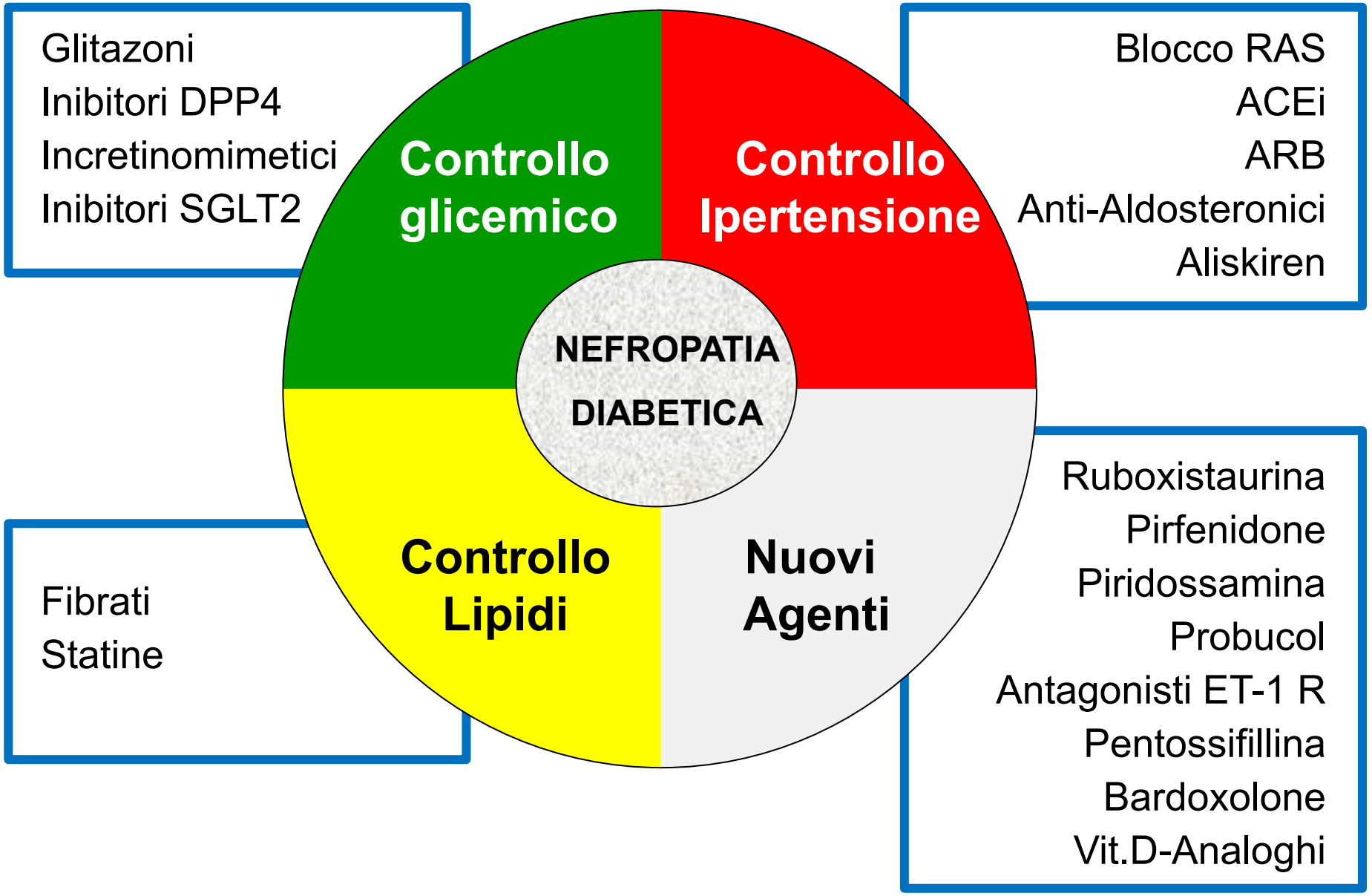
NUOVI FARMACI PER LA NEFROPATIA DIABETICA

S. Di Paolo

Ospedale Dimiccoli-Barletta

Asl BAT
BARLETTA-ANDRIA-TRANI

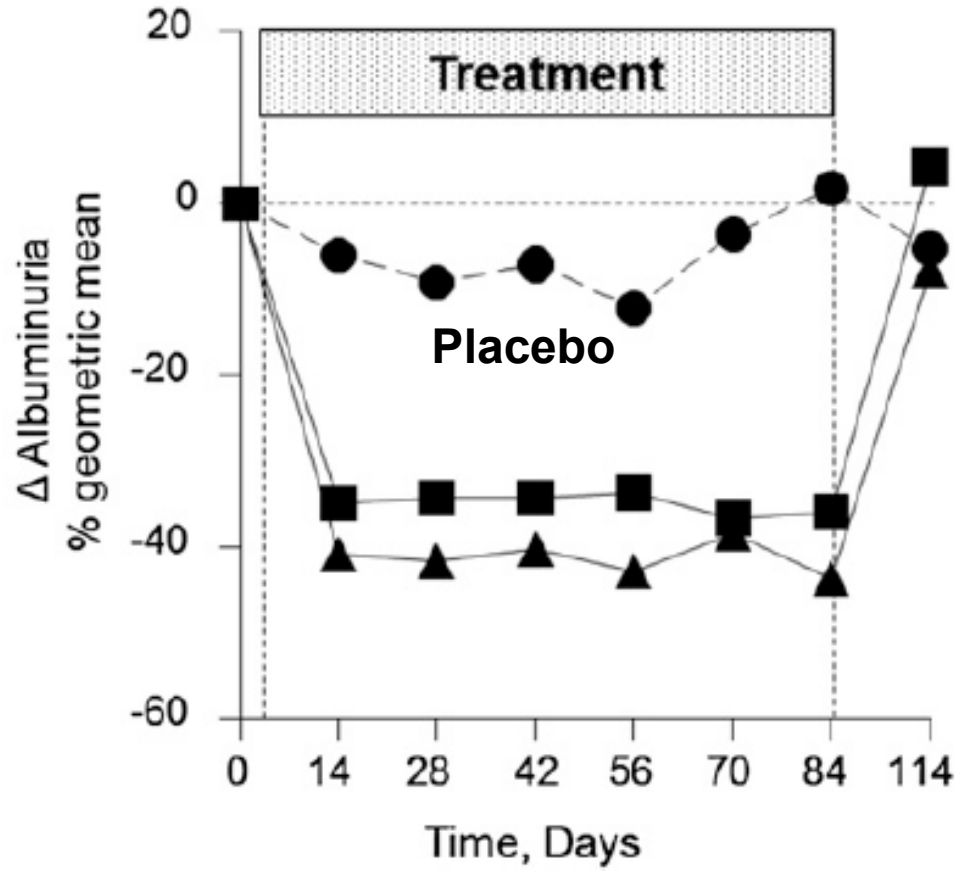
Nefropatia diabetica: Nuove prospettive terapeutiche

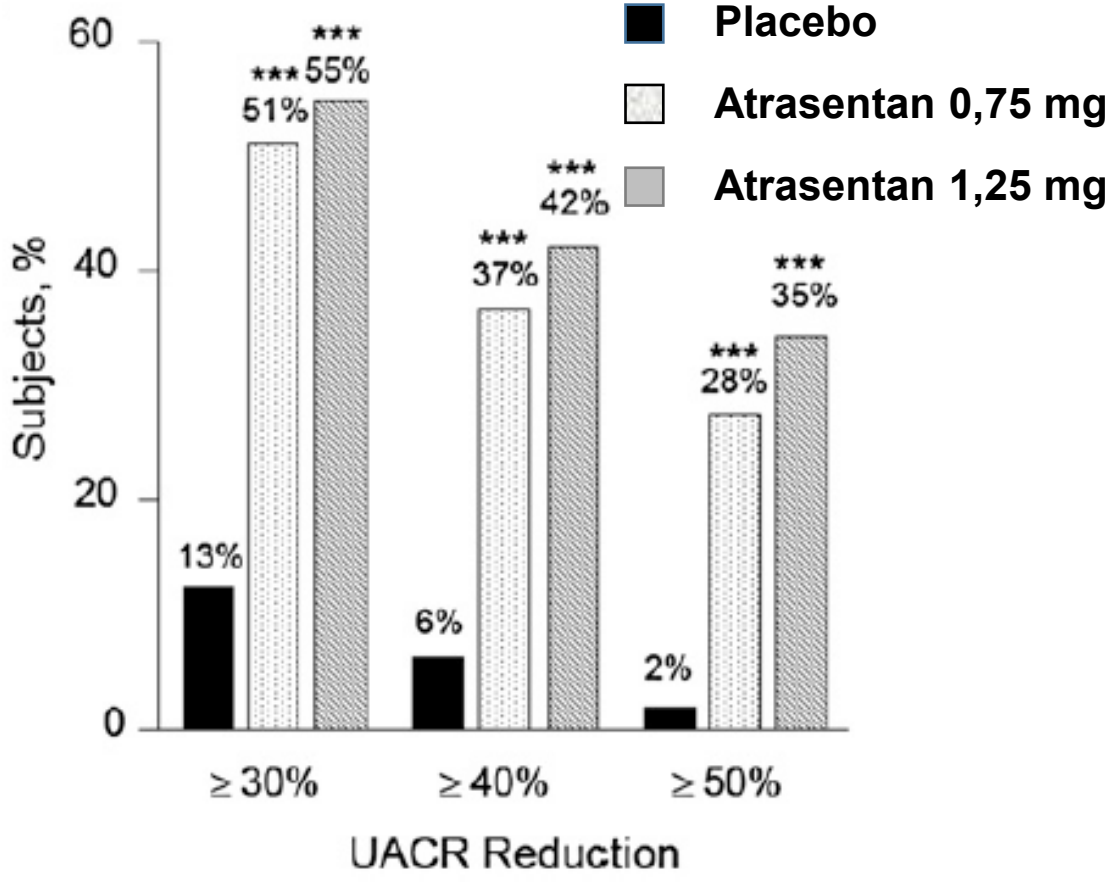


The Endothelin Antagonist Atrasentan Lowers Residual Albuminuria in Patients with Type 2 Diabetic Nephropathy

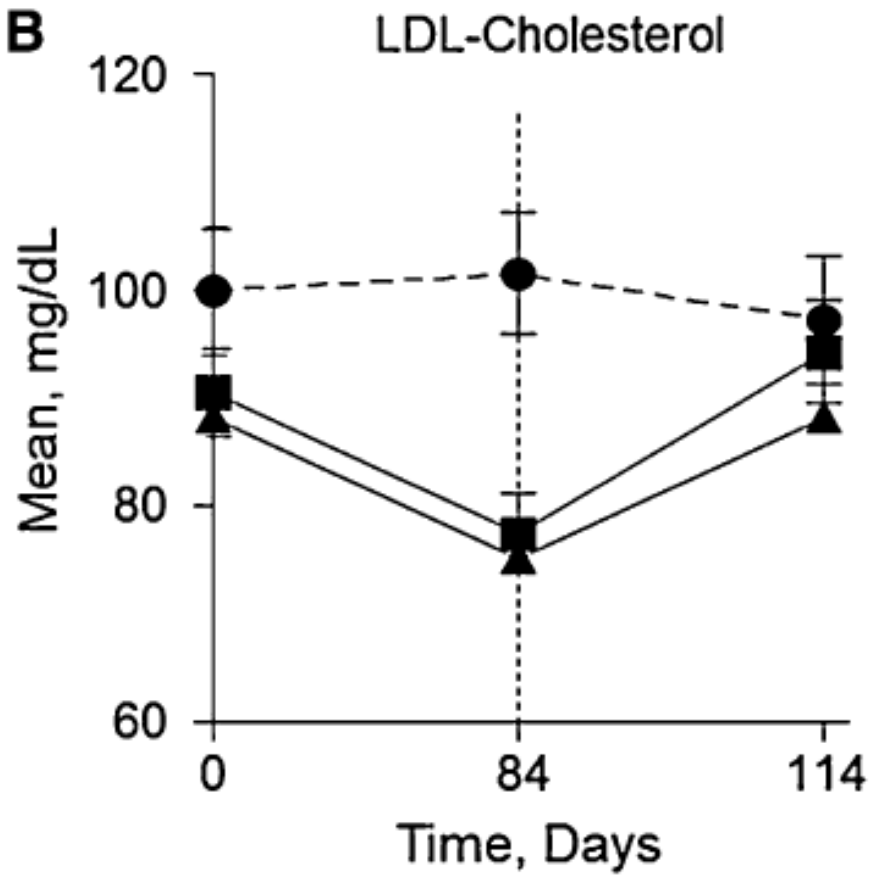
de Zeeuw D, JASN 2014

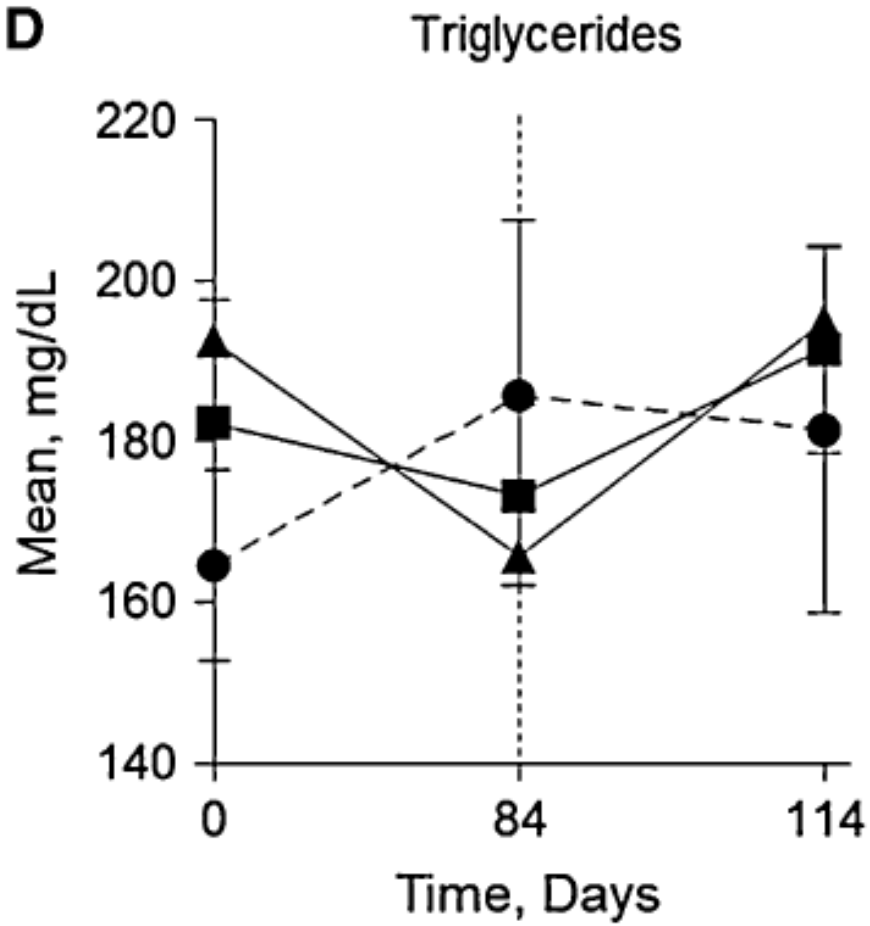
N= 211 T2DM. eGFR 30-75 ml/min. UACR 300 to 3500 mg/g. F-U: 12 settimane





