Aggiornamenti sulla Nefropatia Diabetica

SINL, June 10th 2022

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Disclosures

Conflict of interest	Yes
Relevant relationship with companies	Hoffman La Roche, Genentech, Bristol Myers Squibb, Abbvie, Jenssen, Boehringer Ingelheim, Astra Zeneca, Pfizer, Dimerix, ONO, Chemocentrix, Mallinkrodt, Kyowa Hakko Kirin, L&F Health, Novartis, Reata, Horizon, Kaneka
Sponsored research	• NIH • Hoffman La Roche • Boehringer Ingelheim • Aurinia • Alport Syndrome Foundation
Shareholder/officer	• ZyVersa Therapeutic • Renal 3 River Corporation • L&F Health • UpToDate

Caso clinico

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Obiettivi della presentazione

- Stratificazione, definizione e screening del rischio
- Linee guida 2022 per il trattamento
- Strumenti per approcci personalizzati e nuove scoperte

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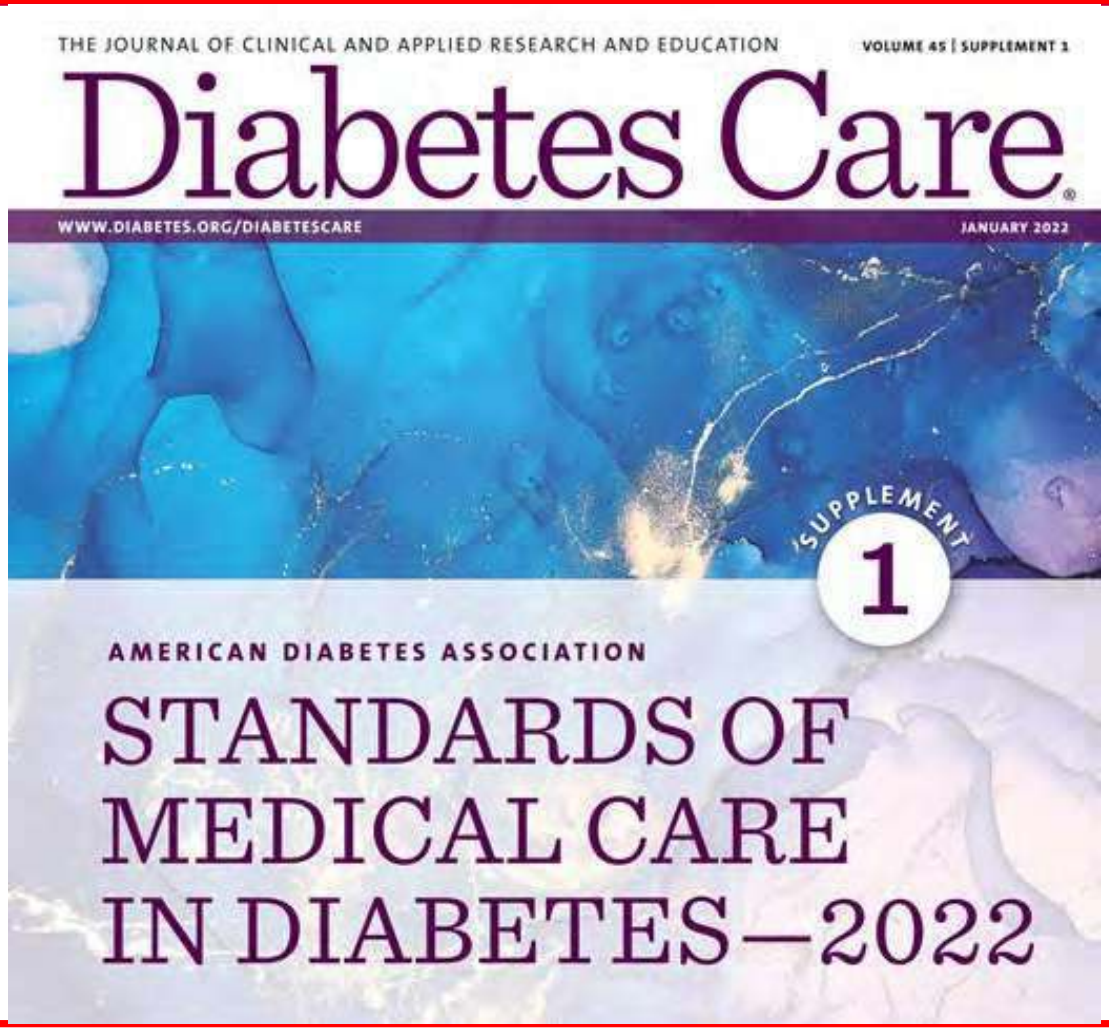
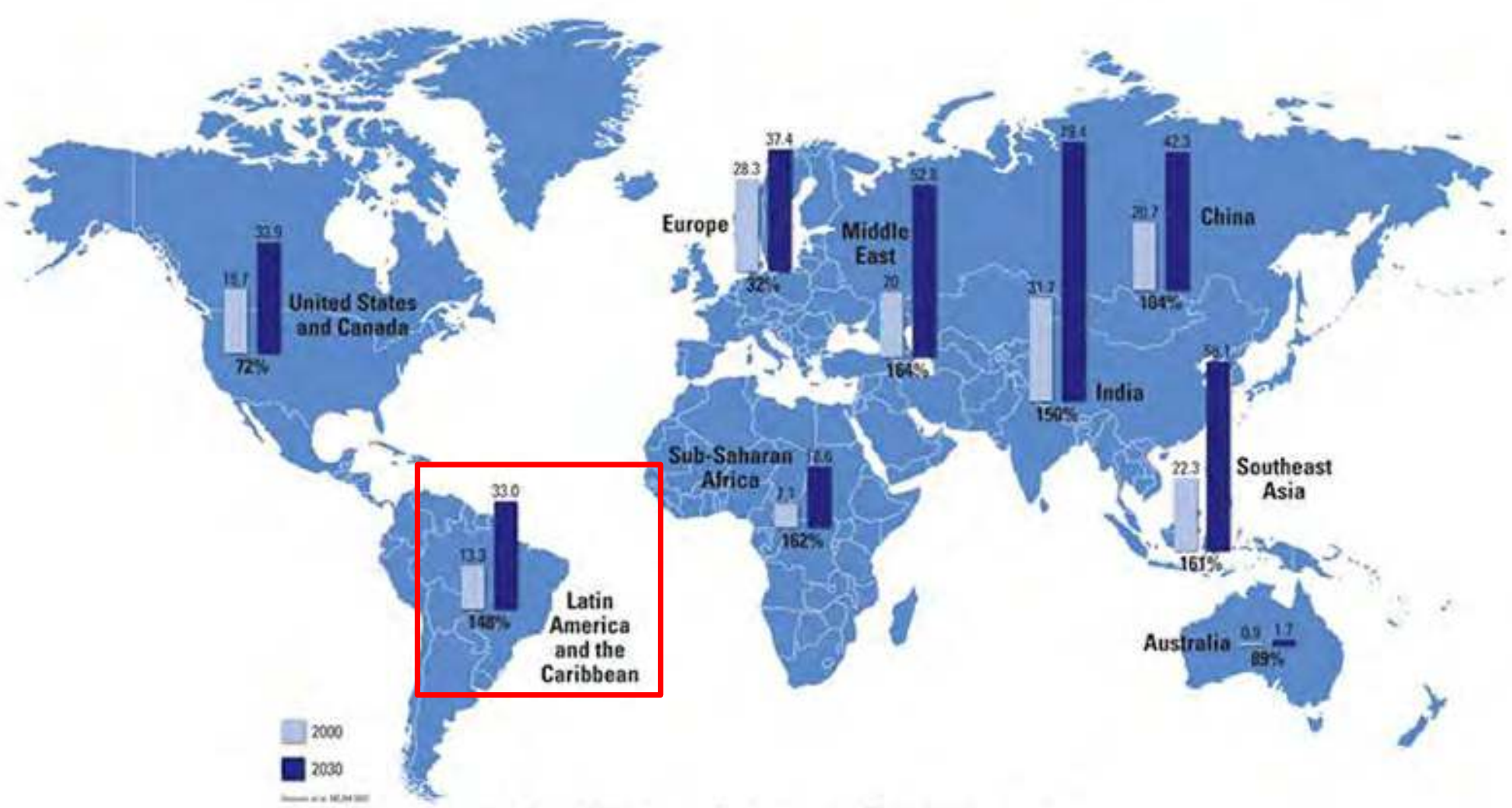
Aggiornamenti annuali



Page S175-185: Chronic Kidney Disease

Diabetes Care, 2022, Supplement 1

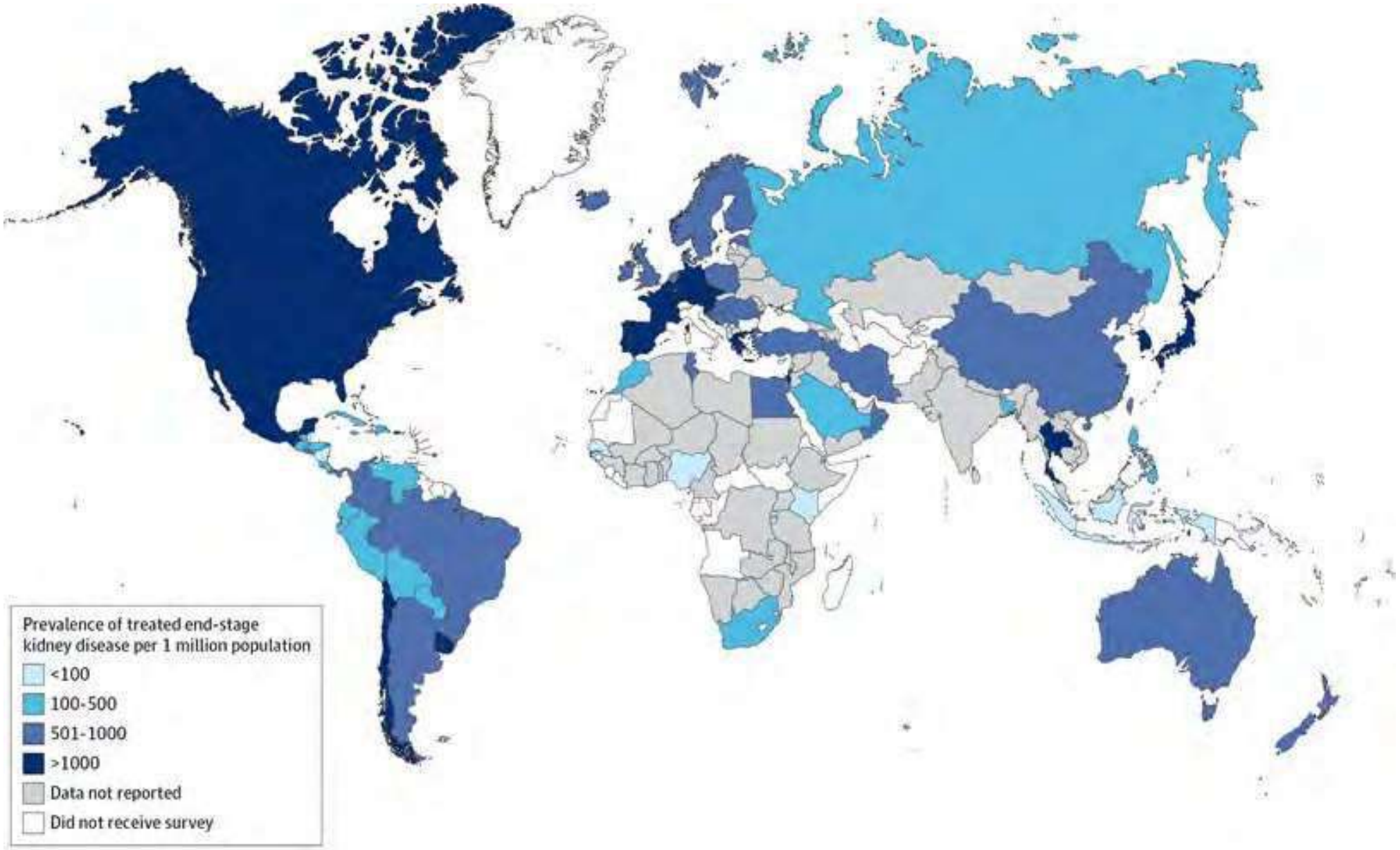
Diabete: una epidemia globale



Global Prevalence of Diabetes

Source: Hossain et al. NEJM 2007 *(million people)*

Prevalenza globale di ESKD

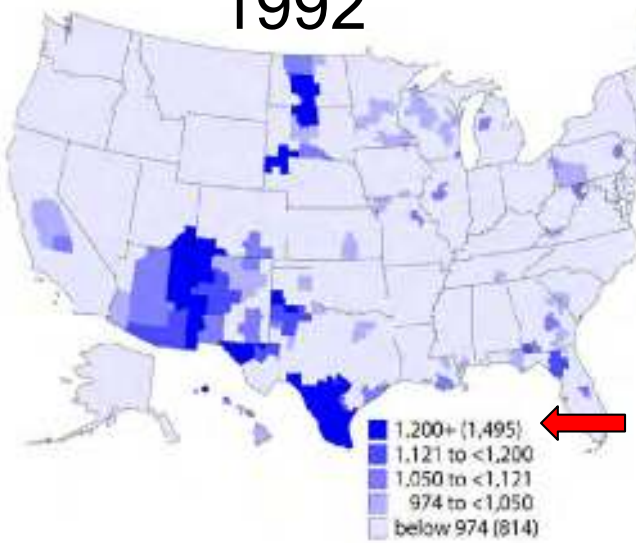


Bello AK et al, JAMA, 317: 1864, 2017

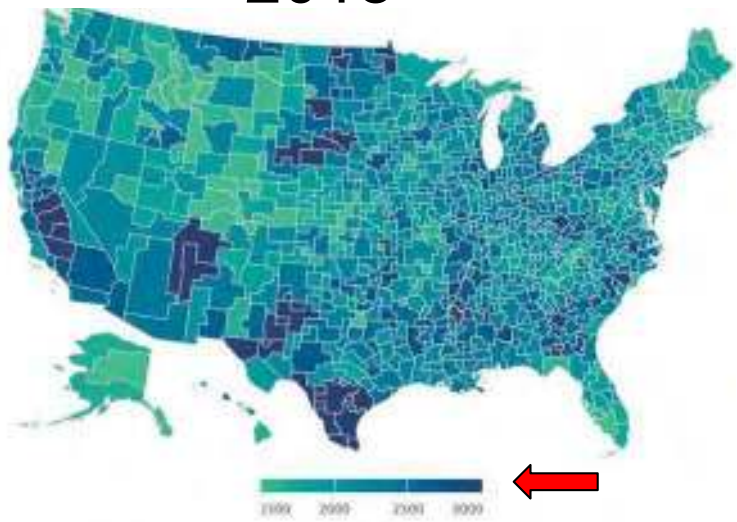
DKD causa primaria di ESKD in USA

ESRD prevalence (per M)

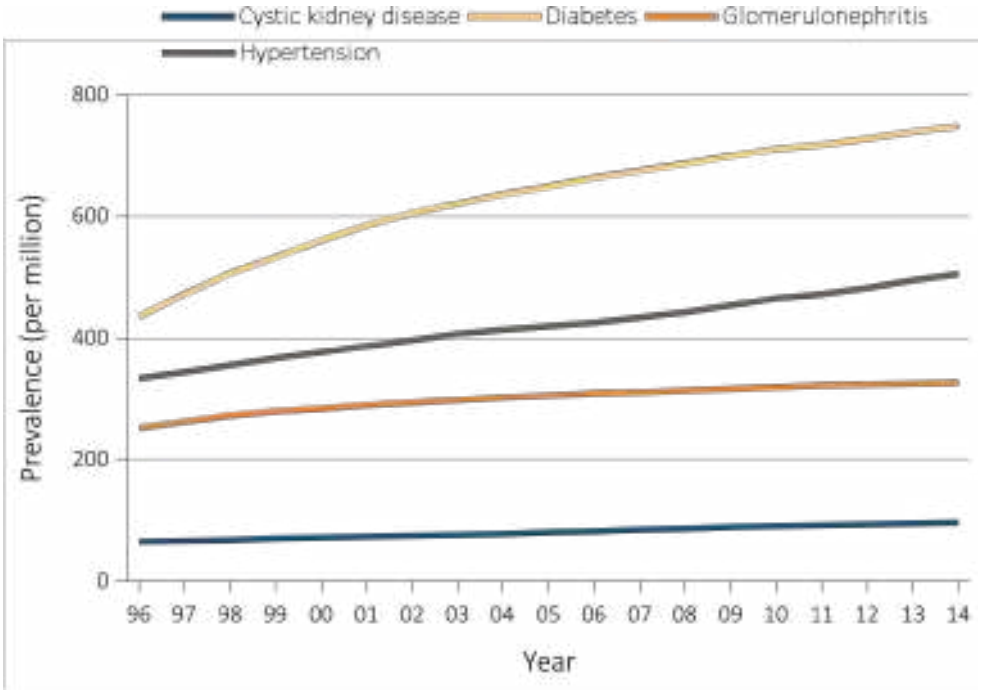
1992



2018

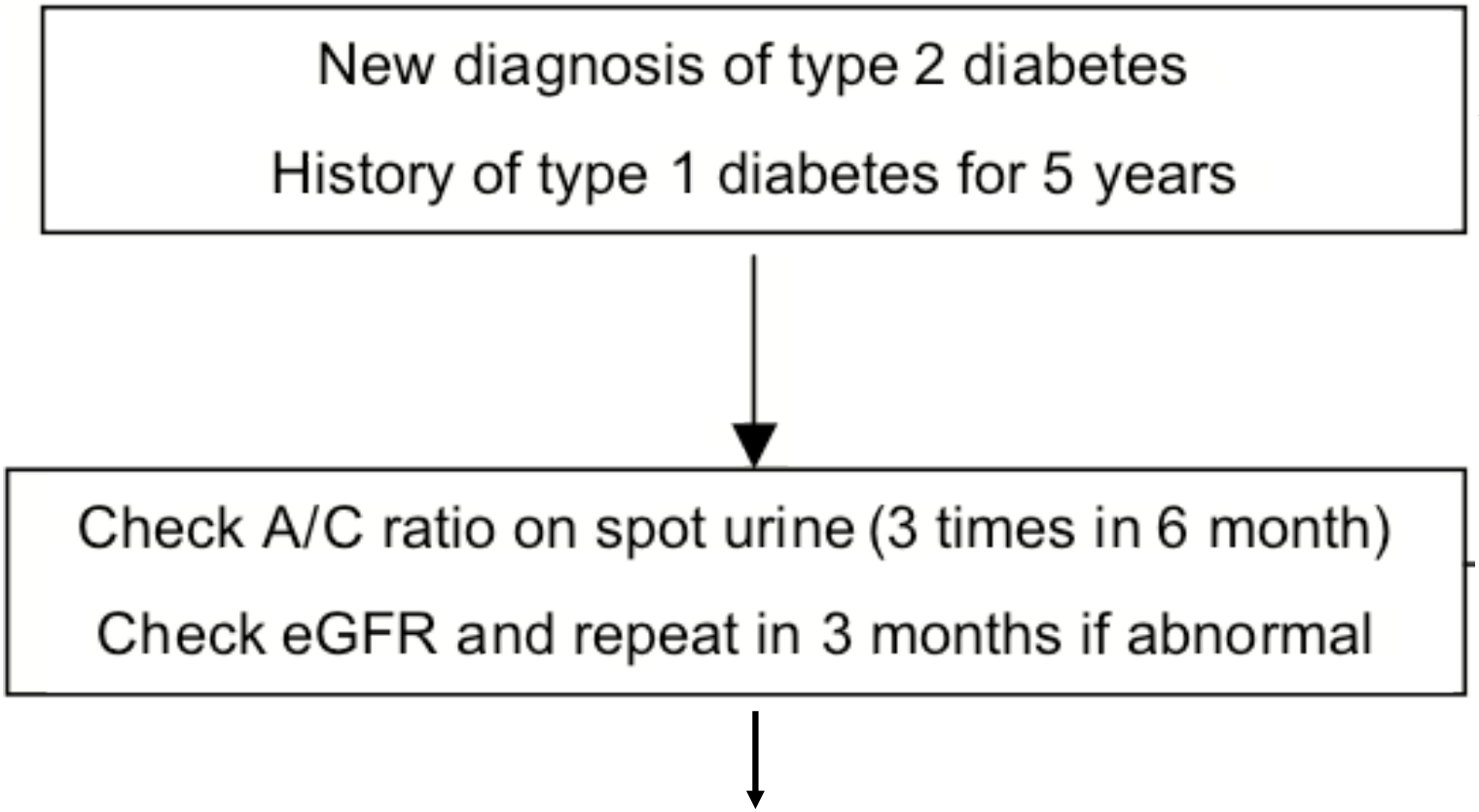


ESRD prevalence by cause



USRDS 2018

Screening



ADA recommendations, Diabetes Care, January 2022

Definizione

DIABETES with:

Abnormal urine albumin excretion

- >30 mg/24 hours
- >30 mg/g creatinine (preferred)
- >20 μg/min

and/or

- diabetic glomerular lesions

and/or

- loss of glomerular filtration rate (CKD-EPI preferred)

ADA recommendations, Diabetes Care, January 2022

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Case

JD is a 55 year old male with a 15 year history of type 2 DM and no retinopathy. His estimated GFR is 50 cc/min/1.73 m^2. A urine dipstick is negative for protein, but spot urine for albumin shows a concentration of 10 mg/dl ("normal" values 0-15 mg/dl) in two of three urine collections over a six months period. Urine creatinine is 0.04 g/dl for both collections: ACR is 250 mg/g creatinine.

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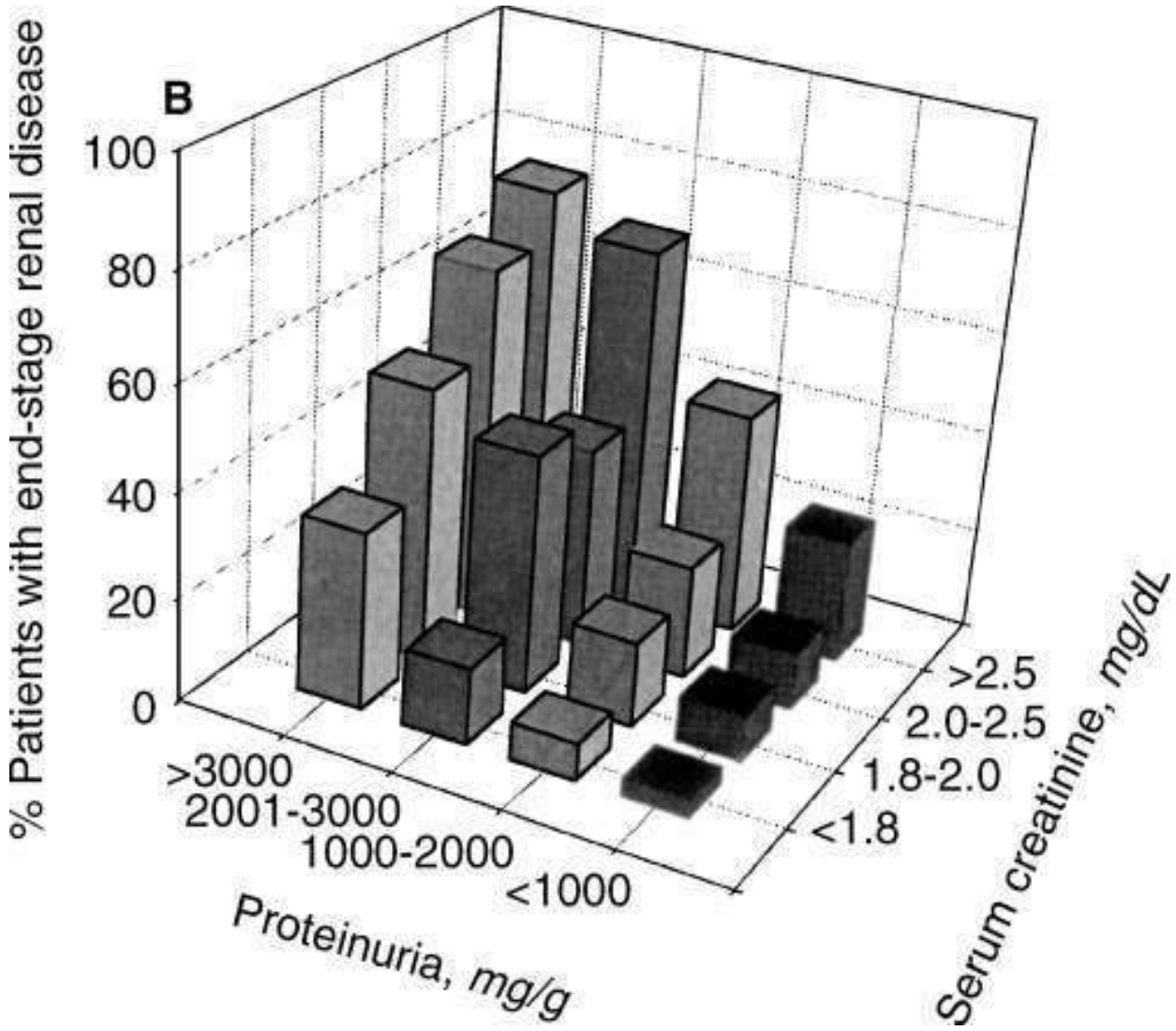
Proteinuria and GFR: risk factors for ESRD



Shahinfar S et al, Kidney Int: S48-S51, RENAAL Baseline Characteristics

Albuminuria e rischio di insufficienza renale

Risk calculator: kidneyfailurerisk.com

Chronic Kidney Disease Prognosis Consortium
721357 participants
30 countries

Tangri N et al, JAMA. 2016 Jan 12;315(2):164-74

Stratificazione del rischio

CKD is classified based on: • Cause (C) • GFR (G) • Albuminuria (A)				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73m²) Description and range	G1	Normal to high	≥90	1 If CKD	Treat 1	Refer* 2
	G2	Mildly decreased	60-89	1 If CKD	Treat 1	Refer* 2
	G3a	Mildly to moderately decreased	45-59	Treat 1	Treat 2	Refer 3
	G3b	Moderately to severely decreased	30-44	Treat 2	Treat 3	Refer 3
	G4	Severely decreased	15-29	Refer* 3	Refer* 3	Refer 4+
	G5	Kidney failure	<15	Refer 4+	Refer 4+	Refer 4+

Numbers indicate the suggested number of visits/year
Refer = initiate nephrology referral

ADA, Diabetes Care, 2022, Supplement 1
KDIGO 2012, Kidney International, Issue 1, 2013

