S.I.Te.C.S.
Società Italiana di Terapia Clinica e Sperimentale
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Four Points by Sheraton Milan Center

IL SOGGETTO NEFROPATICO

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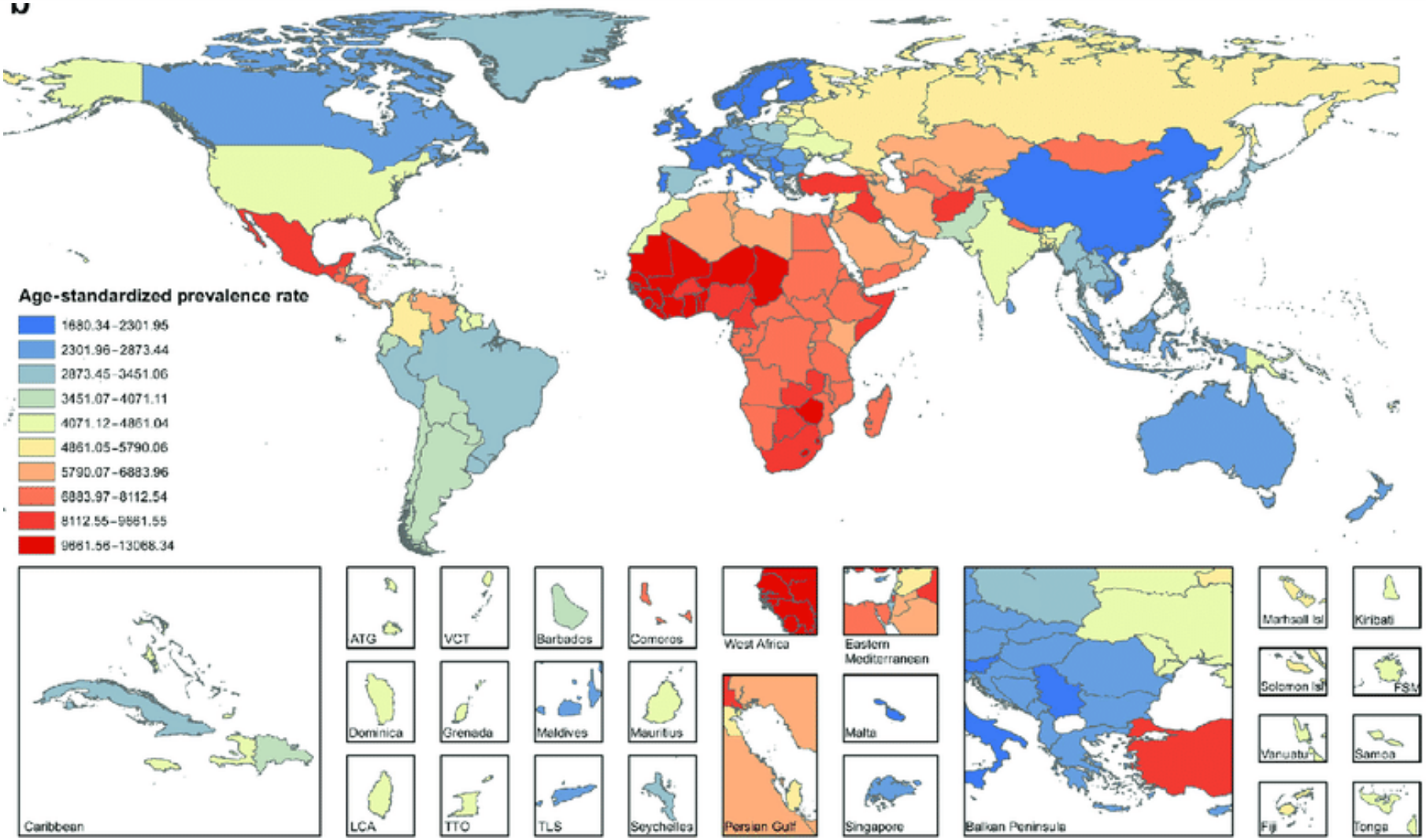
SOCIETA' ITALIANA PER LO STUDIO DELL'ARTERIOSCLEROSI

DICHIARAZIONE CONFLITTO DI INTERESSI:

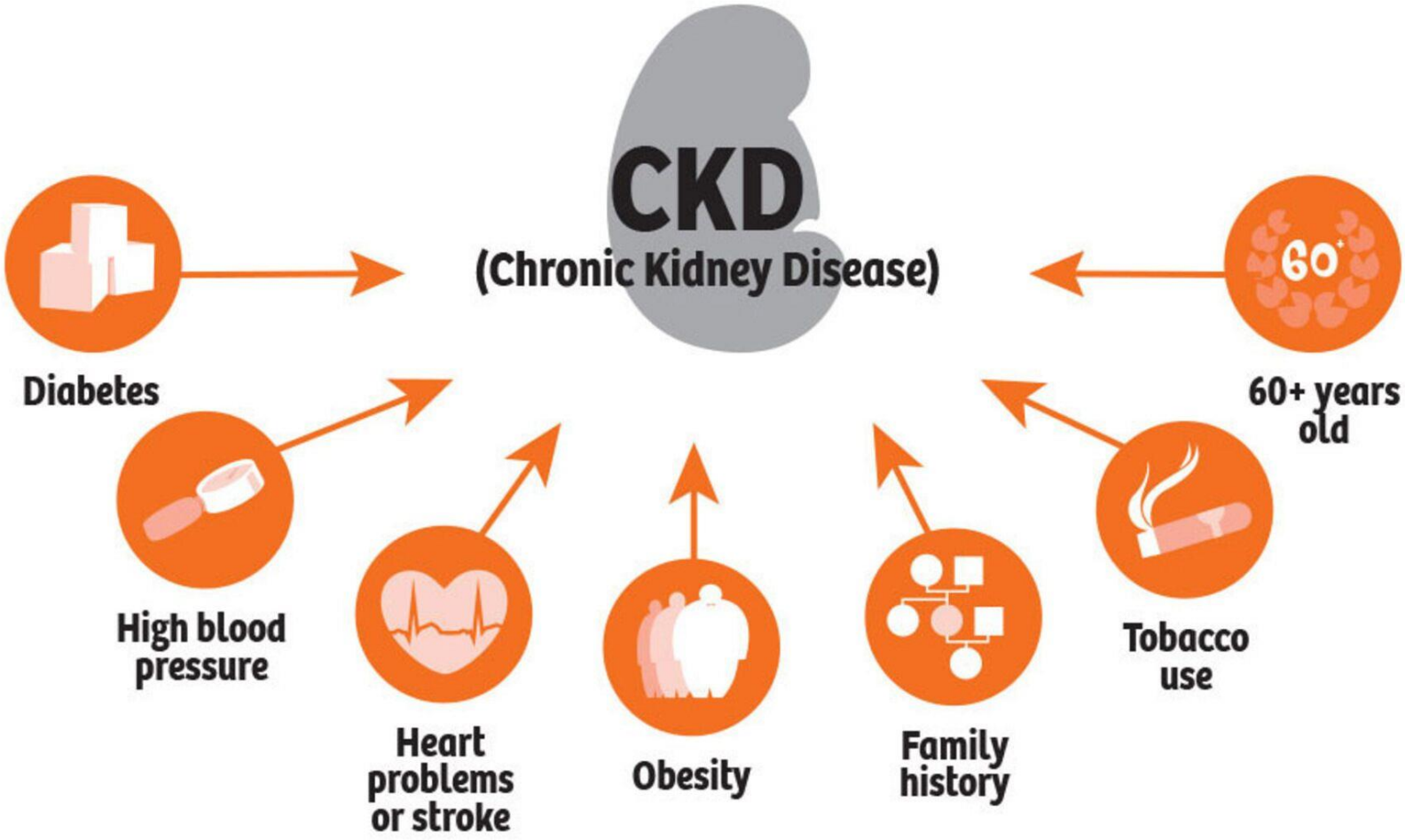
Nessun conflitto di interessi da dichiarare.

RILEVANZA EPIDEMIOLOGICA DELLA PATOLOGIA RENALE



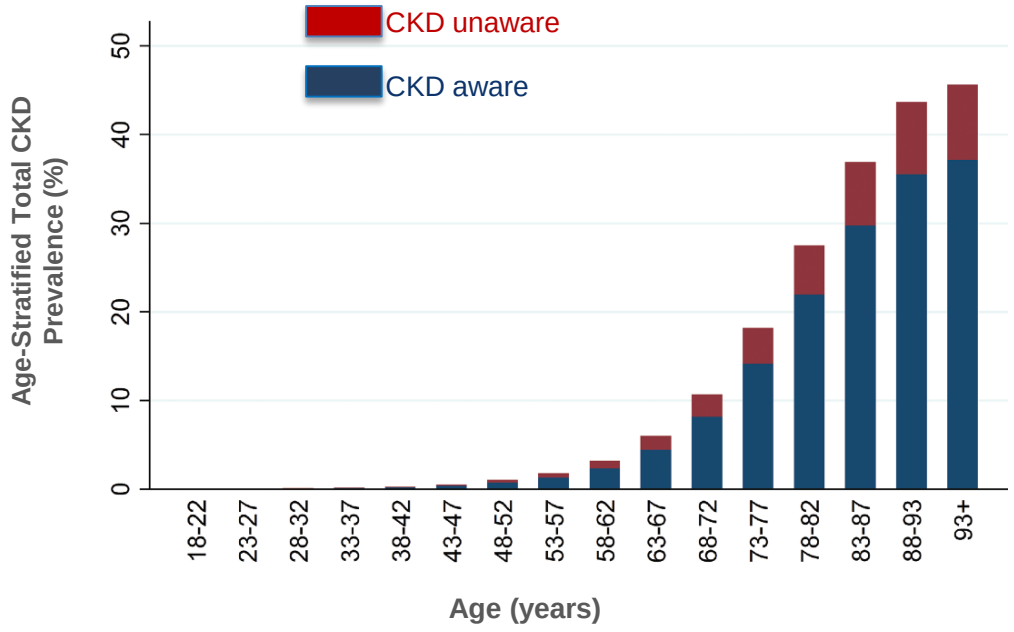
Fox CS. et al. Lancet 2012
Age standardized prevalenc rate: n per 100,000 population.