■ Atrasentan 0,75 mg ▲ Atrasentan 1,25 mg





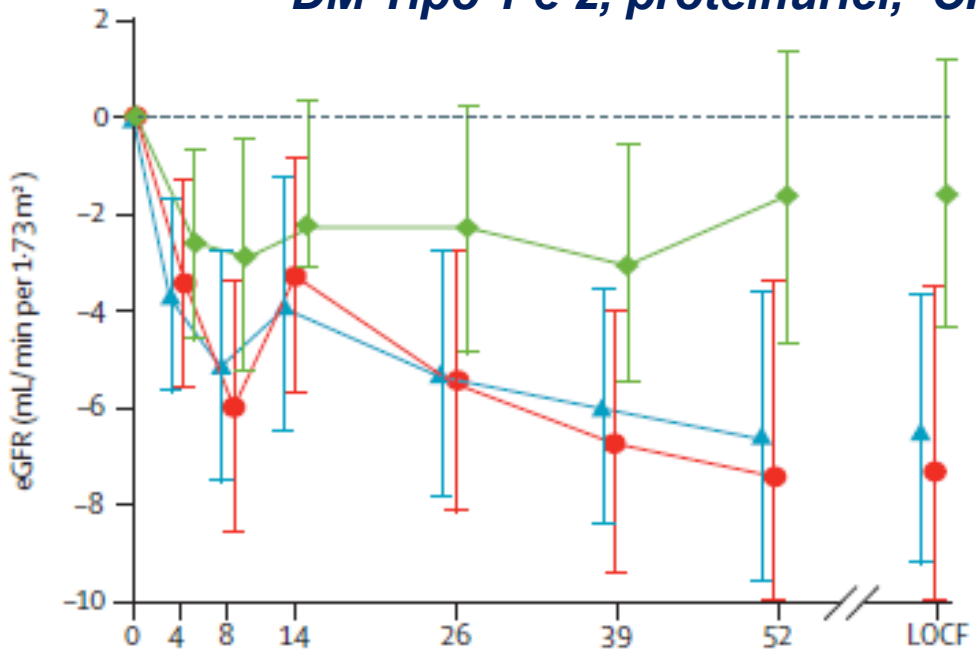
In pazienti T2DM con Nefropatia Diabetica trattati con dosi massimali di RAS inibitori, Atrasentan ha ridotto l'Albuminuria e migliorato la PA ed il profilo lipidico. Effetto avverso principale: edemi da ritenzione idrica

Renal effects of atorvastatin and rosuvastatin in patients with diabetes who have progressive renal disease (PLANET I): a randomised clinical trial

Lancet Diabetes Endocrinol 2015

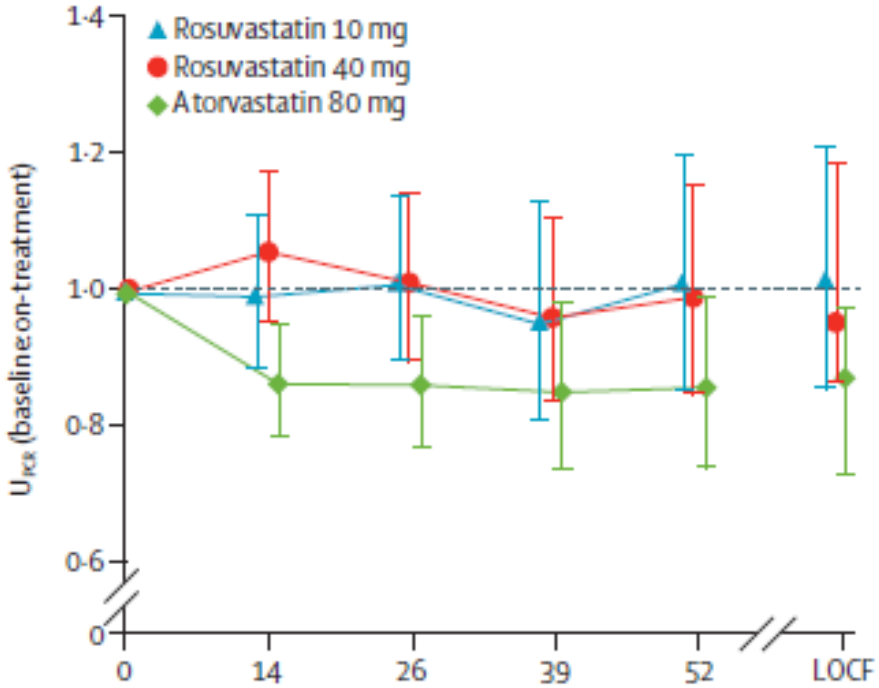
*Dick de Zeeuw, Deborah A Anzalone, Valerie A Cain, Michael D Cressman, Hiddo J Lambers Heerspink, Bruce A Molitoris, John T Monyak, Hans-Henrik Parving, Giuseppe Remuzzi, James R Sowers, Donald G Vidt**

DM Tipo 1 e 2, proteinurici, CKD Stadio 1-3



Number of patients								
Rosuvastatin 10 mg	107	106	104	103	99	95	95	107
Rosuvastatin 40 mg	116	115	112	111	109	104	109	116
Atorvastatin 80 mg	102	99	98	97	92	86	86	102

Time (weeks)



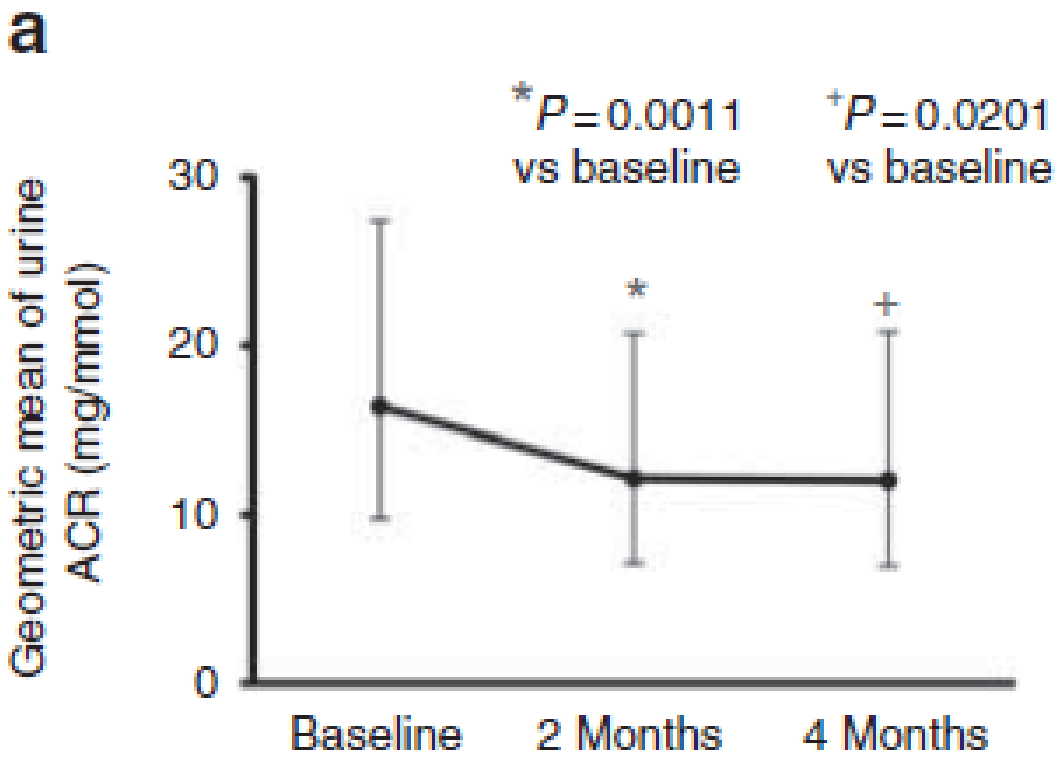
Number of patients						
Rosuvastatin 10 mg	107	103	97	96	95	107
Rosuvastatin 40 mg	116	112	107	106	106	116
Atorvastatin 80 mg	102	96	91	88	82	102

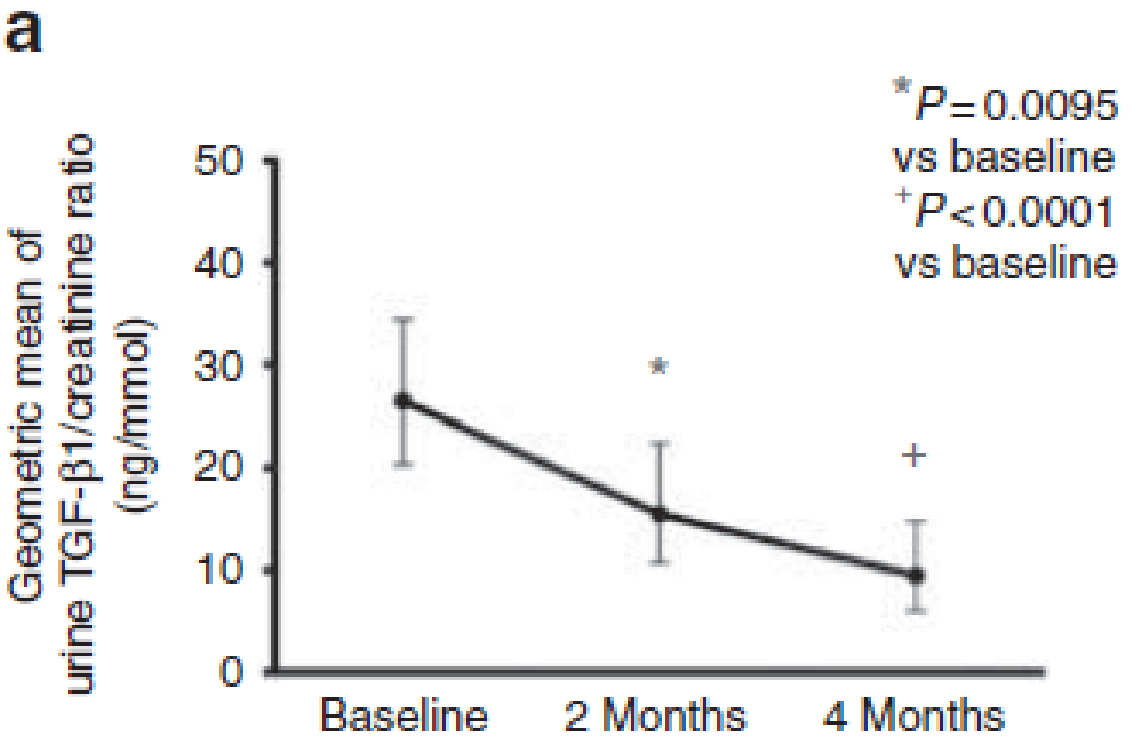
Time (weeks)

Oral cholecalciferol decreases albuminuria and urinary TGF-β1 in patients with type 2 diabetic nephropathy on established renin–angiotensin–aldosterone system inhibition

kidney INTERNATIONAL

Kim M J, 2011



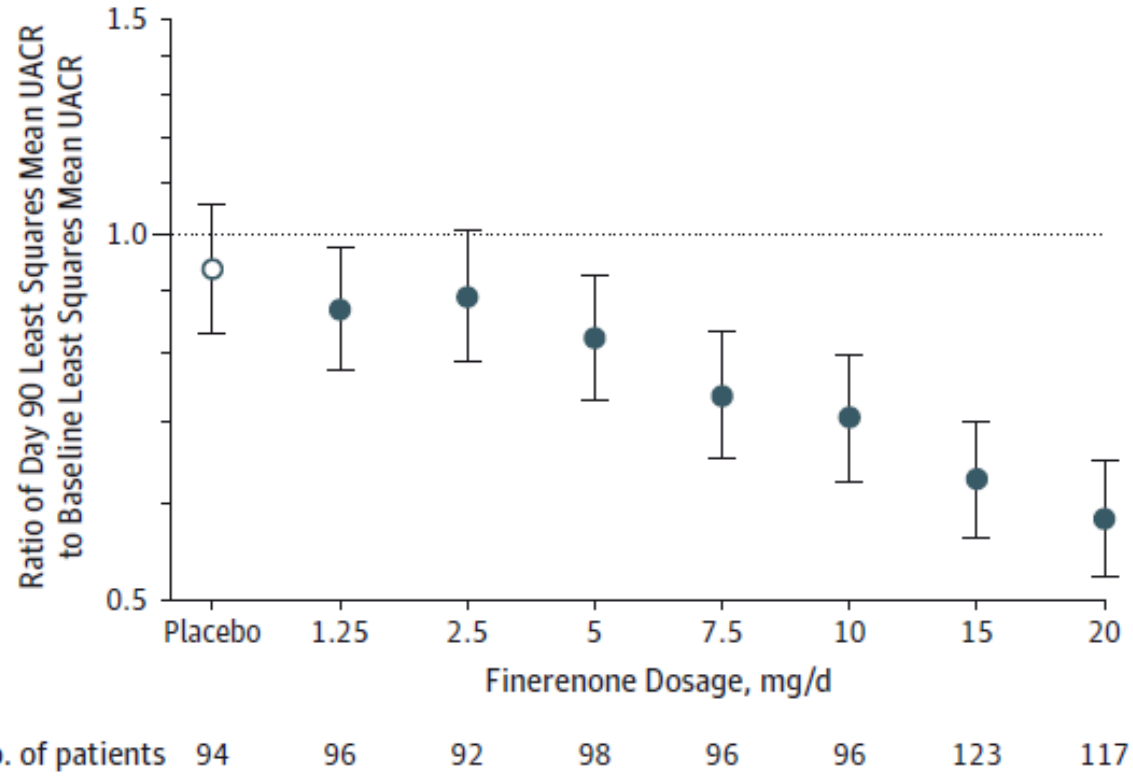


Effect of Finerenone on Albuminuria in Patients With Diabetic Nephropathy
A Randomized Clinical Trial

JAMA The Journal of the American Medical Association

Bakris GL, 2015

Figure 2. Change in Least Squares Mean UACR at Day 90 Relative to Baseline in Patients Treated With Finerenone, 1.25-20 mg/d, or Placebo