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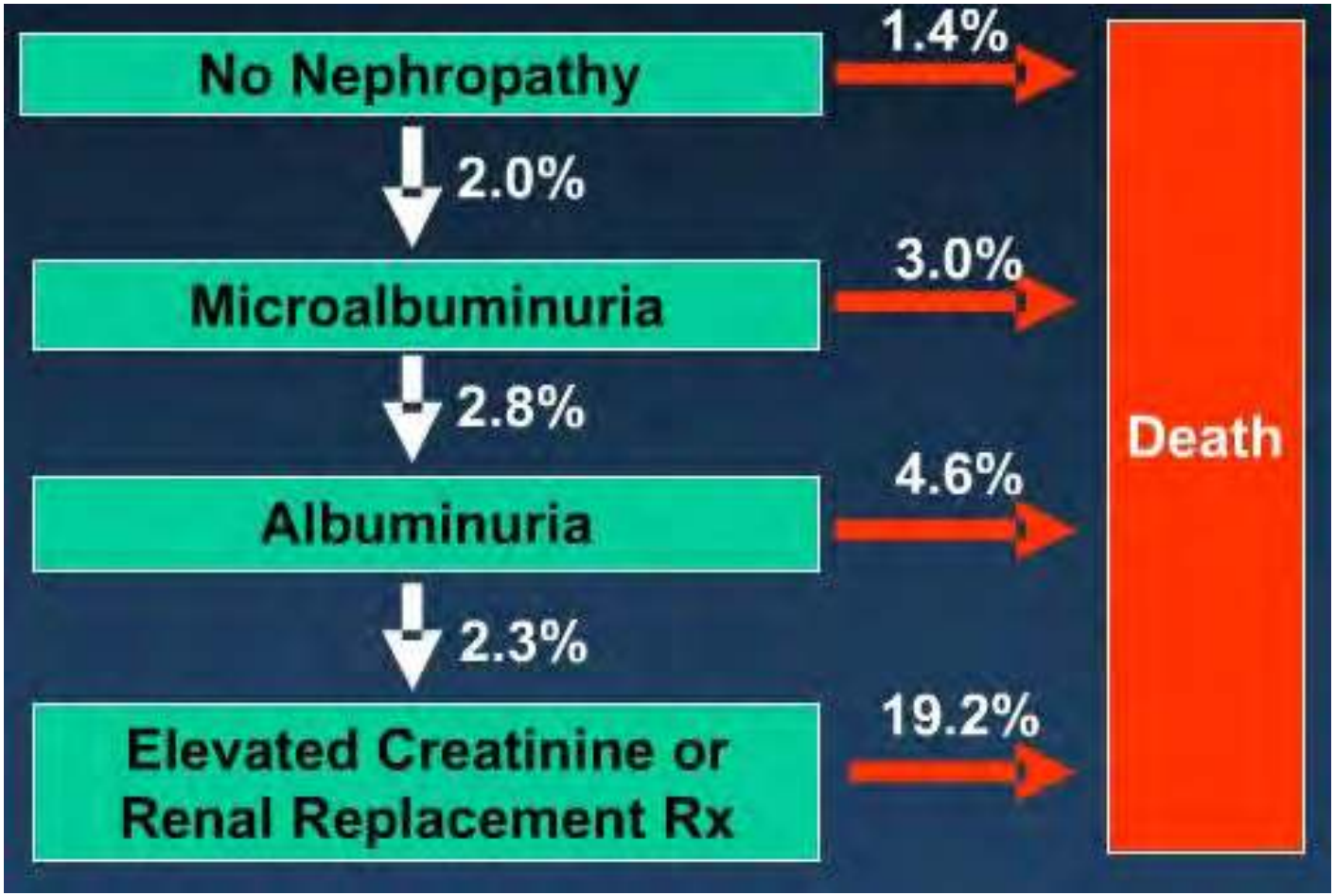
CKD e' tra le maggiori cause di morte

Cause of Death	Deaths (N =2664)		Years of Life Lost (N =45,145)		Years Lived with Disability (N =36,689)		DALYs (N =81,835)	
	Rank	No. (%) in thousands	Rank	No. (%) in thousands	Rank	No. (%) in thousands	Rank	No. (%) in thousands
Ischemic heart disease	1	563 (21.1)	1	7165 (15.9)	16	685 (1.9)	1	7850 (9.6)
Chronic obstructive pulmonary disease	5	154 (5.8)	4	1913 (4.2)	6	1745 (4.8)	2	3659 (4.5)
Low back pain	—	—	—	—	1	3181 (8.7)	3	3181 (3.9)
Cancer of the trachea, bronchus, or lung	3	163 (6.1)	2	2988 (6.6)	73	45 (0.1)	4	3033 (3.7)
Major depressive disorder	—	—	—	—	2	3049 (8.3)	5	3049 (3.7)
Diabetes mellitus	6	86 (3.2)	7	1392 (3.1)	8	1165 (3.2)	8	2557 (3.1)
Chronic kidney disease	9	60 (2.3)	16	780 (1.7)	22	410 (1.1)	17	1191 (1.5)

Murray et al NEJM 2013; 369: 5

DKD e rischio di morte annuale



> 5000 Type 2 Diabetes patients

Yearly risk associated

CVD risk protection needs early implementation

Adler et al, Kidney International, 2003;63:225

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Nephrology referral and biopsy

eGFR<30 cc/min/1.73m^2 at diagnosis

ADA

Worsening proteinuria despite treatment
Loss of eGFR> 1cc/min/1.73m^2/month
Active urine sediment
Absence of retinopathy

QDOQI

biopsy

>30% reduction in eGFR after initiation of ACEi/ARB
Refractory hypertension

CKD care and referral for renal replacement strategies

KDIGO 2020: No mention

ADA recommendations, Diabetes Care, January 2022
NKF QDOQI guidelines for diabetes, AJKD 2014

Limitazioni delle biopsie ad uso clinico

Table 2 Comparison of diabetic nephropathy and non-diabetic renal disease prevalence reported in the literature

Ref.	Country	Population	Type 1 or 2 DM	% DN	% NDRD	% Mixed
Mazzucco *et al*[25]	Italy	393	2	39.7	43	17.3
Christensen *et al*[24]	Denmark	51	2	68.6	13.8	NR
Zhang *et al*[37]	China	130	2	73.9	26.1	NR
Zhuo *et al*[50]	China/Japan	216	2	6.5	82.9	10.7
Sharma *et al*[51]	United States	620	2	37	36	27
Hironaka *et al*[52]	Japan	35	1 and 2	71.4	14.3	14.3
Wong *et al*[53]	China	68	2	35	46	19
Prakash *et al*[55]	India	23	2	56.5	30.5	13
Mak *et al*[56]	China	51	2	67	16	17
Biensebach *et al*[57]	Austria	84	2	78.5	21.5	NR
Richards *et al*[58]	United Kingdom	68	1 and 2	61	32	3
Parving *et al*[59]	Denmark	35	2	77.1	20	2.9
Cordonnier *et al*[60]	United Kingdom	26	2	85	15	NR
Nzerue *et al*[61]	United States	31	2	41.9	19.4	38.7
Lee *et al*[62]	South Korea	22	2	36.4	50	13.6
Izzedine *et al*[63]	France	21	1 and 2	62	38	NR
Castellano *et al*[64]	Spain	20	2	45	55	NR
Serra *et al*[65]	Spain	35	2	74.3	17.2	8.5
Premalatha *et al*[66]	India	18	2	50	50	NR
Rychlik *et al*[67]	Czech Republic	163	2	42.4	47.5	10.1
Tone *et al*[68]	Japan	97	2	36	16.5	47.5
Moger *et al*[69]	India	26	2	34.6	23.1	42.3
Soni *et al*[70]	India	160	2	42.5	27.5	30
Pham *et al*[71]	United States	233	2	27.5	53.2	19.3
Kharrat *et al*[72]	Tunisia	72	2	34.1	69.5	NR
Akimoto *et al*[73]	Japan	50	2	68	26	6
Huang *et al*[74]	China	52	2	55.7	38.5	5.8
Lin *et al*[75]	Taiwan, China	50	2	48	22	30
Ghani *et al*[76]	Kuwait	31	2	54.8	NR	45.2
Arif *et al*[77]	Pakistan	73	2	27.3	49.3	NR
Hashim Al-Saedi *et al*[78]	Iraq	80	1 and 2	NR	NR	100
Mou *et al*[79]	China	69	2	47.8	52.2	NR
Haider *et al*[80]	Austria	567	1 and 2	68	17.4	NR
Chang *et al*[81]	South Korea	119	2	36.2	53.8	10
Bi *et al*[82]	China	220	2	54.5	NR	45.5
Chong *et al*[83]	Malaysia	110	2	62.7	18.2	19.1
Harada *et al*[84]	Japan	55	2	54.5	34.5	10.9
Oh *et al*[85]	South Korea	126	2	39.7	51.6	8.7
Yaqub *et al*[86]	Pakistan	68	2	31	52	17

Often the diagnosis in clinically indicated kidney biopsies differs from DKD

Protocol kidney biopsies are needed to understand the disease

Gonzalez Suarez ML, Thomas DB, Barisoni L, Fornoni A., World J Diabetes, 2013

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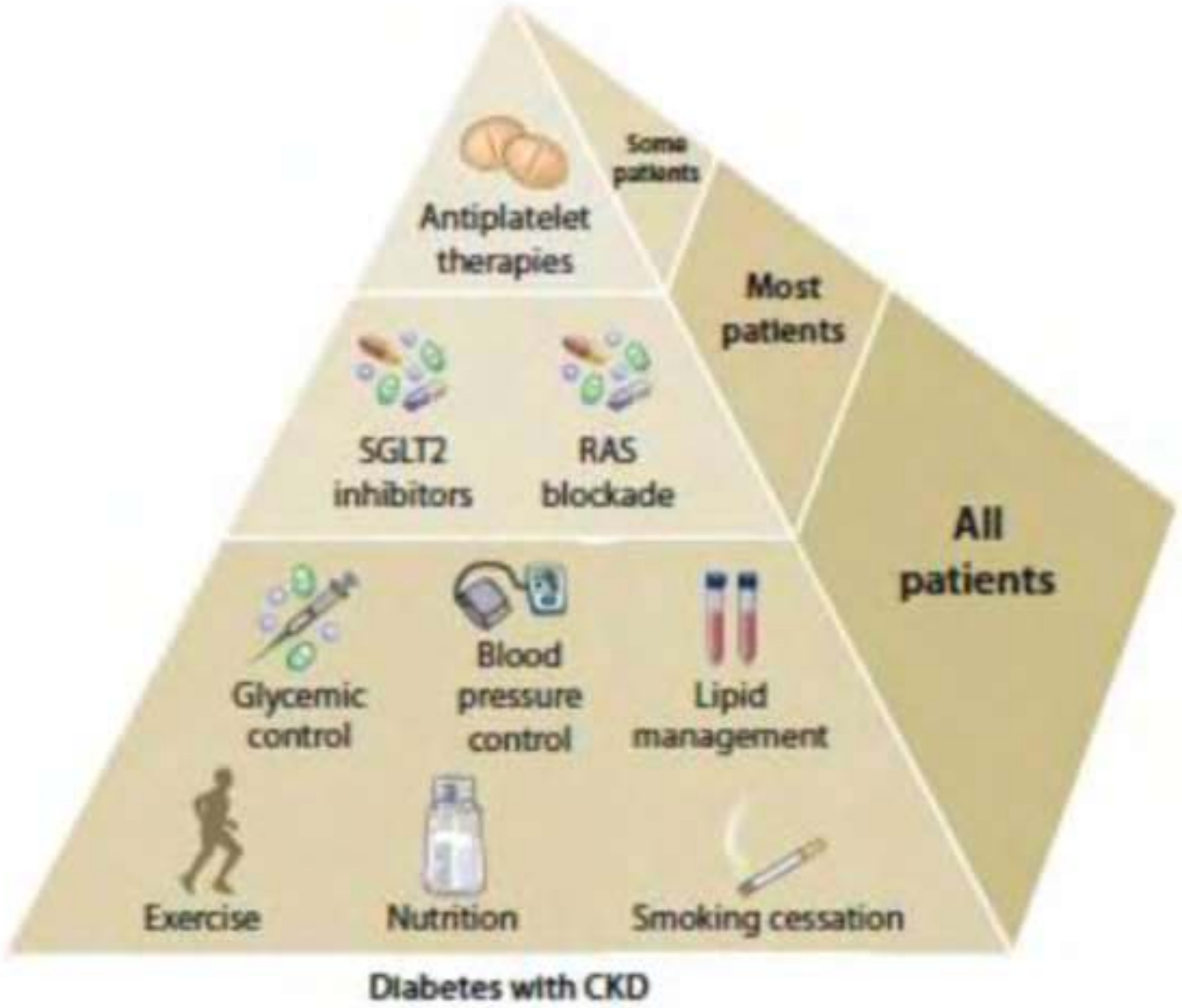
Prevenzione e trattamento



KDIGO 2020, Diabetes Management in CKD

Prevenzione e trattamento

American Diabetes Association recommendations 2022

Level of evidence A:

control BP with appropriate agents (goal <140/90mmHg, <130/80 if high risk for CVD)
control glycemia (A1C about 7%, personalized)
control dyslipidemia (LDL goal <70-100 mg/dl)
counsel about smoking cessation
education
protein intake to 0.8 g/kg/day (more if dialysis)

ADA recommendations, Diabetes Care, January 2022

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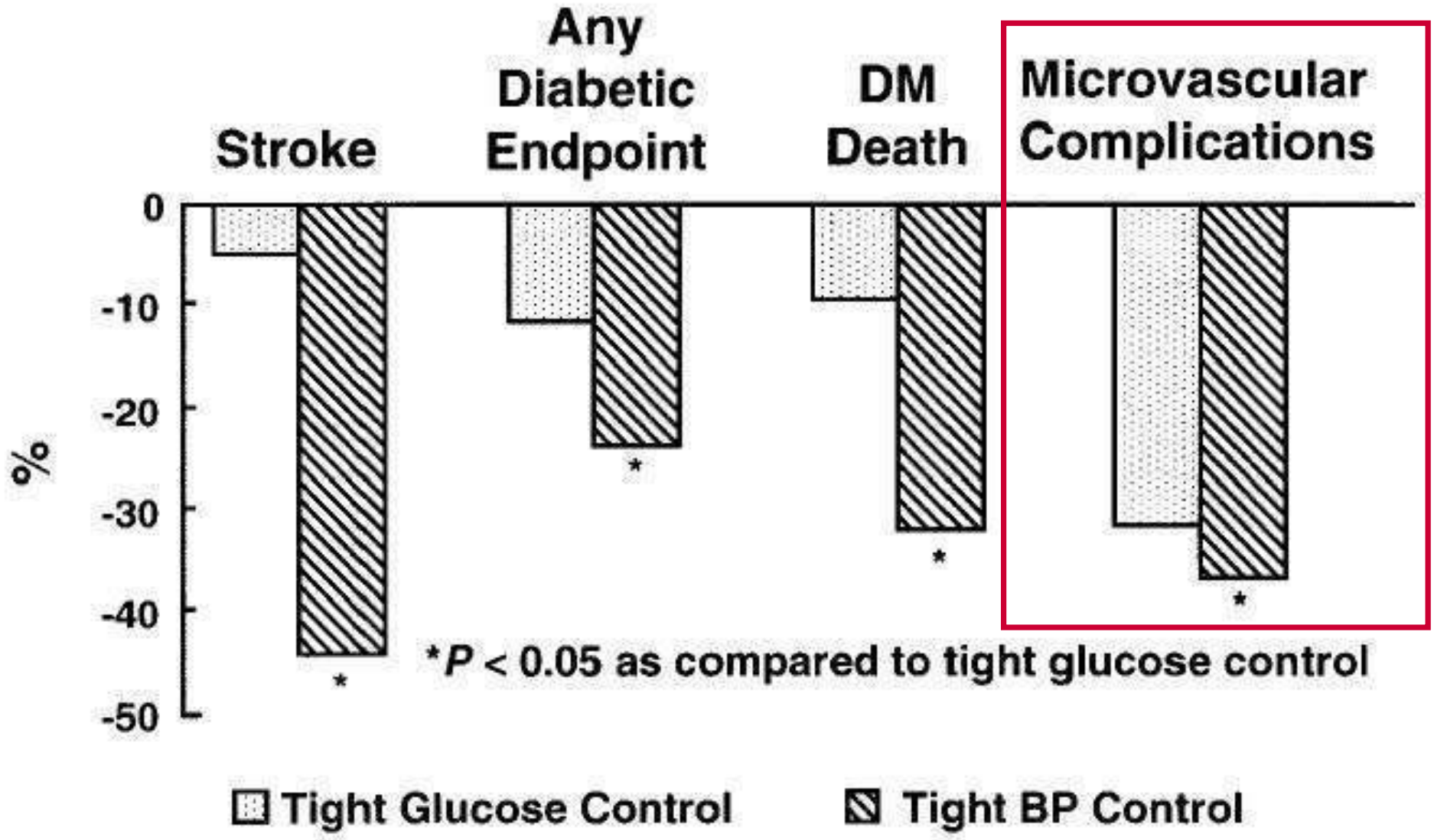
ADA recommendations, Diabetes Care, January 2022

Fattori emodinamici e metabolici in DKD



Bakris, AJKD, 36:646, 2000

Linee guida:
JNC7 - ACC/AHA 2017 - KDIGO 2021

SBP/DBP mm Hg	JNC7	2017 ACC/AHA
<120 and <80	Normal	Normal
120 – 129 and <80	Prehypertension	Elevated BP
130 – 139 or 80 – 89	Prehypertension	Stage 1 HTN
140 -159 or 90 – 99	Stage 1 HTN	Stage 2 HTN
≥ 160 or ≥ 100	Stage 2 HTN	Stage 2 HTN

Chapter 3: Blood pressure management in patients with CKD, with or without diabetes, not receiving dialysis	
• Recommendation 3.1.1	We suggest that adults with high BP and CKD be treated with a target systolic blood pressure (SBP) of <120 mm Hg, when tolerated, using standardized office BP measurement *(2B)*.

KDIGO 2021, Kidney Int, 99:559-569
ACC/AHA recommendations Nov 13 2017

Razionale per BP targets <140/90

Table 9.1—Randomized controlled trials of intensive versus standard hypertension treatment strategies

Clinical trial	Population	Intensive	Standard	Outcomes
ACCORD BP (16)	4,733 participants with T2D aged 40–79 years with prior evidence of CVD or multiple cardiovascular risk factors	Systolic blood pressure target: <120 mmHg Achieved (mean) systolic/diastolic: 119.3/64.4 mmHg	Systolic blood pressure target: 130–140 mmHg Achieved (mean) systolic/diastolic: 133.5/70.5 mmHg	• No benefit in primary end point: composite of nonfatal MI, nonfatal stroke, and CVD death • Stroke risk reduced 41% with intensive control, not sustained through follow-up beyond the period of active treatment • Adverse events more common in intensive group, particularly elevated serum creatinine and electrolyte abnormalities
ADVANCE BP (17)	11,140 participants with T2D aged 55 years and older with prior evidence of CVD or multiple cardiovascular risk factors	Intervention: a single-pill, fixed-dose combination of perindopril and indapamide Achieved (mean) systolic/diastolic: 136/73 mmHg	Control: placebo Achieved (mean) systolic/diastolic: 141.6/75.2 mmHg	• Intervention reduced risk of primary composite end point of major macrovascular and microvascular events (9%), death from any cause (14%), and death from CVD (18%) • 6-year observational follow-up found reduction in risk of death in intervention group attenuated but still significant (142)
HOT (143)	18,790 participants, including 1,501 with diabetes	Diastolic blood pressure target: ≤80 mmHg	Diastolic blood pressure target: ≤90 mmHg	• In the overall trial, there was no cardiovascular benefit with more intensive targets • In the subpopulation with diabetes, an intensive diastolic target was associated with a significantly reduced risk (51%) of CVD events
SPRINT (144)	9,361 participants without diabetes	Systolic blood pressure target: <120 mmHg Achieved (mean): 121.4 mmHg	Systolic blood pressure target: <140 mmHg Achieved (mean): 136.2 mmHg	• Intensive systolic blood pressure target lowered risk of the primary composite outcome 25% (MI, ACS, stroke, heart failure, and death due to CVD) • Intensive target reduced risk of death 27% • Intensive therapy increased risks of electrolyte abnormalities and AKI

CVD, cardiovascular disease; T2D, type 2 diabetes. Data from this table can also be found in the ADA position statement "Diabetes and Hypertension" (5).

ADA recommendations, Diabetes Care, January 2022

Ruolo della pressione in DKD

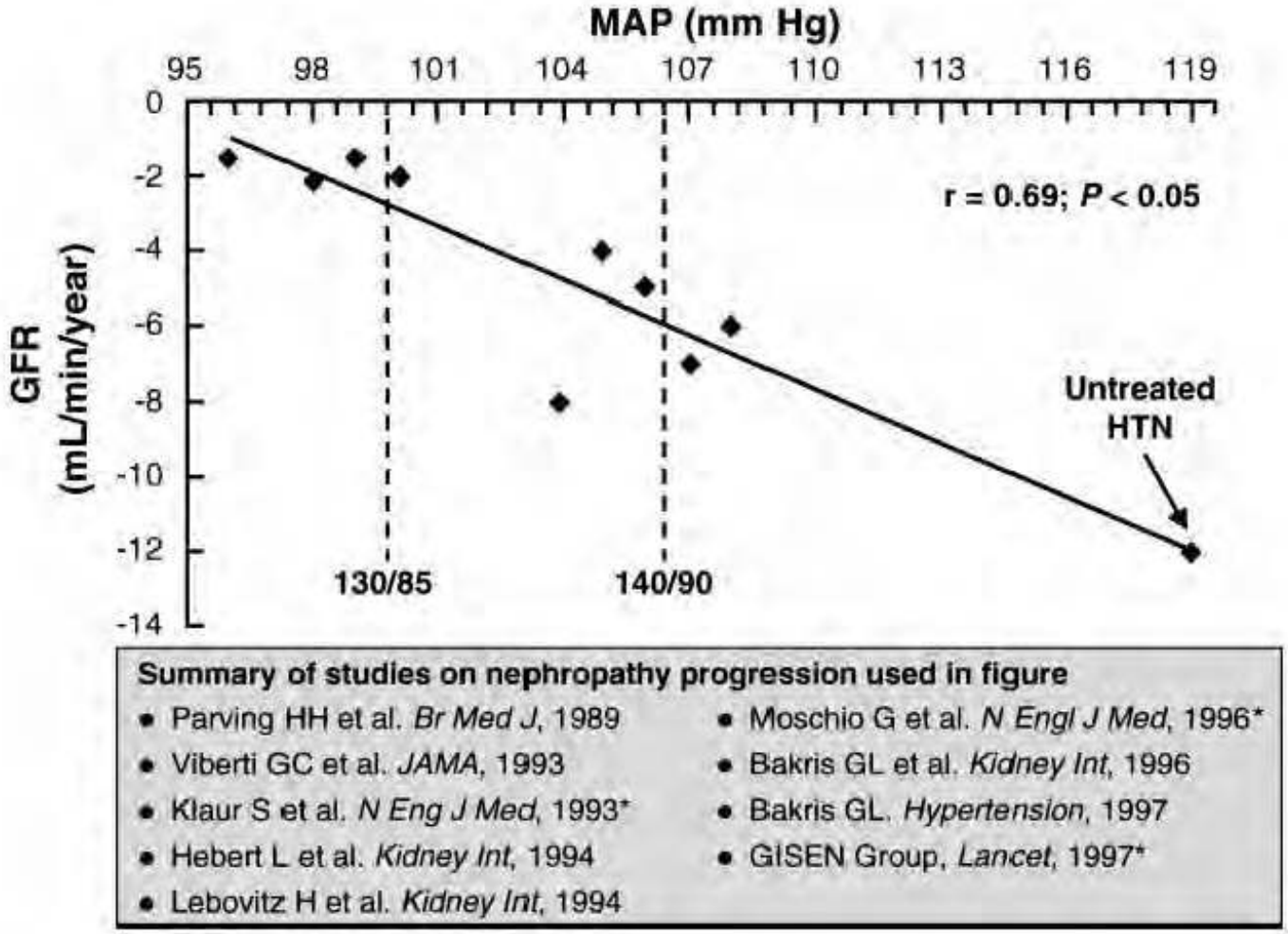
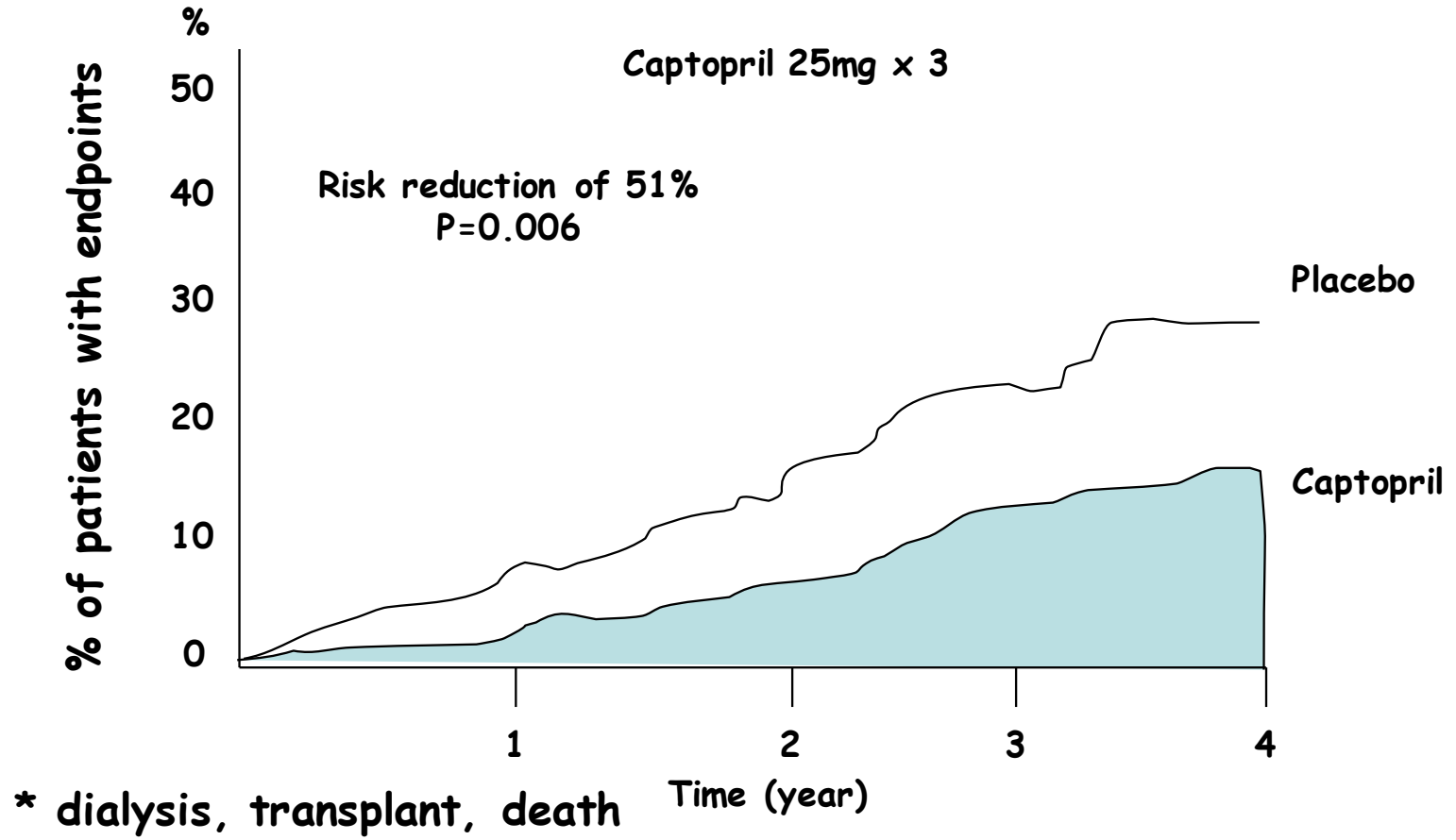


Fig 3. Relationship between achieved blood pressure control and declines in GFR in clinical trials of diabetic and nondiabetic renal disease.[30] In the table, the trials marked by an asterisk are those in nondiabetic renal disease patients.