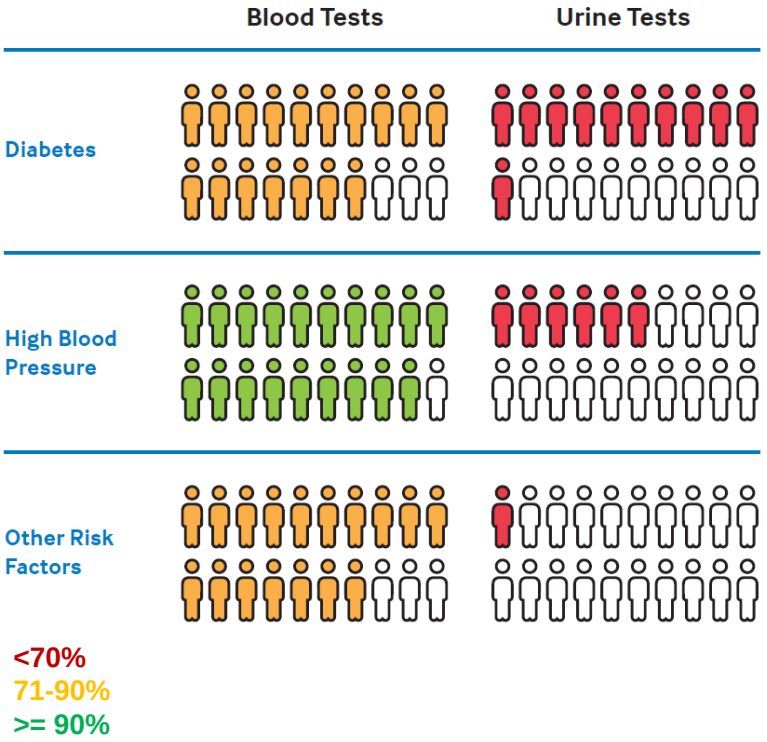
RILEVANZA EPIDEMIOLOGICA DELLA PATOLOGIA RENALE



http://thelancet.com/pb/assets/pbassets/raw/lancet/campaigns/kidney/chroni-ckidney-disease-facts.jpg.
Siemens Healthcare diagnostics

RILEVANZA EPIDEMIOLOGICA DELLA MANCATA DIAGNOSI E CONTROLLO CLINICO DELLA PATOLOGIA RENALE





Data from UK Data CKD Audit.
Delivered by Queen's Mary University of London – Department of Hygene and Tropical Medicine

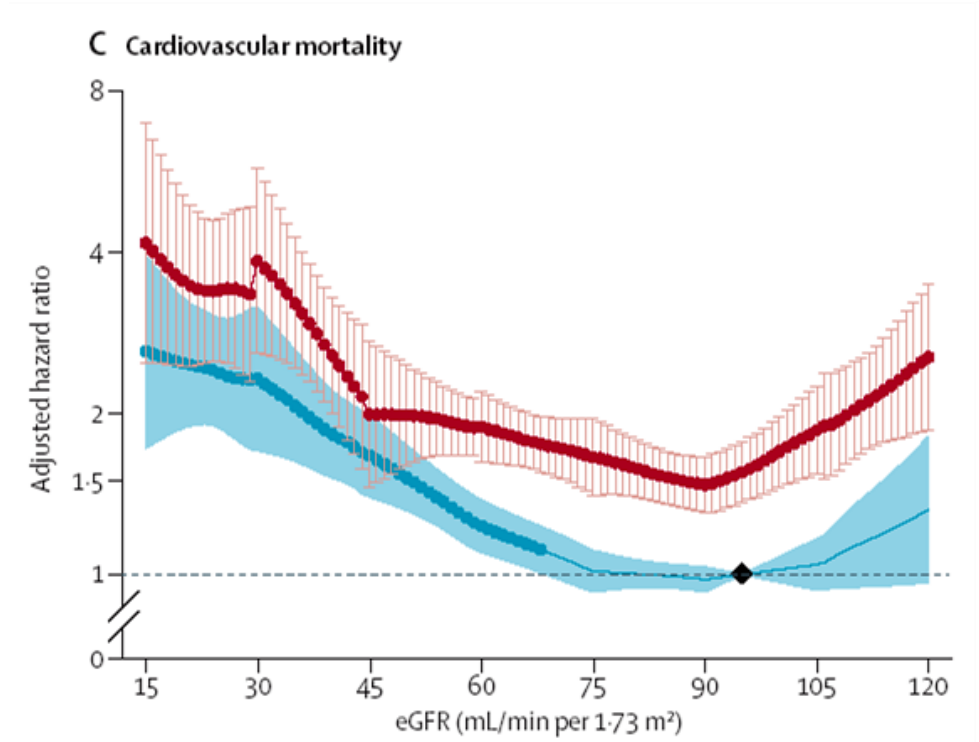
STADAZIONE DELLA MALATTIA RENALE

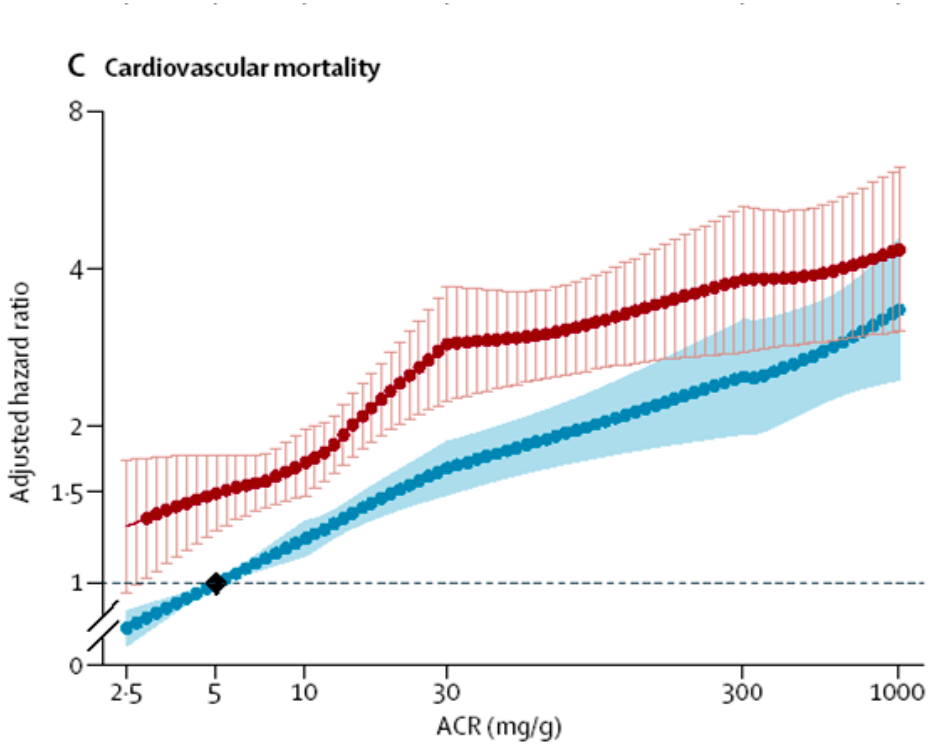
Kidney function stage eGFR (ml/min/1.73m) Description and range			Kidney damage stage albumin/creatinine ratio Description and range		
			A1	A2	A3
			Normal to mild increase <30mg/g "Normo-"	Moderate increase 30-300mg/g "Micro-"	Severe increase >300mg/g "Macro-"
STADIO 1	Normal or high	≥90			
STADIO 2	Mild decrease	60-89			
STADIO 3a	Mild to moderate decrease	45-59			
STADIO 3b	Moderate to severe decrease	30-44			
STADIO 4	Severe decrease	15-29			
STADIO 5	Kidney failure	<15			

Coresh J. et al. Lancet 2013

LA PERDITA DI FUNZIONALITÁ RENALE E PROGRESSIONE DELLA DANNO GLOMERULARE E DIABETE: EFFETTO SUL RISCHIO EVENTI CVD

Data for 1,024,977 participants (128,505 with diabetes) from 30 general population and high-risk cardiovascular cohorts and 13 chronic kidney disease cohorts