1501 T2DM, albuminurici (UACR≥30mg/g) eGFR> 30 mL/min/1.73m2
in trattamento con RAS inibitori almeno al minimo dosaggio

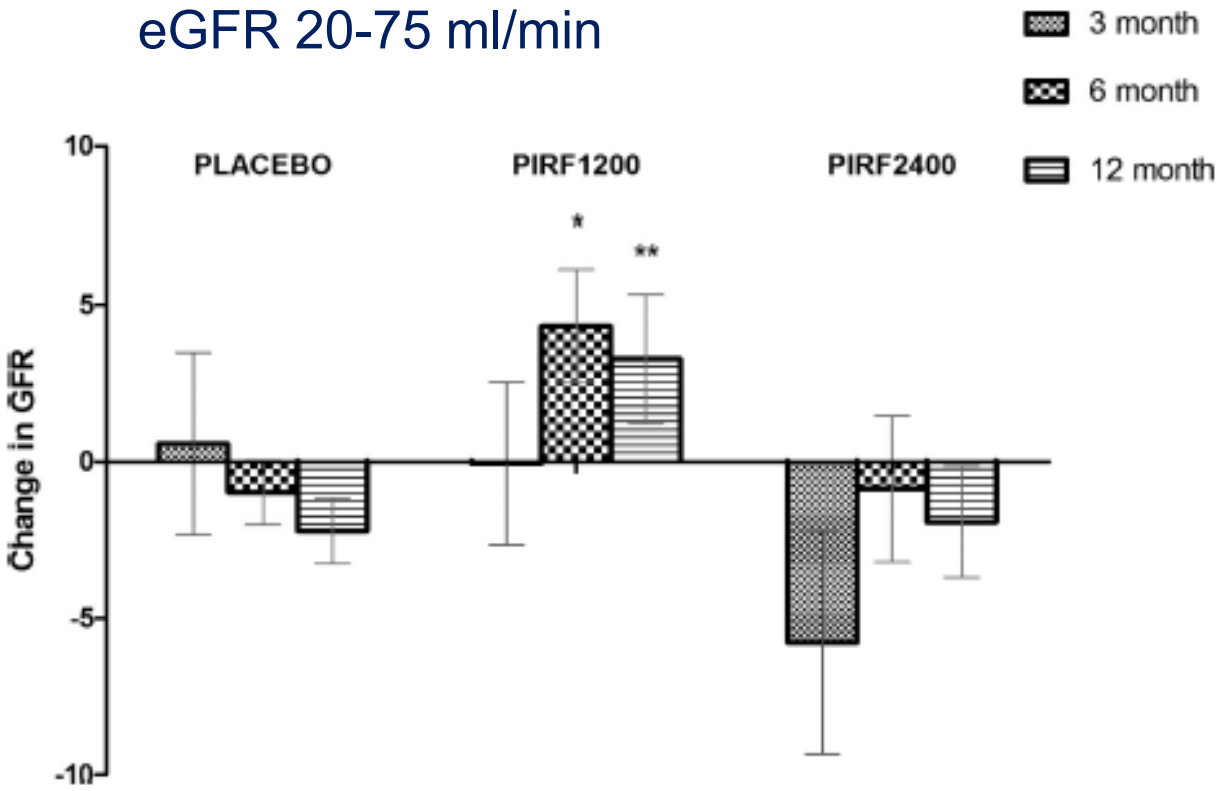
L'aggiunta di Finerenone per 90 giorni ridusse la proteinuria del 21% [7.5mg/d, *P* = .004]; del 24% [10mg/d, *P* = .001] del 33% [15mg/d, *P*<.001]; e del 38% [20mg/d, *P*<.001]

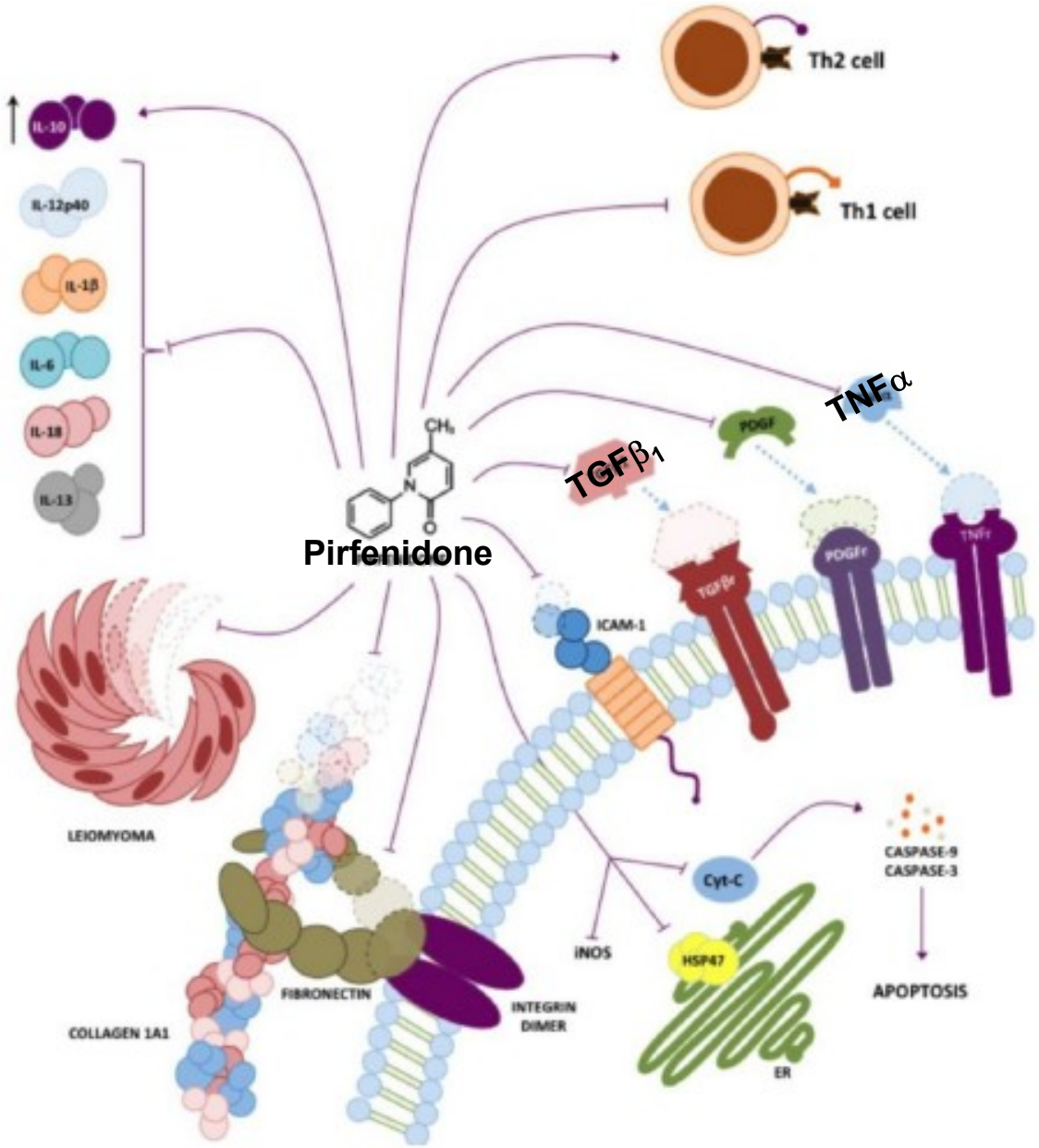
Pirfenidone for Diabetic Nephropathy

Sharma K, JASN 2011

77 DMT2 con macroalbuminuria

eGFR 20-75 ml/min





[Esbriet→Fibrosi polmonare]

Probucol Suppresses Initiation of Chronic Hemodialysis Therapy and Renal Dysfunction-Related Death in Diabetic Nephropathy Patients: Sakura Study

Endo K, J Atheroscler Thromb 2013

Probucol 500 mg/die: anti-ossidante e ipocolesterolemizzante

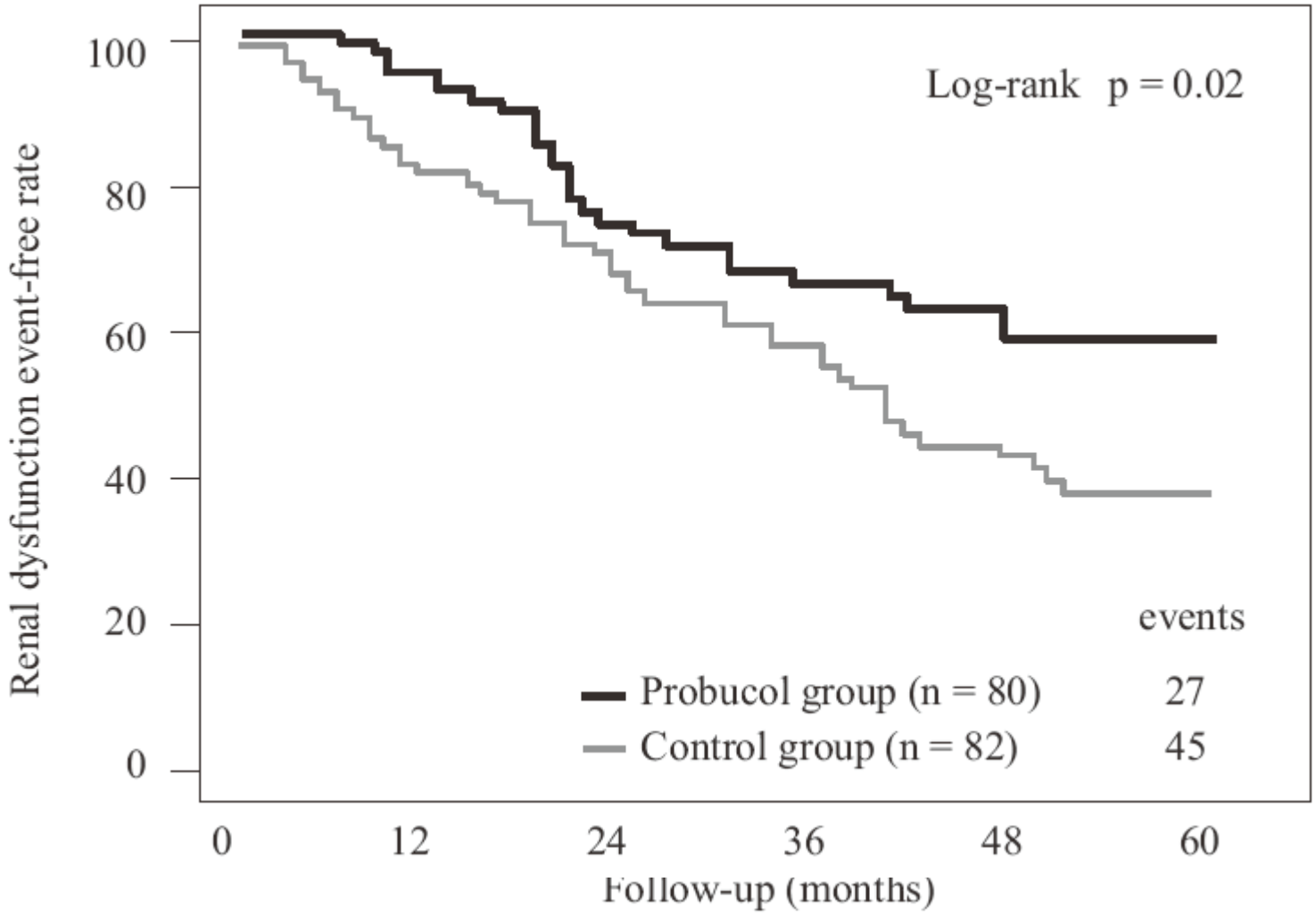
162 paz DMT2

Macroalbuminuria (UACR>300 mg/g)

sCr media: 1,7 mg/dl

<u>*Outcome primario*</u>:

HD o morte da cause renali



CLINICAL RESEARCH www.jasn.org

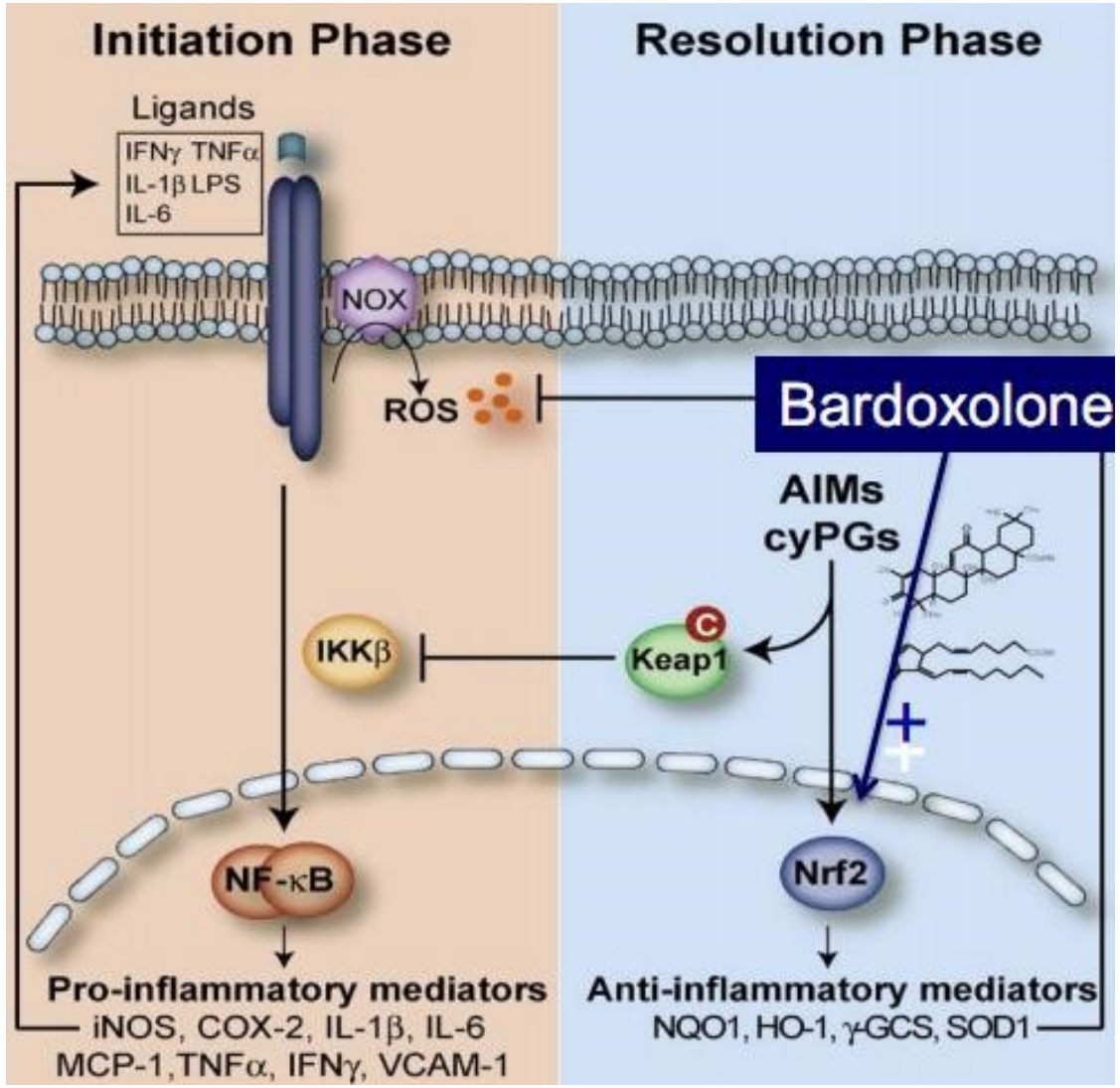
JASN

2012

Pyridorin in Type 2 Diabetic Nephropathy

Edmund J. Lewis,* Tom Greene,† Samuel Spitalewiz,‡ Samuel Blumenthal,§ Tomas Berl,‖ Lawrence G. Hunsicker,¶ Marc A. Pohl,** Richard D. Rohde,†† Itamar Raz,‡‡ Yair Yerushalmy,§§ Yoram Yagil,‖‖ Tommy Herskovits,¶¶ Robert C. Atkins,*** Anne T. Reutens,*** David K. Packham,††† and Julia B. Lewis,‡‡‡ for the Collaborative Study Group

This trial failed to detect an effect of Pyridoxamine dihydrochloride, which inhibits formation of advanced glycation end products and scavenges reactive oxygen species and toxic carbonyls, on the progression of serum creatinine at 1 year



La pathway Nrf2 è soppressa in modelli di fibrosi renale. ***Bardoxolone*** *attiva Nrf2, incrementa la produzione di 250 enzimi anti-ossidanti e inibisce la trascrizione di TF proinfiammatori, quali NFκB e STAT3.*

The NEW ENGLAND JOURNAL of MEDICINE

De Zeeuw D, 2013

ORIGINAL ARTICLE

Bardoxolone Methyl in Type 2 Diabetes and Stage 4 Chronic Kidney Disease

Among patients with type 2 diabetes mellitus and stage 4 chronic kidney disease, bardoxolone methyl did not reduce the risk of ESRD or death from cardiovascular causes.