Bakris GL, AJKD, 36:646, 2000

Ruolo di ACEi per il trattamento della DKD



Type I DM (207 captopril and 202 placebo)

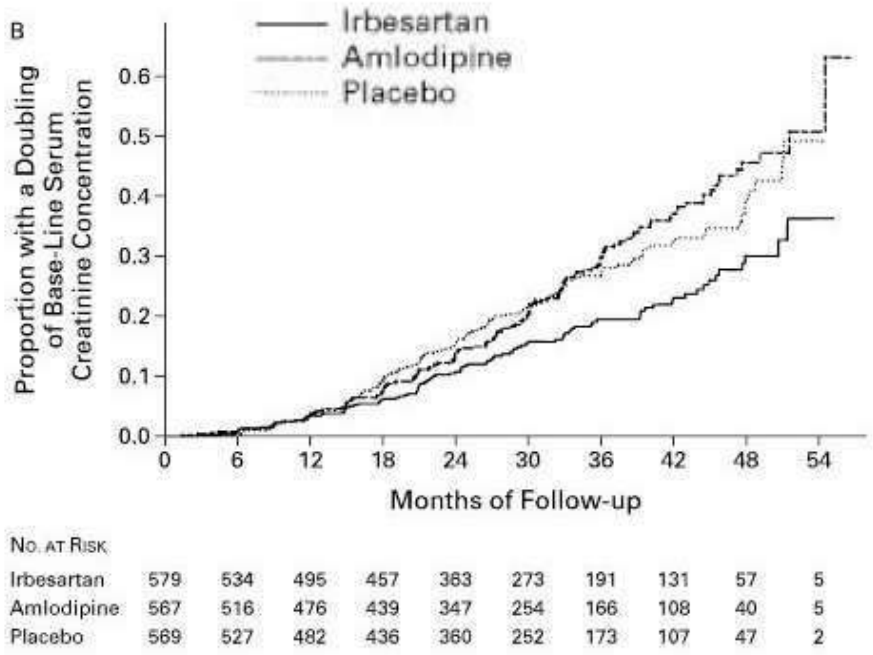
Proteinuria>500 mg/24 h

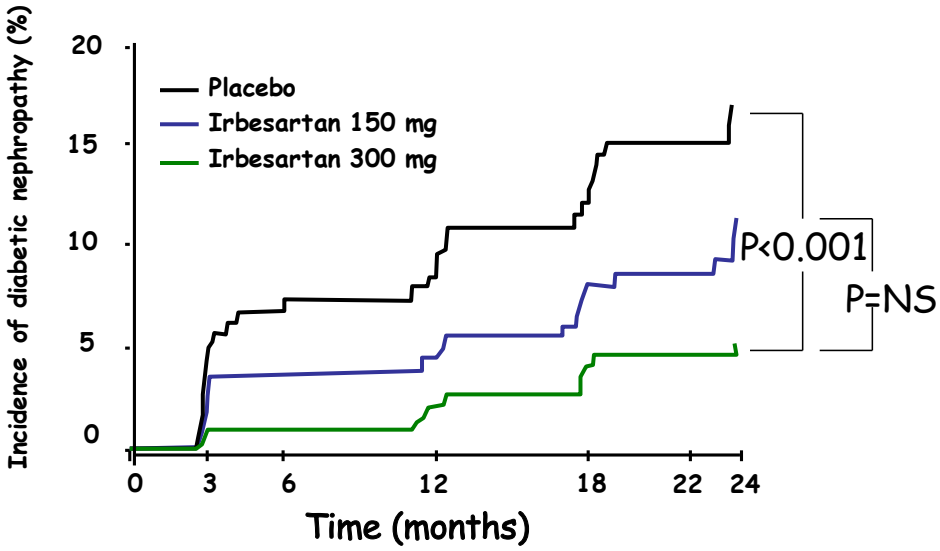
Creat <2.5 mg/dl

Significant effect of captopril on blood pressure

The Collaborative Study Group, NEJM, 329:1456, 1993

Ruolo di ARB per il trattamento della DKD





1715 pt type 2 DM + HTN

Irb 300 mg vs amlo 10 mg vs placebo

End points:

- doubling creatinine
- ESRD
- death

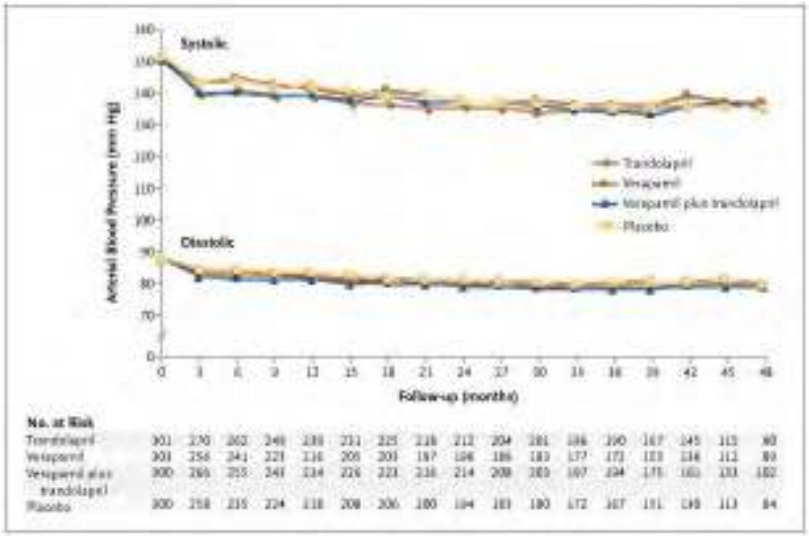
F/u 2.6 years

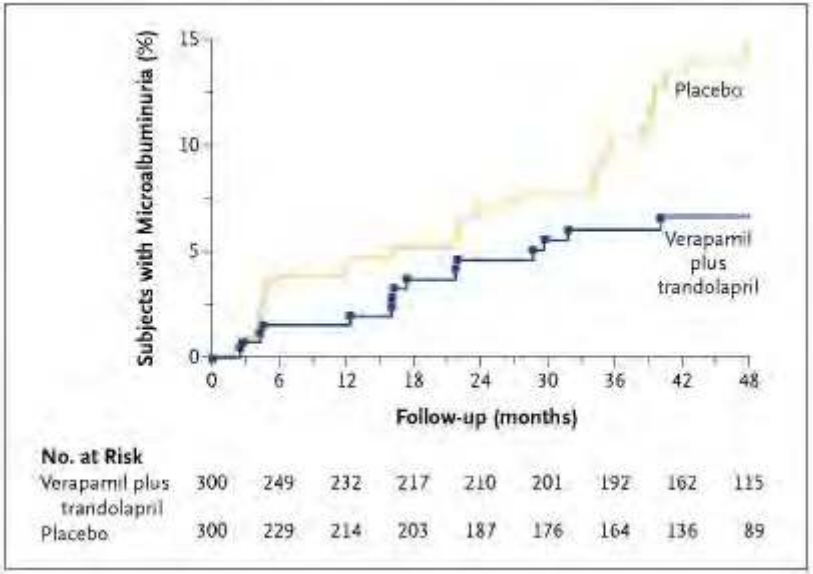
-3.3 mmHg mean BP in tx vs placebo

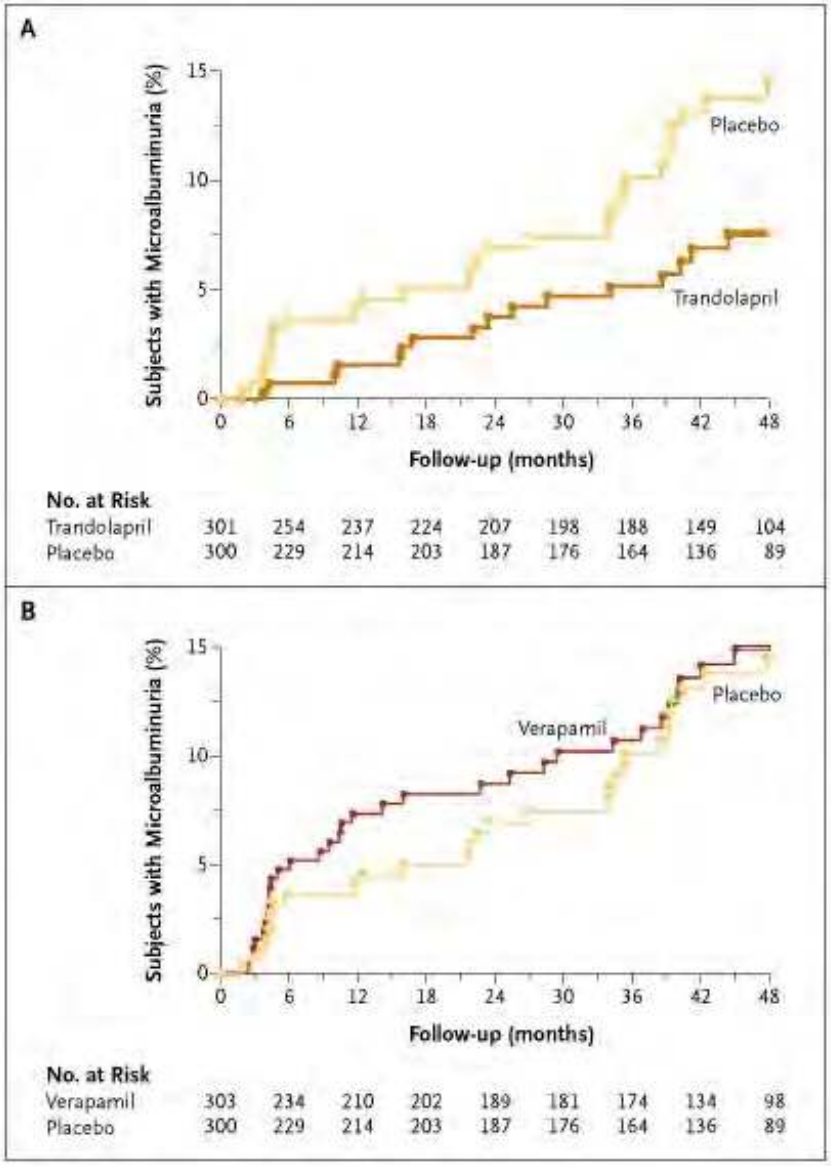
IDNT trial, NEJM 345:851, 2001

IRMA-2. Parving et al. N Engl J Med 2001;345:870-8

ACEi vs CCB nella prevenzione primaria di DKD con ipertensione minima





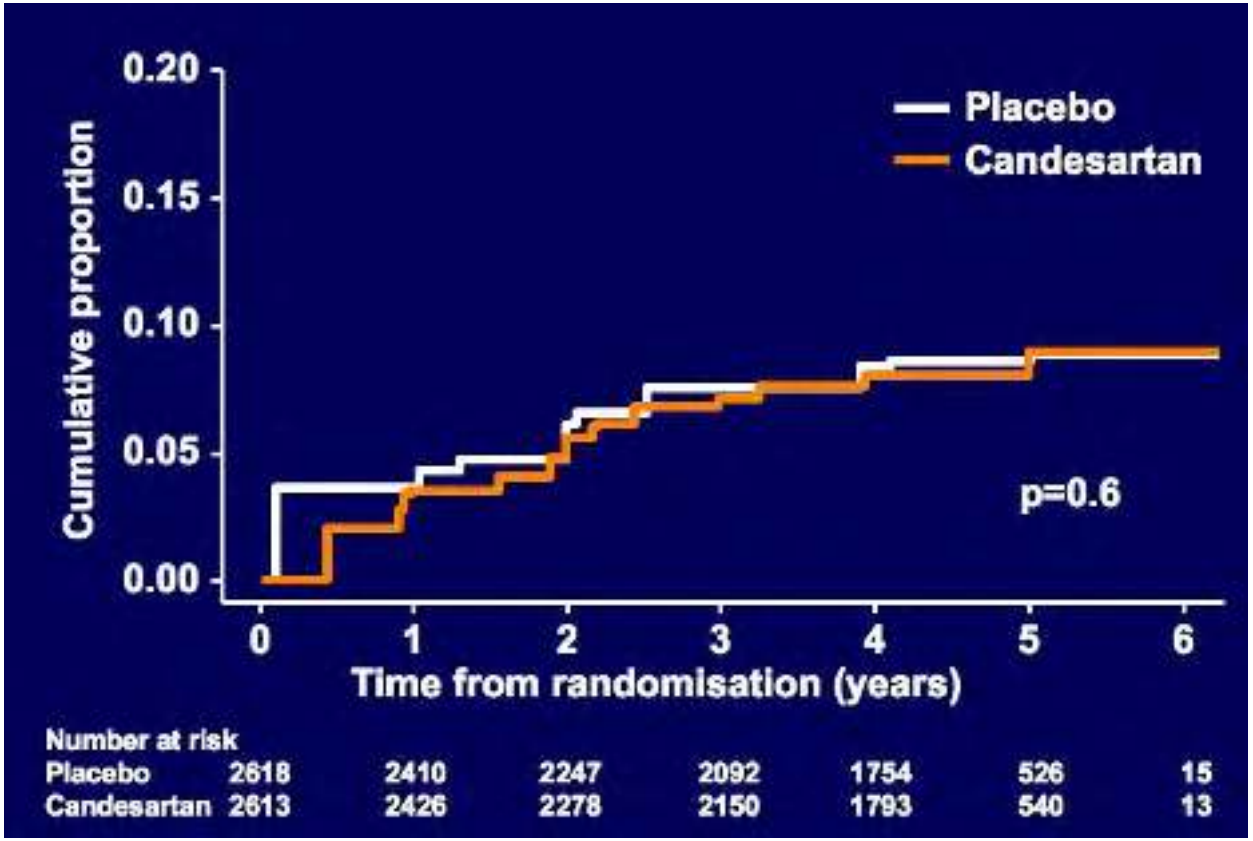


1204 patients, type 2 DM

Primary end point: persistent MA

BENEDICT, NEJM, 251:1941, 2004

ARB vs placebo nella prevenzione primaria di DKD con normotensione



3326/1905 (type 1/type2) patients.

Normotensive with normoalbuminuria

Candesartan versus placebo (significant effect on BP)

4.7 years follow up

Primary end point: development of MA

Secondary: Change in UAER

Bilius R et al, DIRECT, Annals of internal medicine, 2009; 151:11-20

ACEi o ARB?

Table 3. Secondary Renal End Points after Five Years of Treatment, According to Analysis of the Last Observation Carried Forward.*

End Point	Change from Baseline		Difference between Groups (95% CI)
	Telmisartan Group	Enalapril Group	
Serum creatinine (mg/dl)	0.10	0.10	0 (–0.66 to 0.65)
Urinary albumin excretion (ratio)†	1.03	0.99	1.04 (0.71 to 1.51)‡

* One hundred sixteen subjects (35 with the last observation carried forward) in the telmisartan group and 128 (44 with the last observation carried forward) in the enalapril group were included in the analysis of serum creatinine, and 115 (35 with the last observation carried forward) and 125 (42 with the last observation carried forward), respectively, were included in the analysis of urinary albumin excretion.

† Urinary albumin excretion rates were determined as the ratio of the final value to the baseline value.

‡ The ratio of the difference between treatment groups is shown. Because of the skewed distribution of the albumin excretion rate, the log analysis (when log values are converted back to nonlog values, or "anti-logged") yields treatment ratios, both for treatment means (ratio of year 5 value to baseline value) and treatment differences (ratio of telmisartan to enalapril).

Prospective, multicentered, double-blind study
250 patients with type 2 DM and DN
Telmisartan 80 mg vs enalapril 20 mg.
Five year follow-up
Primary end-point: change in iohexol GFR
Secondary end-points: creat, UAE, BP

no difference!

Barnett AH, NEJM, 351:1952, 2004

ACEi o ARB?

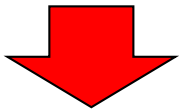
ADA 2022:

Type 1 DM with HTN and albuminuria: ACEi

Type 2 DM with HTN and microalbuminuria: either ACEi or ARBs

Type 2 DM with HTN and overt nephropathy: ARBs

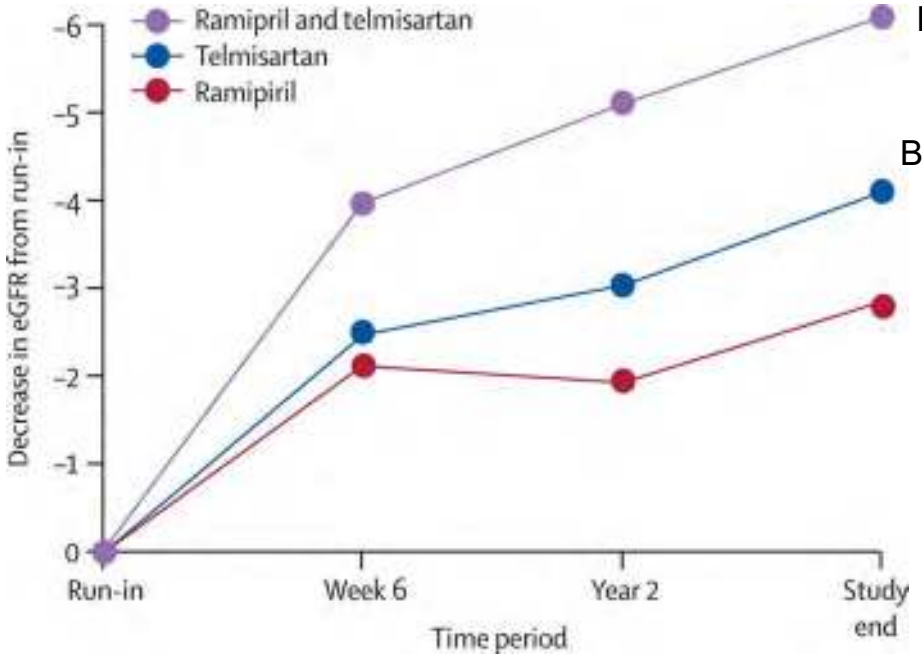
When not tolerated, substitute one for the other



Combinazione non raccomandata

ADA recommendations, Diabetes Care, January 2022

ACEi/ARB combination in DKD in T2DM
ON TARGET



BP -2.4/1.4 mmHg

BP -0.9/0.6 mmHg

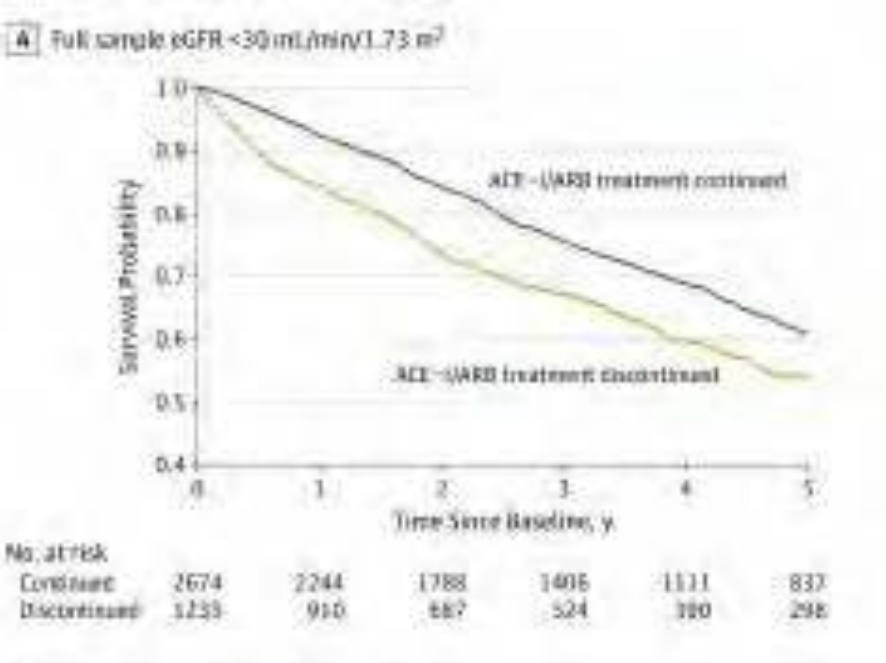
25620 patients with CV disease or high risk diabetes
Follow up for 5 years
Primary renal outcome: dialysis, x2 creat, death

	Ramipril gMean (95% CI)	Telmisartan gMean (95% CI)	Ramipril+telmisartan gMean (95% CI)	Telmisa *vs* ramipril
UACR, Baseline	0·81 (0·78–0·84)	0·83 (0·80–0·86)	0·81 (0·78–0·84)	0·246
2-year ratio to baseline	1·17 (1·13–1·20)	1·08 (1·05–1·12)	1·05 (1·02–1·08)	0·0013

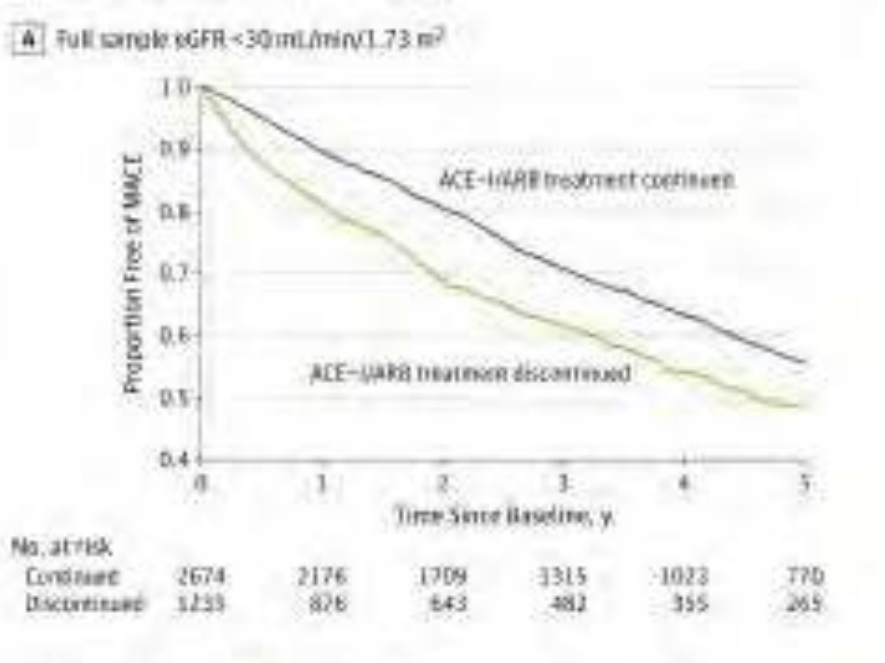
Mann J et al, ONTARGET trial, The Lancet, 2008, 372: 547-562

ACEi/ARB: STOP in CKD avanzata?

Mortality



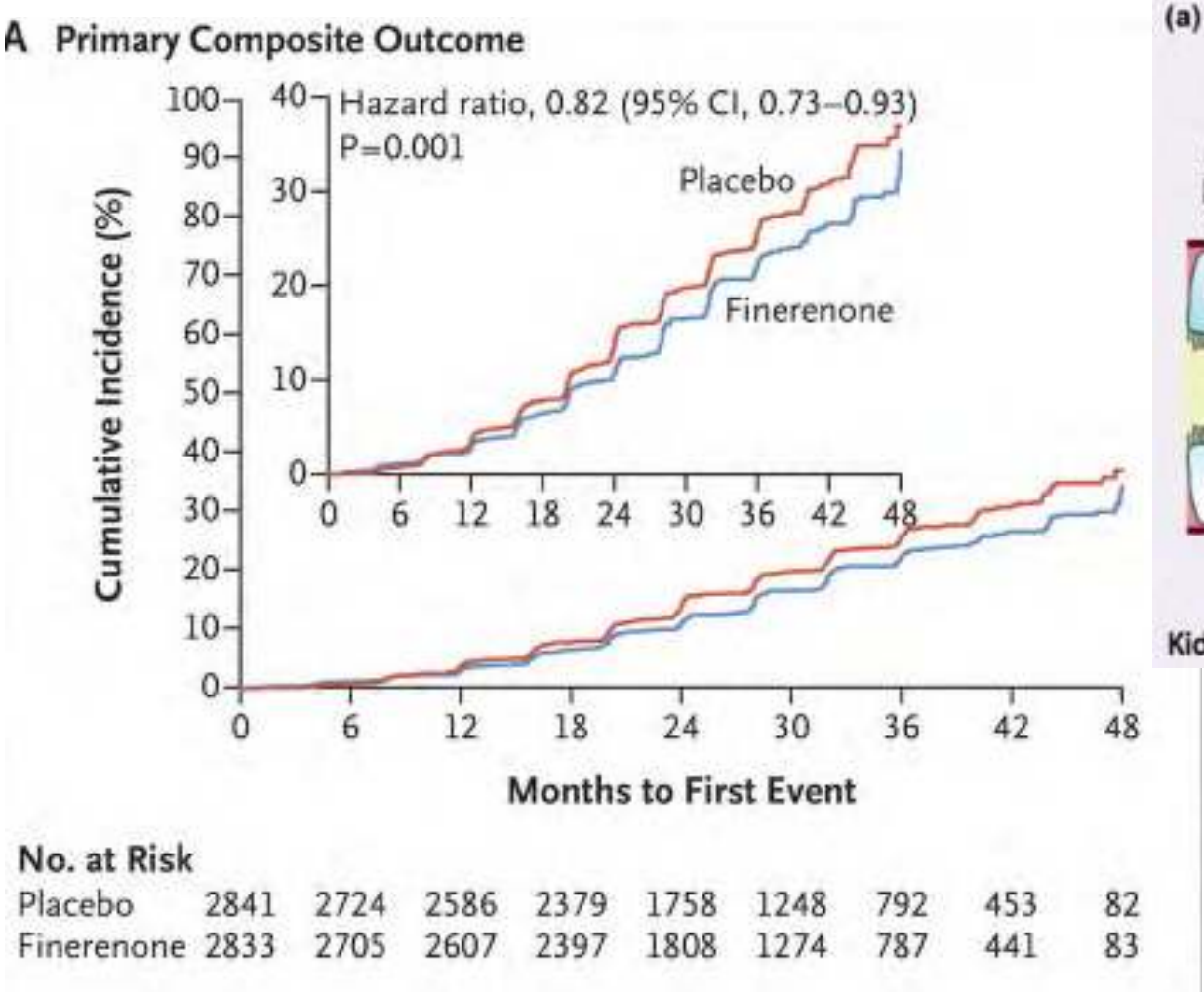
CVD

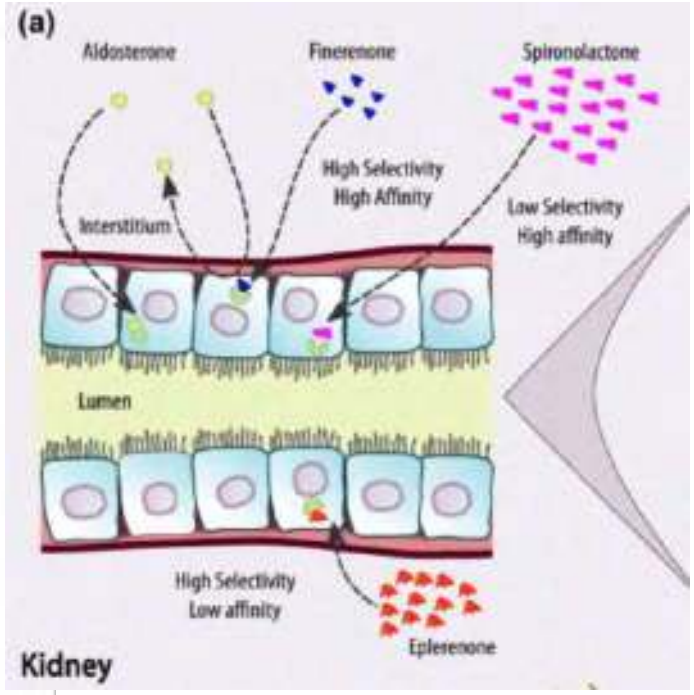


3909 patients
eGFR<30
Follow-up for 5 years

Qiao Y et al, JAMA, 180:718-726, 2020

Antagonisti dell' Aldosterone (MRA): finerenone and DKD

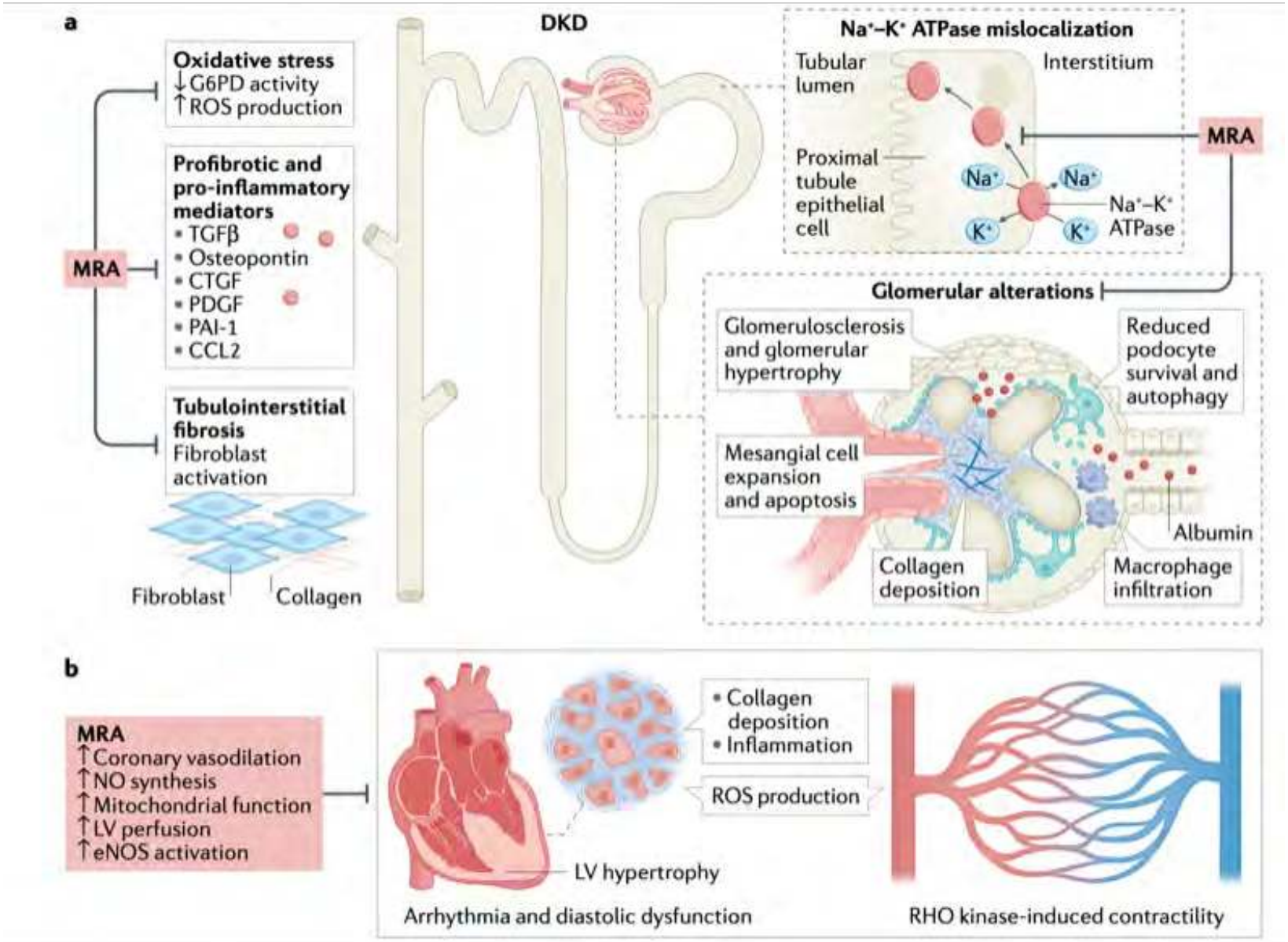




5734 T2D pt with CKD3/4A2 on RAS blockade
Primary outcomes: renal death, ESKD, 40% decrease in eGFR
Follow up: 2.6 years

FIDELIO-DKD, Bakris et al, NEJM, 383:2219-2229
Cappelli et al, J of Neph, 33, 2020