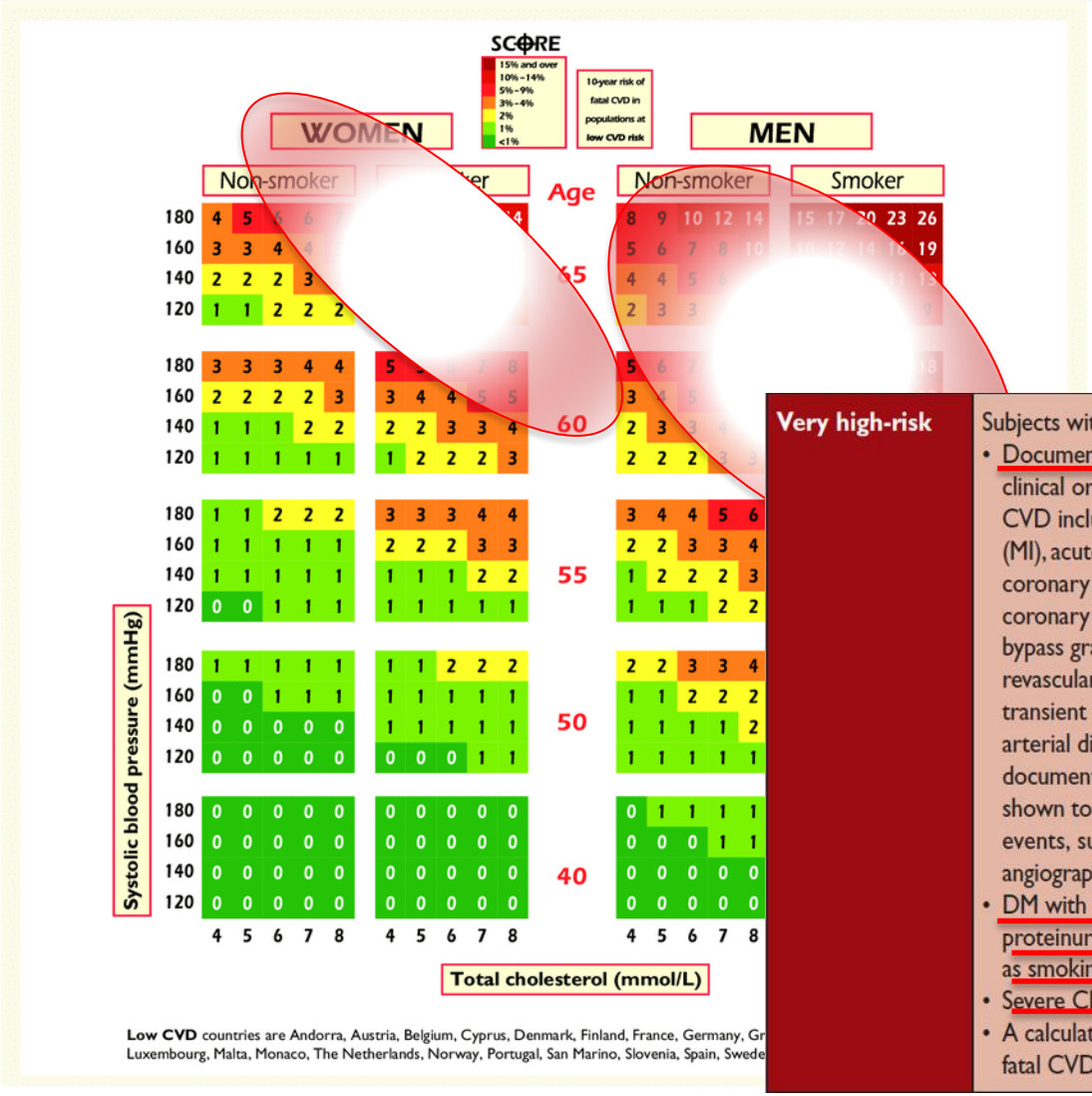




eGFR = estimated Glomerular Filtration Rate
ACR = urinary albumin/creatinine ratio

Diabetes
No Diabetes

IL RISCHIO CARDIOVASCOLARE NEL PAZIENTE NEFROPATICO



SCORE ≥10%

Very high-risk

Subjects with any of the following:

- Documented cardiovascular disease (CVD), clinical or unequivocal on imaging. Documented CVD includes previous myocardial infarction (MI), acute coronary syndrome (ACS), coronary revascularisation (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG)) and other arterial revascularization procedures, stroke and transient ischaemic attack (TIA), and peripheral arterial disease (PAD). Unequivocally documented CVD on imaging is what has been shown to be strongly predisposed to clinical events, such as significant plaque on coronary angiography or carotid ultrasound.
- DM with target organ damage such as proteinuria or with a major risk factor such as smoking, hypertension or dyslipidaemia.
- Severe CKD (GFR <30 mL/min/1.73 m^2).
- A calculated SCORE ≥10% for 10-year risk of fatal CVD.

EVIDENZE DALLE NUOVE TERAPIE IPOGLICEMIZZANTI E ANTI-IPERTENSIVE PER IL PAZIENTE NEFROPATICO

SGLT2 inhibitors

	<30	30-300	>300
≥90			
60-89	A B C		
45-59			
30-44			D
15-29			
<15			

	CVD events reduction	GFR	ACR (mg/g)
A DECLARE	V	85	13
B CANVAS	V	76	12
C EMPA-REG	V	74	18
D CREDENCE	V	56	927

EVIDENZE DALLE NUOVE TERAPIE IPOGLICEMIZZANTI E ANTI-IPERTENSIVE PER IL PAZIENTE NEFROPATICO

SGLT2 inhibitors

	<30	30-300	>300
≥90			
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	CVD events reduction	GFR	ACR (mg/g)
A DECLARE	V	85	13
B CANVAS	V	76	12
C EMPA-REG	V	74	18
D CREDENCE	V	56	927

Sacubitril/ Valsartan

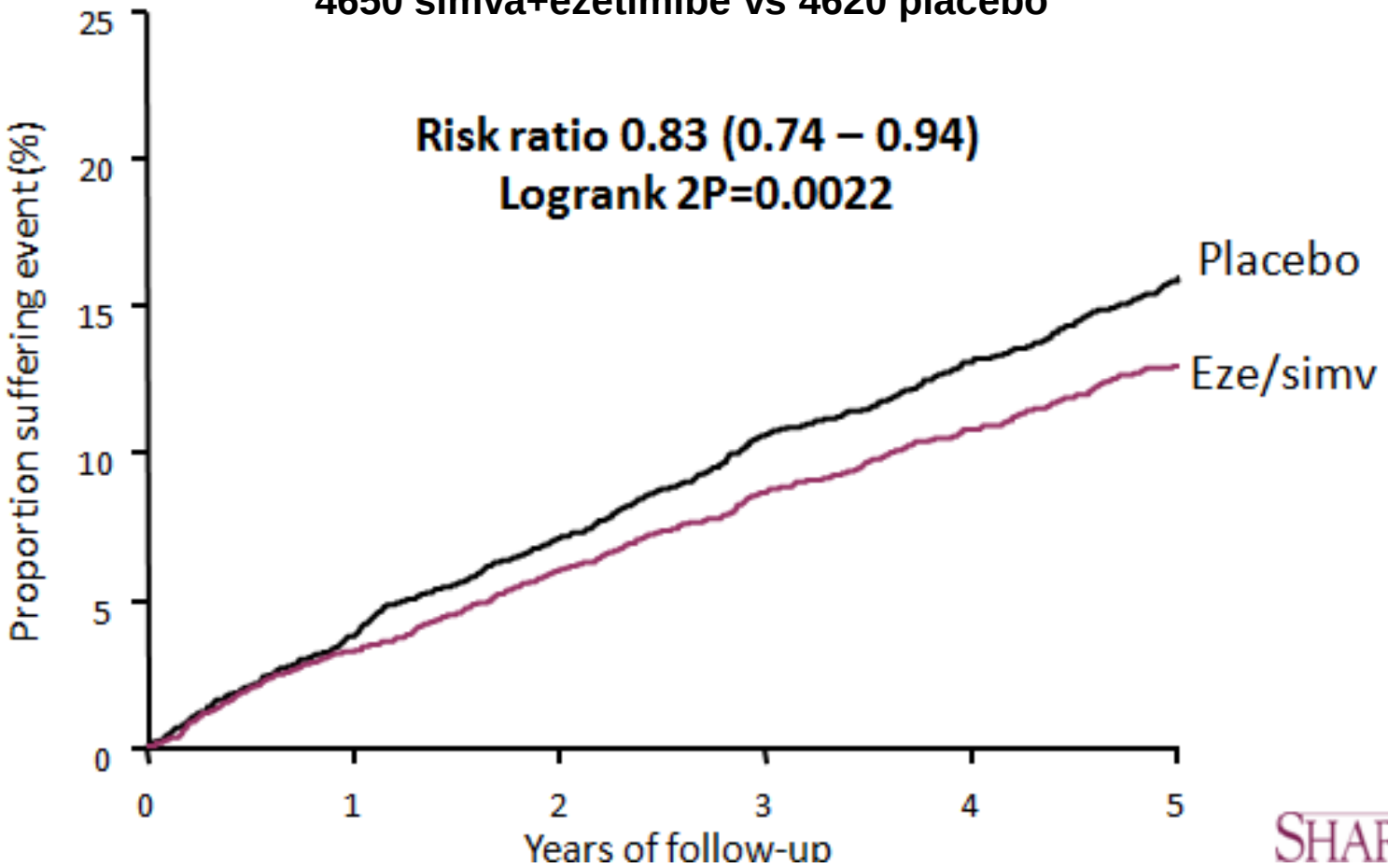
	<30	30-300	>300
≥90			
60-89	E F		
45-59			
30-44			
15-29			
<15			

	CVD events reduction	GFR	ACR (mg/g)
E PARADIGM-HF	V	55-75	?
F PARAGON	X	55-75	?

La terapia ipolipemizzante per la prevenzione cardiovascolare del paziente CKD non in dialisi: the lower, the better

SHARP Trial: Study of Heart and Renal Protection

4650 simva+ezetimibe vs 4620 placebo

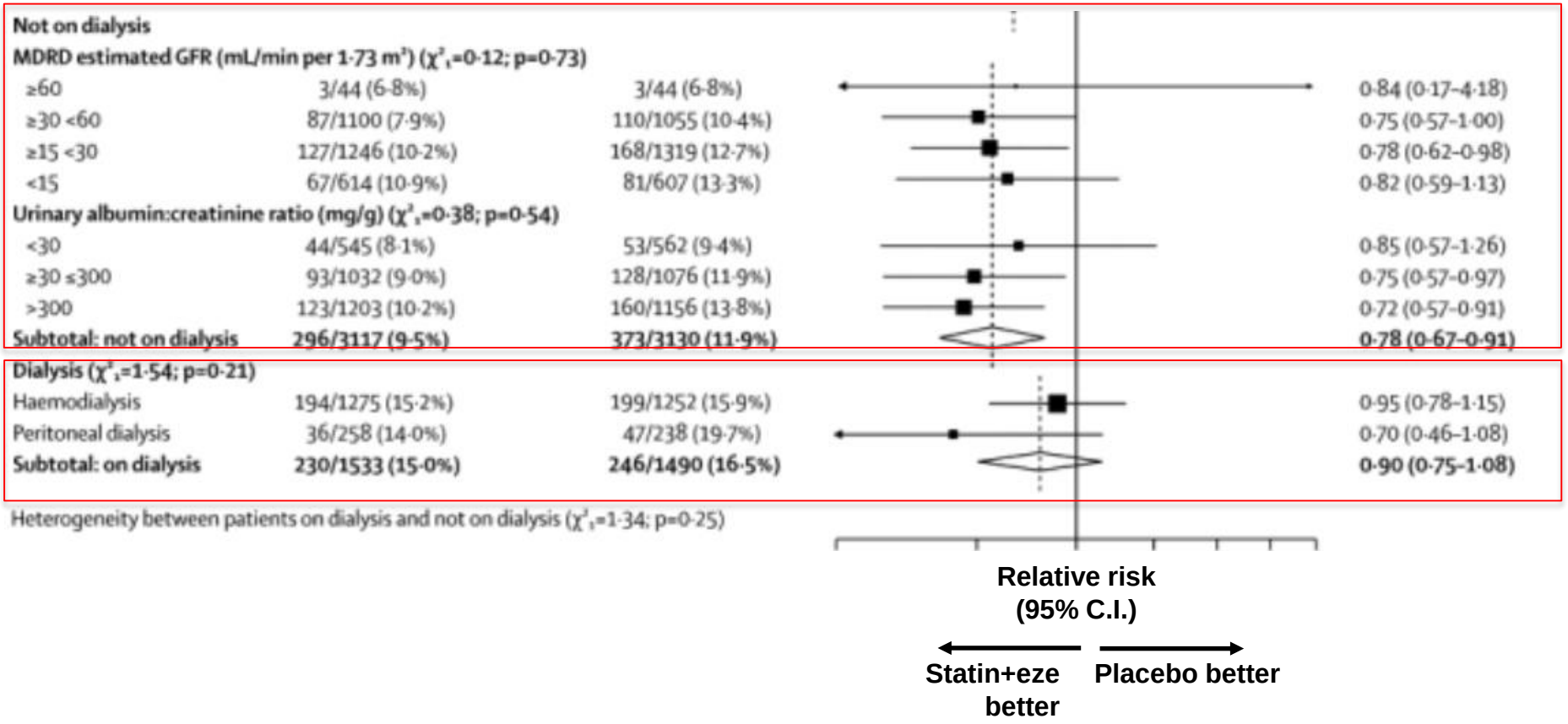


Baigent et al. SHARP Study Lancet 2011

Paziente CKD in dialisi: ridotto beneficio della terapia con statina nella prevenzione cardiovascolare