A higher rate of cardiovascular events with bardoxolone methyl than with placebo prompted termination of the trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Parving H-H, 2012

Cardiorenal End Points in a Trial of Aliskiren for Type 2 Diabetes

BACKGROUND

This study was undertaken to determine whether use of the direct renin inhibitor aliskiren would reduce cardiovascular and renal events in patients with type 2 diabetes and chronic kidney disease, cardiovascular disease, or both.

CONCLUSIONS

The addition of aliskiren to standard therapy with renin–angiotensin system blockade in patients with type 2 diabetes who are at high risk for cardiovascular and renal events is not supported by these data and may even be harmful. (Funded by Novartis; ALTITUDE ClinicalTrials.gov number, NCT00549757.)

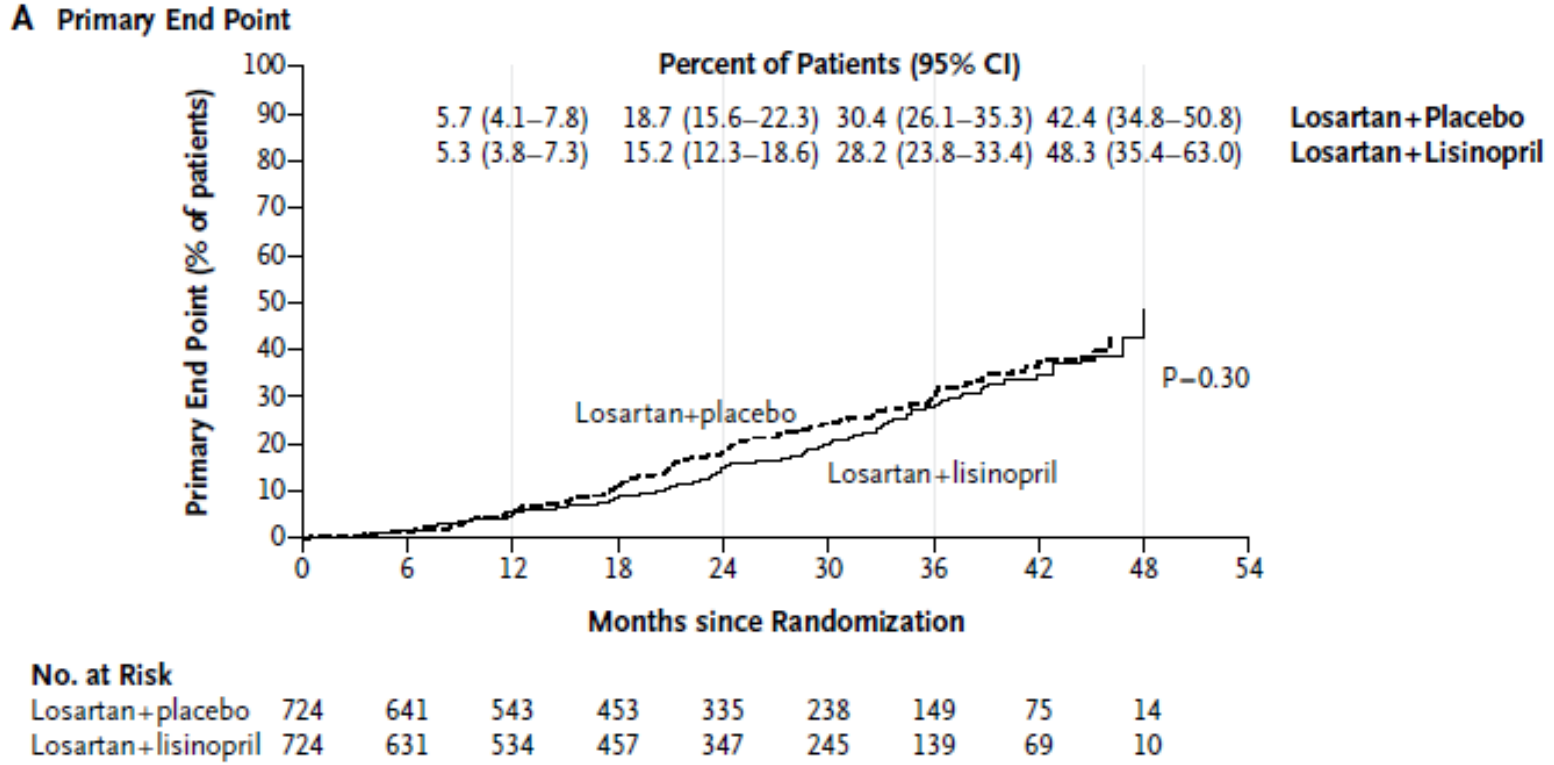
The NEW ENGLAND JOURNAL of MEDICINE

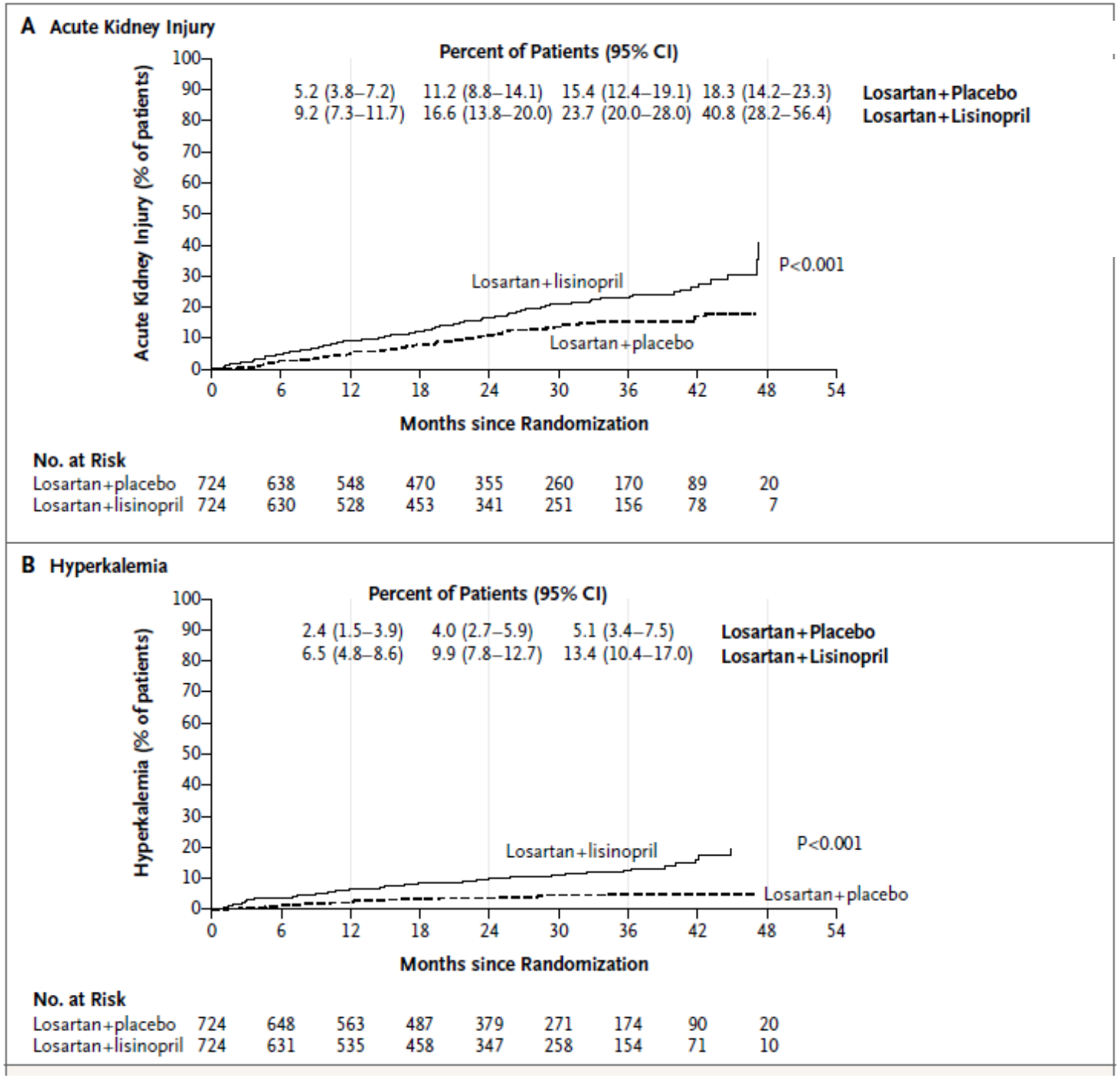
ORIGINAL ARTICLE

Fried LF for VA NEPHRON-D Investigators-2013

Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy

Primary end-point: ↓ eGFR >50%, ESRD o morte





The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

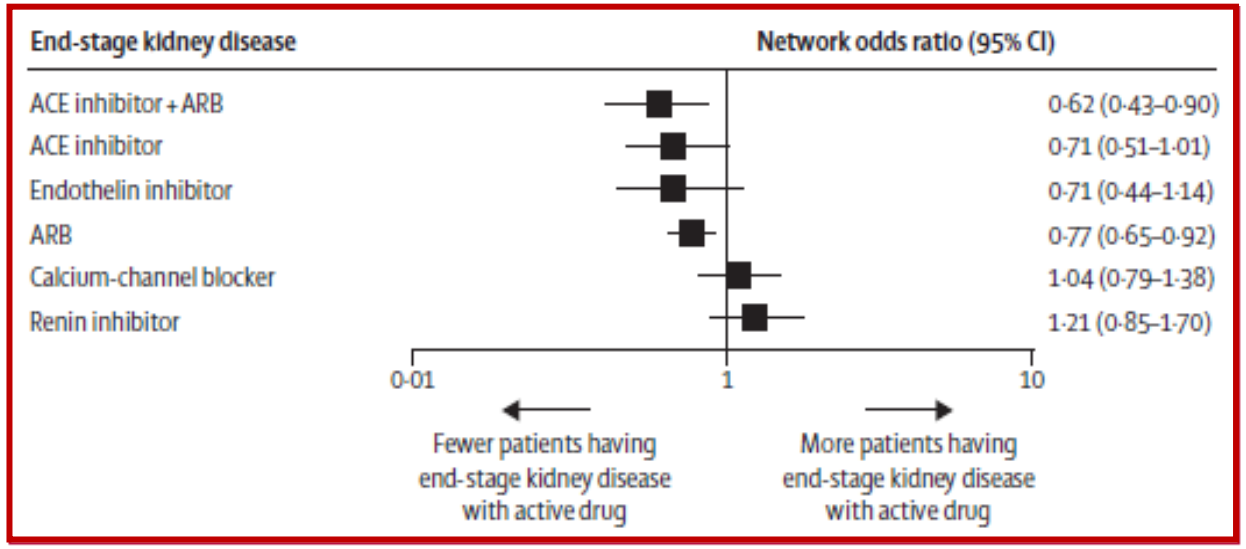
Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy

Fried LF for VA NEPHON-D Investigators-2013

Nei pazienti con Nefropatia Diabetica la terapia combinata ACE inibitori + Sartani si associava ad incremento di rischio di eventi avversi

Comparative efficacy and safety of blood pressure-lowering agents in adults with diabetes and kidney disease: a network meta-analysis

Palmer SC, Lancet 2015



RAS BLOCKADE

Nephroprotection by dual RAS blockade—a welcome back

Piero Ruggenenti and Giuseppe Remuzzi

Kidney Int 2015

A new meta-analysis shows that dual blockade of the RAAS is the most effective approach to prevent ESRD in patients with diabetes and kidney disease. Combination therapy should be reconsidered as the most powerful tool for nephroprotection, provided that treatment is individually tailored by careful dose-titration.

ACE inhibitors and ARBs, alone or in combination, were the most effective strategies against end-stage kidney disease. Any benefits of combined ACE inhibitor and ARB treatment need to be balanced against potential harms of hyperkalaemia and acute kidney injury

NEFROPATIA DIABETICA: STATO DELL'ARTE

- *I 3 pilastri principali del trattamento della Nefropatia diabetica sono il controllo della proteinuria, della pressione arteriosa e del compenso glicemico, con l'avvertenza che i trattamenti aggressivi possono non essere idonei per alcuni sottogruppi di pazienti.*
- *Il blocco del RAAS rappresenta a tutt'oggi la pietra angolare del trattamento, e può essere potenziato dalla restrizione del Sodio e/o dall'uso dei diuretici.*
- *Inoltre, il blocco dell'Aldosterone appare assicurare un potenziamento degli effetti protettivi*

Le effettive novità cliniche su Diabete Mellito Tipo 2 e Danno Renale

Cross-sectional analysis of the Renal Insufficiency and CV Events (RIACE) Italian multicenter study

Patients stratification

		Cases			
N		A1	A2	A3	Total
G1	>90	3,610 (22.9)	932 (5.9)	120 (0.8)	4,662 (29.6)
G2	60-90	6,255 (39.7)	1,653 (10.5)	244 (1.6)	8,152 (51.7)
G3a	45-60				1,951 (12.4)
G3b	30-45				750 (4.8)
G4	15-30				229 (1.5)
G5	<15				29 (0.2)
Total		11,538 (73.2)	3,497 (22.2)	738 (4.7)	15,773 (100.0)
		<30 mg/g	>30 <300 mg/g	>300 mg/g	

eGFR ml/min

Tra i pazienti con CKD (eGFR<60 ml/min) 56% erano Normoalbuminurici, 31% Microalbuminurici, e solo 13% presentavano Macroalbuminuria

ALBUMINURIA

Pugliese *et al. Cardiovascular Diabetology* 2014, **13**:59

CARDIO VASCULAR DIABETOLOGY

Clinical significance of nonalbuminuric renal impairment in type 2 diabetes

G Penno, for the RIACE Study Group, J Hypertens 2011

L'insufficienza renale cronica normoalbuminurica;

- non si associa ai livelli di HbA1c
- si associa debolmente alla Retinopatia e all'Ipertensione, se confrontata all'albuminuria, isolata o associata a CKD.
- si associa ad un'alta prevalenza di eventi CV, maggiore dell'albuminuria isolata, ma inferiore alla CKD albuminurica.
- E' più frequente nel sesso femminile