MRA: protezione pleiotropica (BP independent)



Barrera-Chimal et al, Nature Review Nephrology, 18:56, 2022

Prevenzione e trattamento

American Diabetes Association recommendations 2022

Level of evidence A:

control BP with appropriate agents (goal <140/90mmHg, <130/80 if high risk for CVD)

control glycemia (A1C about 7%, personalized)

control dyslipidemia (LDL goal <70-100 mg/dl)

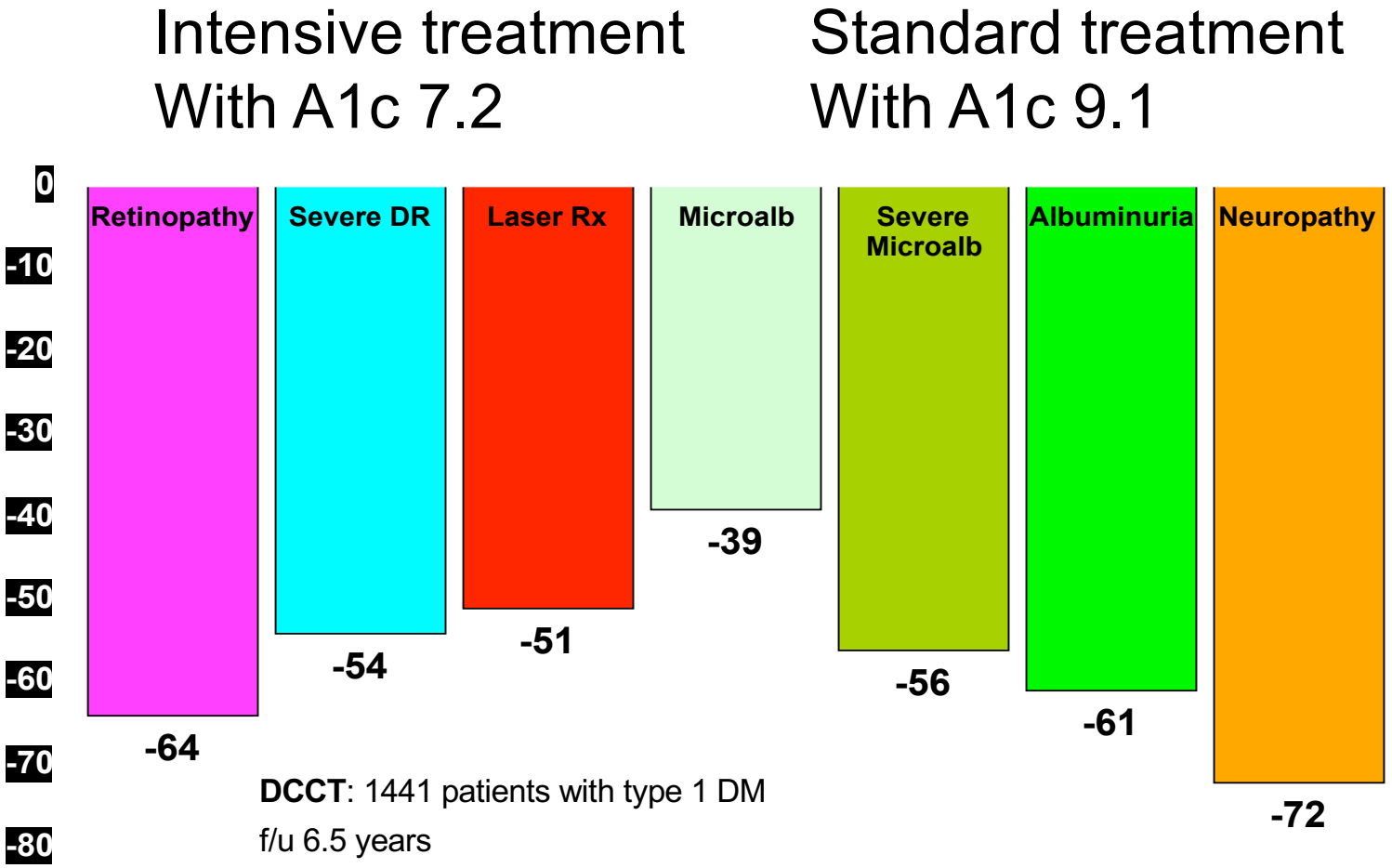
counsel about smoking cessation

education

protein intake to 0.8 g/kg/day (more if dialysis)

ADA recommendations, Diabetes Care, January 2022

Ruolo della glycemia in T1D-DKD



DCCT: 1441 patients with type 1 DM

f/u 6.5 years

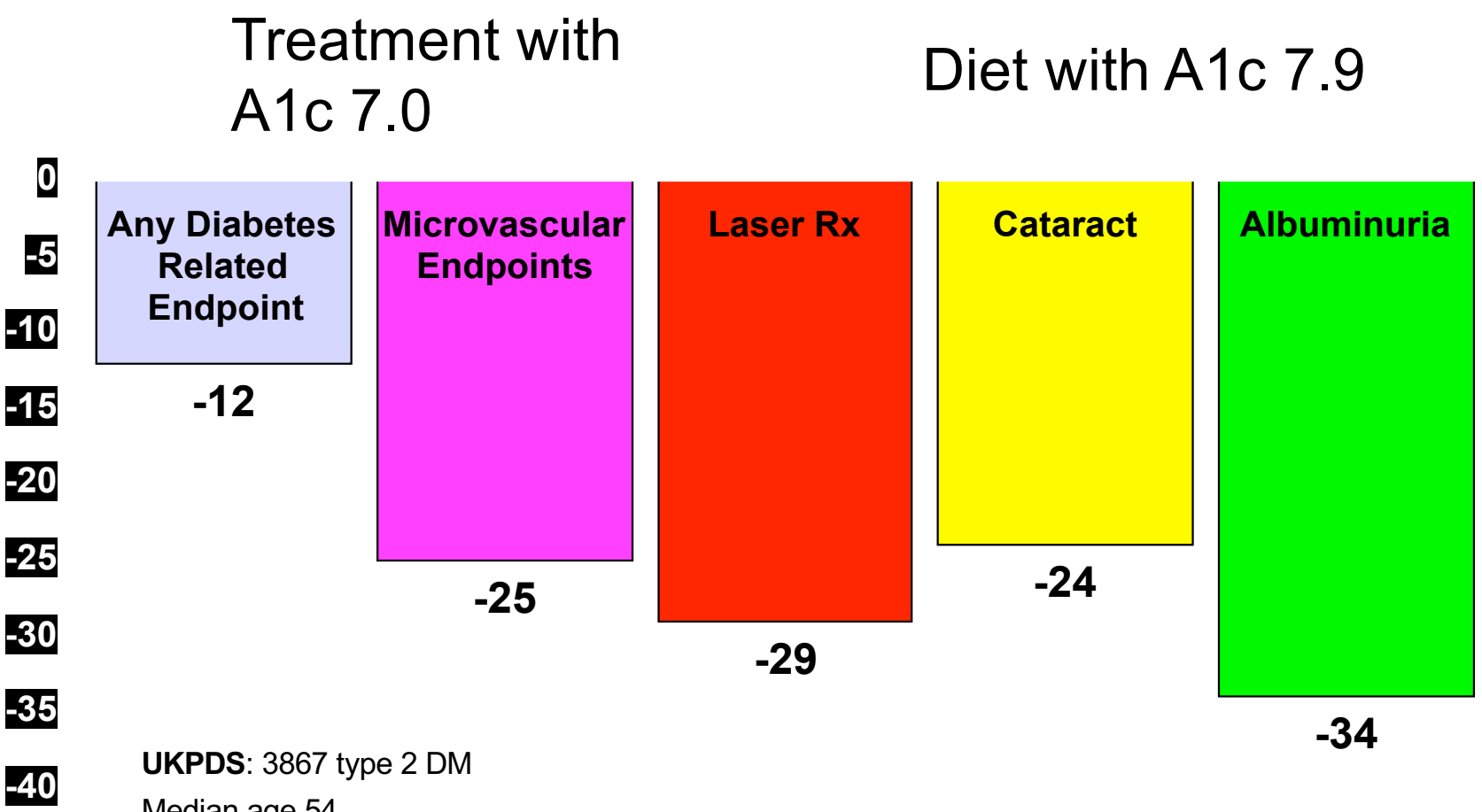
Insulin 3 x day or pump vs conventional (1 or 2 daily insulin injection)

Primary prevention/secondary prevention

Difference maintained after discontinuation of tx (7 yr follow up)

NEJM 1993; 329:977

Ruolo della glycemia in T2D-DKD



UKPDS: 3867 type 2 DM

Median age 54

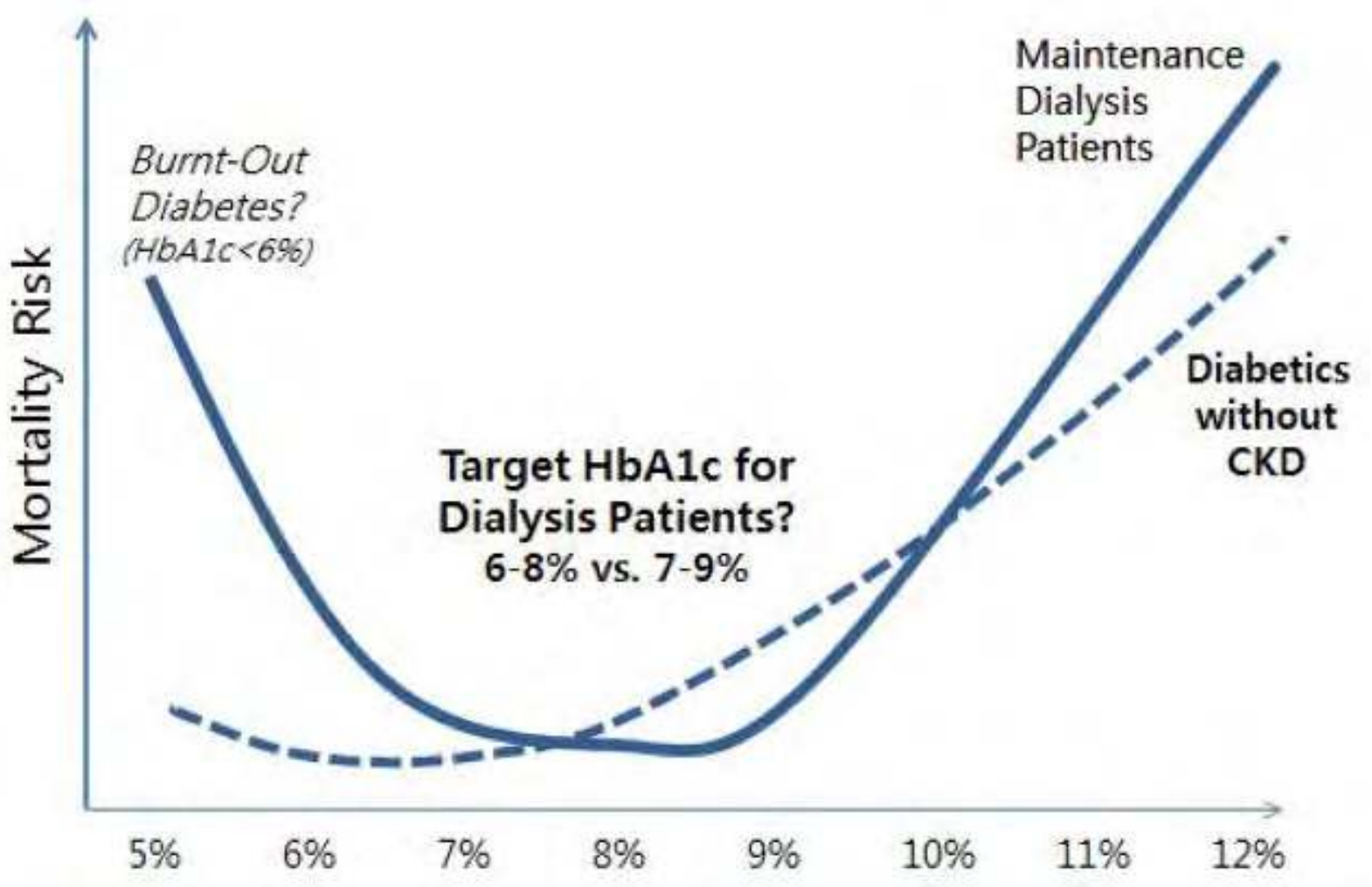
Intensive tx (sulpha or insulin) versus diet

End points: any DM related end-point, diabetes related death and all cause mortality

F/u 10 years (15 years f/u had no difference in diabetes related death)

Lancet 1998; 352: 837-853

Target glicemici nella DKD avanzata



Ricks et al., Diabetes 61(30): 708–715, 2012

Regressione della microalbuminuria in T1DM

Table 3. Results of the Cox Regression Analysis of Regression of Microalbuminuria with the Use of Time-Dependent Factors.*

Factor	Adjusted Hazard Ratio (95% CI)	P Value†
Nonmodifiable		
Age (≤26 vs. >26 yr)	1.6 (1.2–2.2)	0.004
Incidence cohort (vs. prevalence cohort)‡	1.8 (1.2–2.6)	0.003
Modifiable		
Lipid status§		0.002
Cholesterol <198 mg/dl, triglycerides <145 mg/dl	2.4 (1.4–4.0)	
Cholesterol <198 mg/dl, triglycerides ≥145 mg/dl	1.9 (1.0–3.8)	
Cholesterol ≥198 mg/dl, triglycerides <145 mg/dl	2.1 (1.2–3.5)	
Cholesterol ≥198 mg/dl, triglycerides ≥145 mg/dl¶	1.0	
Glycosylated hemoglobin		0.02
<8.0 %	1.9 (1.2–2.9)	
8.0–8.9 %	1.5 (1.0–2.3)	
9.0–9.9 %	1.2 (0.8–1.9)	
≥10.0 %¶	1.0	
Systolic blood pressure‖		0.02
<115 mm Hg	1.4 (1.0–1.9)	
≥115 mm Hg¶**	1.0	

386 patients with persistent MA
Total f/u of 4 periods of 2 years each
Regression defined as 50% reduction in UAE from one period to the other

Perkins, NEJM, 2003;348:2285

Regressione della MA in T2DM

TABLE 3 The ORs of factors associated with the regression and remission of microalbuminuria with the pooled logistic regression model

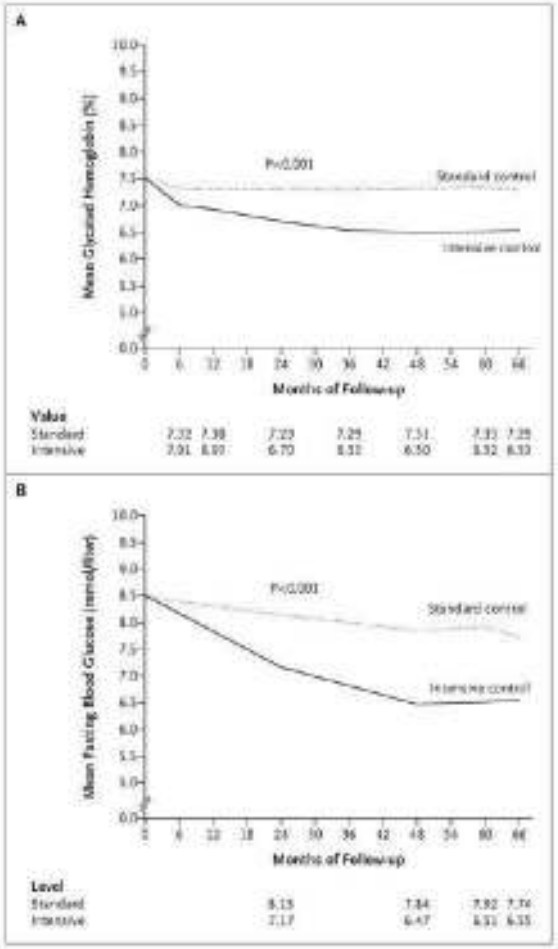
	Adjusted OR (95% CI)*	
	Regression	Remission
Nonmodifiable factors		
Incidence cohort (vs. prevalence)	2.0 (1.03–3.9)	2.0 (1.1–3.9)
Modifiable factors		
Use of ACE inhibitors or ARBs (vs. none)	2.3 (1.4–4.0)	1.9 (1.1–3.3)
A1C (%)		
A1C < 6.95	2.2 (1.2–4.2)	3.0 (1.5–6.0)
6.95 ≤ A1C < 7.75	1.2 (0.6–2.3)	2.1 (1.01–4.2)
7.75 ≤ A1C	1.0 (ref.)	1.0 (ref.)
SBP (mmHg)		
SBP < 129	2.0 (1.04–3.9)	2.7 (1.4–5.2)
129 ≤ SBP < 143	1.6 (0.8–3.0)	1.8 (0.9–3.5)
143 ≤ SBP	1.0 (ref.)	1.0 (ref.)

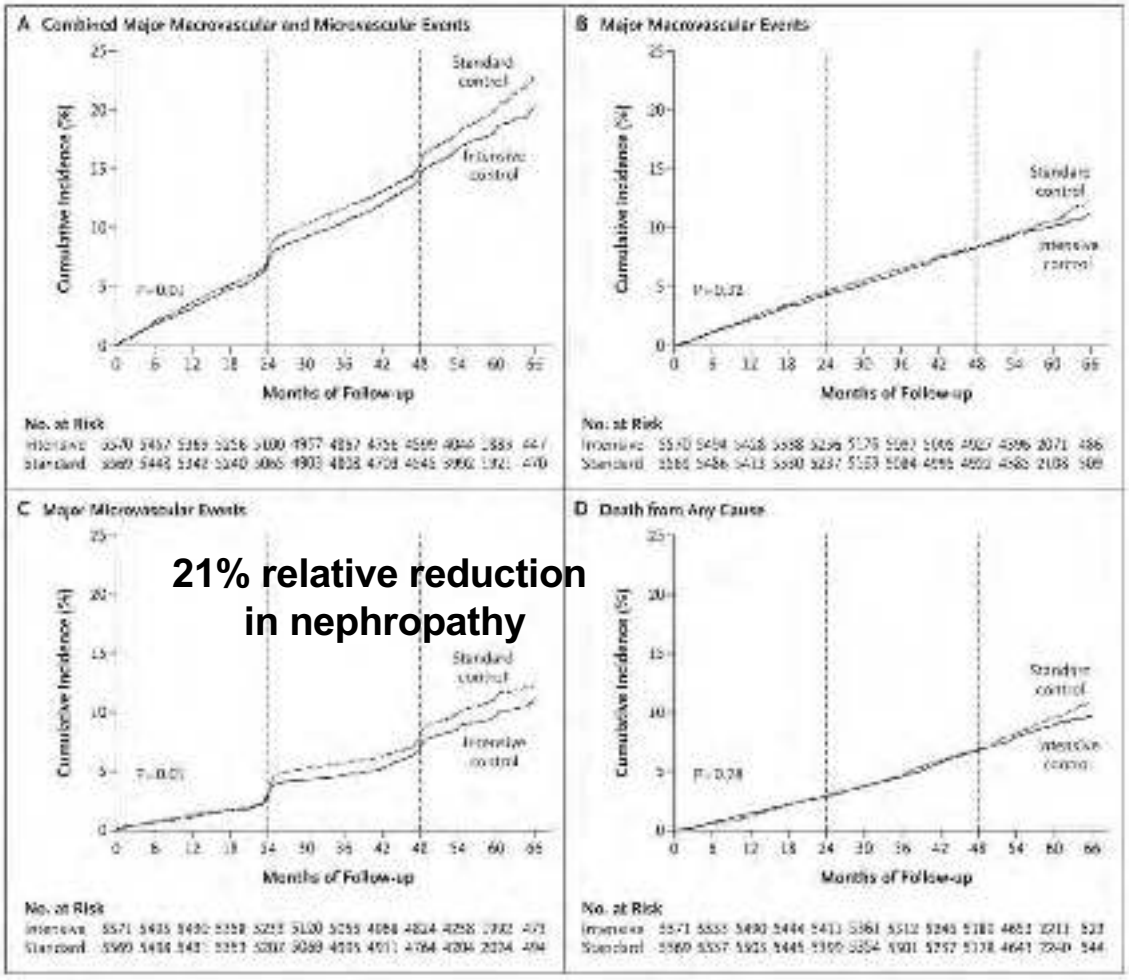
* The multivariate model was adjusted for sex, mean urinary albumin excretion in the initial evaluation period, total cholesterol, estimated sodium intake, and estimated protein intake. ref., reference category.

216 Japanese patients with type 2 DM
F/u 6 years, 3 periods of 2 years each
Regression: 50% reduction MA
Remission: back to NA

Araki, Diabetes, 2005;54:2983

A_1C: quale target raggiungere?



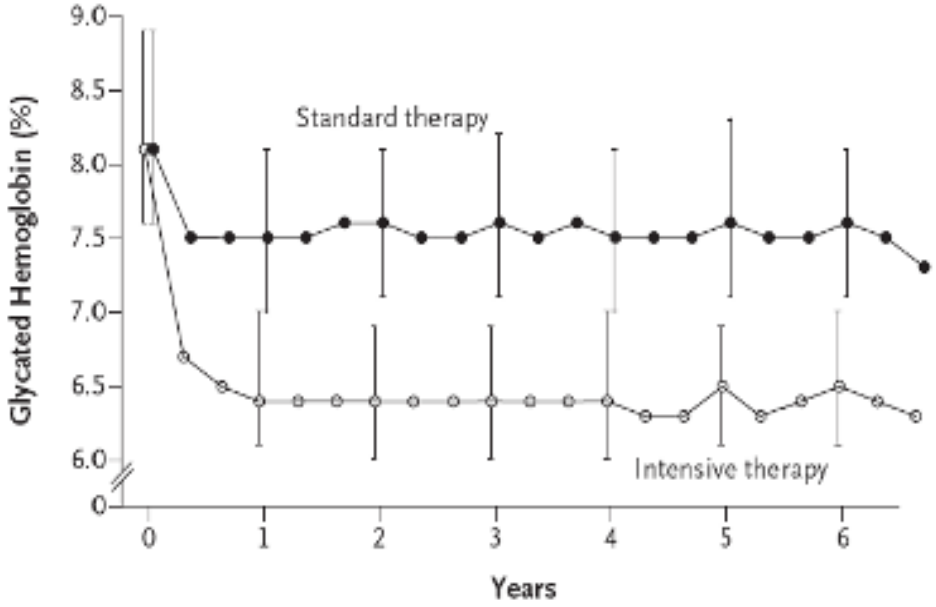


21% relative reduction in nephropathy

11140 patients, standard vs intensive (sulfa + other drugs to achieve A1C less than 6.5).
Macro: CV death, MI, stroke
Micro: development of alb, x 2 creat, ESRD

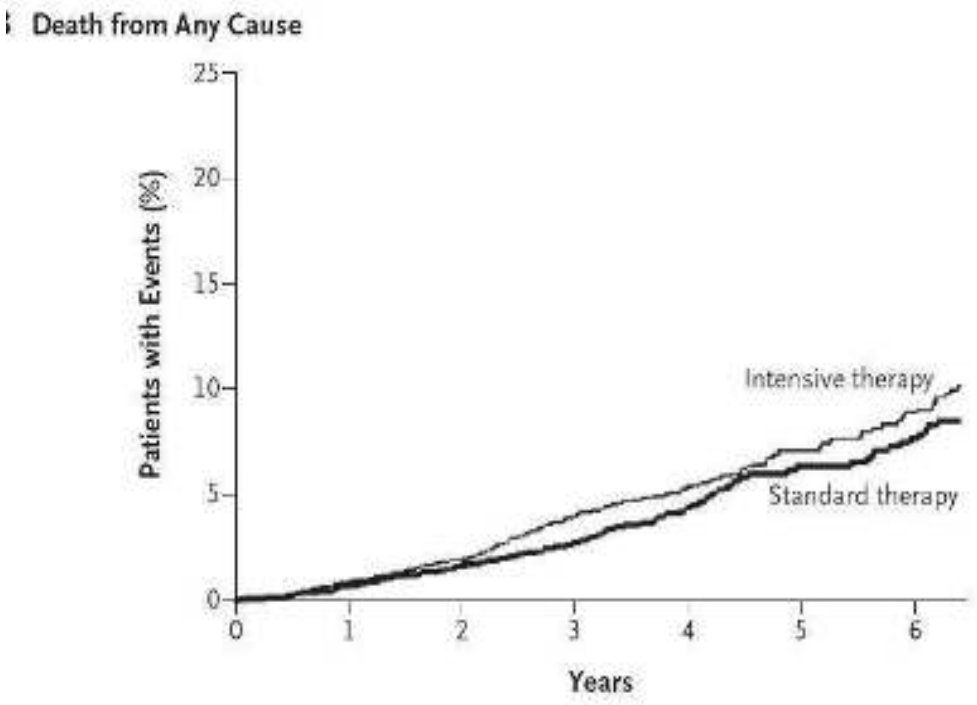
ADVANCE trial, NEJM, 358:24, 2008

A_1C: quale target raggiungere?



No. at Risk

Standard therapy	5109	4774	4588	3186	1744	455	436
Intensive therapy	5119	4768	4585	3165	1706	476	471



No. at Risk

Intensive therapy	5128	4972	4803	3250	1748	523	506
Standard therapy	5123	4971	4700	3180	1642	499	480

10,251 patients, standard vs intensive (mainly insulin and TZDs).
1/3 patients had prior CV event
End point: CV death, MI, stroke
Discontinued after 3.5 years f/u for high mortality in intensive arm.