SHARP Trial: Study of Heart and Renal Protection

4650 simva+ezetimibe vs 4620 placebo
(3023 patients in dialysis)



Baigent et al. SHARP Study Lancet 2011

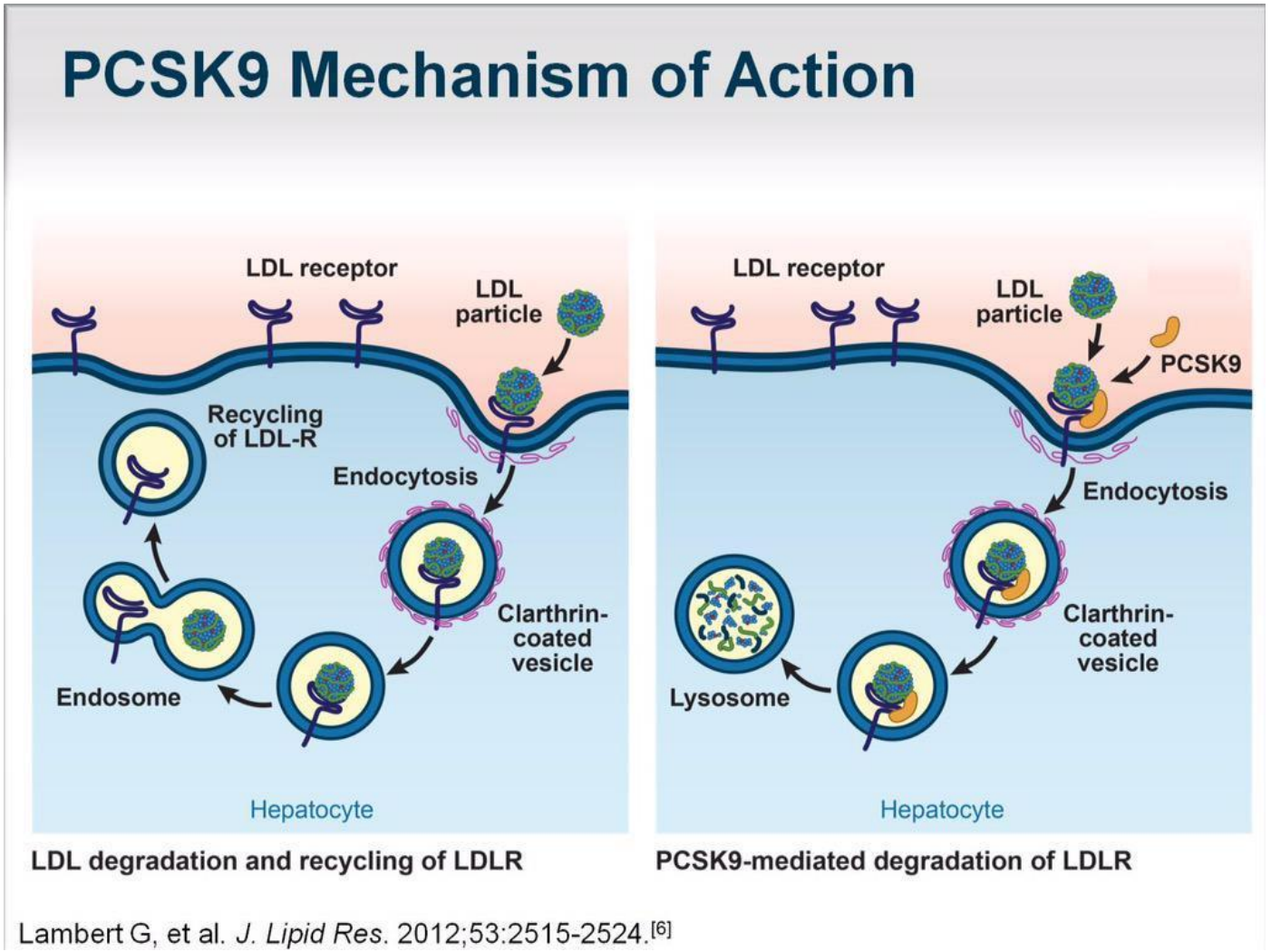
INDICAZIONI DA PARTE DELLE LINEE GUIDA EAS/ESC PER IL TRATTAMENTO IPOLIPEMIZZANTE DEL PAZIENTE NEFROPATICO

Recommendations for lipid management in patients with moderate-to-severe (Kidney Disease Outcomes Quality Initiative stages 3–5) chronic kidney disease

Recommendations	Class[a]	Level[b]
It is recommended that patients with Kidney Disease Outcomes Quality Initiative stage 3–5[c] CKD are considered to be at high or very-high risk of ASCVD.[489–493]	I	A
The use of statins or statin/ezetimibe combination is recommended in patients with non-dialysis-dependent stage 3–5 CKD.[214,222,495,496]	I	A
In patients already on statins, ezetimibe, or a statin/ezetimibe combination at the time of dialysis initiation, continuation of these drugs should be considered, particularly in patients with ASCVD.	IIa	C
In patients with dialysis-dependent CKD who are free of ASCVD, commencement of statin therapy is not recommended.[220,221]	III	A

Mach F. et al. Eur Heart J 2019 EAS/ESC Guidelines for the management of dyslipidemias

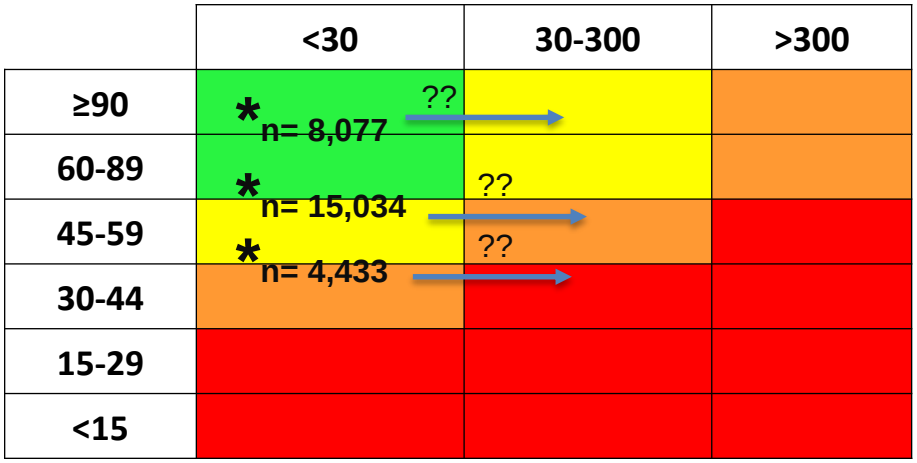
TERAPIE IPOLIPEMIZZANTI NELLA PREVENZIONE CARDIOVASCOLARE DEL PAZIENTE NEFROPATICO: QUALE SPAZIO PER PCSK9?



Lambert G, et al. *J. Lipid Res.* 2012;53:2515-2524.[6]

mAbs anti-PCSK9 NELLA PREVENZIONE CARDIOVASCOLARE: IN ATTESA DI TRIALS SPECIFICI PER IL PAZIENTE NEFROPATICO

Analisi Post-Hoc studio FOURIER



Follow-up:

38 months.

Primary endpoint:

CV death, MI, stroke, hospitalization, unstable angina, coronary revascularization

Secondary endpoint:

