Vinuesa,† Manuel Praga,§ Marian Goicoechea,† Vicente Lahera,‖ Luisa Casas,* and Jesús Oliva,¶ on behalf of the PRONEDI Study Group*

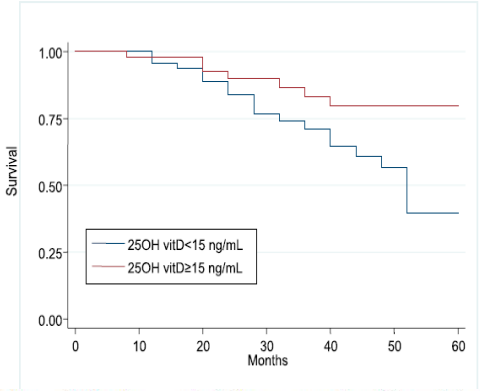
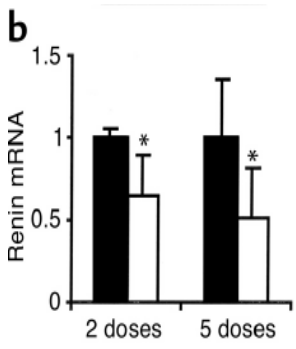


Figure 1. | Kaplan Meier survival curves for the primary end point (increase more than 50% creatinine, dialysis, or death) comparing patients with 25 OH vitamin D deficiency (<15 ng/ml) to those with 25 OH vitamin D levels ≥15 ng/ml.

1,25-Dihydroxyvitamin D_3 is a negative endocrine regulator of the renin-angiotensin system

J. Clin. Invest. 110:229–238 (2002)

Yan Chun Li,[1] Juan Kong,[1] Minjie Wei,[1] Zhou-Feng Chen,[2] Shu Q. Liu,[3] and Li-Ping Cao[1]



Quantitation of renin mRNA levels.
Black bars, vehicle treatment;
white bars, 1,25(OH)2D3 treatment. **P* < 0.05

Lancet. 2010 Nov 6;376(9752):1543-51.

Selective vitamin D receptor activation with paricalcitol for reduction of albuminuria in patients with type 2 diabetes (VITAL study): a randomised controlled trial.

de Zeeuw D, Agarwal R, Amdahl M, Audhya P, Coyne D, Garimella T, Parving HH, Pritchett Y, Remuzzi G, Ritz E, Andress D.

Multinational, placebo-controlled, double-blind trial, patients with type 2 diabetes and albuminuria **who were receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers**

281 patients x 24 weeks

placebo(n=93), **– 3%** from 61 to 60 mg/mmol;

1 µg paricalcitol (n=93), **–14%** from 63 to 54 mg/mmol ; p=0.23 — **18%** p=0.053

2 µg paricalcitol (n=95);' **–20%** from 61 to 49 mg/mmol

Addition of 2 µg/day paricalcitol to RAAS inhibition safely lowers residual albuminuria in patients with diabetic nephropathy, and could be a novel approach to lower residual renal risk in diabetes.

Prevenzione della nefropatia diabetica: from bench to bedside

Dapagliflozin

Maria Elena Liberti, Adelia Sagliocca, Raffaele Palmisano, Laura Pirro, Michele Provenzano, Roberto Minutolo, Giuseppe Conte, **Luca De Nicola**

Cattedra di Nefrologia, Seconda Università di Napoli

Tabella 1. Effetti terapeutici e caratteristiche cliniche degli inibitori del trasportatore tubulare del glucosio SGLT2.

Ridotto rischio di ipoglicemia
Assenza di effetti gastrointestinali
Riduzione dell'iperglicemia e della glucotossicità
Lieve riduzione dei livelli plasmatici di trigliceridi (studi su animali)
Riduzione dei valori di HbA1c di 0,5-1,5% a seconda dei livelli iniziali di HbA1c)
Miglioramento della risposta all'ipoglicemia per aumento del contenuto di glucagone nelle isole pancreatiche
Miglioramento del quadro isto-patologico dei reni diabetici
Prevenzione della nefropatia diabetica (?)

- L’ambiente diabetico conferisce al RAAS specificità che costituiscono la plausibilità biologica delle favorevoli risposte osservate sulla prevenzione di nuovi casi di DM II e sugli outcomes cardiovascolari e renali nei trials clinici con gli inibitori del sistema.
- L’impatto dell’ inibizione del RAAS sull’istologia renale è evidente solo nelle fasi avanzate di malattia.
- Il paradigma del RAAS come via metabolica univoca su cui esercitare un blocco farmacologico è sostituito dal concetto di rete da modulare agendo su più punti (stato del sodio compreso) per ottenere un’ulteriore riduzione del rischio.
- I risultati negativi di alcuni trials con associazioni di farmaci orientano per identificare i sottogruppi a rischio di sviluppare effetti collaterali e per l’esigenza di individualizzare la terapia e aumentare l’accuratezza del follow up nei pazienti da trattare con schemi ad alta attività (es.proteinuria grave, HT resistente), piuttosto che per l’ abbandono dell’idea di base.Nuovi trials.
- Studi recenti esibiscono risultati confortanti dell’associazione con inibitori dell’endotelina (limitati questi dall’incidenza di pesanti effetti collaterali) e con gli analoghi della Vit D.
- L’inibizione del cotrasporto Na – Glucosio SGTL2 può interrompere l’iperfiltrazione da attivazione del feed back tubulo glomerulare ed essere sinergica con i bloccanti dell’attività del RAAS.