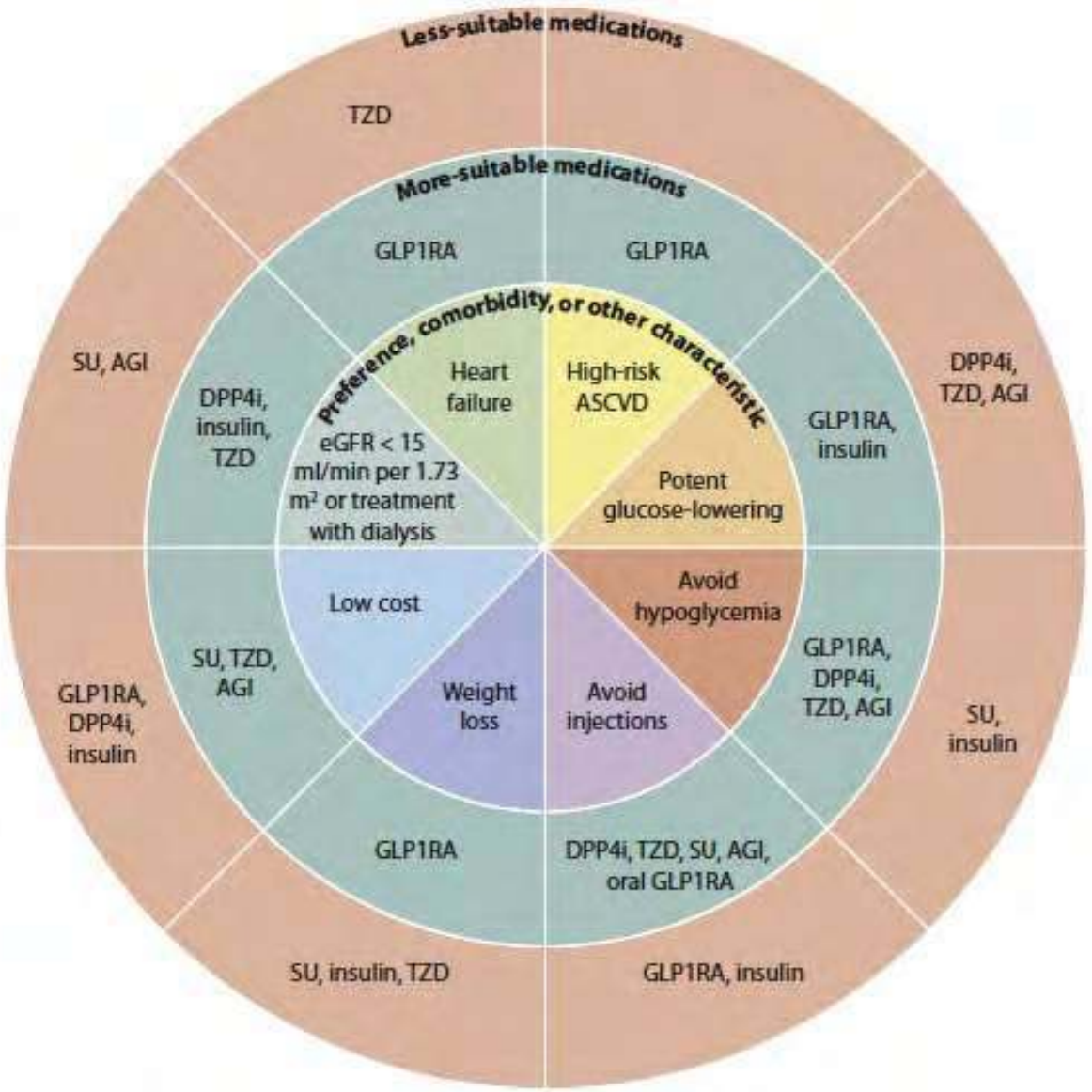
ACCORD, NEJM, 358:24, 2008

Storia naturale della malattia

GD viene in ambulatorio e ti chiede quanto segue

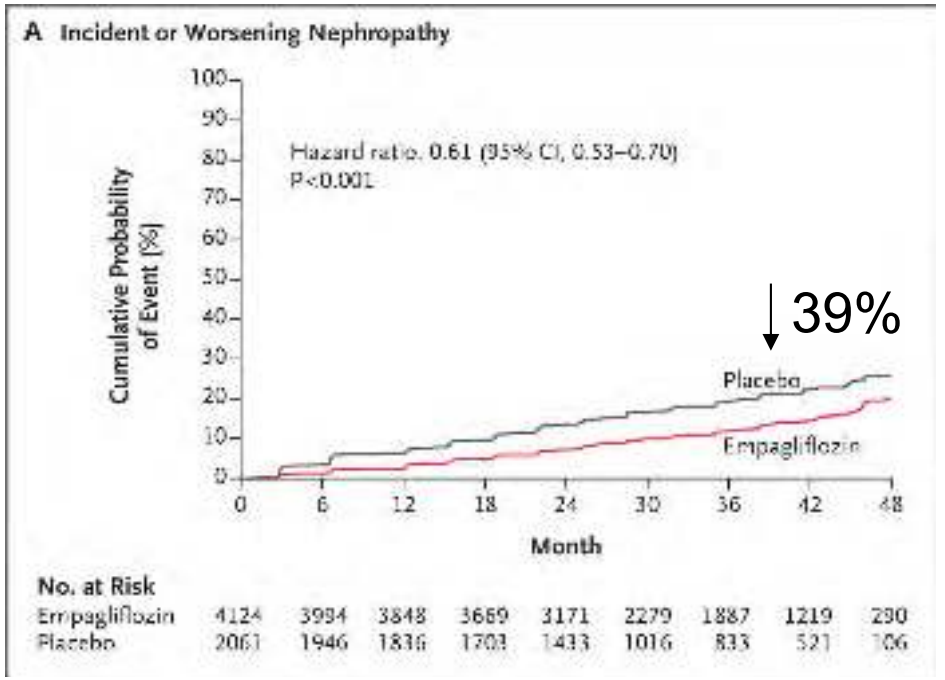
- I miei reni sono affetti da diabete?
- Qual è la mia possibilità di entrare in dialisi?
- Qual è il mio rischio di morire di malattie renali?
- Sarebbe utile una biopsia renale?
- Come devo essere trattato?
- Gli anti-iperglicemizzanti sono tutti uguali?
- Qualche nuovo strumento per capire i miei rischi?
- Qualche nuova terapia all'orizzonte?

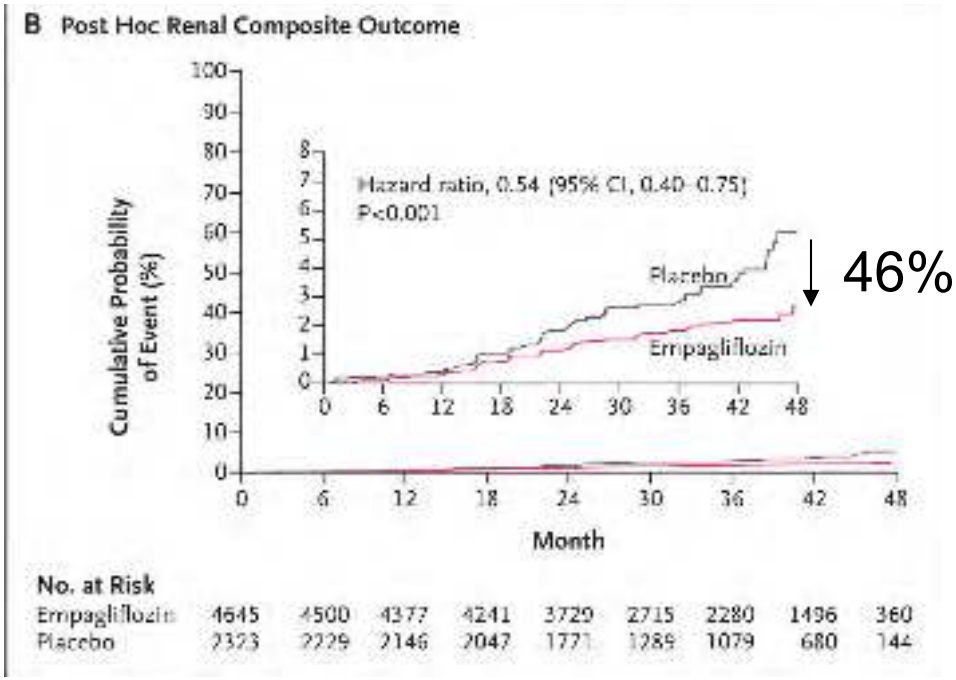
KDIGO2020: Diabetes Management:
Sono gli antidiabetici tutti uguali?



KDIGO 2020 Clinical Practice Guidelines for Diabetes Management

SGLT2 inhibitors and DKD: EMPA-REG





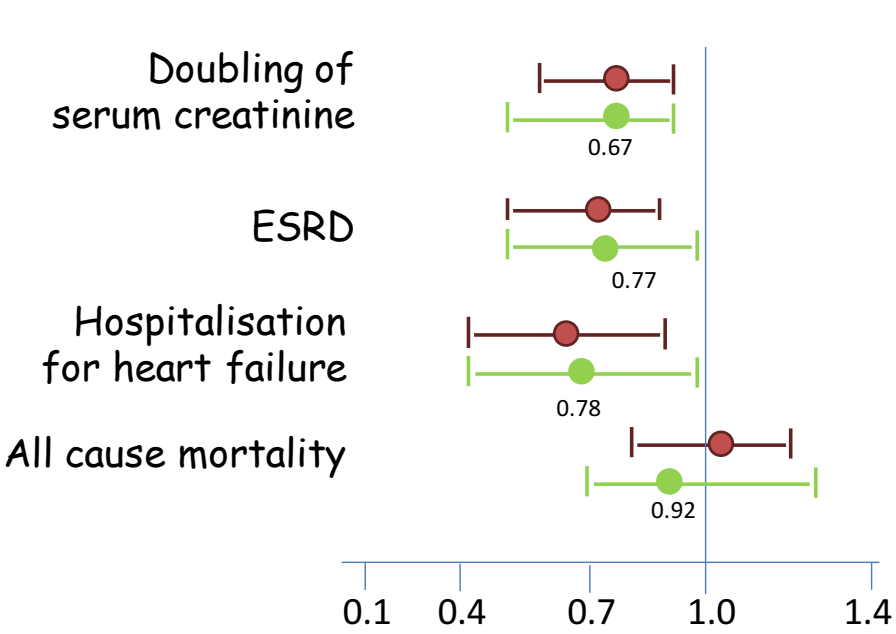
Worsening Nephropathy:
eGFR<60 ml/min and/or ACR>300 mg/g

Composite outcome:
doubling of the serum creatinine
initiation of renal-replacement therapy
death from renal disease

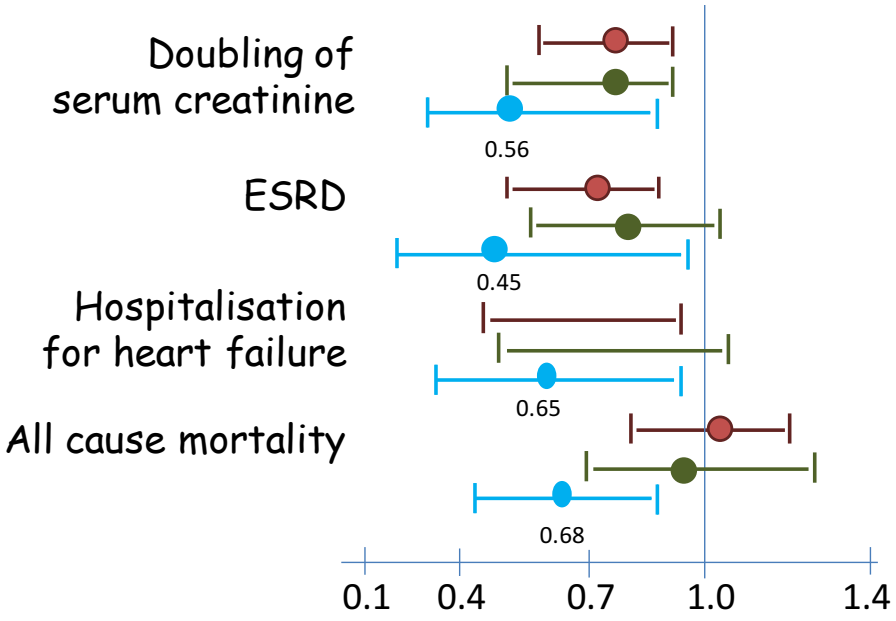
Wanner C et al. N Eng J Med 2016. DOI: 10.1056/NEJMoa1515920

ARB versus SGLT2i

IDNT



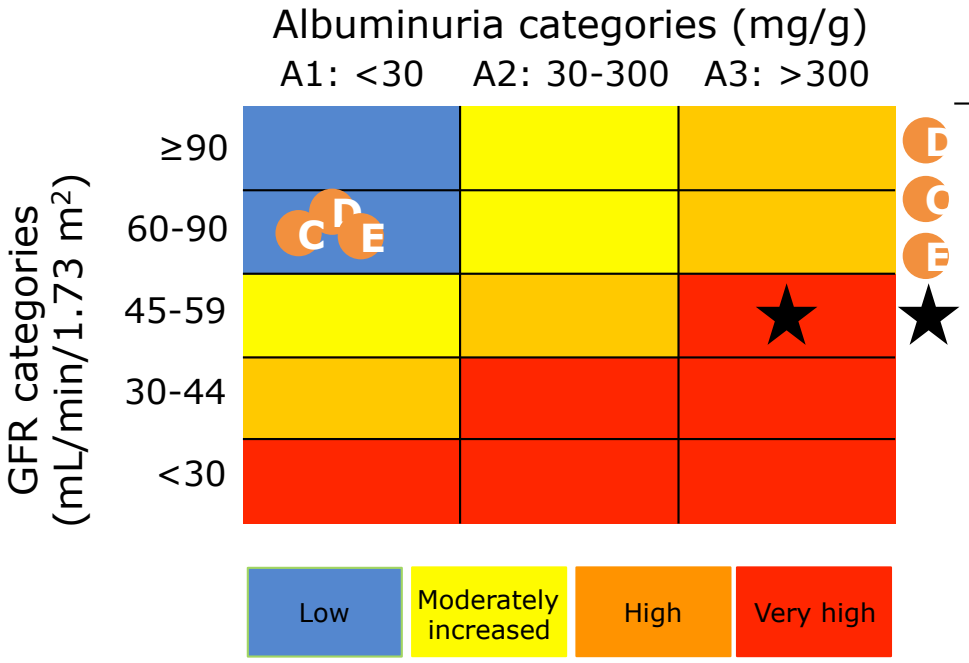
EMPA-REG



Courtesy of Dr Per-Henrik Groop

SGLT2 inhibitors and DKD: CREDENCE

Higher Renal Risk Population in CREDENCE



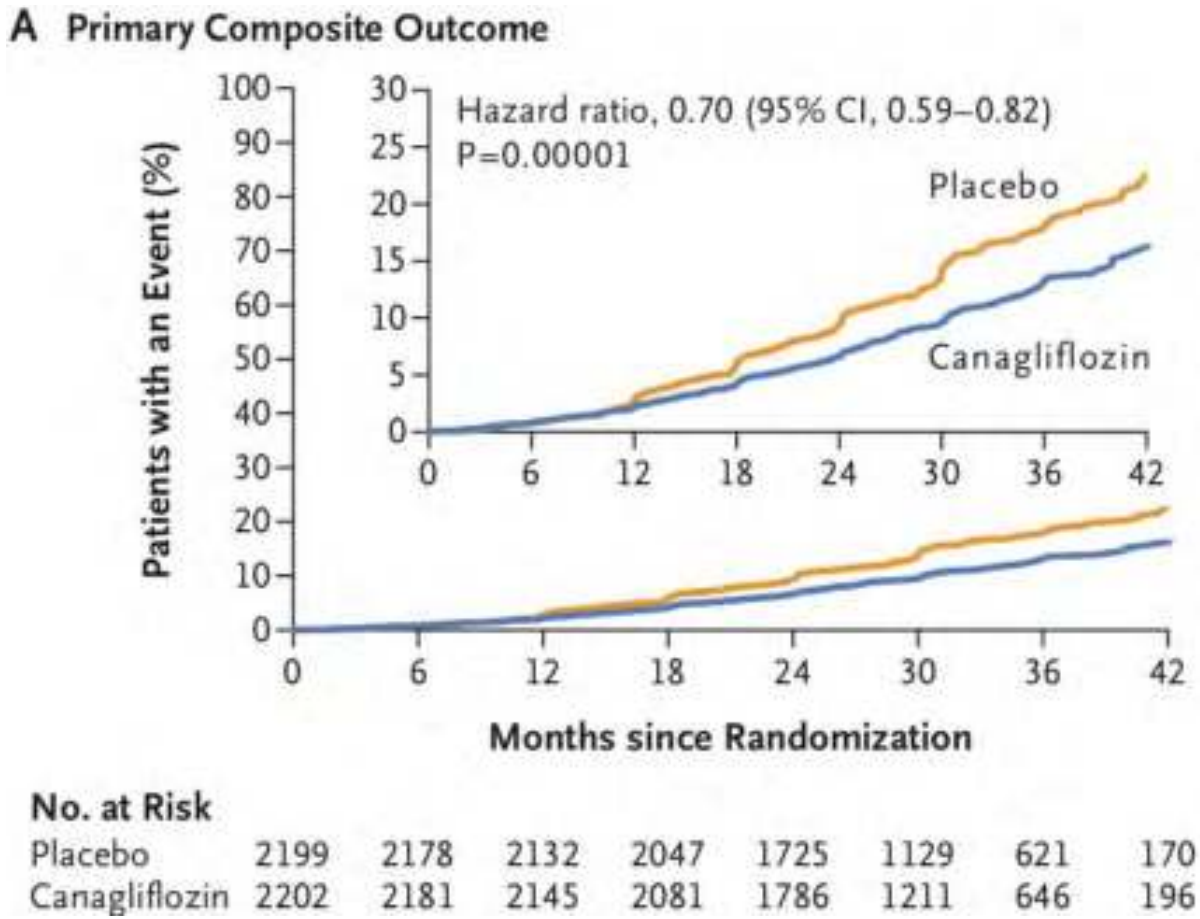
	Mean eGFR (mL/min/1.73 m²)	MedianU ACR (mg/g)
DECLARE	85	13
CANVAS Program	76	12
EMPA-REG OUTCOME	74	18

Sustained RRT Events

DECLARE	Not reported
CANVAS Program	18
EMPA-REG OUTCOME	11
CREDENCE	**176**

Perkovic et al, April 14, 2019, NEJM

SGLT2 inhibitors and DKD: CREDENCE



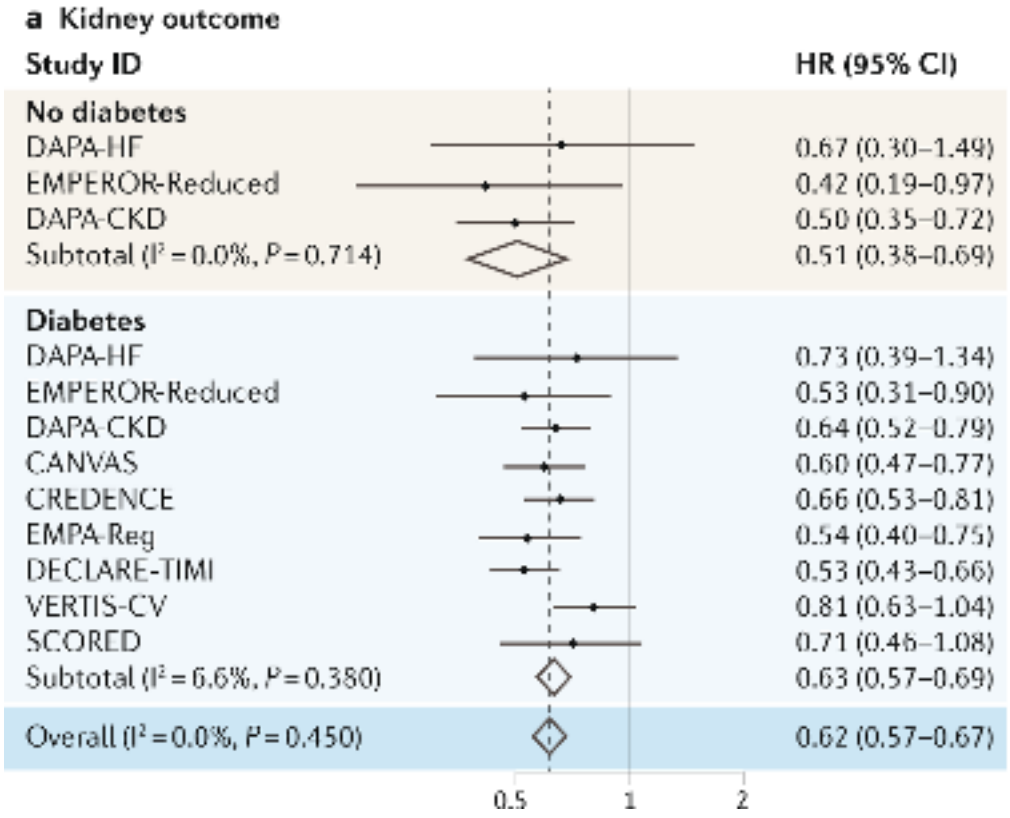
↓44%

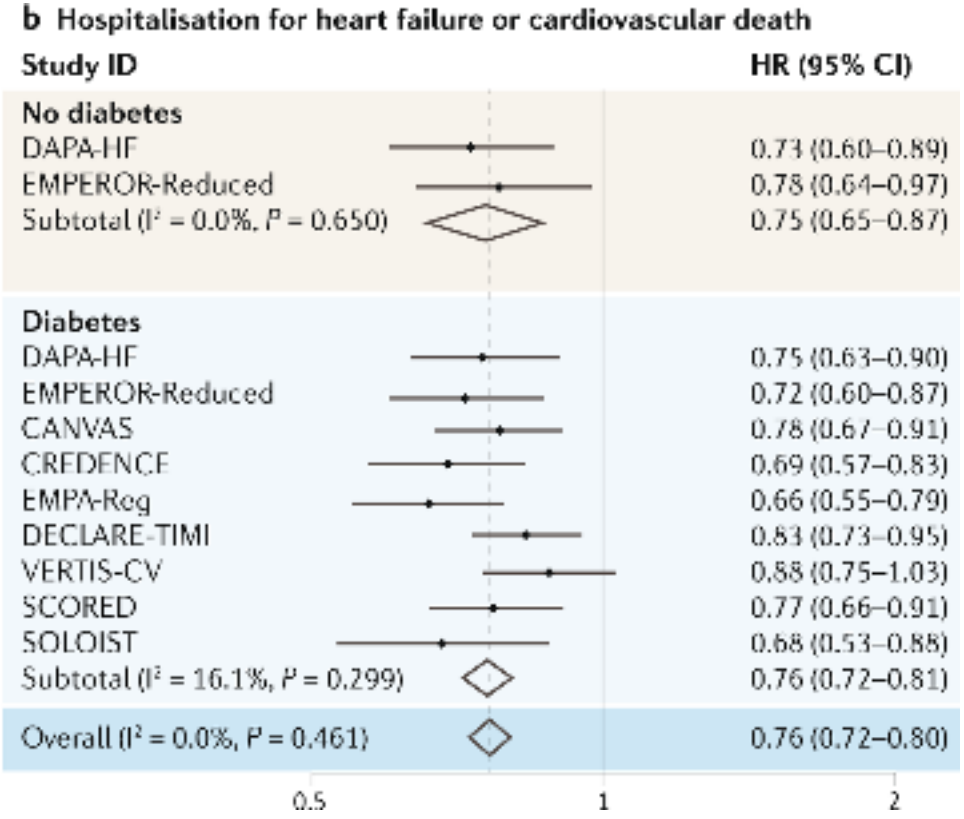
Composite EP: ERSD, sustained eGFR <15ml/min, X2 Creat (x 30 days) or death (renal and CV)

Perkovic et al, April 14, 2019, at NEJM.org

The NEW ENGLAND JOURNAL of MEDICINE

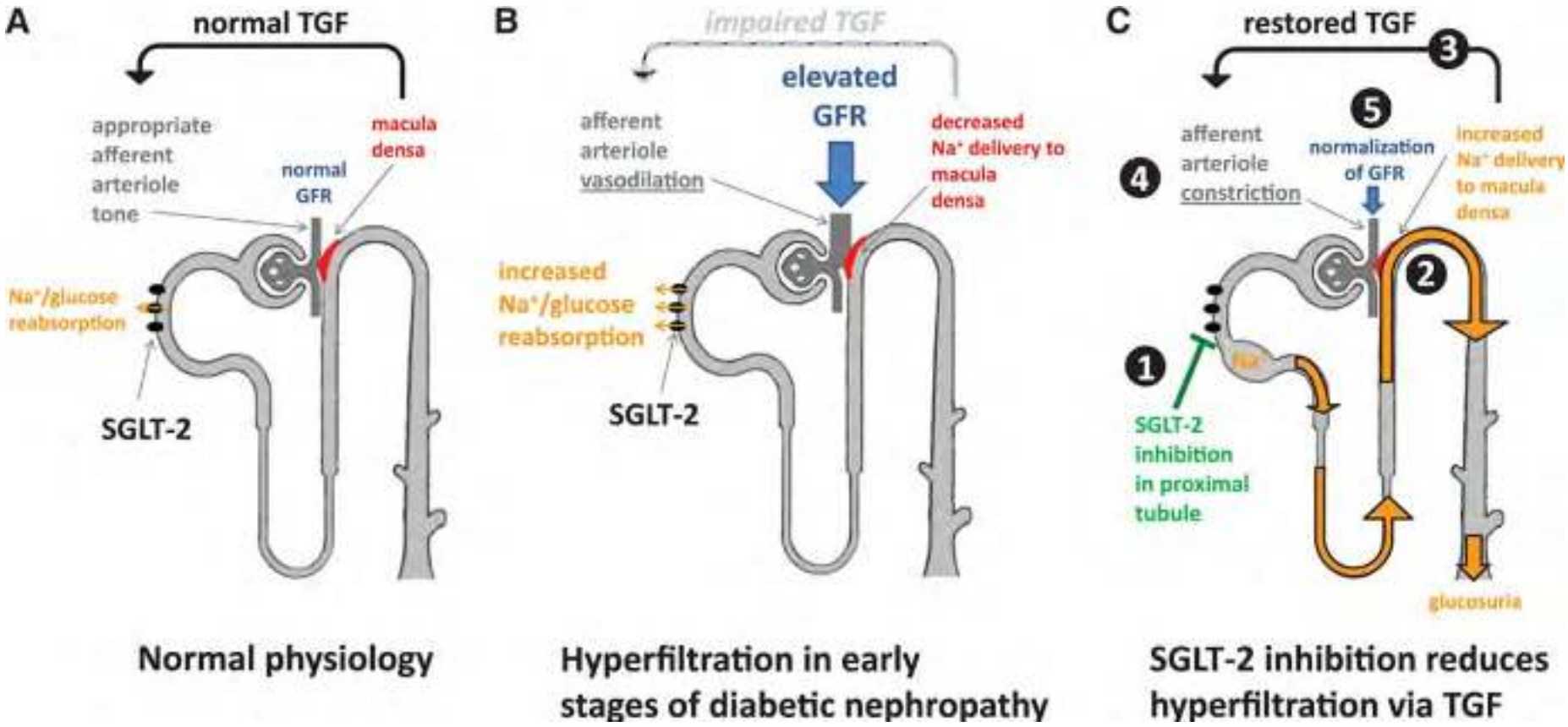
Meta-analysis: SGLT2i e outcomes renali





Kang A et al, Nature Rev Neph, 17: 83-84, 2021

SGLT2 inhibitors: effecti emodinamici



No difference in incident albuminuria!

Other effects?