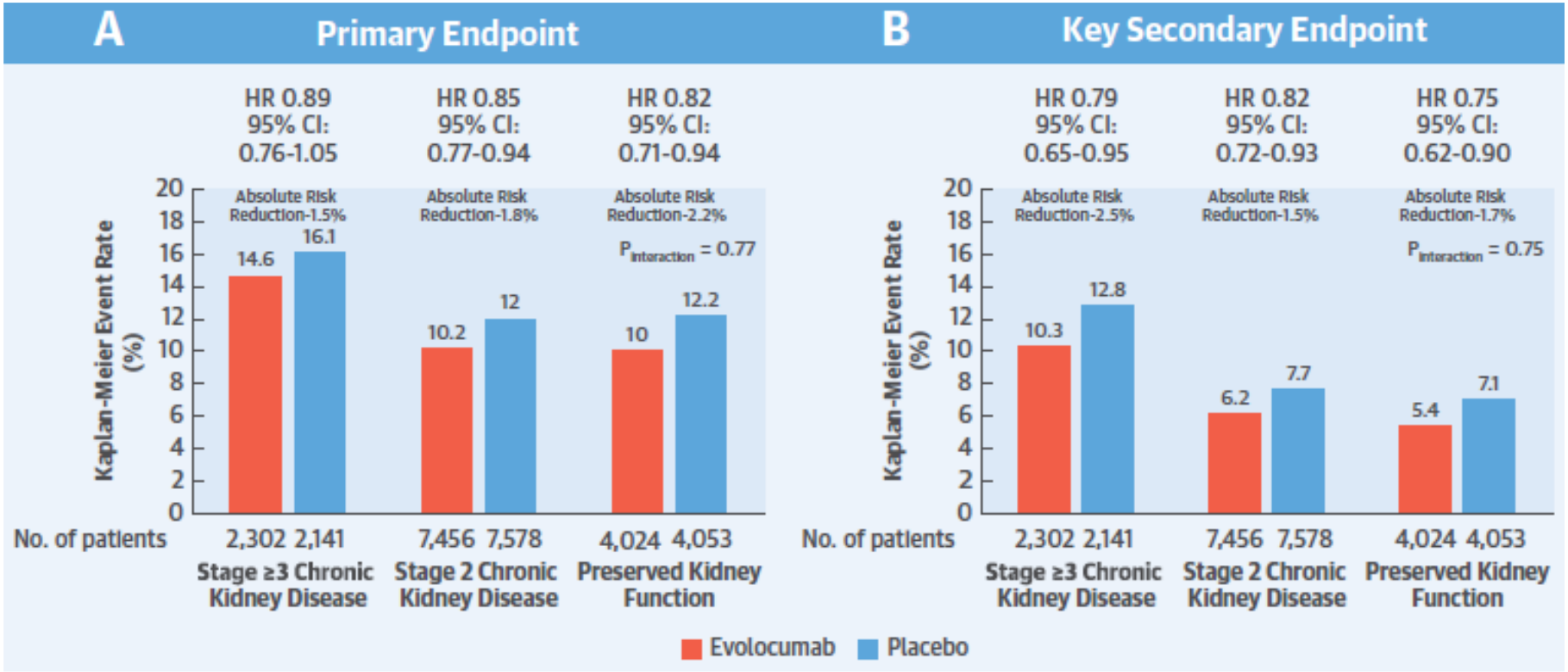
Composite CV death, MI or stroke.

Renal endpoint:

>= 30% GFR decline
>= 40% GFR decline
>= 50% GFR decline
(either by diabetes y/n)

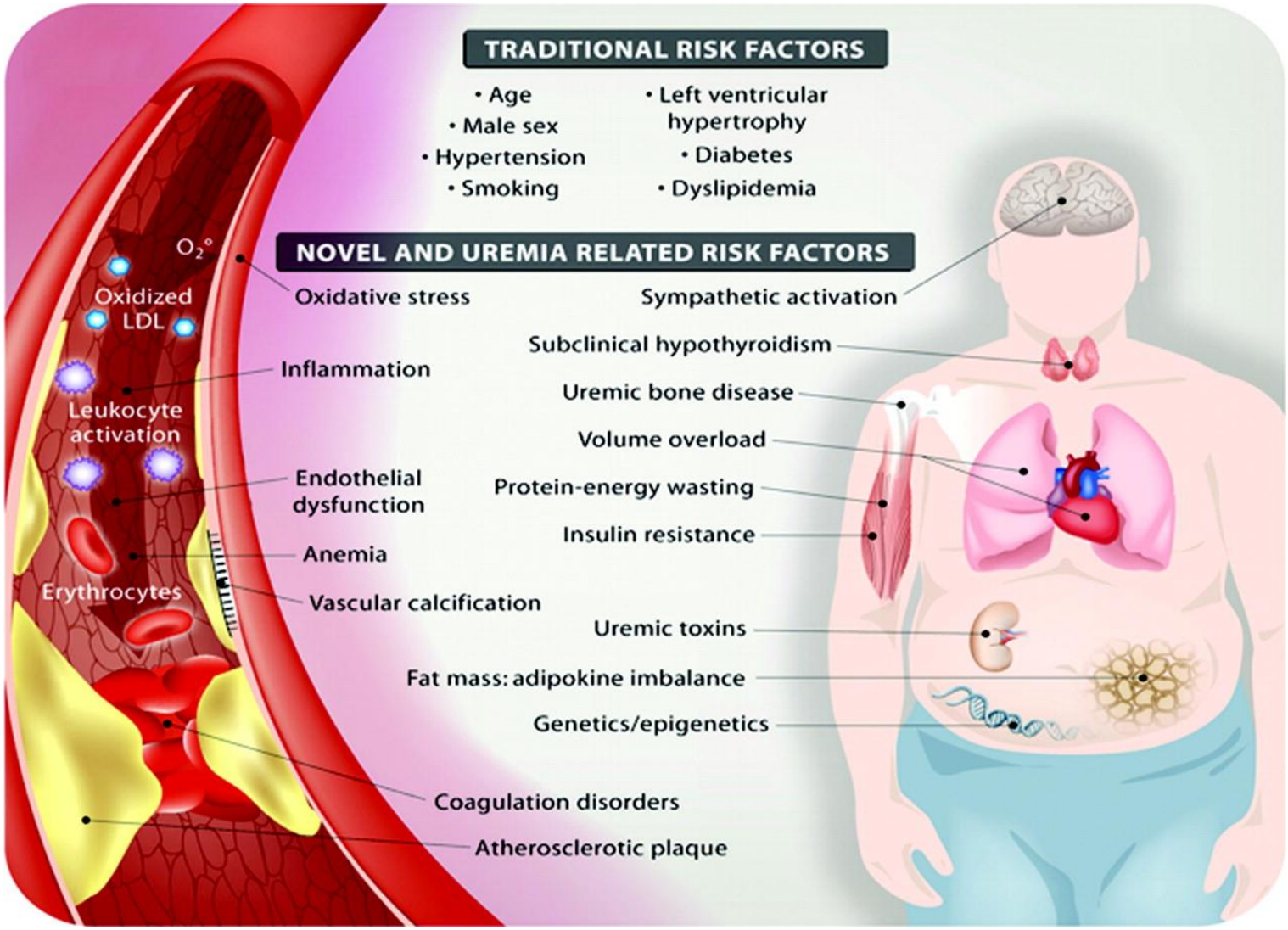
mAbs anti-PCSK9 NELLA PREVENZIONE CARDIOVASCOLARE: IN ATTESA DI TRIALS SPECIFICI PER IL PAZIENTE NEFROPATICO

Analisi Post-Hoc studio FOURIER



Charytan DM et al. FOURIER Trial JACC 2019

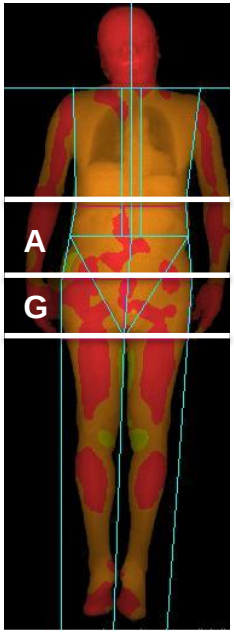
IL PUZZLE DI FATTORI DI RISCHIO CHE INSORGONO CONTESTUALMENTE AL DECORSO DELLA MALATTIA RENALE



Stenvinkel P. et al. CJASN 2009

DALL'OBESITÁ ALLA MALNUTRIZIONE: IL RIMODELLAMENTO METABOLICO DURANTE IL DECORSO DELLA MALATTIA RENALE

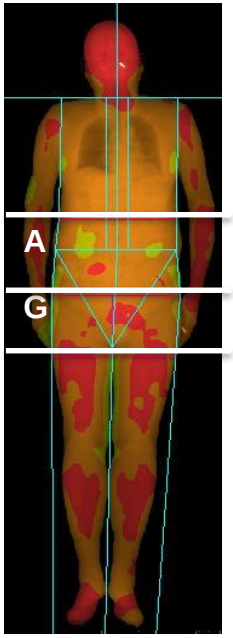
GFR 90.2 mL/min/1.73 m²



Uomo Età: 74

BMI: 26,8 Kg/m²
%FM: 30.6
%LM: 69,4
A: 39,8
G: 31.1
A/G: 1,28

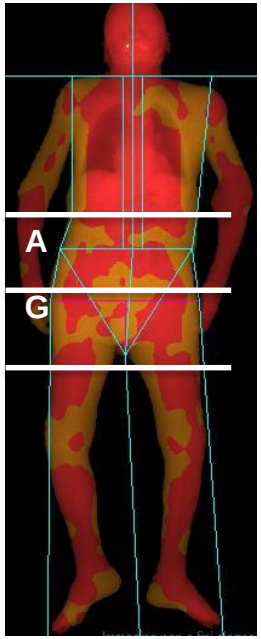
GFR 40.0 mL/min/1.73 m²



Uomo Età: 75,8

BMI: 26,9 Kg/m²
%FM: 40.0
%LM: 59,9
A: 52,4
G: 35,2
A/G: 1,49

Dialysis (pre-dialysis session)



Uomo Età: 75,2

BMI: 26,0 Kg/m²
%FM: 25.0
%LM: 74.9
A: 27.0
G: 28.8
A/G: 0.49

FM Fat mass

LM Lean mass (+water)

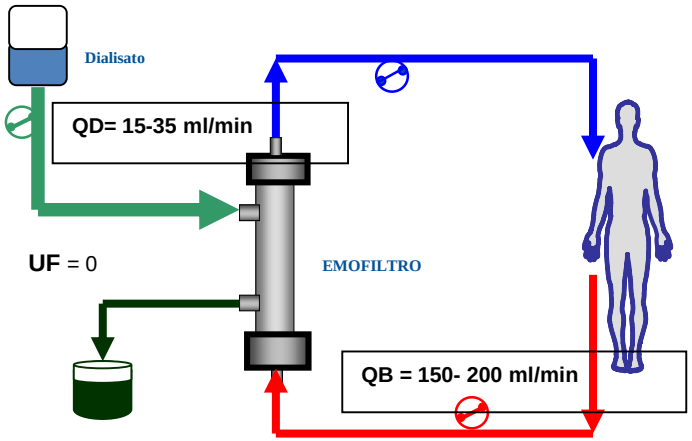
A Android (abdominal) fat

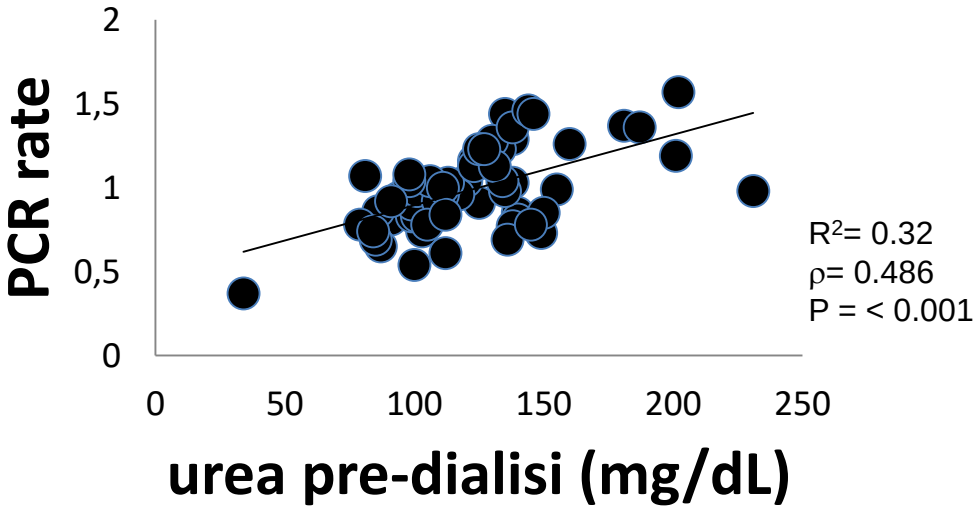
G Gynoid (gluteal) fat

Ringrazio Dr. I. Baragetti per pazienti (U.O. Nefrologia/Dialisi Bassini)