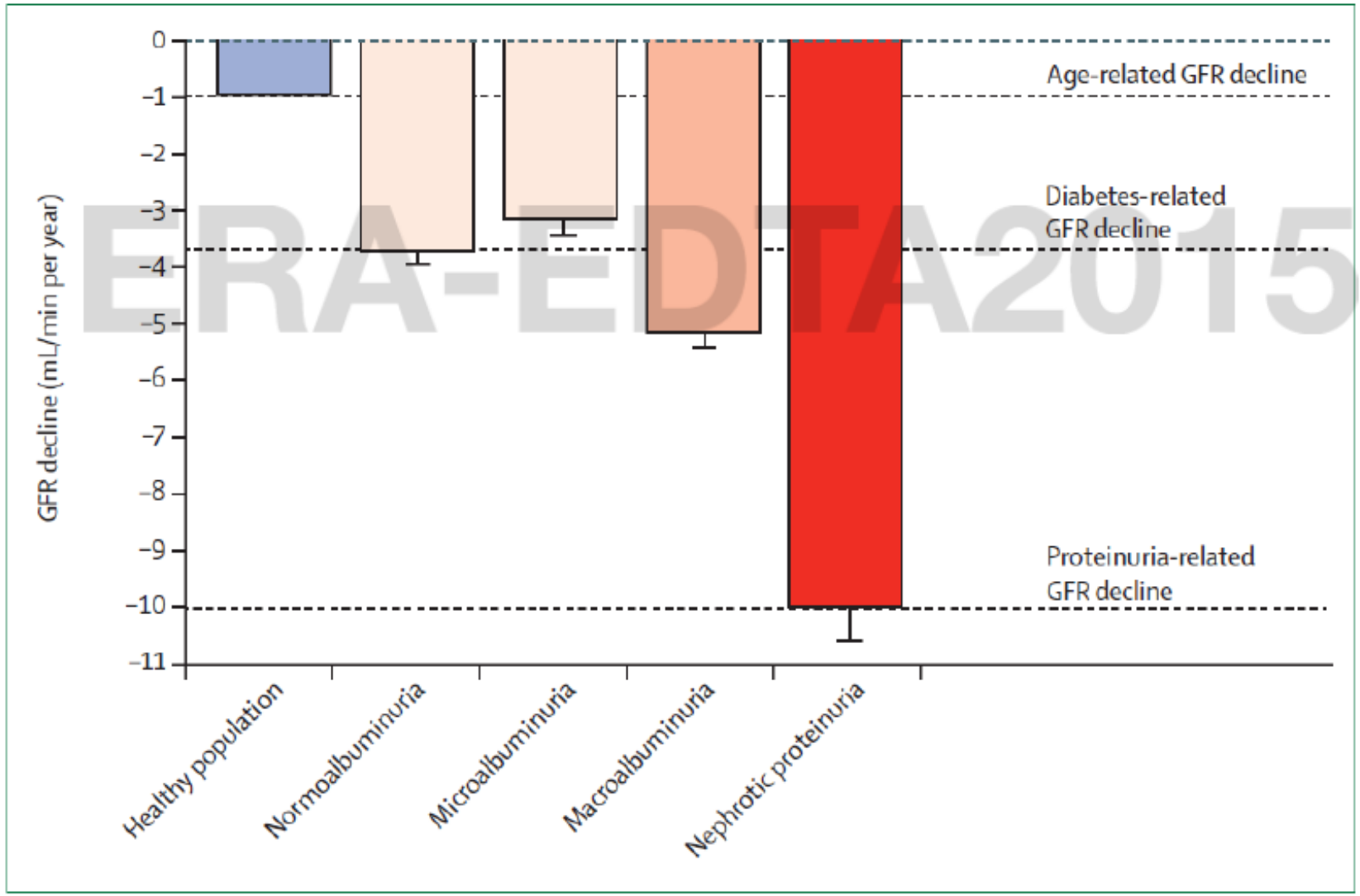
Conclusioni

I pazienti T2DM con CKD normoalbuminurica presentano un fenotipo clinico distinto, che suggerisce la prevalenza delle lesioni macroangiopatiche nel danno renale e CV

Non-proteinuric pathways in loss of renal function in patients with type 2 diabetes

Lancet Diabetes Endocrinol
2015; 3: 382–91

Esteban Porrini, Piero Ruggenenti, Carl Erik Mogensen, Drazenka Pongrac Barlovic, Manuel Praga, Josep M Cruzado, Radovan Hojs, Manuela Abbate, Aiko P J de Vries, for the ERA-EDTA diabesity working group.



ndt NEPHROLOGY DIALYSIS TRANSPLANTATION

Nephrol Dial Transplant (2015) 30: 155–157
doi: 10.1093/ndt/gfu372
Advance Access publication 10 December 2014

In Focus

Renal lesions in patients with type 2 diabetes: a puzzle waiting to be solved

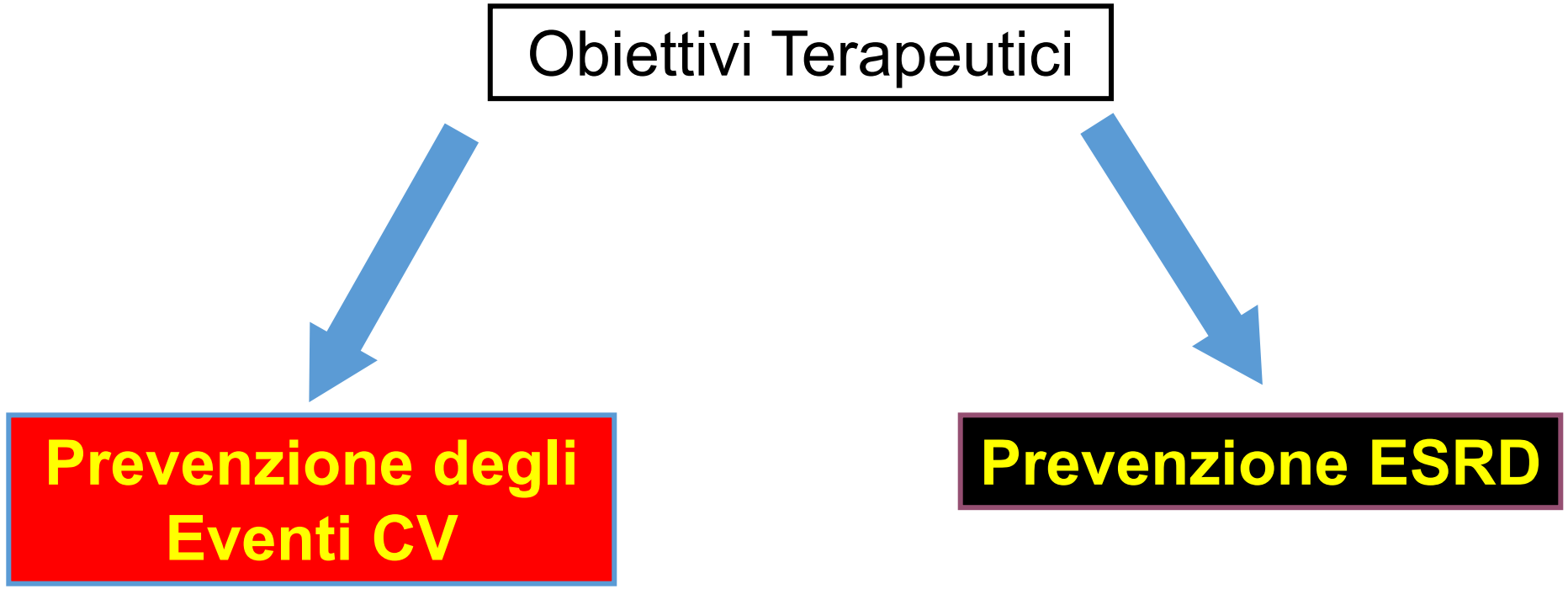
Loreto Gesualdo[1] and Salvatore Di Paolo[2]

[1]Department of Nephrology, Dialysis and Transplantation Unit 'Aldo Moro' University of Bari, Bari, Italy and [2]Nephrology and Dialysis Unit, Hospital Dimiccoli, Barletta, Italy

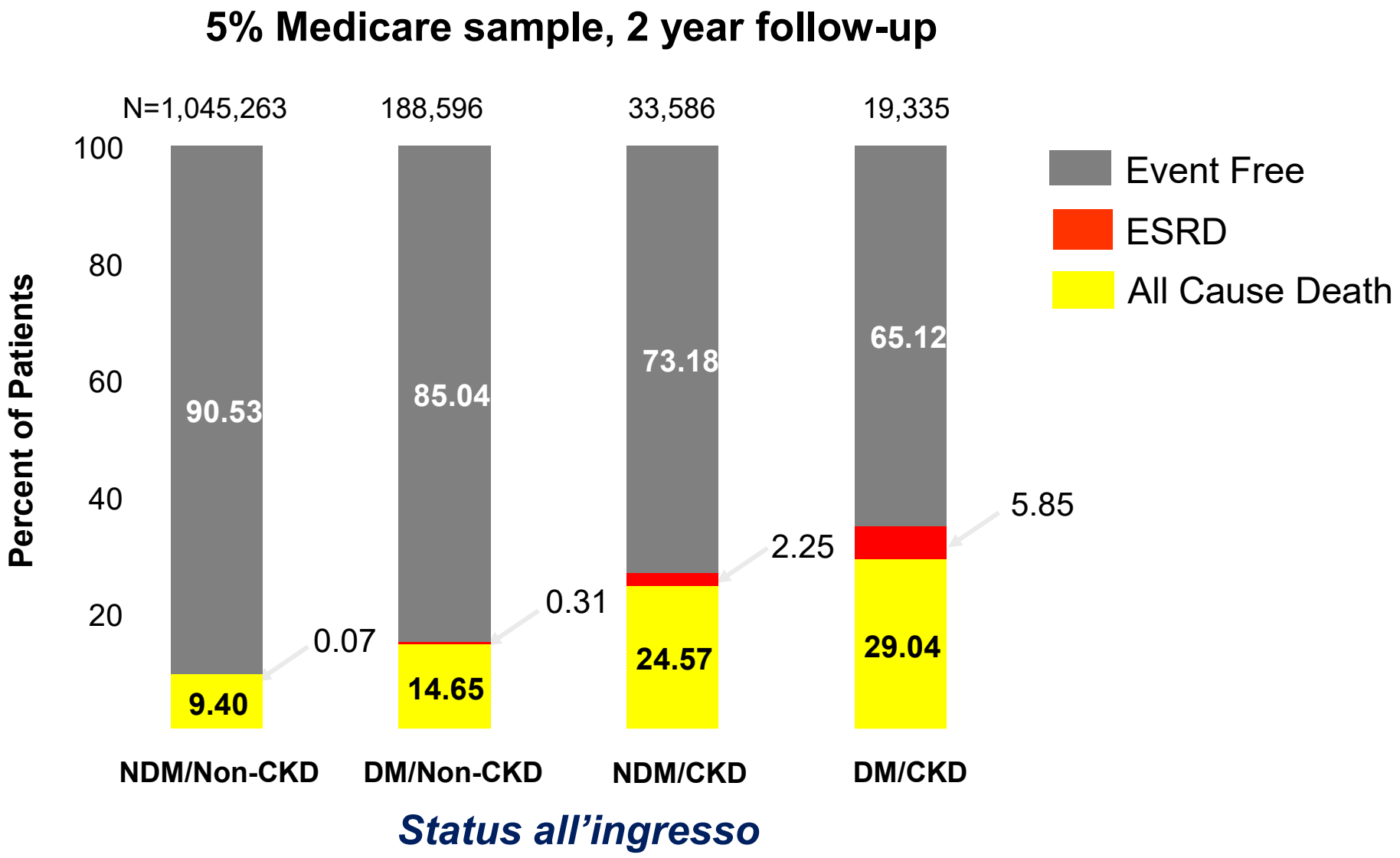
C'è urgente necessità di individuare biomarkers specifici non invasivi e non costosi che siano in grado di discriminare la ND dalle Nefropatie Non-Diabetiche

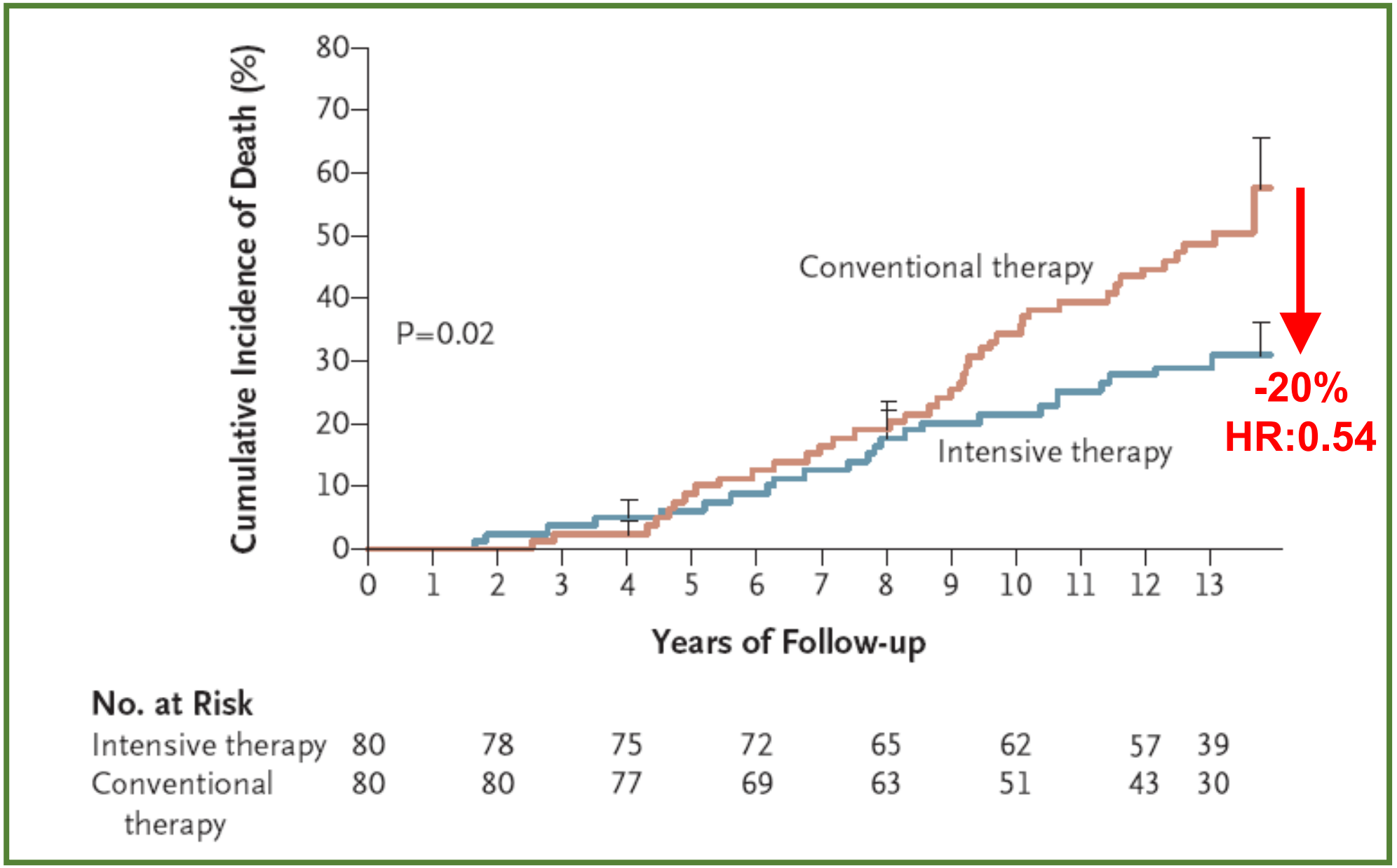
APPROCCI TERAPEUTICI DIVERSI?