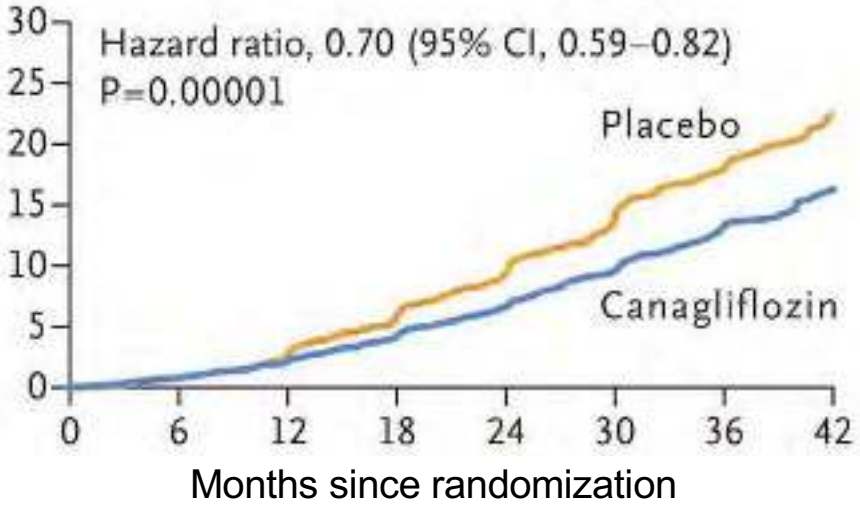
Cherney D et al, Circulation, AHA 2013

SGLT2 inhibitors: protezione indipendente dalla presenza di iperglicemia

DIABETES

CREDENCE

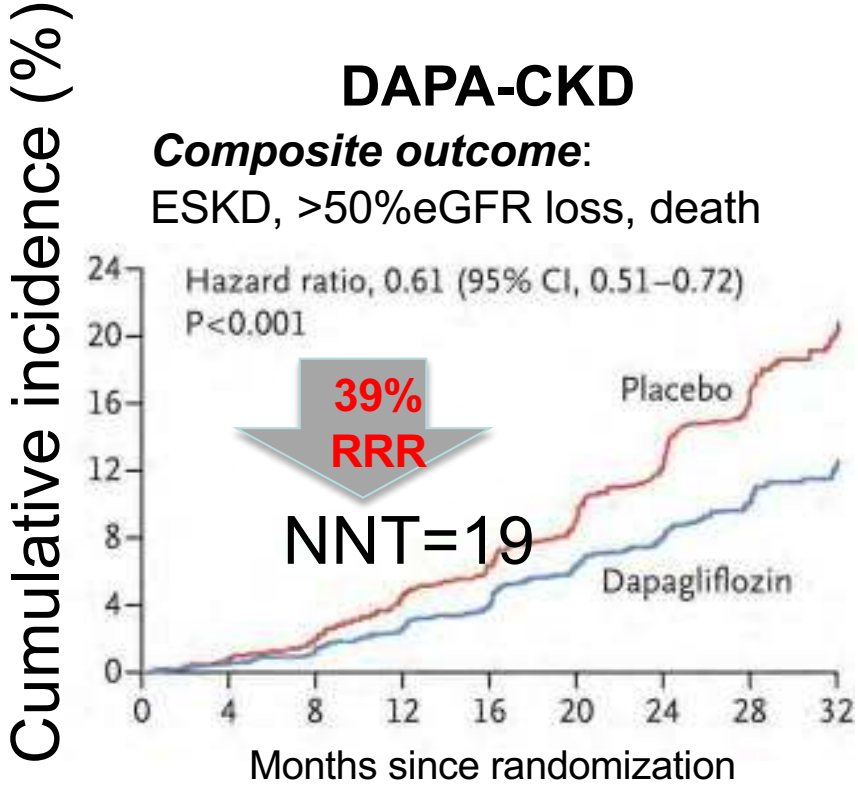
Composite outcome:
ESKD, x2 creat, renal or CV death



CKD

DAPA-CKD

Composite outcome:
ESKD, >50%eGFR loss, death

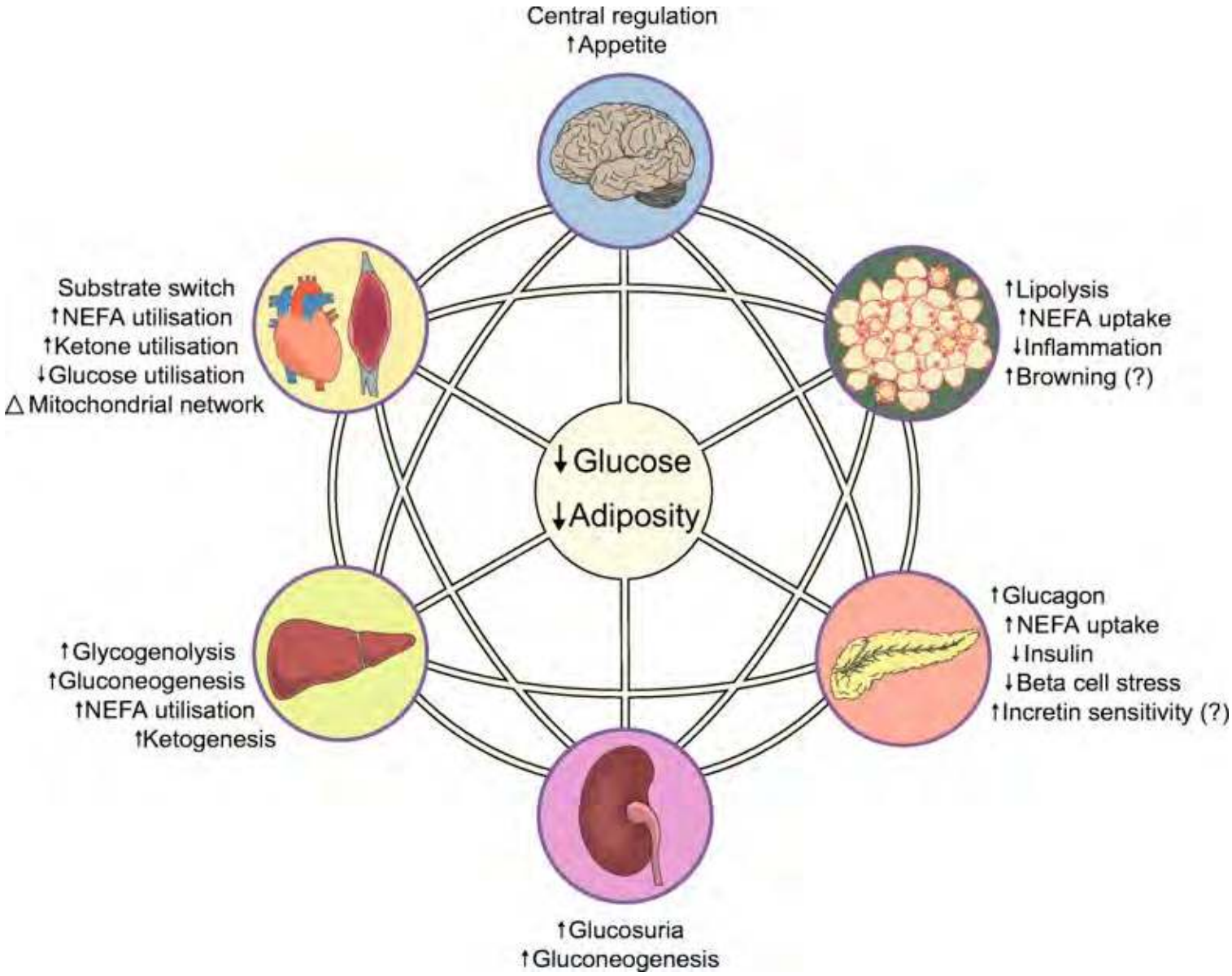


Renoprotection independent of glucose control!

Perkovic, NEJM July 2019, 380:2295

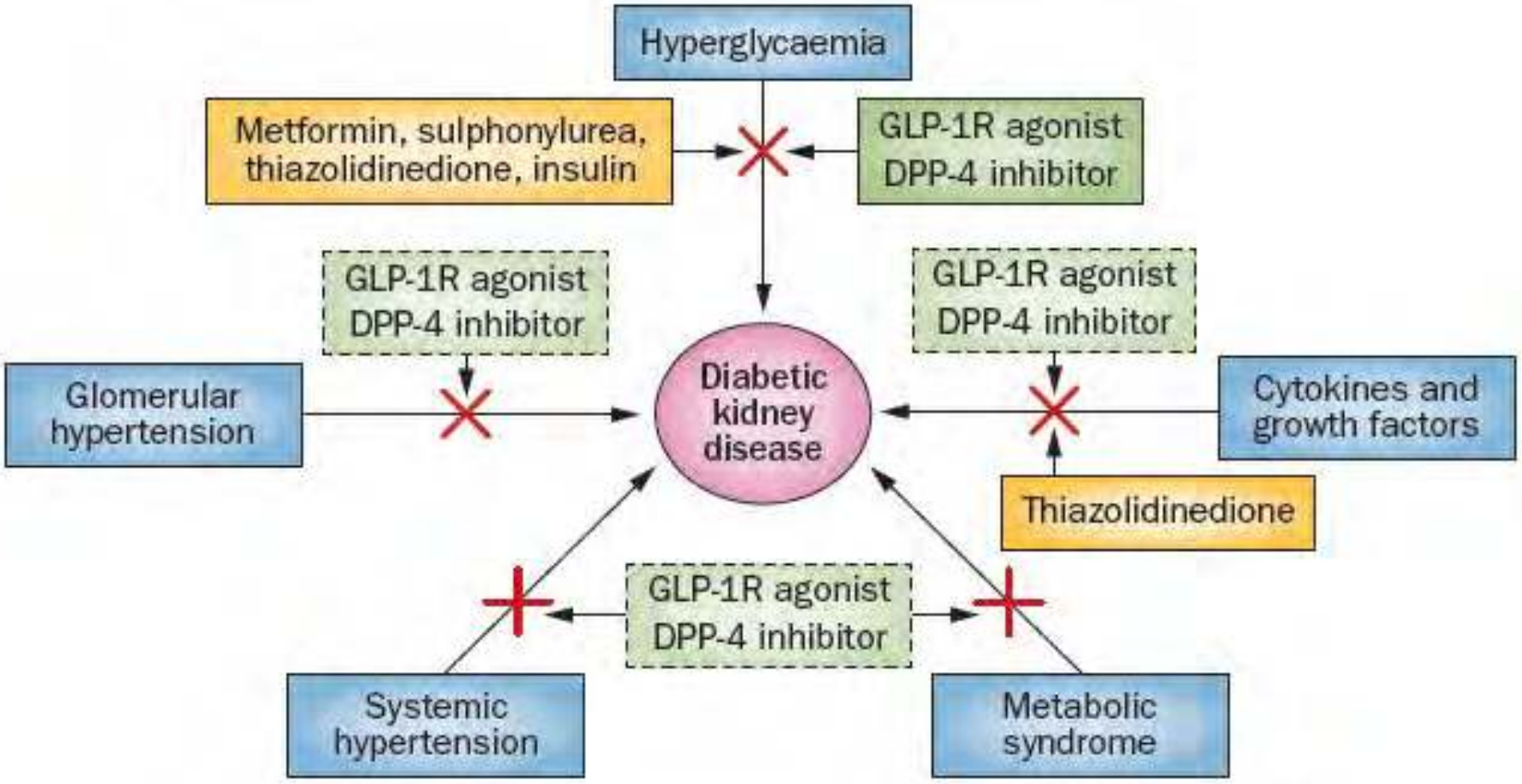
Heerspink H, NEJM Oct 2020, 383:1436

SGLT2 inhibitors: effetti metabolici



Thomas M and Cherney D, Diabetologia, 10:2098-2107, 2018

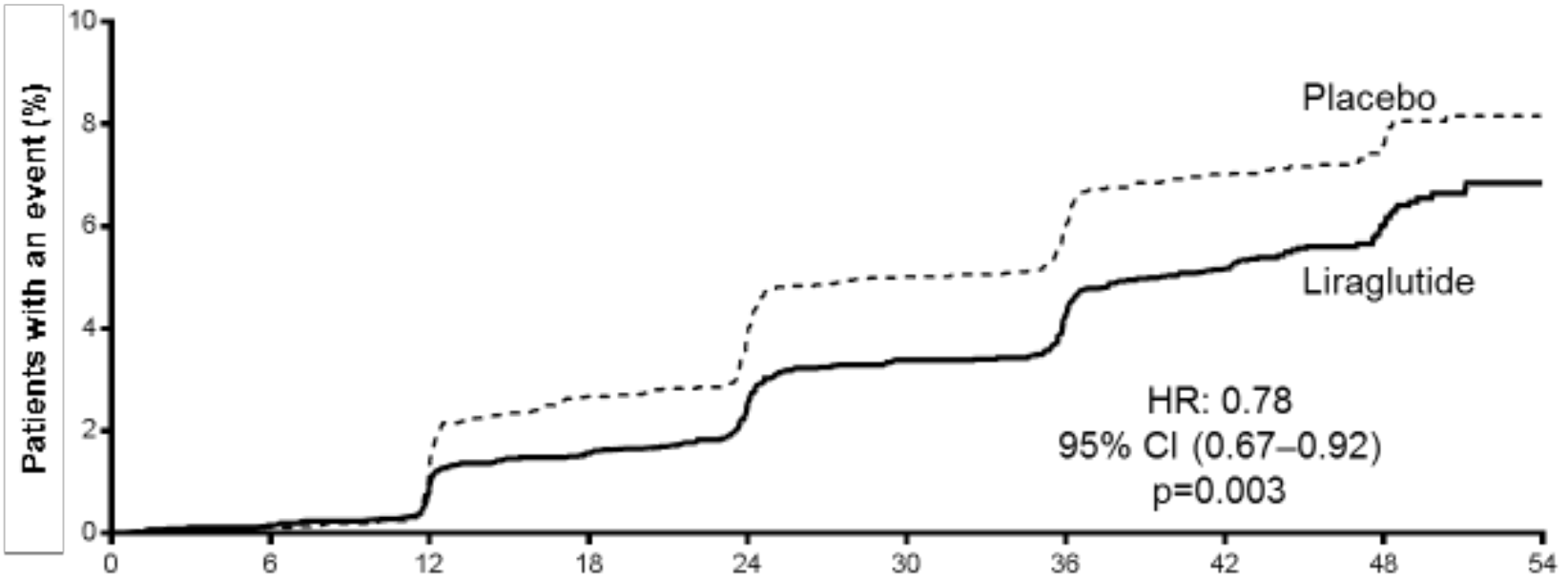
DKD: connessione intestino-rene via GLP1



Muskiet et al, Nature Review, 10:88-103, 2014

Liraglutide in DKD: LEADER trial

Time to first renal event: ACR>300, x2 creat, ESRD, renal death



Patients at risk										
Liraglutide	4668	4635	4561	4492	4400	4304	4210	4114	1632	454
Placebo	4672	4643	4540	4428	4316	4196	4094	3990	1613	433

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months. CI: confidence interval; ESRD: end-stage renal disease; HR: hazard ratio.

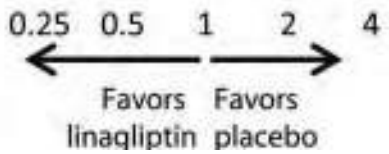
9340 T2DM patients
3.8 yrs f/u
CKD1 35%, CKD2 42%, CKD3 20%

Mann J et al, NEJM 2017, 377:839-848, 2017l

DPP4 inhibition and DKD: linagliptin

B

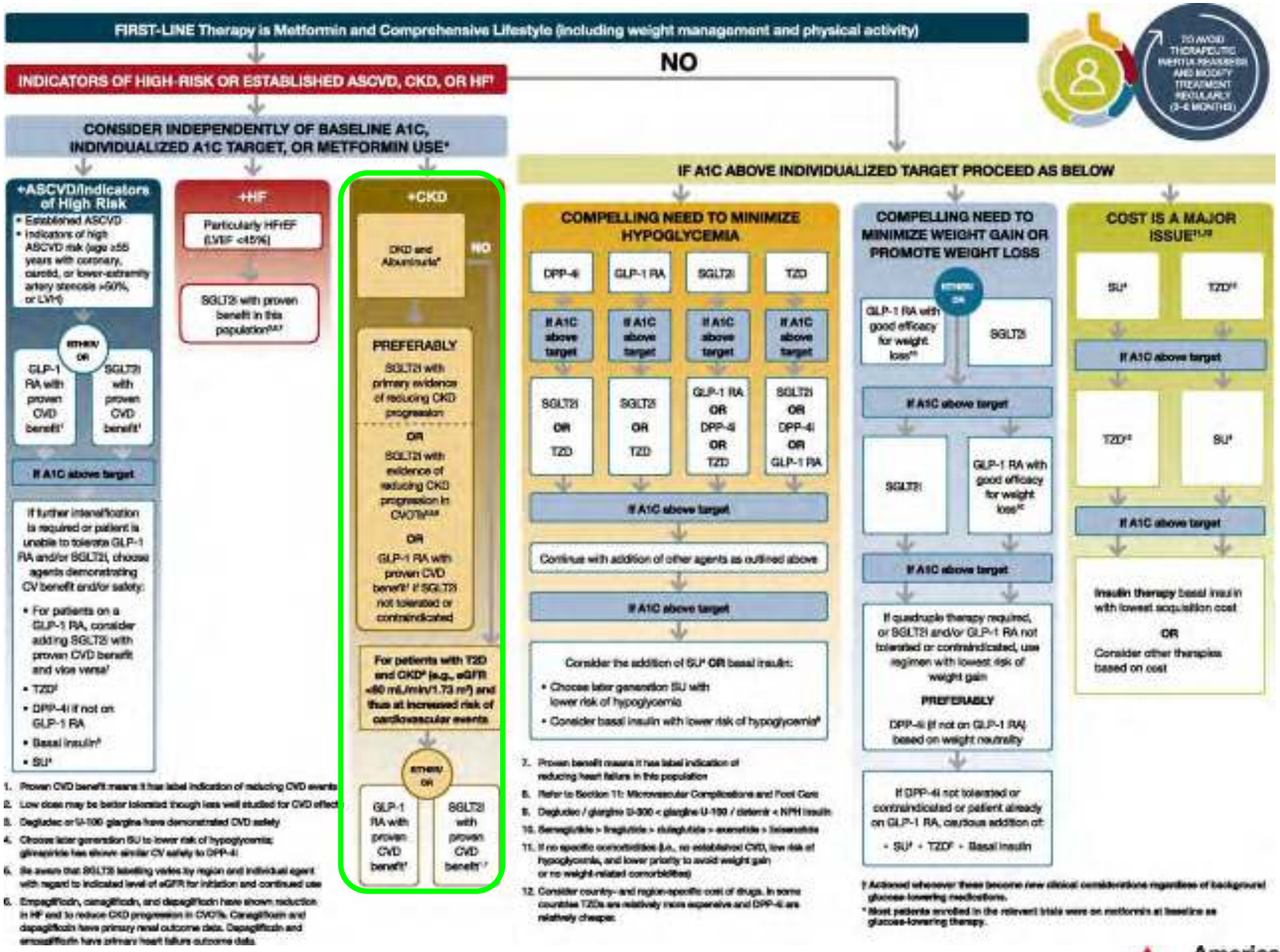
	Linagliptin	Placebo	HR (95% CI)	HR (95% CI)	*P*-value
	n with event / N analyzed (%)				
Kidney composite: overall	**327/3494 (9.4)**	**306/3485 (8.8)**	**1.04 (0.89, 1.22)**		**0.6164**
eGFR ≥60 mL/min/1.73 m²	54/1294 (4.2)	38/1337 (2.8)	1.46 (0.97, 2.21)		
eGFR ≥45 to <60 mL/min/1.73 m²	51/690 (7.4)	49/658 (7.4)	0.94 (0.64, 1.39)		0.3591*
eGFR ≥30 to <45 mL/min/1.73 m²	89/994 (9.0)	86/944 (9.1)	0.95 (0.70, 1.27)		
eGFR <30 mL/min/1.73 m²	133/516 (25.8)	133/546 (24.4)	1.05 (0.82, 1.33)		
ESKD or renal death: overall	**136/3494 (3.9)**	**154/3485 (4.4)**	**0.87 (0.69, 1.10)**		**0.2371**
eGFR ≥60 mL/min/1.73 m²	4/1294 (0.3)	2/1337 (0.1)	NC		
eGFR ≥45 to <60 mL/min/1.73 m²	8/690 (1.2)	6/658 (0.9)	1.26 (0.44, 3.62)		0.1710*
eGFR ≥30 to <45 mL/min/1.73 m²	23/994 (2.3)	39/944 (4.1)	0.55 (0.33, 0.92)		
eGFR <30 mL/min/1.73 m²	101/516 (19.6)	107/546 (19.6)	0.97 (0.74, 1.27)		
ESKD, renal death, or eGFR <10: overall	**149/3494 (4.3)**	**172/3485 (4.9)**	**0.84 (0.67, 1.05)**		**0.1189**
eGFR ≥60 mL/min/1.73 m²	4/1294 (0.3)	2/1337 (0.1)	NC		
eGFR ≥45 to <60 mL/min/1.73 m²	8/690 (1.2)	8/658 (1.2)	0.92 (0.34, 2.44)		0.1978*
eGFR ≥30 to <45 mL/min/1.73 m²	26/994 (2.6)	42/944 (4.4)	0.56 (0.34, 0.91)		
eGFR <30 mL/min/1.73 m²	111/516 (21.5)	120/546 (22.0)	0.96 (0.74, 1.24)		



6979 T2D pt
Mean eGFR 54, age 69, 80% A2-A3
Secondary outcome: renal death, ESKD, 40% decrease in eGFR
Follow up: 2.2. years

CARMELINA, Perkovic et al, Diab Care, 43: 1803, 2020

Algoritmo suggerito da ADA



American Diabetes Association Dia Care 2021;44:S111-S124

American Diabetes Association.

Prevenzione e trattamento

American Diabetes Association recommendations 2022

Level of evidence A:

control BP with appropriate agents (goal <140/90mmHg, <130/80 if high risk for CVD)

control glycemia (A1C about 7%, personalized)

control dyslipidemia (LDL goal <70-100 mg/dl)

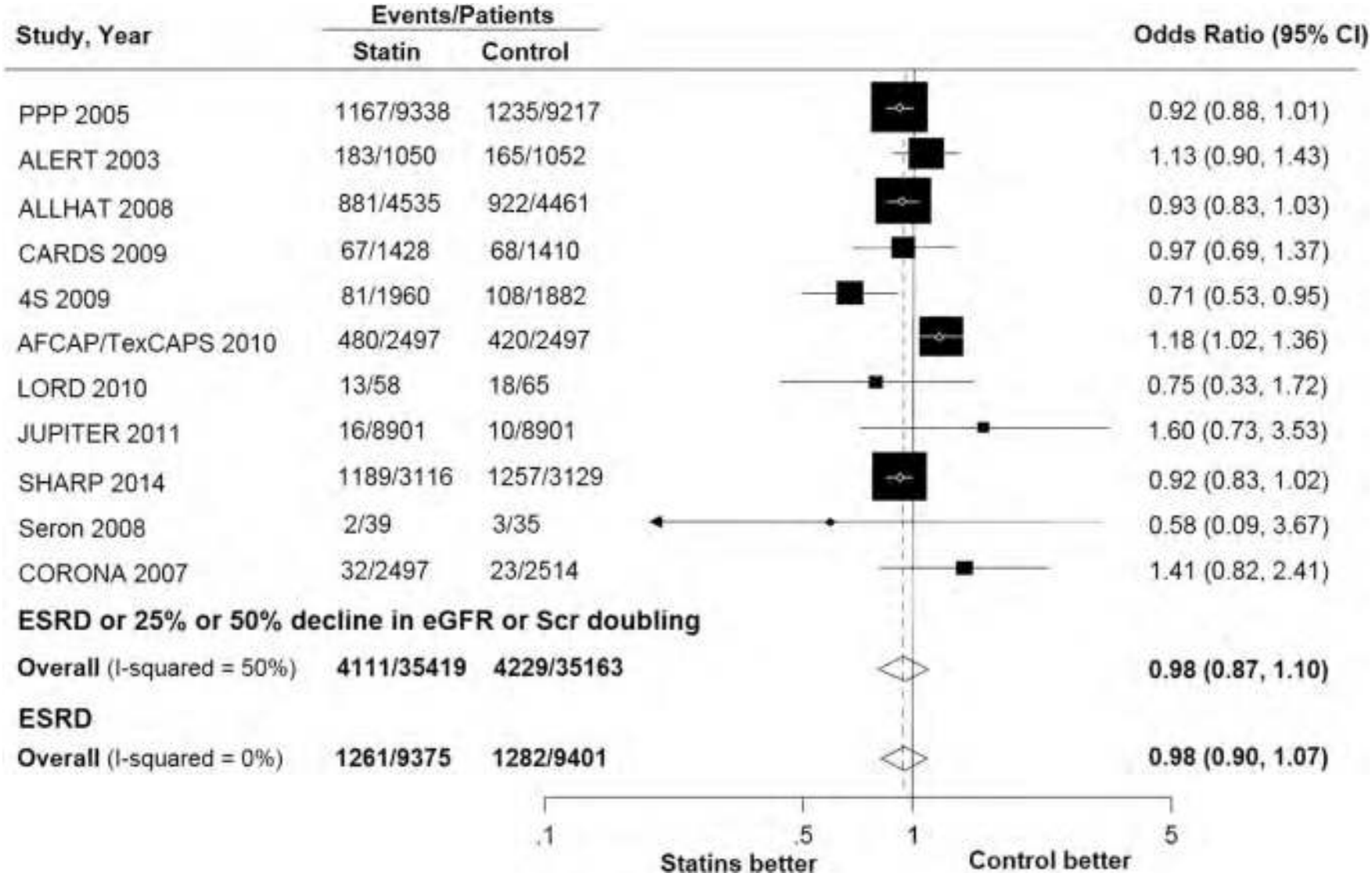
counsel about smoking cessation

education

protein intake to 0.8 g/kg/day (more if dialysis)

ADA recommendations, Diabetes Care, January 2022

Effetto delle Statine su GFR



Su et al, AJKD, 67:881, 2016

Prevenzione e trattamento

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control BP with appropriate agents (goal <140/90mmHg, <130/80 if high risk for CVD)

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counsel about smoking cessation

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protein intake to 0.8 g/kg/day (more if dialysis)

ADA recommendations, Diabetes Care, January 2022

Intake proteico e DKD

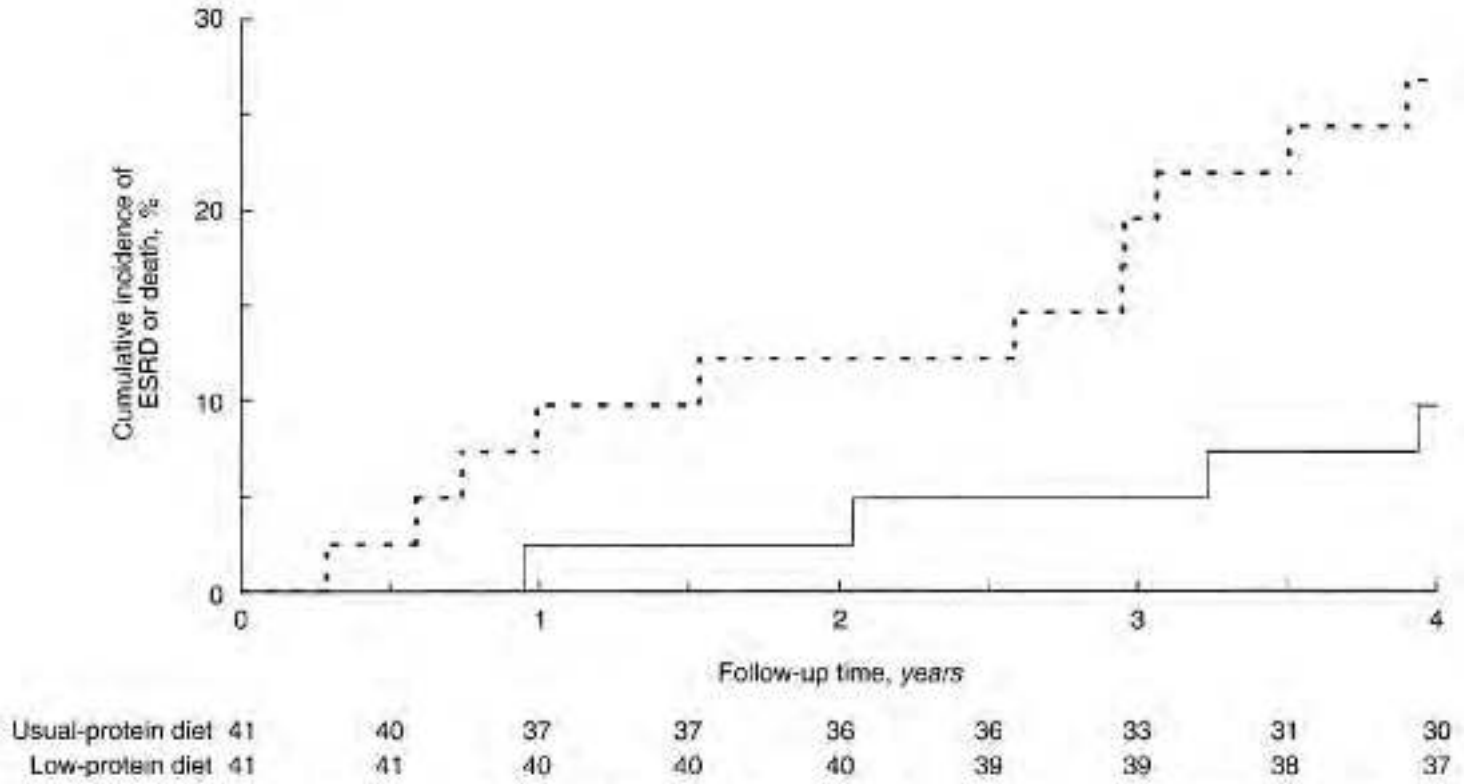


Fig. 3. Cumulative incidence of end-stage renal disease (ESRD) or death in type 1 diabetic patients with progressive diabetic nephropathy in the usual-protein group (dashed lines) and the low-protein diet group (solid line). Log rank test, $P = 0.042$. The numbers at the bottom denote the number of patients in each group at risk for the event at baseline and after each six month period.