UNIVERSITÀ DEGLI STUDI DI MILANO
DIPARTIMENTO DI SCIENZE FARMACOLOGICHE E BIOMOLECOLARI

L'UREMIA FOMENTA LA PERDITA DI MASSA MUSCOLARE E LA CACHESSIA NEL PAZIENTE NEFROPATICO IN DIALISI



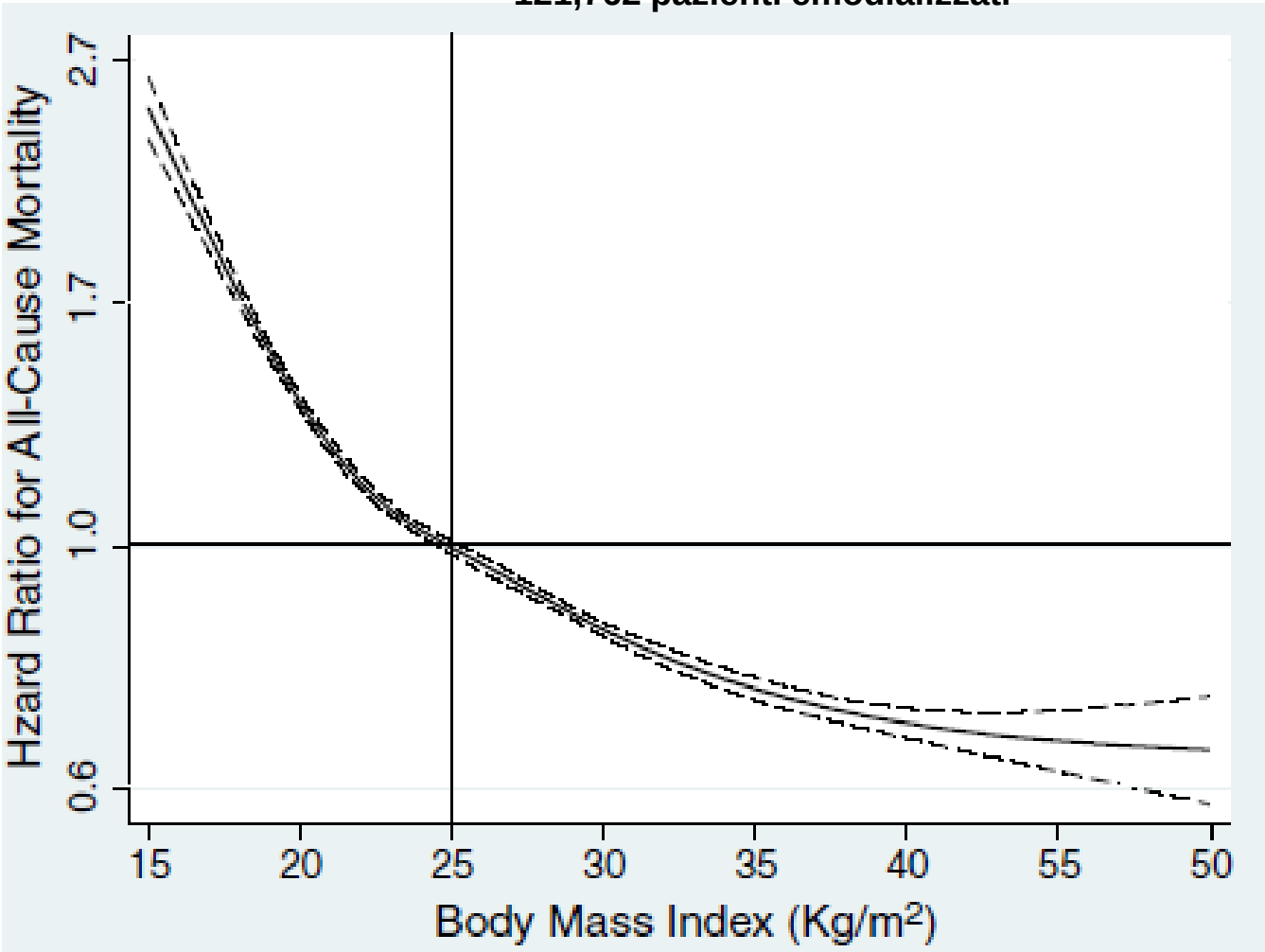


N= 63 HD pazienti
PCR = Protein Catabolic Rate (Indice nutrizionale)
Ringrazio Dr. I. Baragetti per pazienti (U.O. Nefrologia/Dialisi Bassini)

UNIVERSITÀ DEGLI STUDI DI MILANO
DIPARTIMENTO DI SCIENZE FARMACOLOGICHE E BIOMOLECOLARI

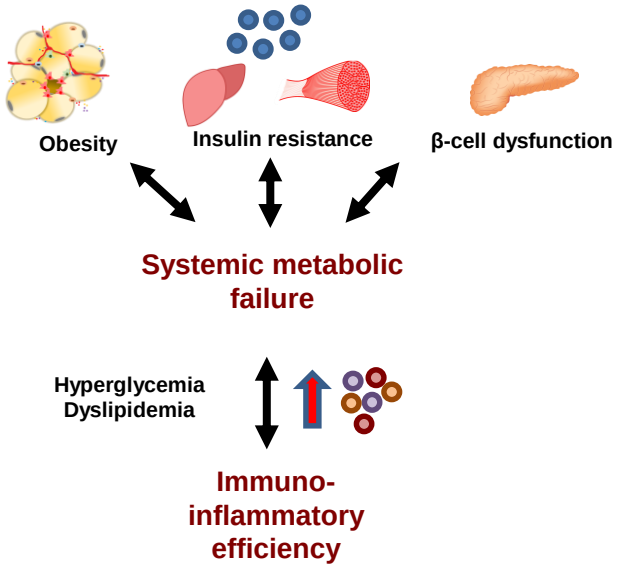
«THE OBESITY PARADOX» NEGLI STADI AVANZATI DELLA PATOLOGIA RENALE

Mortalità per tutte le cause; studio di registro US hemodialysis units
121,762 pazienti emodializzati

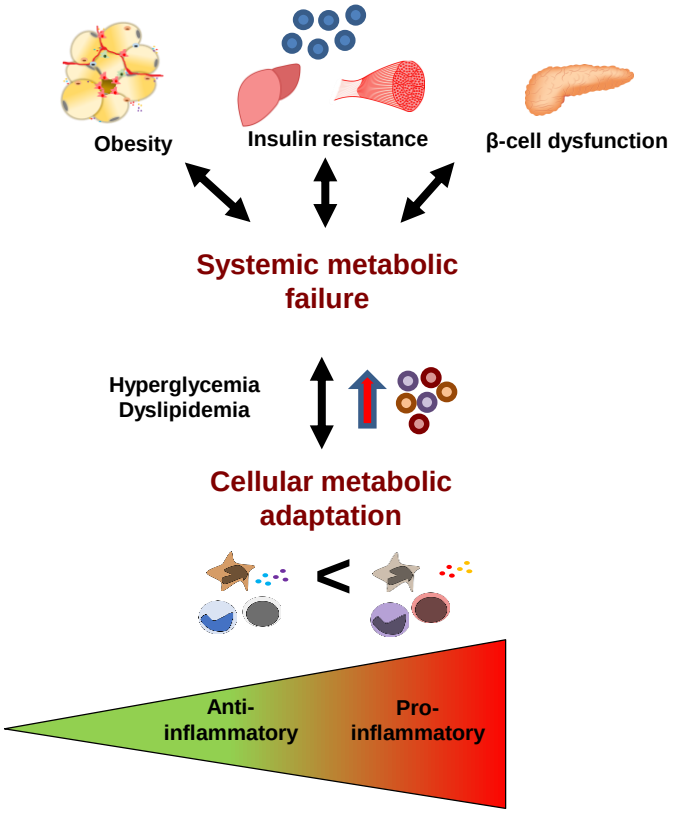


Park J, Kalantar-Zadeh et al. Prog. Cardiovasc Dis 2014
Zoccali N et al. Nat Rev Nephrol 2017