NEFROPATIA DIABETICA



I Diabetici con Nefropatia (DM/CKD) hanno più probabilità di morire che di progredire a ESRD





Effect of a multifactorial intervention on mortality in type 2 diabetes

(Gæde P, N Engl J Med 2008)

MACROALBUMINURIA

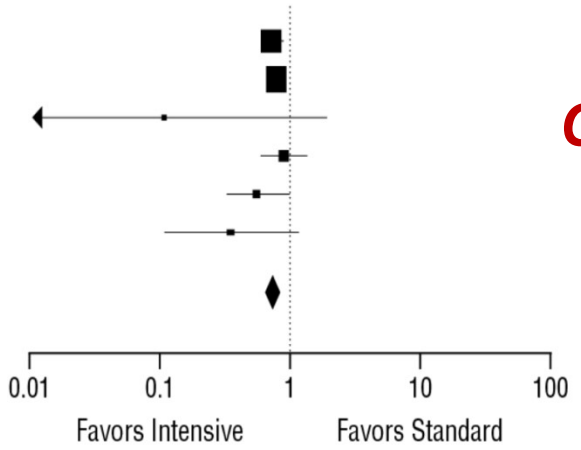
The JAMA Network

Coca SG
Arch Intern Med. 2012

Study or Subgroup	Intensive Therapy Events	Intensive Therapy Total	Standard Therapy Events	Standard Therapy Total	Weight, %	Risk Ratio M-H, Random (95% CI)
ACCORD[8,14]	195	4397	272	4424	39.3	0.72 (0.60-0.86)
ADVANCE[12]	230	5571	292	5569	42.5	0.79 (0.67-0.93)
Kumamoto[4,15]	0	52	4	50	0.2	0.11 (0.01-1.94)
UKPDS 33[16]	72	2277	33	938	10.4	0.90 (0.60-1.35)
VADT[11]	20	693	36	703	6.2	0.56 (0.33-0.96)
VA Feasibility Trial[5]	3	24	10	28	1.4	0.35 (0.11-1.13)
Total (95% CI)		**13014**		**11712**	**100.0**	**0.74 (0.65-0.85)**
Total events	**520**		**647**			

Heterogeneity: $\tau^2=0.00$; $\chi^2_5=5.73$; $P=.33$; $I^2=13\%$
Test for overall effect: $z=4.24$; $P=.001$

-26%



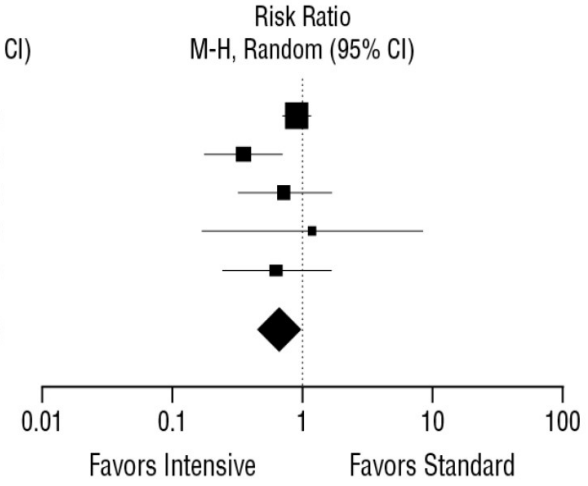
Controllo glicemico intensivo e Outcomes renali

ESRD

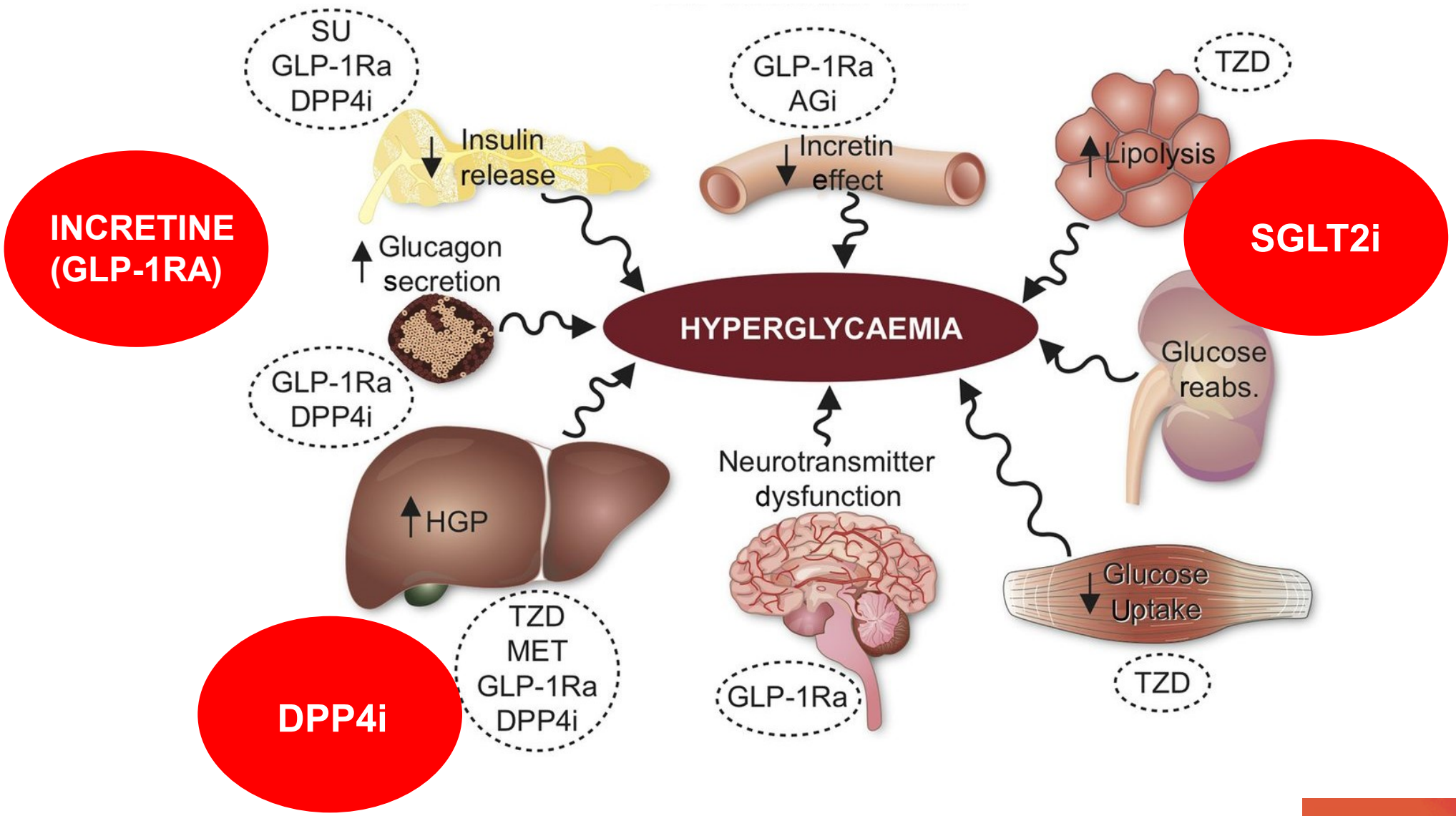
Study or Subgroup	Intensive Therapy Events	Intensive Therapy Total	Standard Therapy Events	Standard Therapy Total	Weight, %	Risk Ratio M-H, Random (95% CI)
ACCORD[8,14]	138	5119	151	5115	43.2	0.91 (0.73-1.15)
ADVANCE[12]	11	5571	31	5569	21.2	0.35 (0.18-0.70)
UKPDS 33[16]	16	2729	9	1138	17.3	0.74 (0.33-1.67)
UKPDS 34[17]	2	342	2	411	4.2	1.20 (0.17-8.49)
VADT[11]	7	882	11	884	14.1	0.64 (0.25-1.64)
Total (95% CI)		**14643**		**13117**	**100.0**	**0.69 (0.46-1.05)**
Total events	**174**		**204**			

Heterogeneity: $\tau^2=0.09$; $\chi^2_4=7.08$; $P=.13$; $I^2=43\%$
Test for overall effect: $z=1.72$; $P=.09$

-31%



FARMACI IPOGLICEMIZZANTI



Ferrannini E, and DeFronzo RA, 2015

European Heart Journal

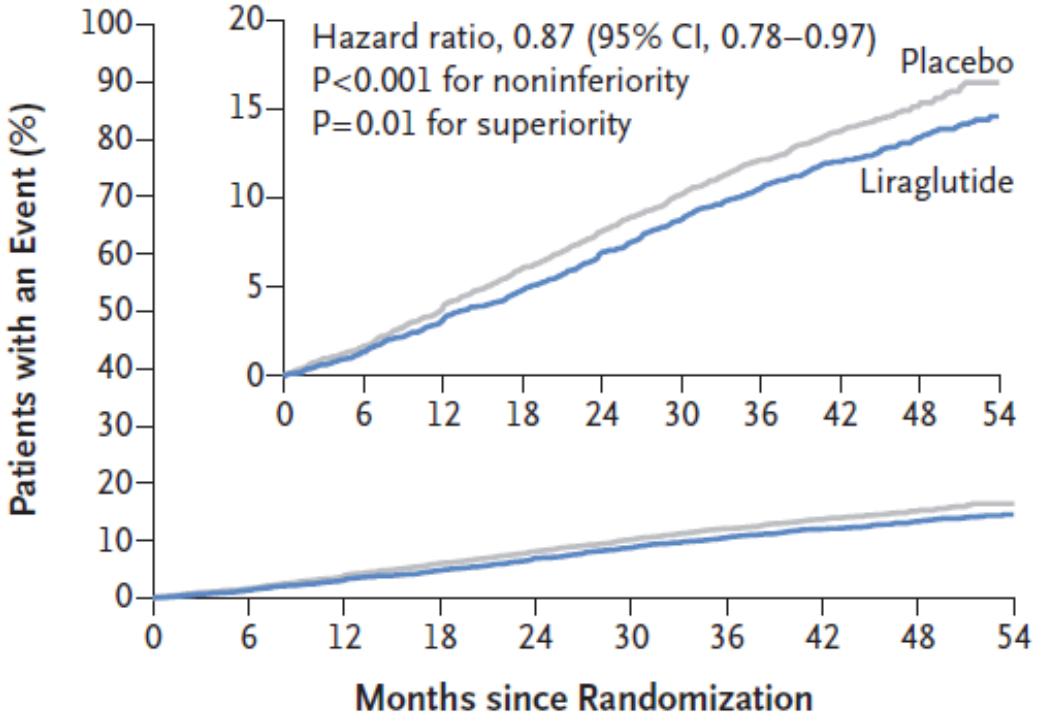
Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

The NEW ENGLAND JOURNAL of MEDICINE

LEADER Trial

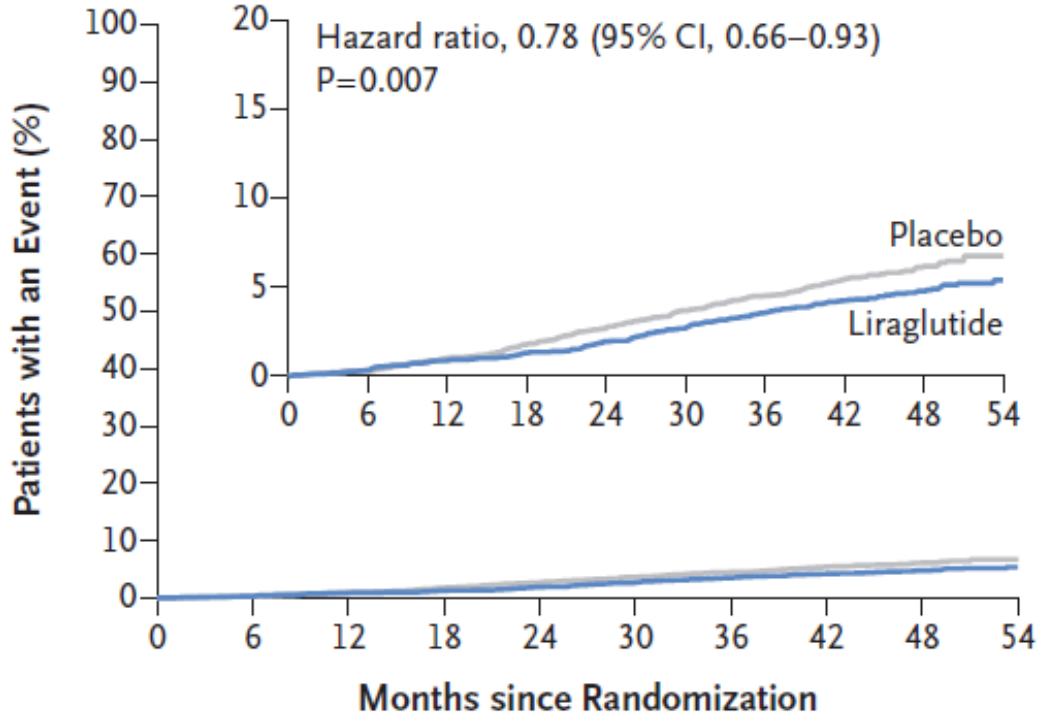
Marso SP, 2016

A Primary Outcome



No. at Risk										
Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

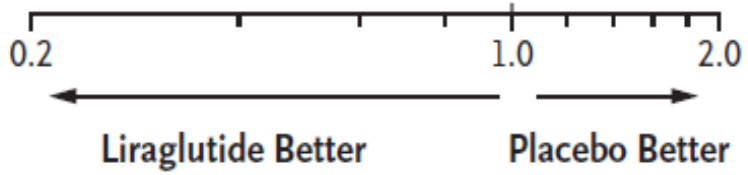
B Death from Cardiovascular Causes



No. at Risk										
Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4267	1709	465

La mortalità da cause CV, l'incidenza di infarto miocardico non fatale e di stroke non fatale in pazienti con DM Tipo 2 risultò significativamente inferiore nei pazienti che assumevano Liraglutide vs placebo *[75% dei pazienti assumevano Metformina]*

Subgroup	No. of Patients	Liraglutide	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
		no. of events/no. of patients (%)			
Renal function					
Severe or moderate disease					0.01
<60 ml/min/1.73 m^2	2158	172/1116 (15.4)	223/1042 (21.4)	0.69 (0.57–0.85)	
≥60 ml/min/1.73 m^2	7182	436/3552 (12.3)	471/3630 (13.0)	0.94 (0.83–1.07)	
Severe disease					0.93
<30 ml/min/1.73 m^2	224	25/117 (21.4)	26/107 (24.3)	0.89 (0.51–1.54)	
≥30 ml/min/1.73 m^2	9116	583/4551 (12.8)	668/4565 (14.6)	0.87 (0.77–0.97)	



- Liraglutide esercita un maggiore effetto protettivo CV con eGFR<60 ml/min
- I pazienti trattati con Liraglutide avevano una minore incidenza di eventi renali (macroalbuminuria, raddoppio creatinina, eGFR<45 ml/min, ESRD): hazard ratio 0.78; 95% CI, 0.67 to 0.92; P = 0.003

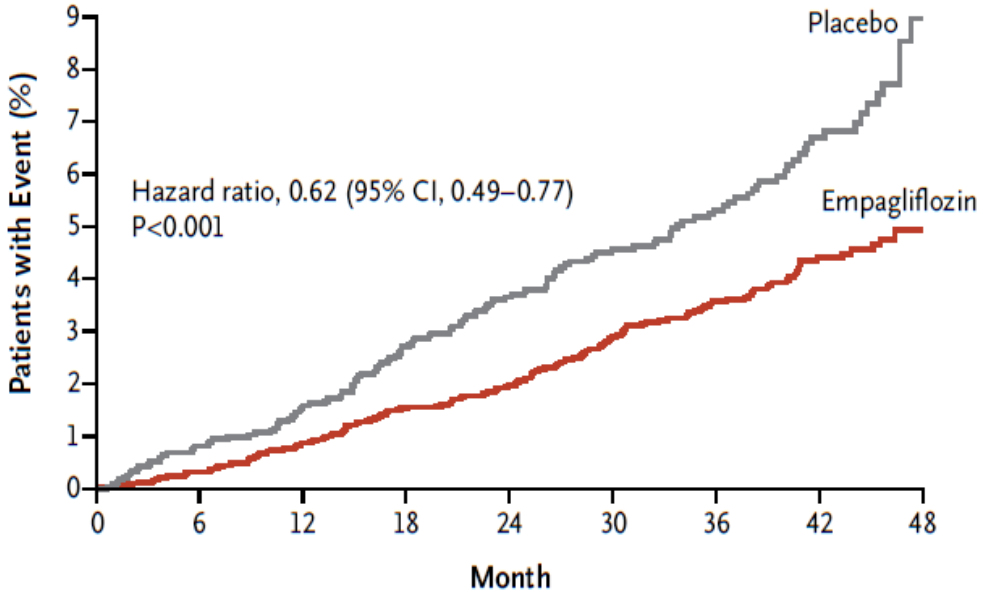
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