Restrizione da liberalizzare in dialisi

Hansen HP et al, Kidney International, 62:220, 2002

Corso della malattia

Mr GD comes to you with GFR 50 cc/min/1.73m^2

Smoker
Obese
BP150/90
A1c 11%
LDL 150
High protein diet

↓

GFR loss 20 cc/min/year

↓

ESRD in 2 year

Non smoker
Exercise TIW
BP130/80
A1c 6.9%
LDL 70
protein diet 0.8 g/kg

↓

GFR loss 2 cc/min/year

↓

ESRD in 20 year

IT'S UP TO MR JD AND TO YOU!

Storia naturale della malattia

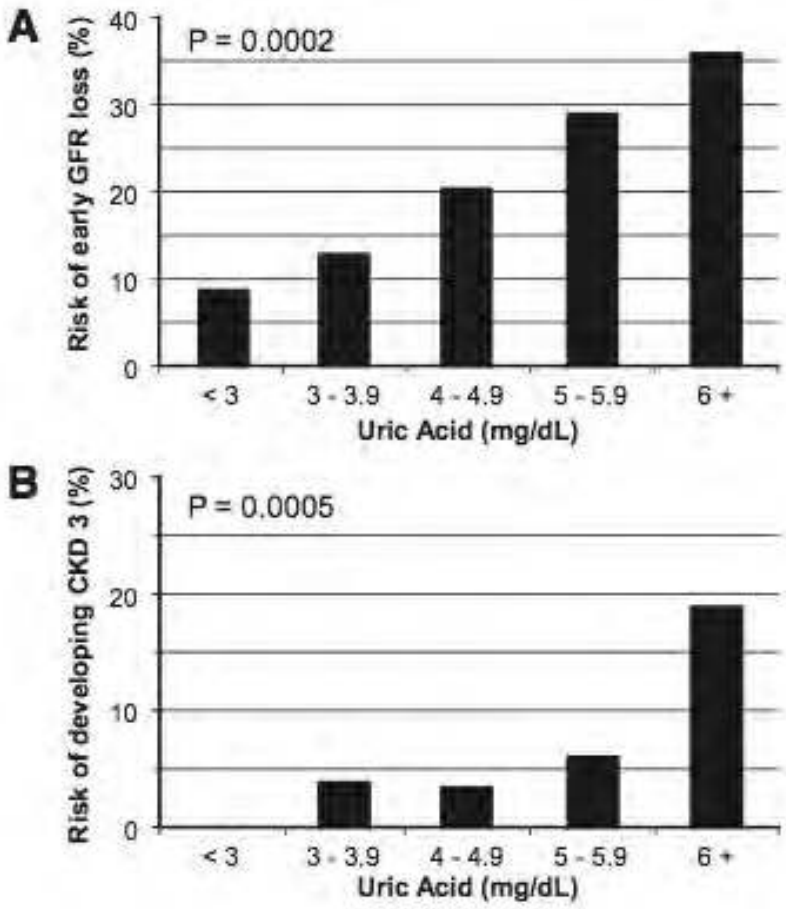
GD viene in ambulatorio e ti chiede quanto segue

- I miei reni sono affetti da diabete?
- Qual è la mia possibilità di entrare in dialisi?
- Qual è il mio rischio di morire di malattie renali?
- Sarebbe utile una biopsia renale?
- Come devo essere trattato?
- Gli anti-iperglicemizzanti sono tutti uguali?
- Qualche nuovo strumento per capire i miei rischi?
- Qualche nuova terapia all'orizzonte?

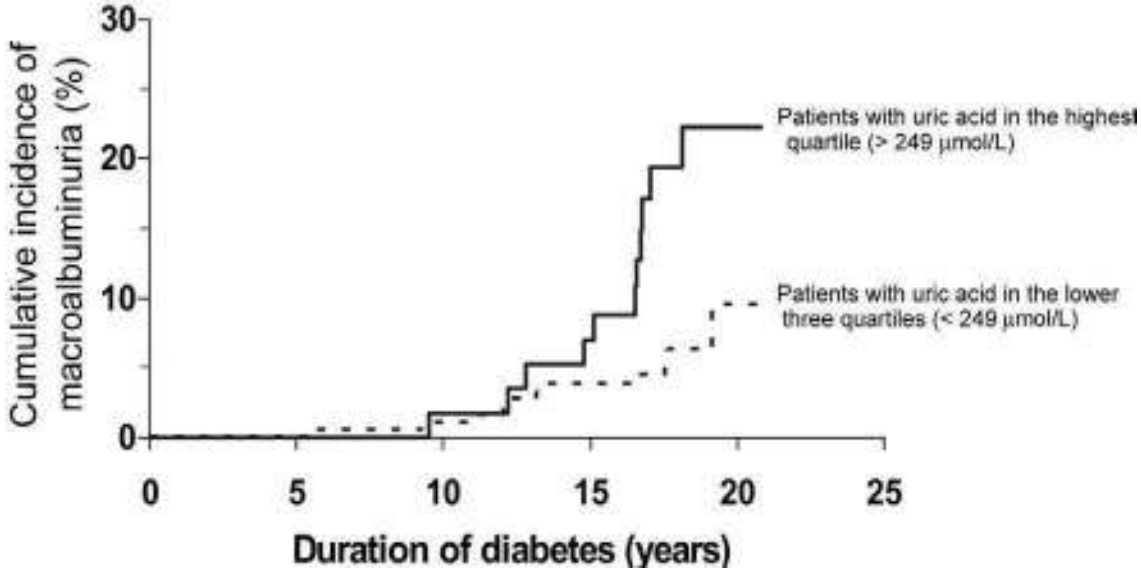
Obiettivi della presentazione

- Stratificazione, definizione e screening del rischio
- Linee guida 2022 per il trattamento
- Strumenti per approcci personalizzati e nuove scoperte

Acido urico come biomarker



355 patients with DM and MA
Baseline uric acid determination
6 years f/u
End points: GFR Cystatin decline albuminuria

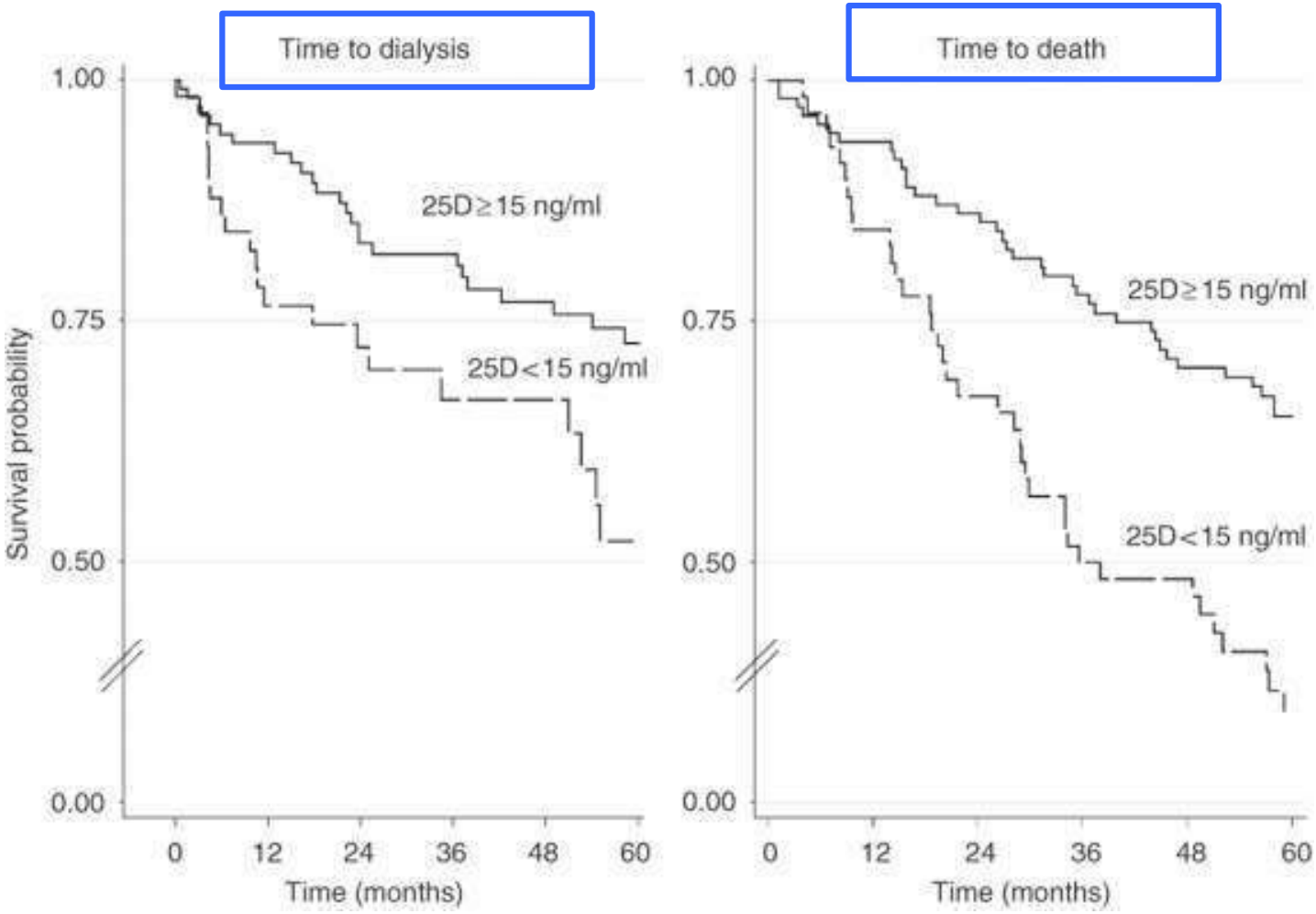


263 patients with type 1 diabetes, 18.1 years f/u
Uric acid measured 3 years after onset of diabetes
All patients NA at enrollment (23 with macroalbuminuria at f/u)

Ficociello et al, Diabetes Care. 2010 Jun;33(6):1337-43.

Hovind P et al, Diabetes, 2009 Jul;58(7):1668-71

Vitamin D come biomarker

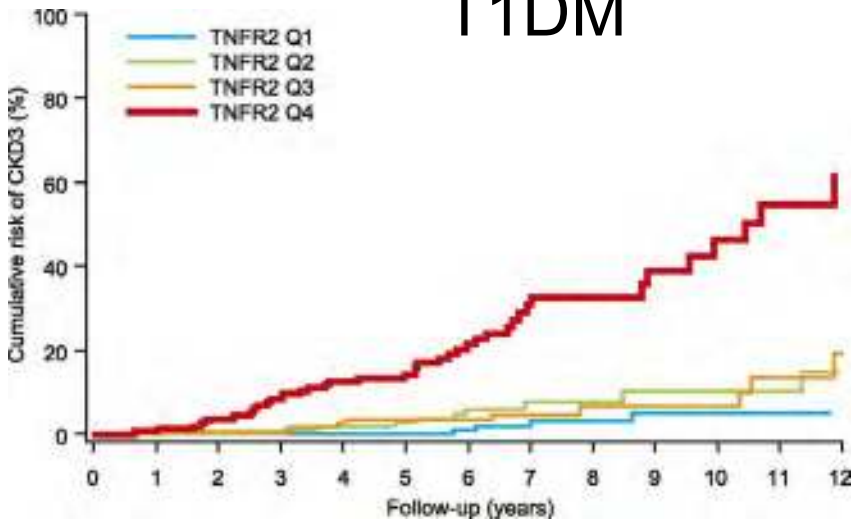


168 consecutive patients in a CKD clinic (28% with DKD)
6 years follow up
Baseline Vitamin D adjusted for age, sex, smoking, CRP, albumin, ACE/ARB usage, eGFR

Ravani P et al, Kidney International (2009) 75, 88–95

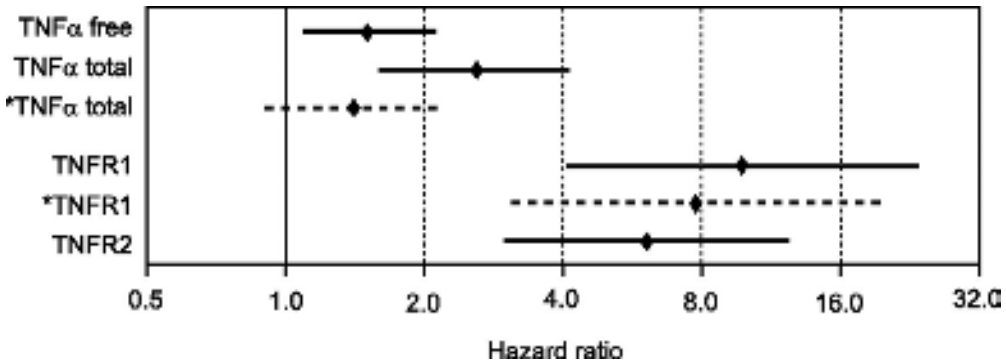
Recettori del TNF come biomarkers

T1DM



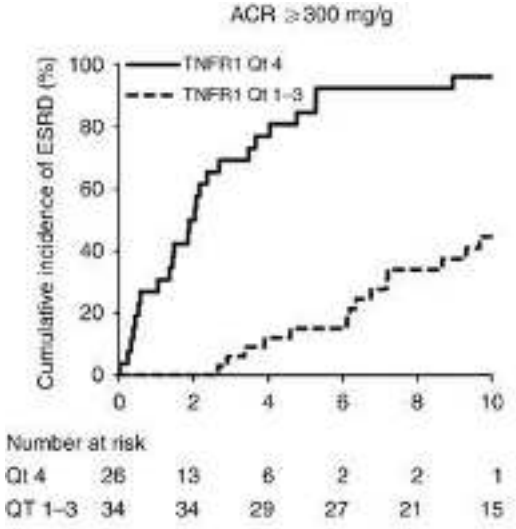
Cumulative risk for CKD>3 in patients with T1D during 12 years of follow-up according to quartile (Q1–Q4) of circulating TNFR2 at baseline.

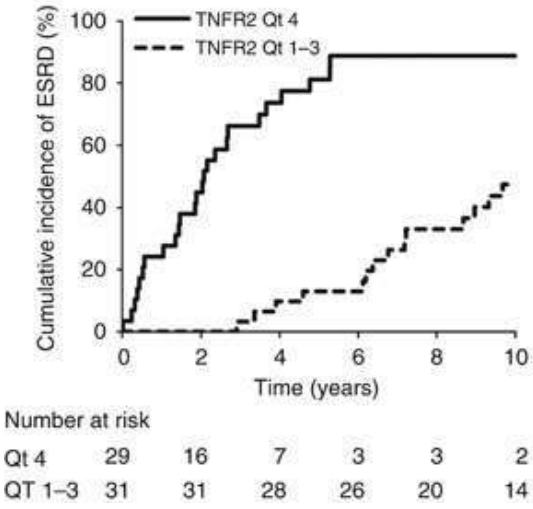
Gohda T and Niewczas M et al, JASN, 23:516-524, 2012



(Caucasian Americans, 410 patients) Adapted from Niewczas MA et al., JASN, 2012.

T2DM





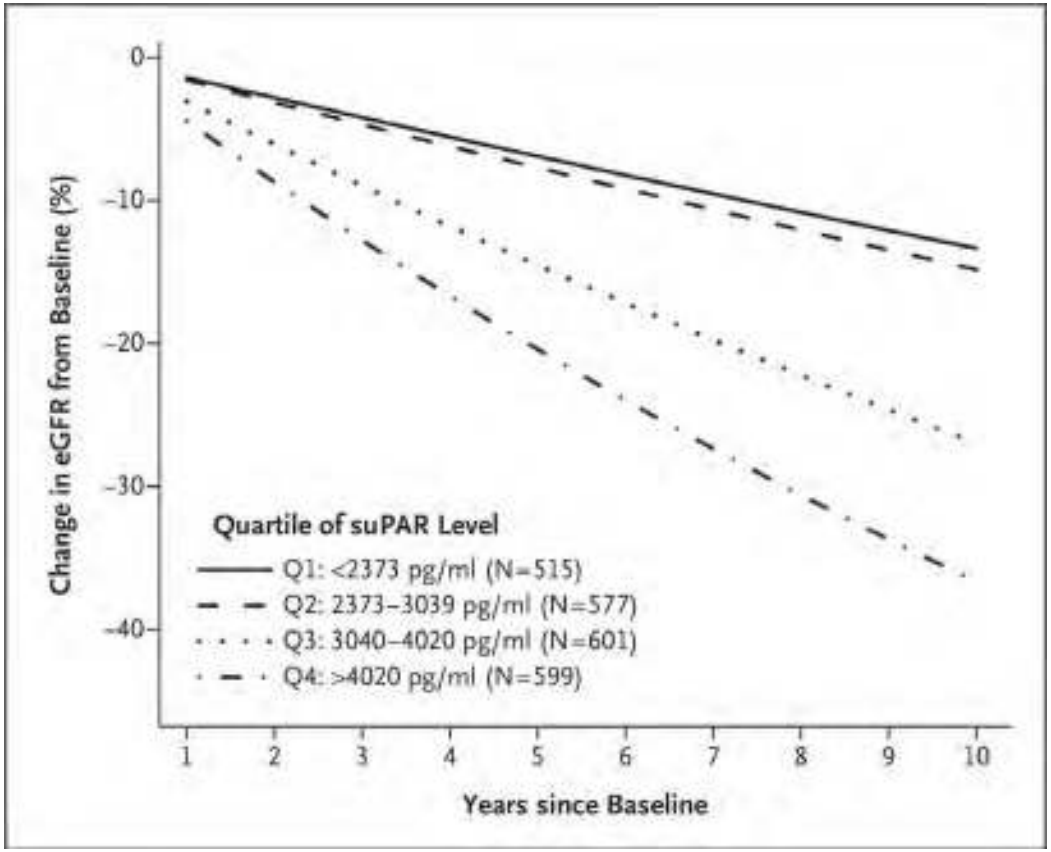
(PIMA Native Americans, 193 patients) Adapted from Pavkov ME et al. KI, 2014.

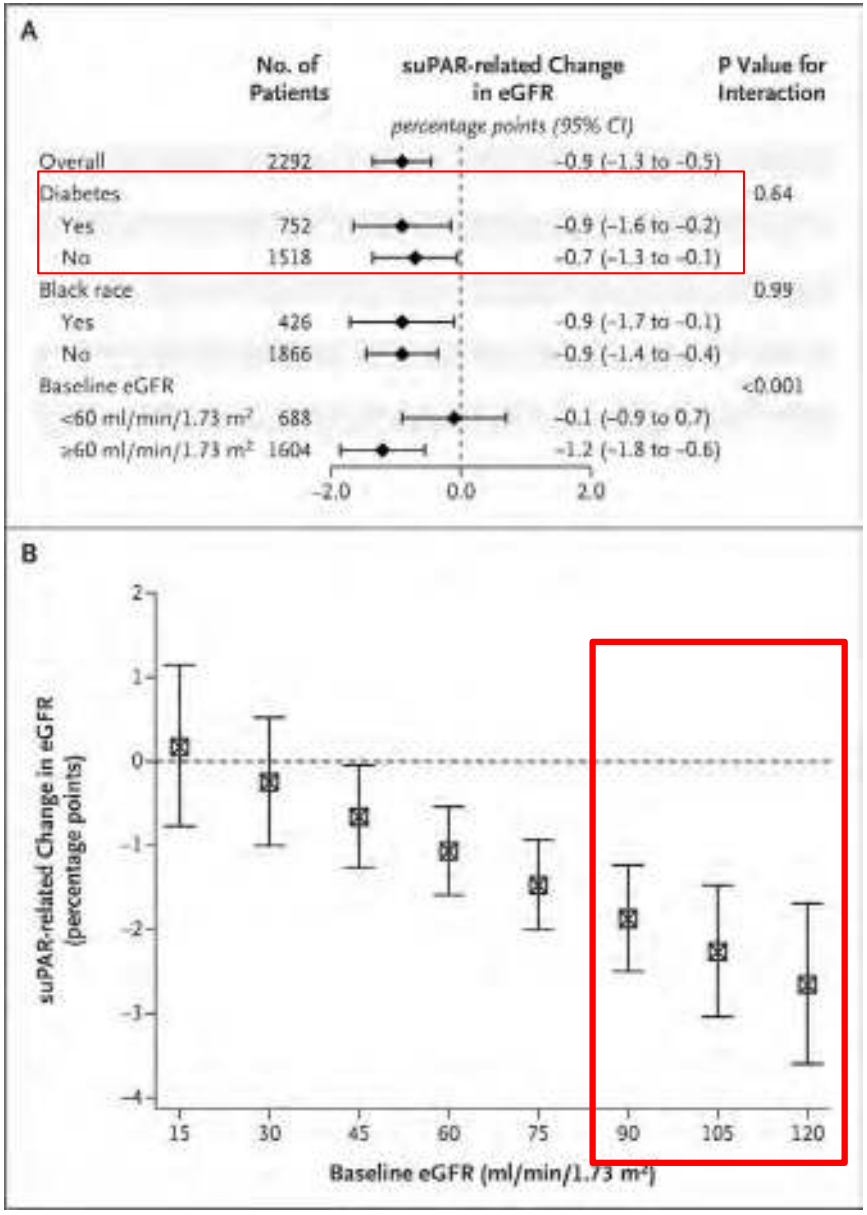
Soluble Urokinase Receptor (suPAR)

2292 patients

Q1: eGFR loss of 0.9 cc/min

Q4: eGFR loss of 4.2 cc/min

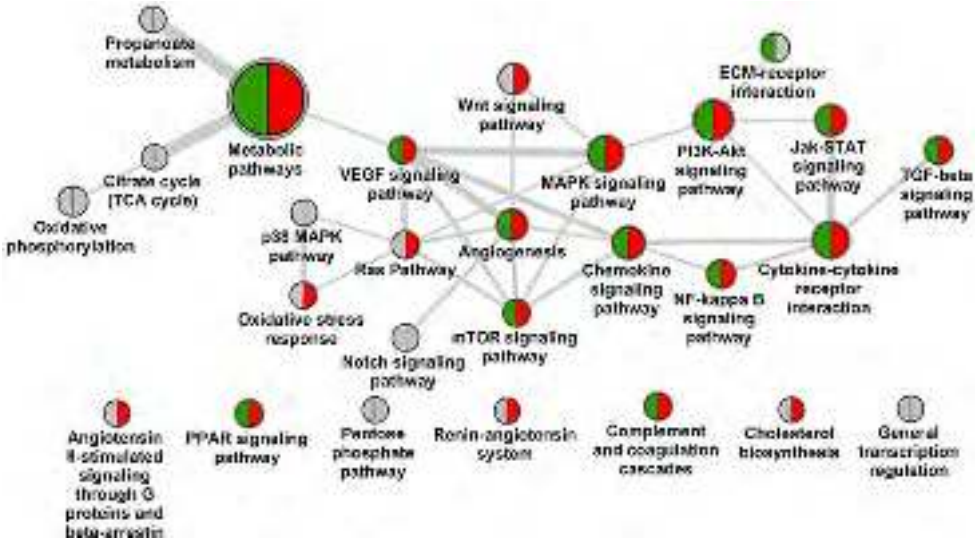




Hayek SS et al. N Engl J Med 2015;373:1916-1925.

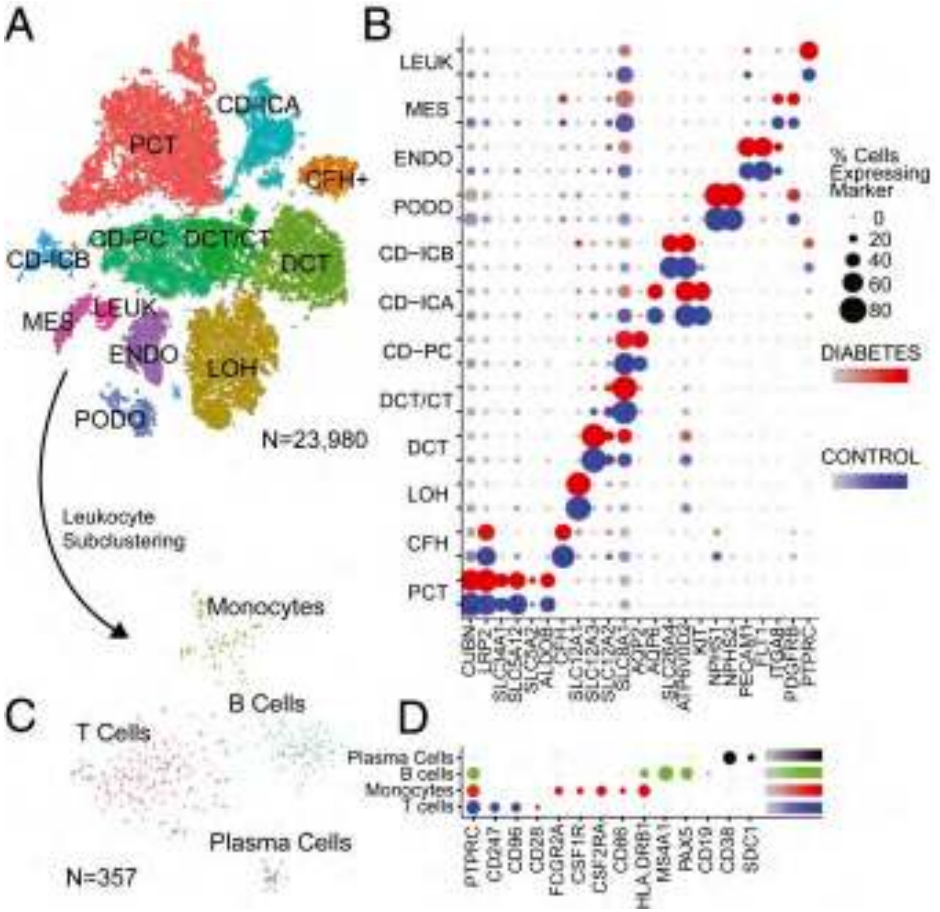
DKD: verso la medicina di precisione

RNA-seq



Fornoni et al, Brenner Rector 11th Edition
Heinzel et al, Frontiers in Cell and Dev Biol, 2014

Single nuclei RNA-seq



Wilson PC et al, PNAS, 116:19619-25, 2019

Storia naturale della malattia

GD viene in ambulatorio e ti chiede quanto segue

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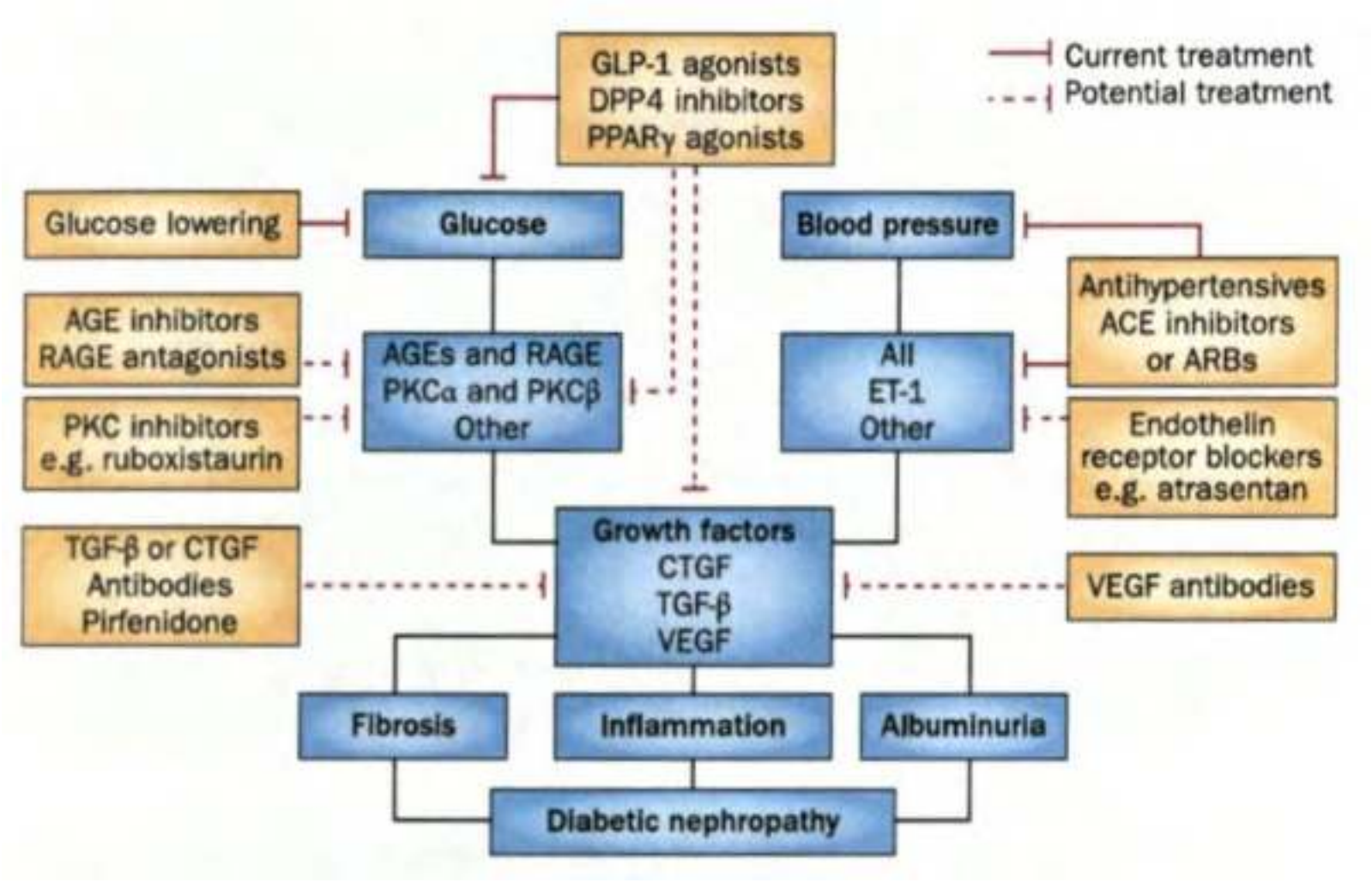
- Qualche nuova terapia all'orizzonte?