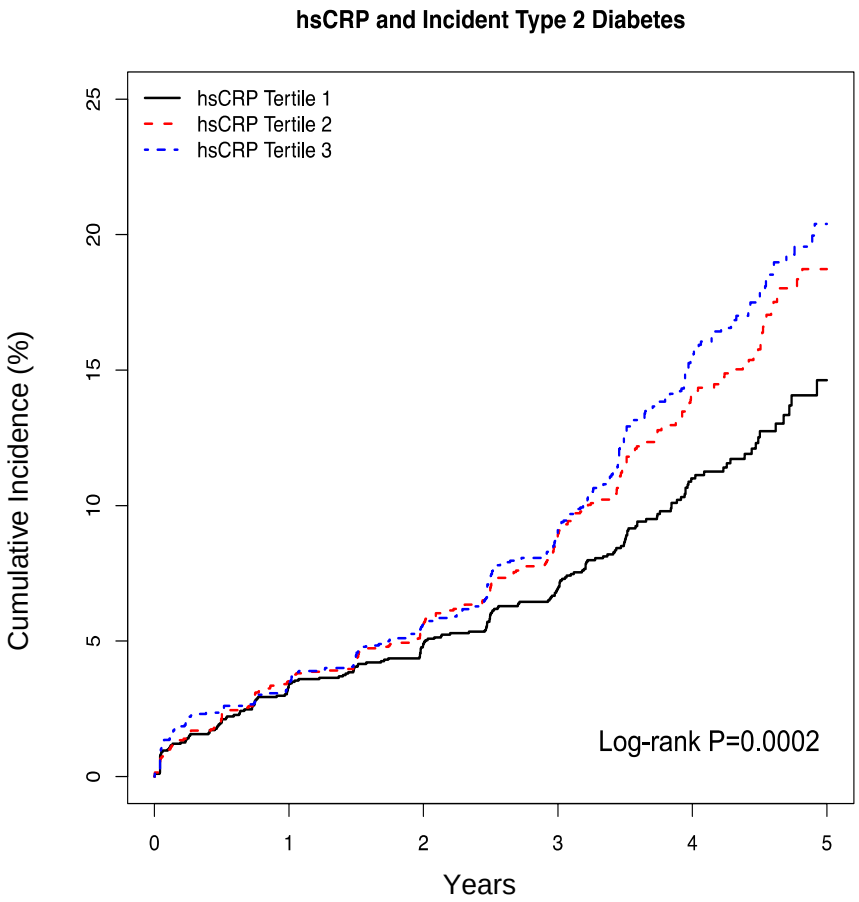
Relazione tra alterazione metabolica e immuno-infiammazione nel rischio CVD del paziente nefropatico

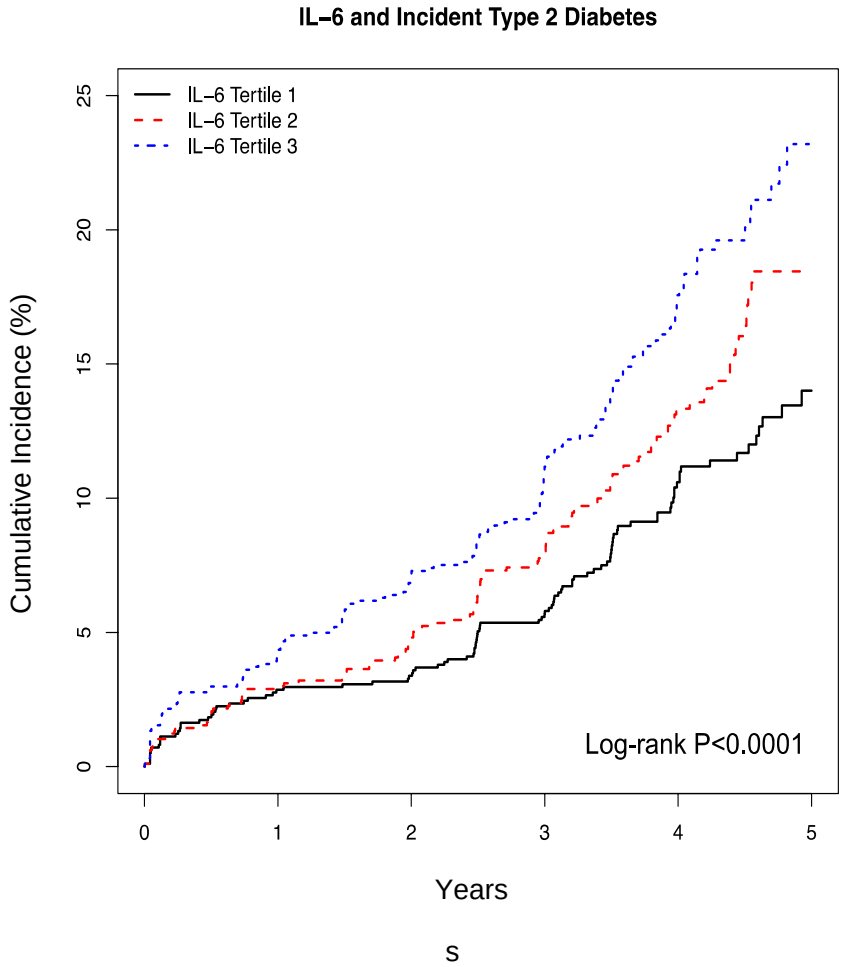


Relazione tra alterazione metabolica e immuno-infiammazione nel rischio CVD del paziente nefropatico



“Low-grade inflammation” predice incidenza di T2D





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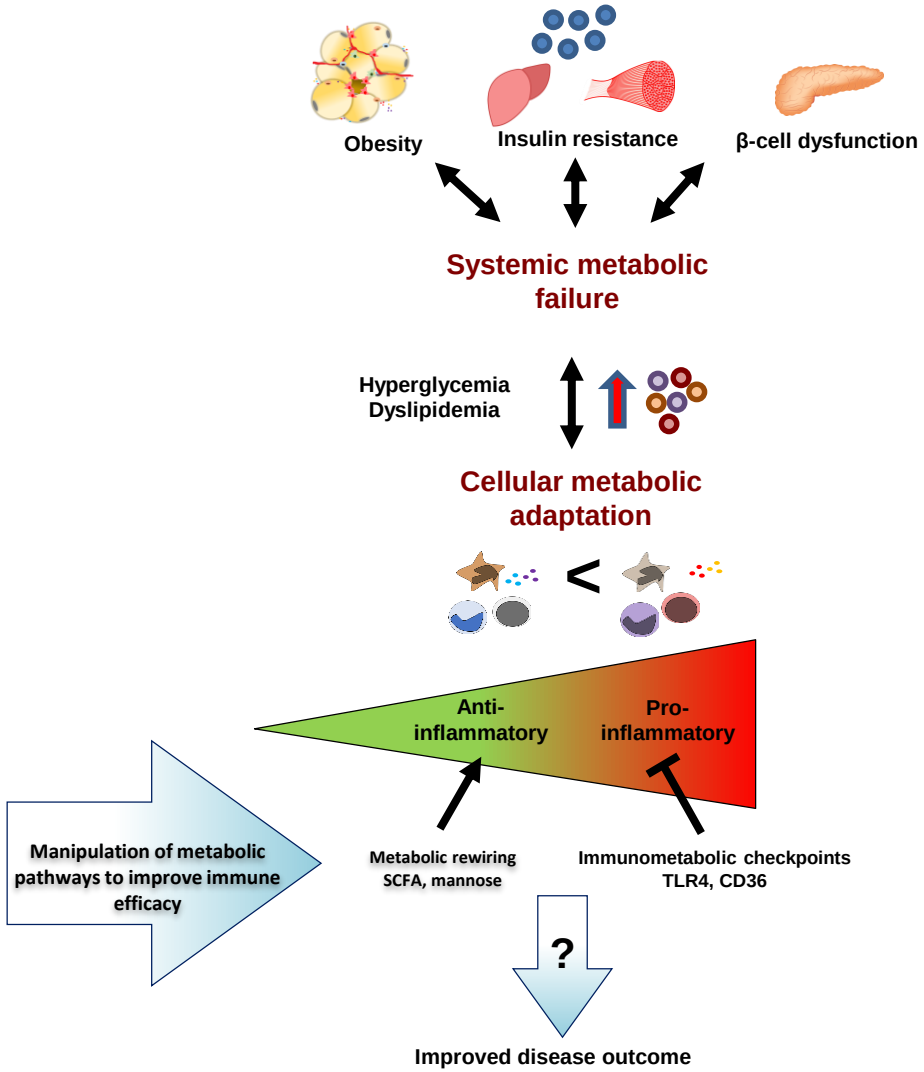
CANTOS
Canakinumab Anti-inflammatory Thrombosis Outcomes Study

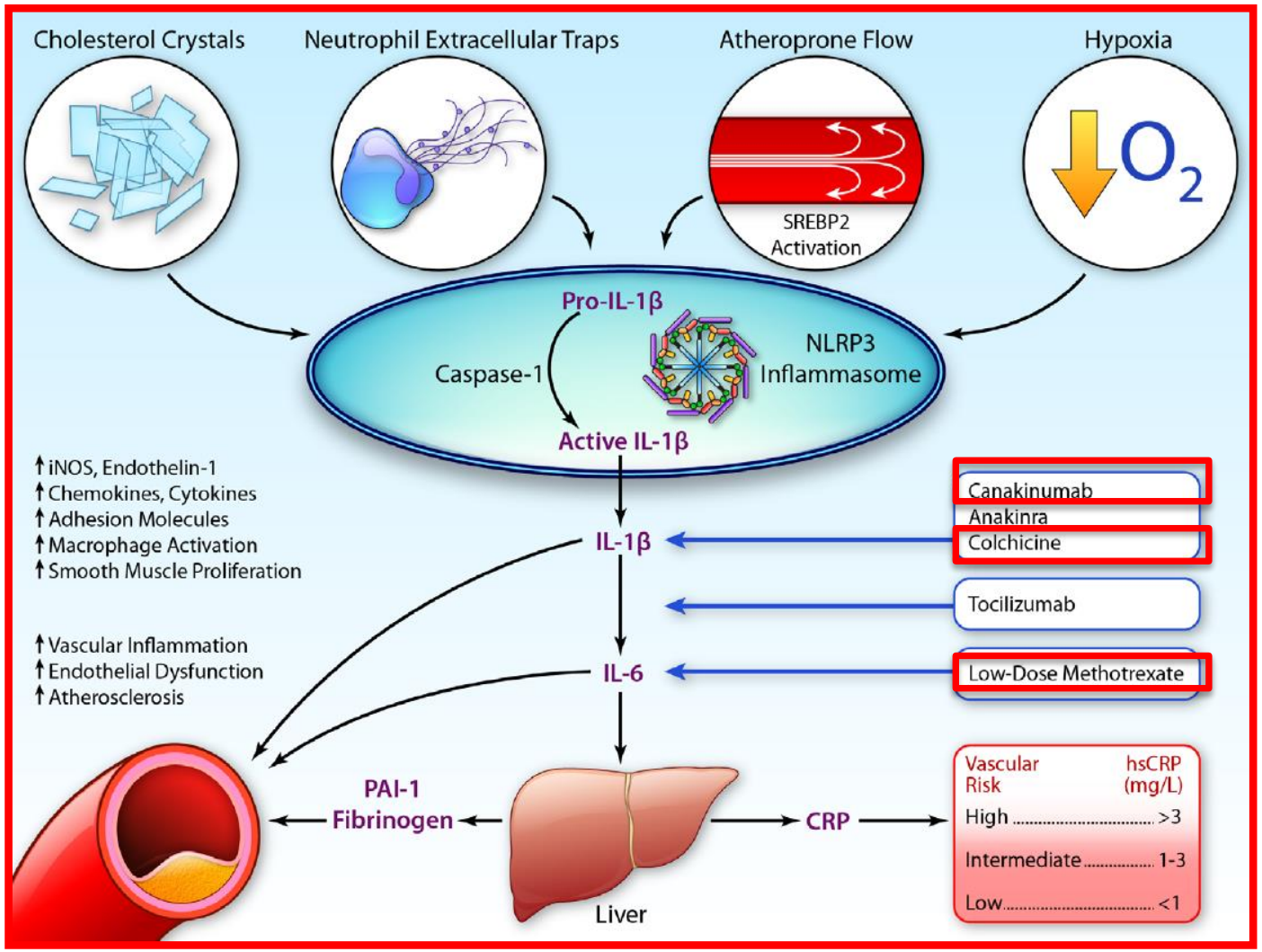
Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)