The NEW ENGLAND JOURNAL of MEDICINE

EMPA-REG OUTCOME Trial

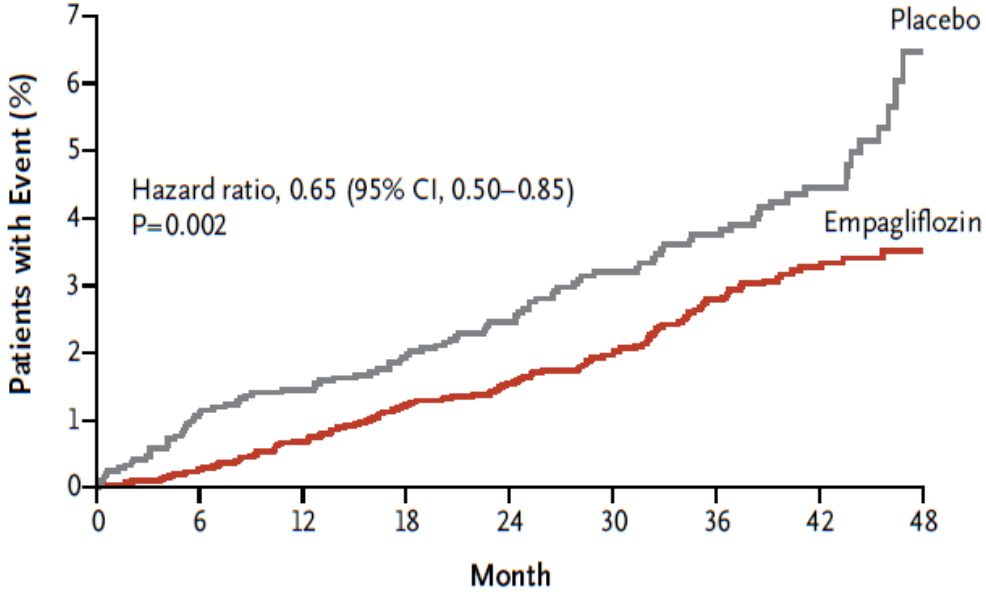
Zinman B, 2015

Death from Cardiovascular Causes



No. at Risk									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

Hospitalization for Heart Failure



No. at Risk									
Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

Pazienti con DM Tipo 2 ad alto rischio CV avevano una significativa riduzione del rischio CV con l'aggiunta di Empagliflozin alla terapia standard

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

The NEW ENGLAND JOURNAL of MEDICINE

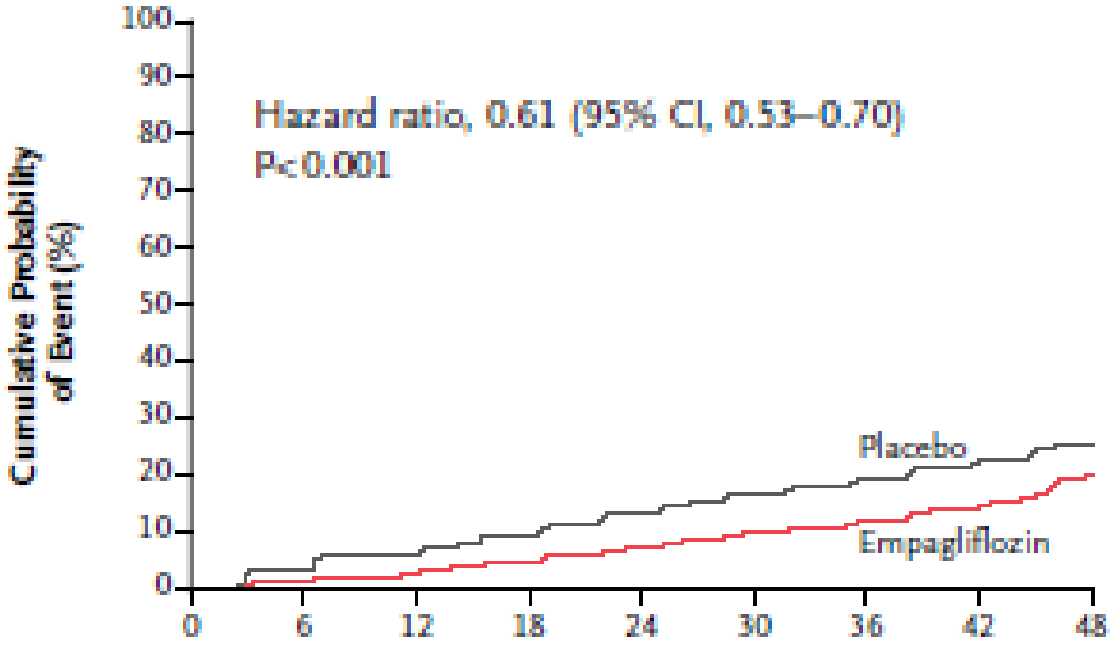
Wanner C, 2016

- 7020 pazienti diabetici ad alto rischio CV
- eGFR: 45-59 ml/min nel 17.8% e 30-44 ml/min nel 7.7%
- Microalbuminuria: 28.7%. Macroalbuminuria: 11.0%.
- Mediana di trattamento: 2,6 anni (osservazione: 3,1 anni)
- [Metformina: 70% nei paz. con eGFR >60 ml/min; 60% nei paz. con eGFR<60 ml/min]

Outcomes renali:

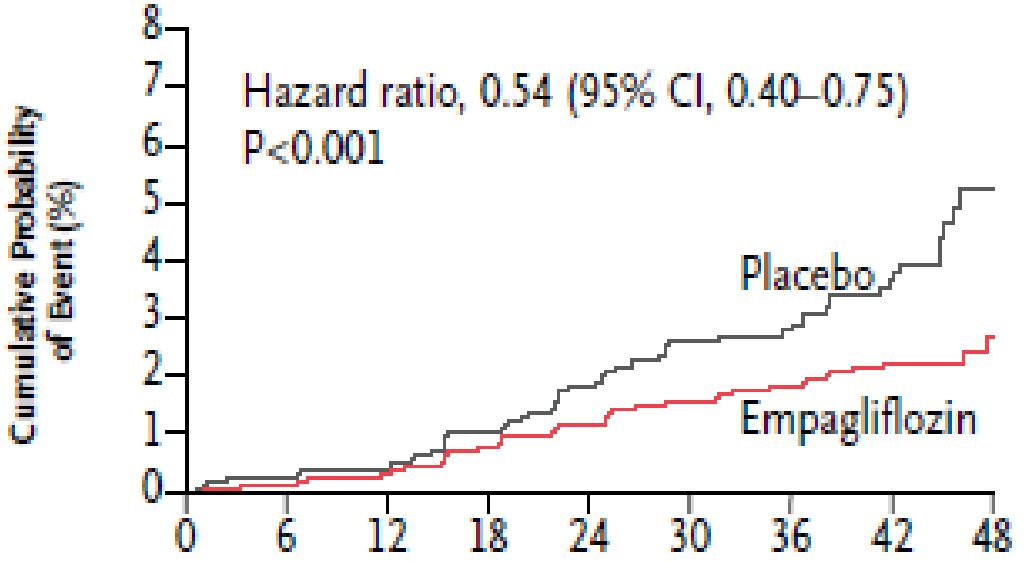
- *insorgenza o peggioramento della nefropatia, definito come progressione a macroalbuminuria;*
- *raddoppio della creatinina associato a eGFR<45 ml/min,*
- *ESRD o morte per malattia renale.*

Insorgenza o peggioramento di Nefropatia



No. at Risk									
Empagliflozin	4124	3994	3848	3669	3171	2279	1887	1219	290
Placebo	2061	1946	1836	1703	1433	1016	833	521	106

Raddoppio creatinina, ESRD, o morte per malattia renale



No. at Risk									
Empagliflozin	4645	4500	4377	4241	3729	2715	2280	1496	360
Placebo	2323	2229	2146	2047	1771	1289	1079	680	144

CONCLUSIONI

Nei pazienti diabetici di Tipo 2 ad alto rischio per eventi cardiovascolari, l'uso di Empagliflozin in aggiunta agli standard di cura (terapia anti-diabetica, ACEi o Sartani, ipolipemizzanti, ASA…) si associava ad una minore incidenza e ad un rallentamento della progressione di malattia renale

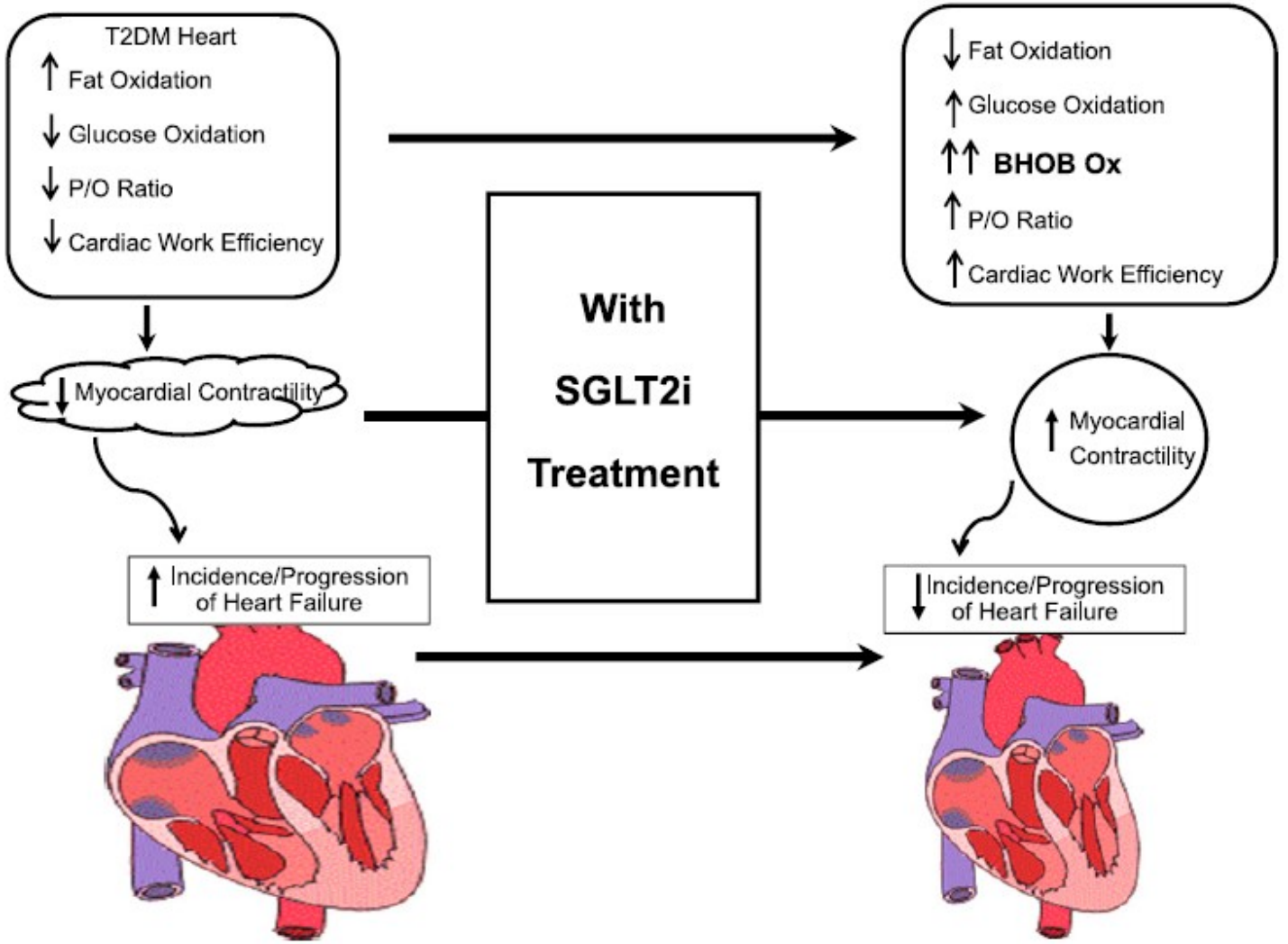
L'uso di Empagliflozin si associava altresì ad una significativa diminuzione del rischio di eventi renali maggiori (raddoppio della creatinina, ESRD o morte per malattia renale)

Diabetes Care Volume 39, July 2016

Sunder Mudaliar, Sindura Alloju, and Robert R. Henry

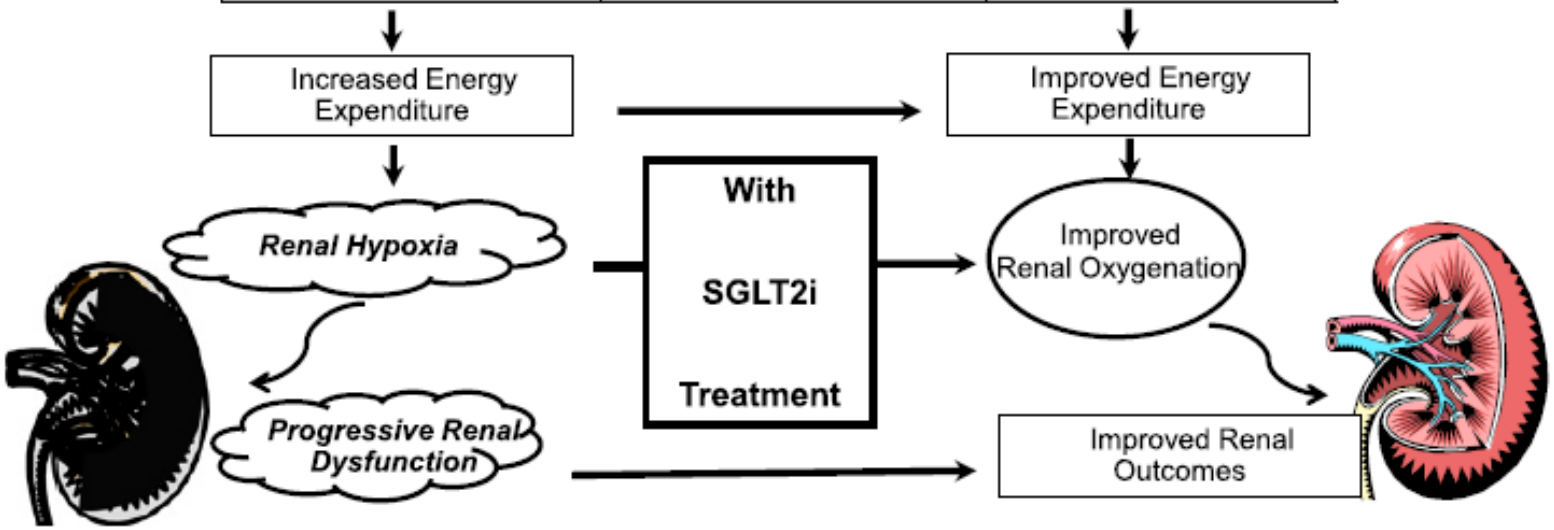
Can a Shift in Fuel Energetics Explain the Beneficial Cardiorenal Outcomes in the EMPA-REG OUTCOME Study? A Unifying Hypothesis