DKD: Targets e trials

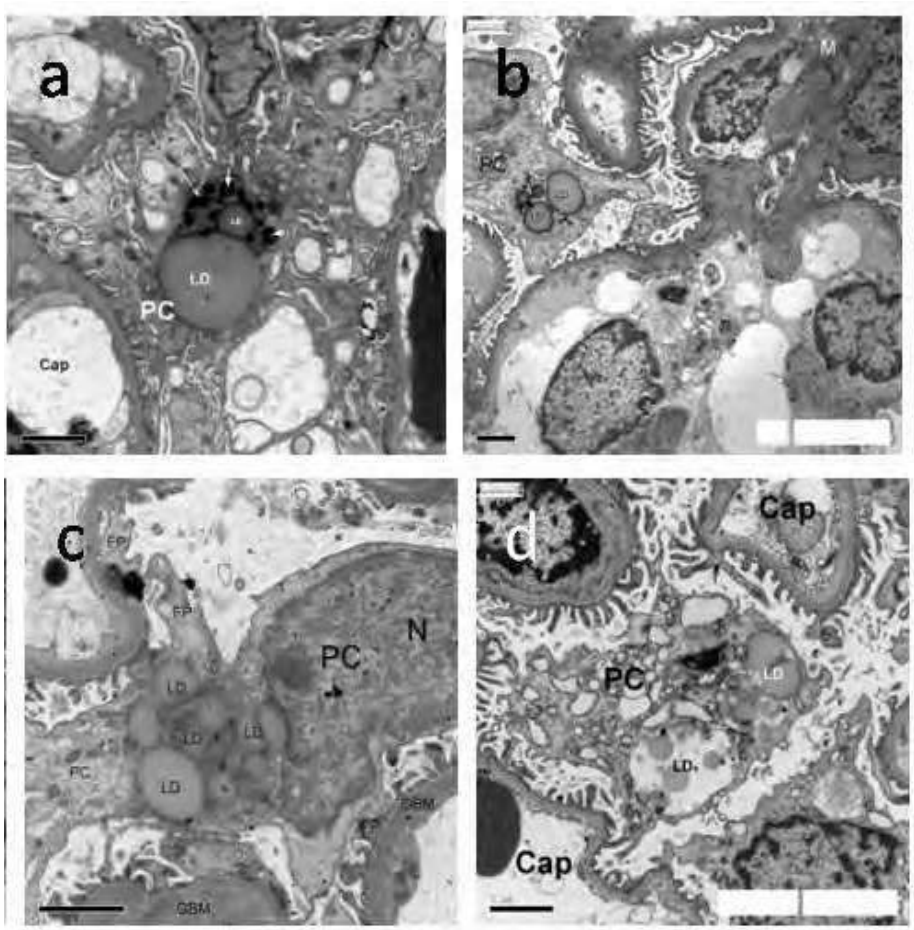


Fornoni et al, Brenner Rector 11th edition.
Adapted from Fineberg, D. *et al.* (2013) *Nat. Rev. Endocrinol.* doi:10.1038/nrendo.2013.184

DKD: una forma di rene grasso?

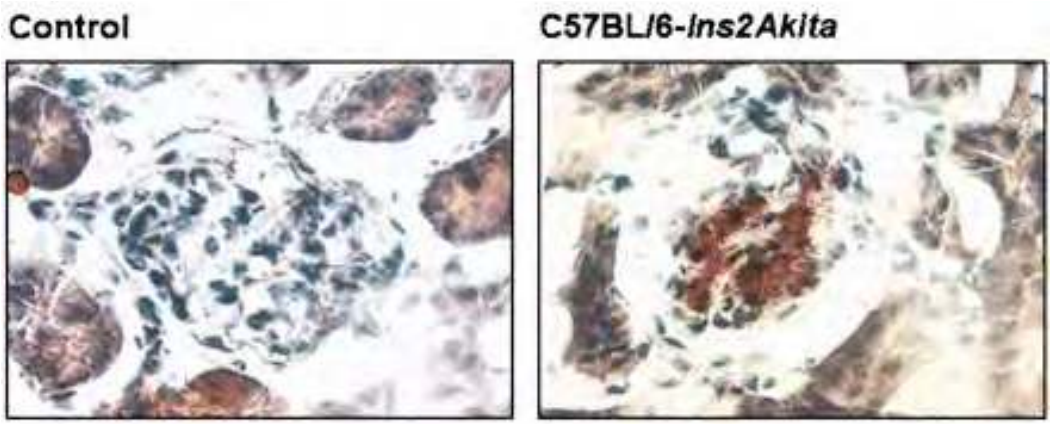
Nuovi targets

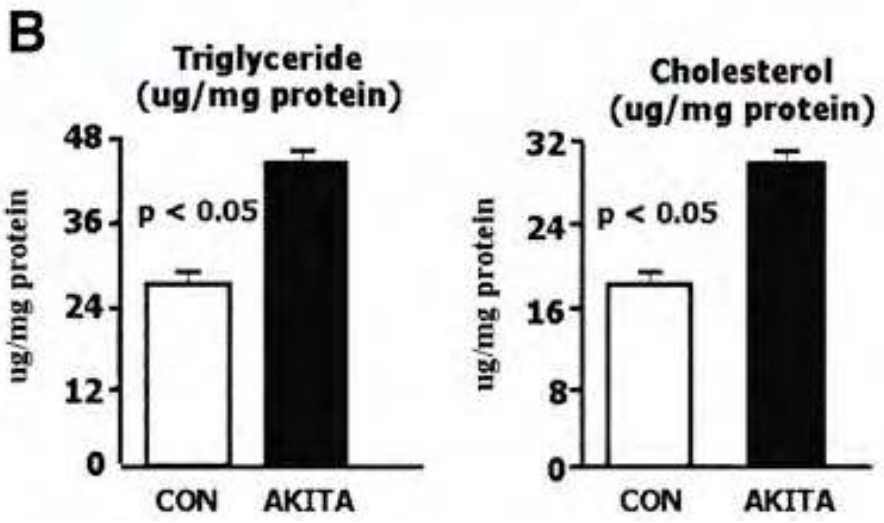
CLINICAL



Herma-Hedelstain et al, J Lipid Res, 55:561, 2013

EXPERIMENTAL





Gregory Proctor et al, Diabetes, 55, 2502-2509, 2005

Osservazioni storiche
causa o consequenza?

British Medical Journal
1883

REMARKS
ON
THE FATTY TRANSFORMATION OF THE KIDNEY.

By EDWIN RICKARDS, M.B.,
Physician to the General Hospital, Birmingham.

In fatty transformation of the kidney, there is a replacement of renal tissue by true adipose tissue, the contour of the organ being, to a varying extent, preserved. The condition is a rare one, and the cases on record are few. It has not, as far as I am aware, been before portrayed, numerous and excellent as are the illustrations of the various morbid changes in the kidney by Bright and others.

The Lancet
1982

Hypothesis

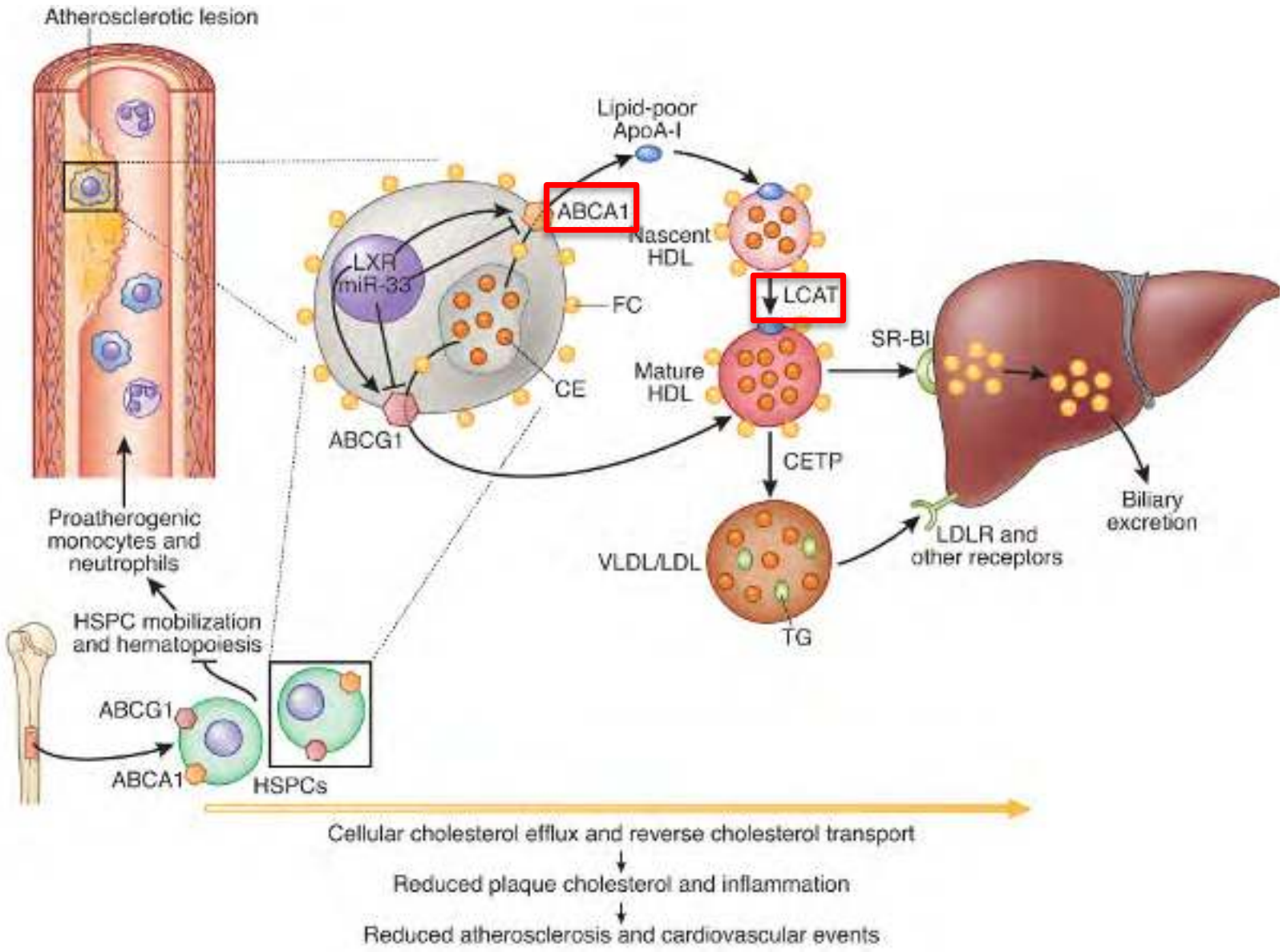
LIPID NEPHROTOXICITY IN CHRONIC PROGRESSIVE GLOMERULAR AND TUBULO-INTERSTITIAL DISEASE

J. F. MOORHEAD, M. K. CHAN, M. EL-NAHAS, Z. VARGHESE

Department of Nephrology and Transplantation, Royal Free Hospital, London NW3 2QG

Summary It is hypothesised that chronic progressive kidney disease may be mediated by abnormalities of lipid metabolism. A series of self-perpetuating secondary events follows an initial glomerular injury. Increased glomerular basement membrane permeability leads to loss of lipoprotein lipase activators, resulting in hyperlipidaemia. Circulating low-density lipoprotein binds with glycosaminoglycans in the glomerular basement membrane and increases its permeability. Filtered lipoprotein accumulates in mesangial cells and stimulates them to proliferate and produce excess basement membrane material. The proximal tubular cells metabolise some of the filtered lipoprotein and the remainder are altered on passage down the nephron. Luminal apoprotein precipitates, initiating or aggravating tubulo-interstitial disease, if the intraluminal pH is close to the isoelectric point of the apoprotein. The hypothesis offers new approaches to the study of chronic progressive kidney disease by proposing a major pathogenetic role for lipid abnormalities.

Ruolo di ABCA1 nell' efflusso di colesterolo nell'aterosclerosi



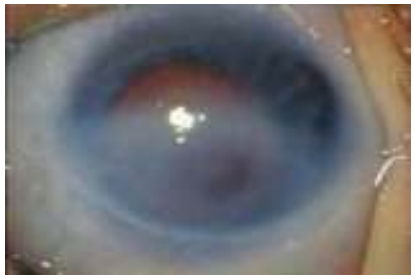
Rader and Tall, Nature Medicine, 18: 1344-1346, 2012

Malattie genetiche rare che suggeriscono un ruolo causale dell' efflusso di colesterolo sulla proteinuria

Tangier disease

ABCA1 deficiency

Inability of the cells to efflux cholesterol

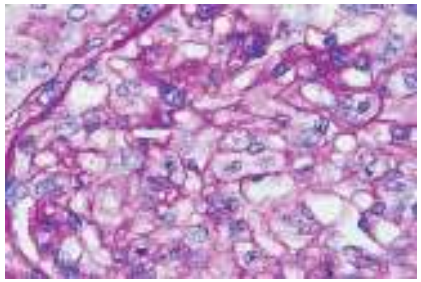


- Very low HDL
- Premature atherosclerosis
- Orange large tonsils
- Hepatosplenomegaly
- Corneal opacity
- **Mild proteinuria**
- **Foamy podocytes**

Am J Pathol, 78:101, 1975

LCAT deficiency/fish-eye dx

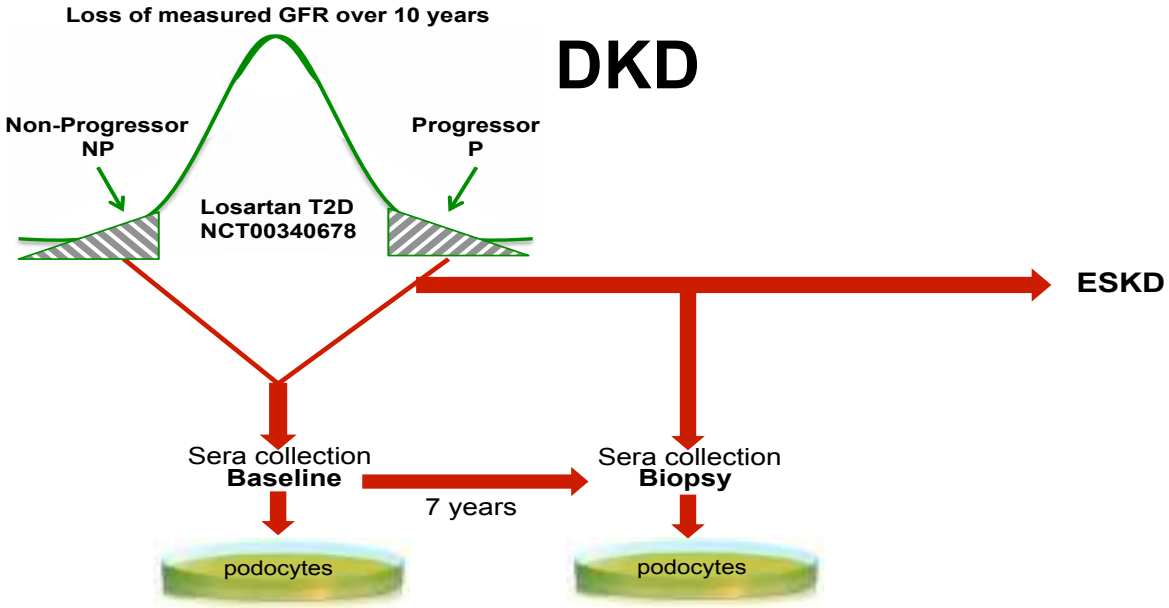
Impairment of cholesterol esterification



- **Nephrotic syndrome leading to ESRD**
- Premature atherosclerosis
- Hepatosplenomegaly
- Corneal opacity

Shamburek RD et al, Circ Res. 2015 Dec

Riduzione di ABCA1 glomerulare nelle fasi precoci di nephropatia



Podocytes+sera

Genes	Progressor
ABCA1	0.4
HMGCoA	0.9
LDL-Rec	2.8
SREBP1	1.2
SREBP2	1.4

Kidney biopsies

	DKD (70)	MN (21)	FSGS (18)
ABCA1	**0.77**	0.88	1.01
HMGCoA	1.1	1.03	1.04
LDL-Rec	1.19	1.07	0.97
SREBP1	**1.23**	1.11	**1.42**
SREBP2	1.09	1.03	0.99

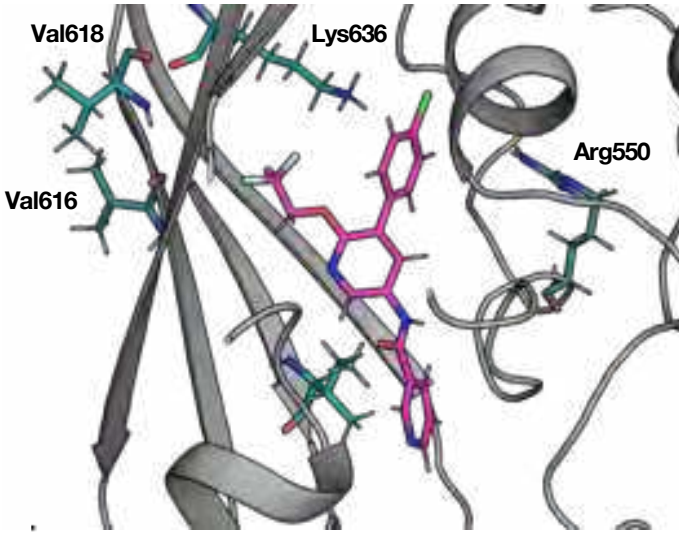
>1.4
>1.3
>1.2
>1.1
<0.9
<0.8
<0.7
<0.6

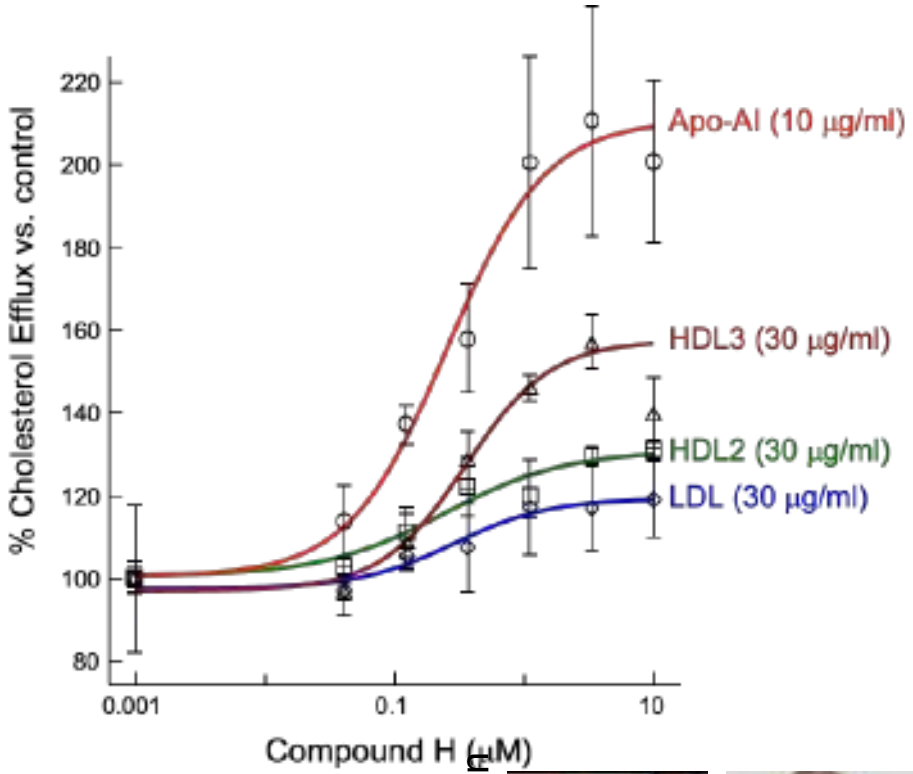
Ducasa GM et al, JCI,129(8):3387-3400, July 2019

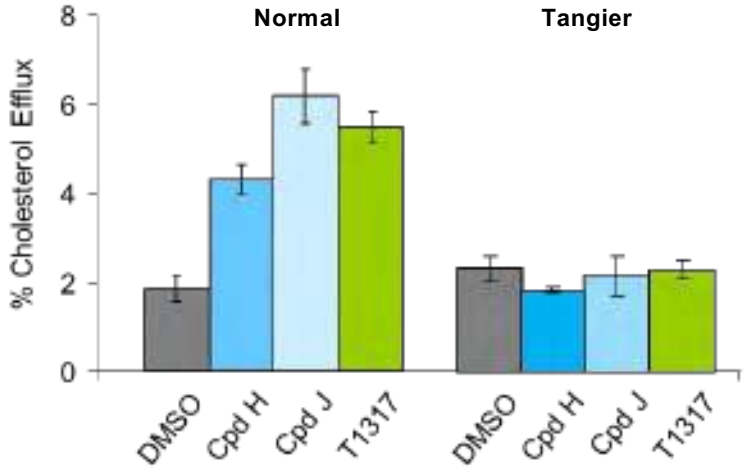
Sviluppo di un farmaco che provoca efflusso di coloesterolo dal rene

Discovery of 5-arylnicotinamides

Cpd G: ABCA1 inducer



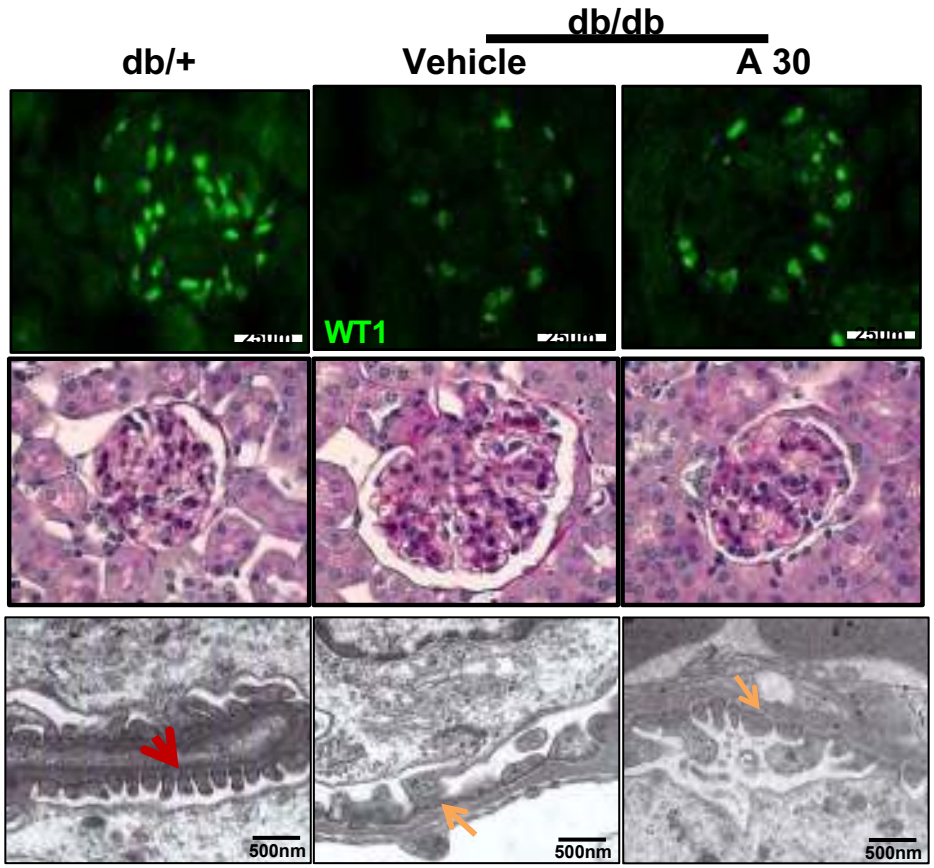


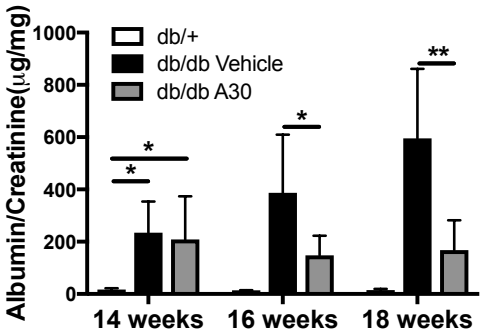


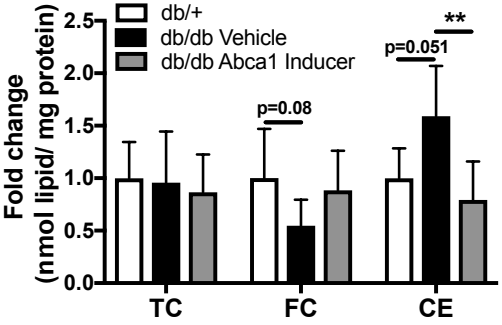
UM-Roche Collaboration

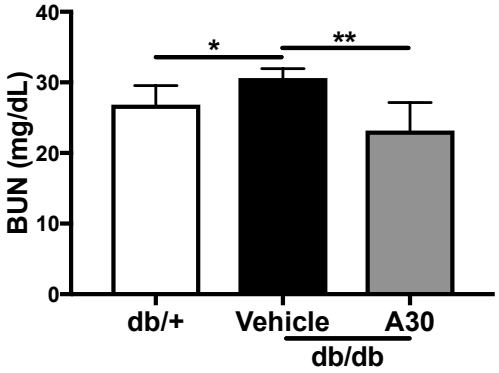
Wright, Varona et al, Nature Communication, 2021, 12:4662

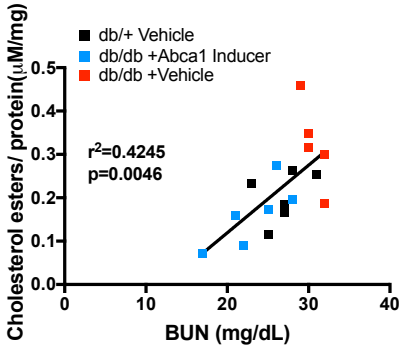
Effetto degli induttori di ABCA1 sulla nefropatia











PHASE II trial 2022

Ducasa GM et al, JCI,129(8):3387-3400, July 2019

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	U24-DK076169 (AMDCC)
	UL1TR000460 (CTSI)
	U54-DK083912 (NEPTUNE)
	UM1-DK100846 (CureGN)
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Questions?