Diabetes Care 2016;39:1115–1122 | DOI: 10.2337/dc16-0542



La protezione Cardio-Renale di Empagliflozin sembra legata allo shift metabolico dall'ossidazione di glucosio e grassi all'utilizzo di chetoni, che migliora la resa ed il lavoro energetico e la funzione d'organo

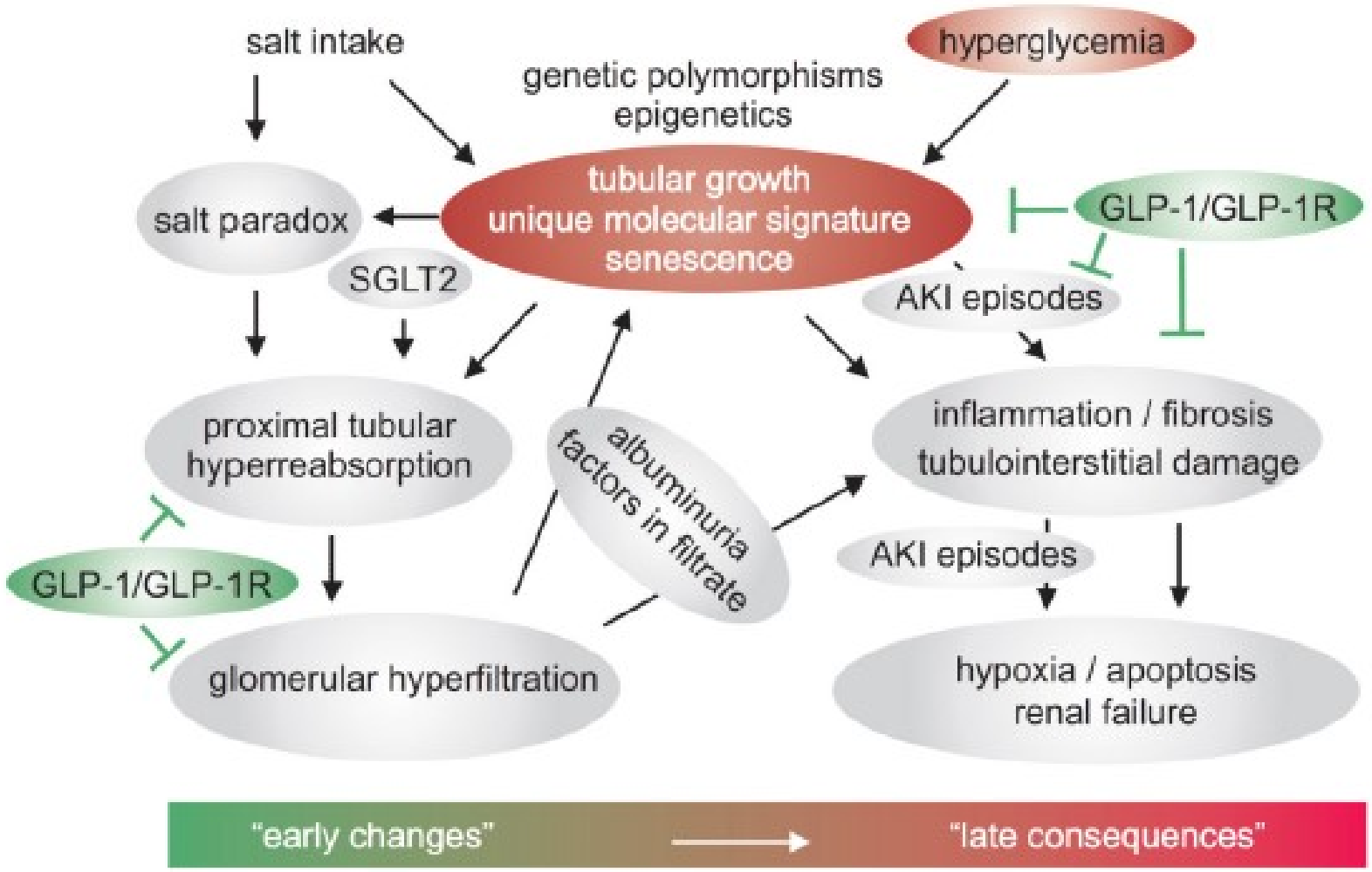
T2DM Kidney	Preferred Substrate In	T2DM Kidney with SGLT2i Rx
Lactate/FFA Glutamate	**S1/S2 Segments**	↓Lactate/FFA ↔ Glutamate
Lactate/FFA Glutamate/Glucose BHOB	**S3 Segment**	↓Lactate/FFA ↓Glutamate/Glucose **↑ BHOB**
Lactate/FFA Glucose BHOB	**Distal Collecting Tubules/Cortical Collecting Tubules**	↓Lactate/FFA ↓Glucose **↑ BHOB**



Nel diabete, l'aumento di GFR è legato all'incremento di assorbimento prossimale di Na^+, secondario all'iperattività di SGLT-2, e si accompagna ad un incremento nel consumo di Ossigeno.
L'inibizione di SGLT-2 può ridurre lievemente il GFR e il carico tubulare di Na^+

L'Ipotesi Tubulare della Iperfiltrazione glomerulare e della Nefropatia nel Diabete

Il ruolo emergente di GLP-1 R, e degli inibitori di DPP-4 e SGLT-2



AJKD
Original Investigation

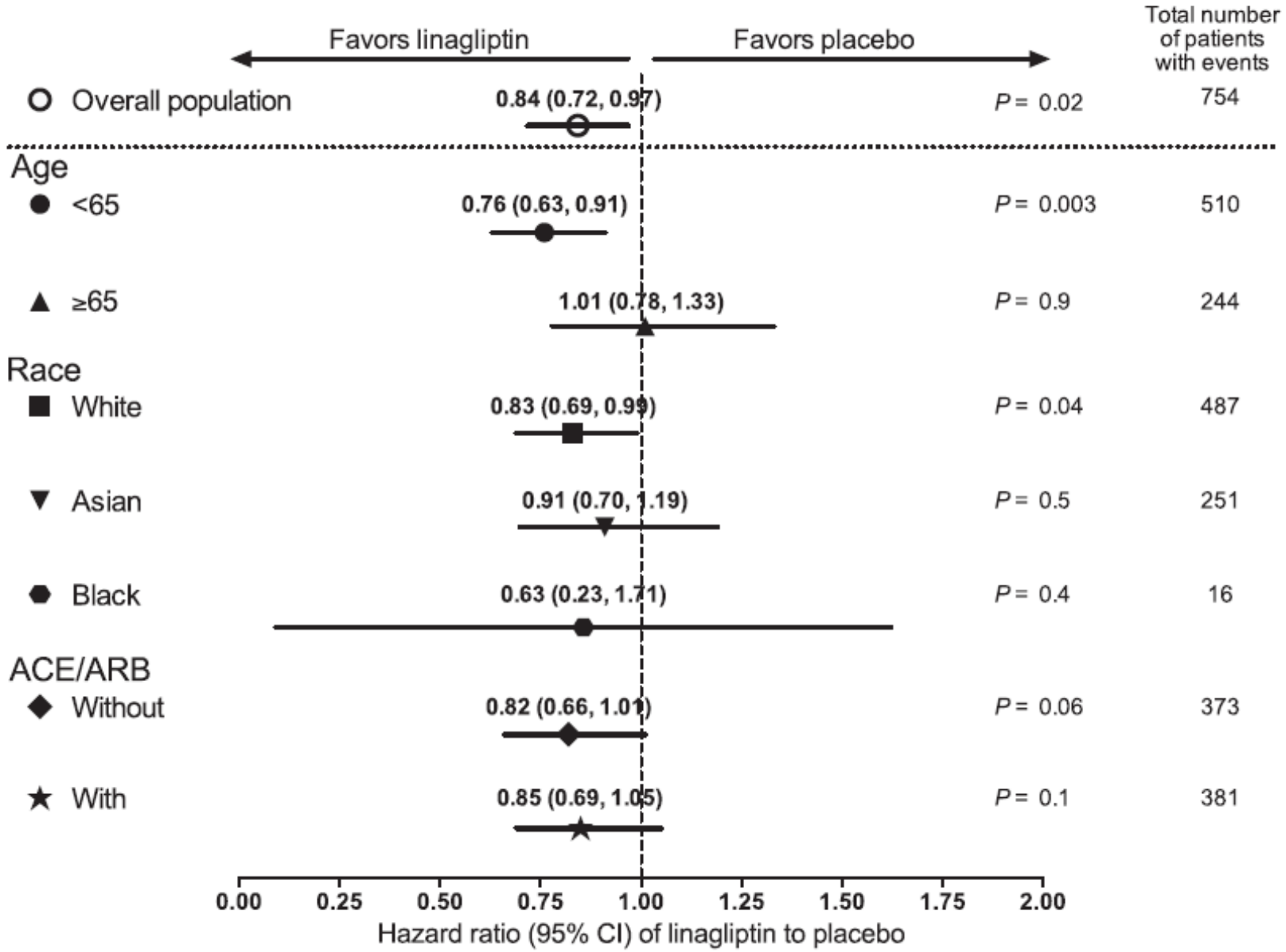
Kidney Disease End Points in a Pooled Analysis of Individual Patient–Level Data From a Large Clinical Trials Program of the Dipeptidyl Peptidase 4 Inhibitor Linagliptin in Type 2 Diabetes

Mark E. Cooper, MBBS, PhD,[1] Vlado Perkovic, MBBS, PhD,[2] Janet B. McGill, MD,[3] Per-Henrik Groop, MD, DMSC,[1,4,5] Christoph Wanner, MD,[6] Julio Rosenstock, MD,[7] Uwe Hehnke, MSc,[8] Hans-Juergen Woerle, MD,[8] and Maximilian von Eynatten, MD[8]

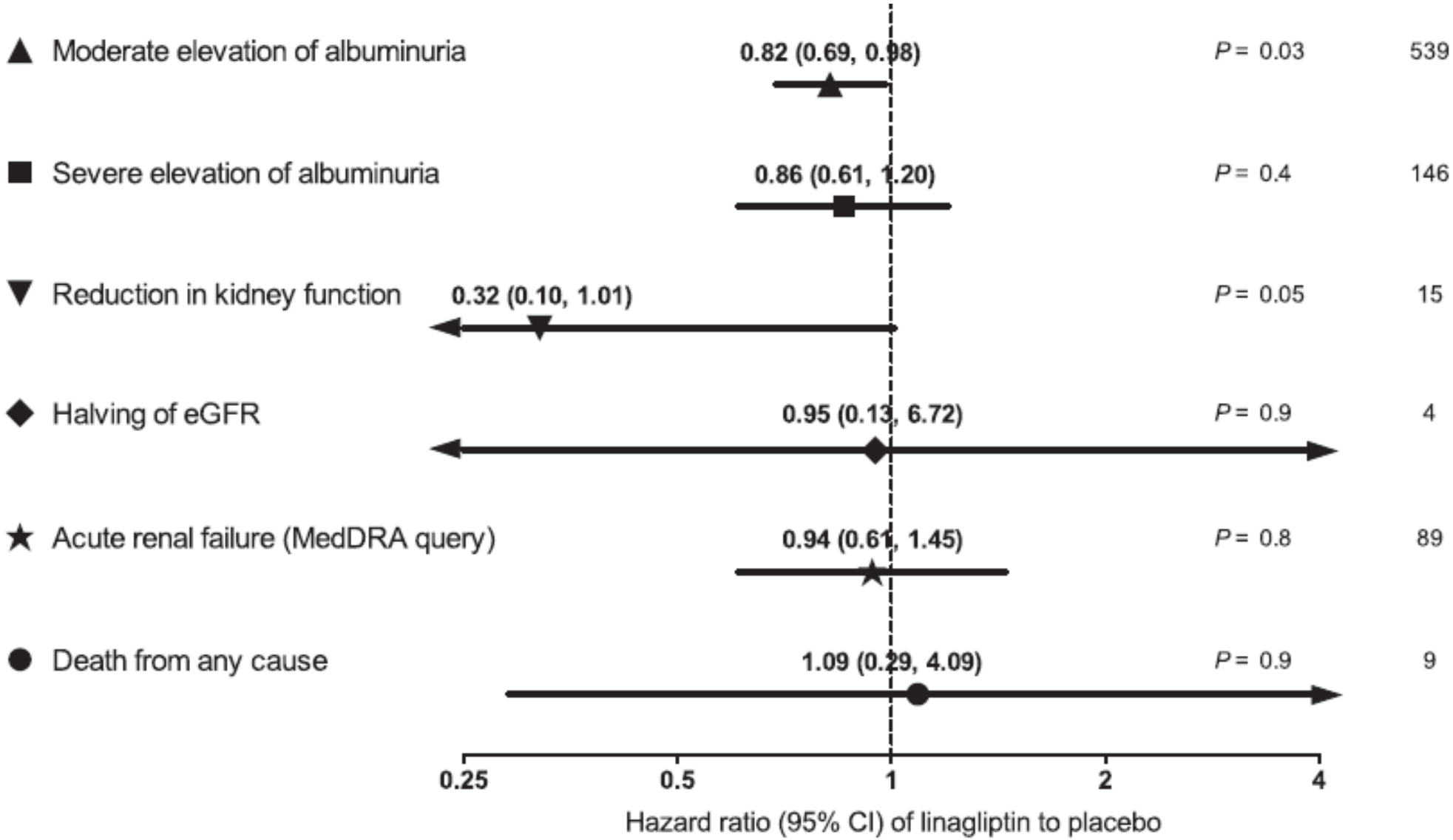
- Pooled analysis di 13 studi randomizzati di fase 2 o 3
- 5.466 pazienti con DMT2 mal controllato: 3.505 con linagliptin, 5 mg/d, e 1.961 con placebo

Outcome renale composito:

- insorgenza de novo o moderata elevazione della albuminuria
- Insorgenza di proteinuria severa (ACR ≥300 mg/g),
- Riduzione della funzione renale (creatininemia ≥ 250 mmol/L [2,84 mg/dl])
- Dimezzamento eGFR
- IRA
- Morte per qualsiasi causa



Linagliptin ridusse significativamente il rischio di eventi renali del 16% (P = 0.02)


Moderate elevation of albuminuria
0.82 (0.69, 0.98)
P = 0.03
539
Severe elevation of albuminuria
0.86 (0.61, 1.20)
P = 0.4
146
Reduction in kidney function
0.32 (0.10, 1.01)
P = 0.05
15
Halving of eGFR
0.95 (0.13, 6.72)
P = 0.9
4
Acute renal failure (MedDRA query)
0.94 (0.61, 1.45)
P = 0.8
89
Death from any cause
1.09 (0.29, 4.09)
P = 0.9
9
0.25
0.5
1
2
4
Hazard ratio (95% CI) of linagliptin to placebo

TAKE HOME MESSAGES

- ***Il danno renale in corso di DM Tipo 2 è eterogeneo: Biopsia renale (?)***
- ***I nuovi anti-diabetici, in specie Incretine e Glifozine, aggiunti a Metformina, riducono significativamente HbA1c e peso corporeo, con modesti decrementi della PA***
- ***Incretine e Glifozine, aggiunte a Metformina, riducono significativamente il rischio CV, l'incidenza di nefropatia de novo e la progressione del danno renale***

COSTI

COLLABORAZIONE CON I DIABETOLOGI