Everett ACC 2018

Infiammazione o metabolismo: quale target terapeutico prioritario nella prevenzione CVD del paziente nefropatico?



Infiammazione: target terapeutico nella prevenzione CVD del paziente nefropatico?



CANTOS trial

LoDoCo trial
(Ongoing)

CIRT trial

Ridker PM. Circ Res 2016

Infiammazione: target terapeutico nella prevenzione? Evidenze cliniche

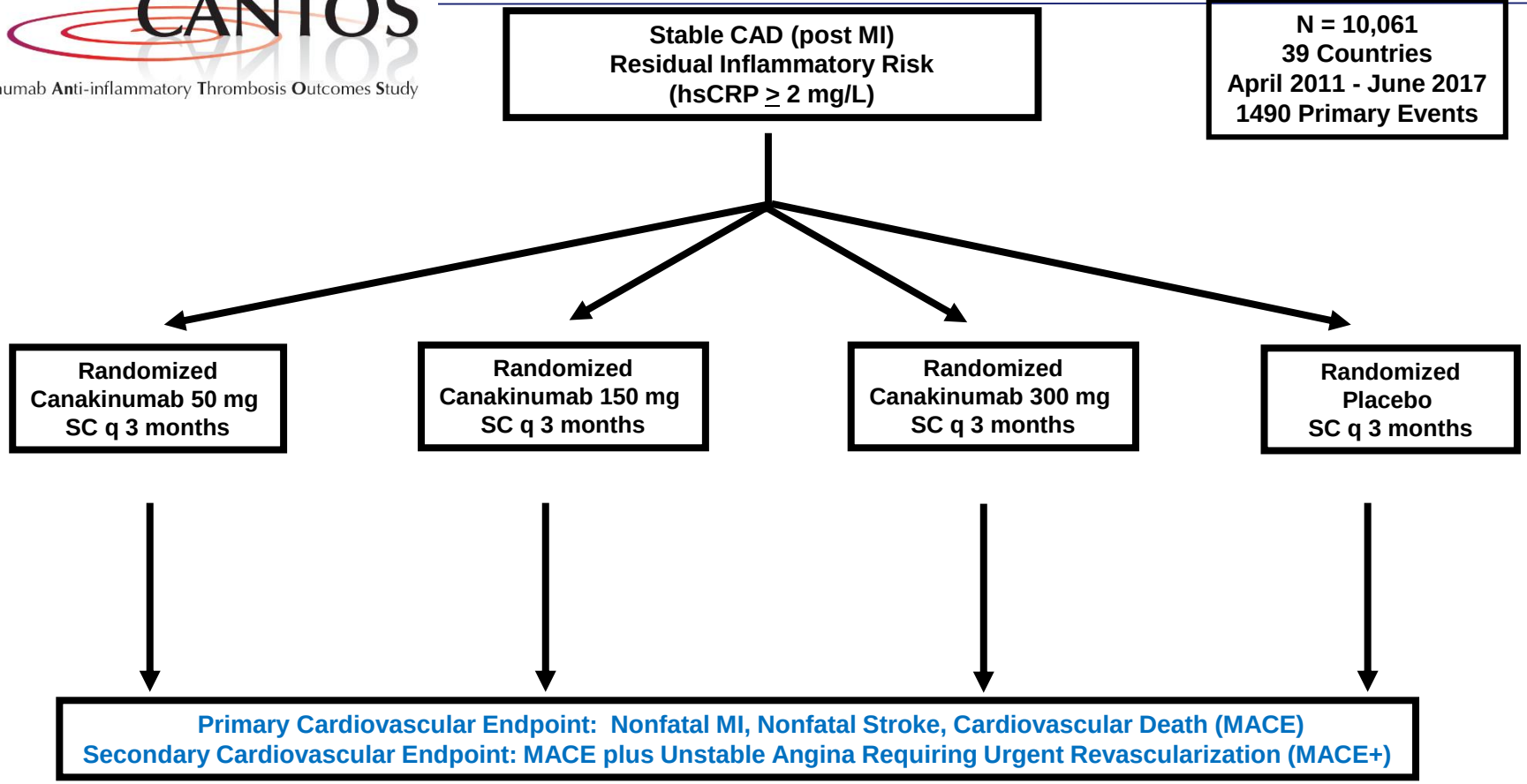
CANTOS
Canakinumab Anti-inflammatory Thrombosis Outcomes Study

Variazioni di hsCRP e IL-6 dopo canakinumab in pazienti dello Studio divisi per dosaggio

	Median Percent (IQR) Reduction Compared to Placebo	
Dose	**hsCRP**	**IL-6**
50 mg	-49.2 (-20.0, -67.2)	-25.7 (0.7, -46.6)
150 mg	-61.5 (-33.3, -75.8)	-37.4 (-9.1, -54.9)
300 mg	-67.1 (-43.2, -80.6)	-43.4 (-21.0, -60.0)

Infiammazione: target terapeutico nella prevenzione? Evidenze cliniche

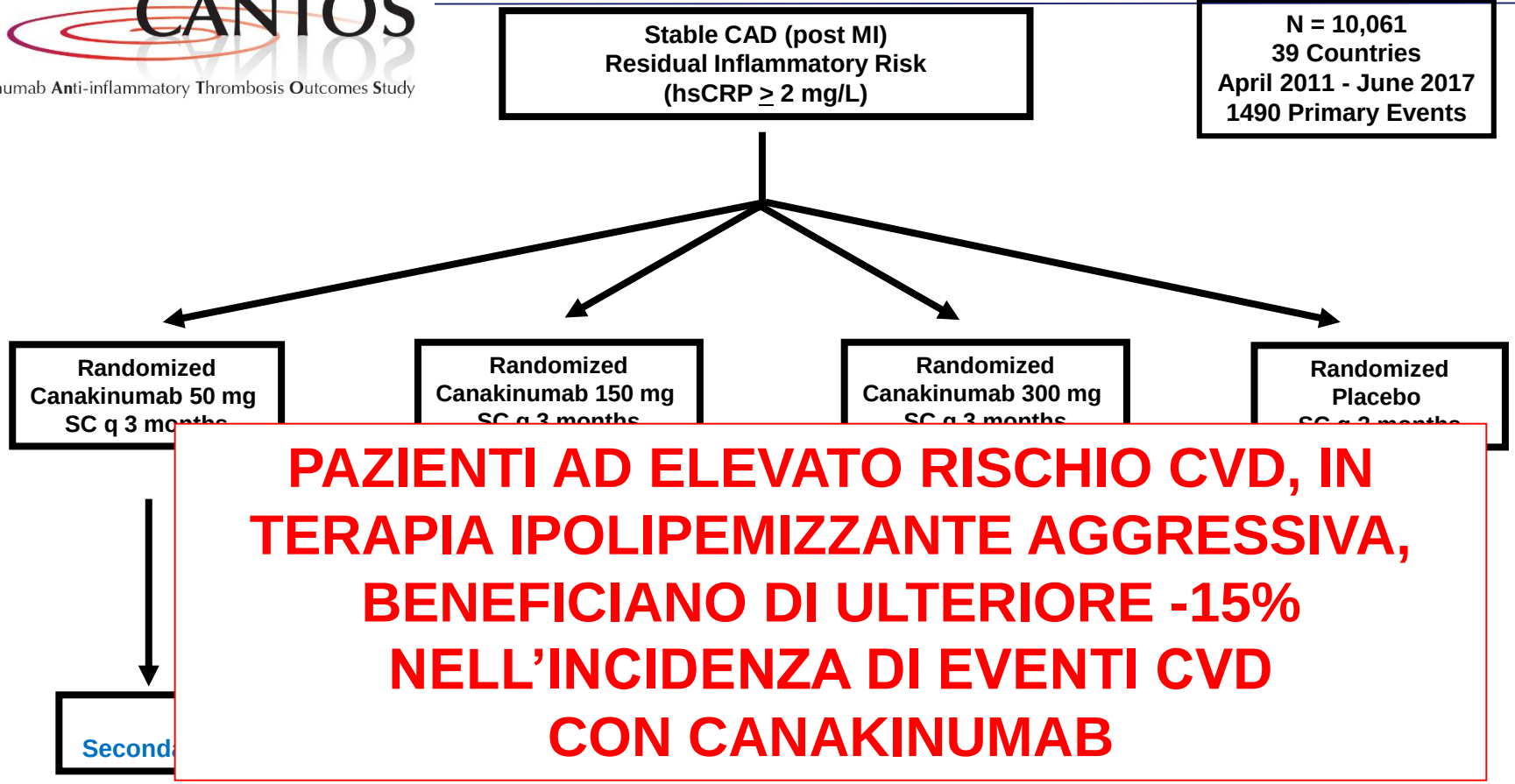
CANTOS
Canakinumab Anti-inflammatory Thrombosis Outcomes Study



Pre-Specified Secondary Endpoint: New Onset Diabetes among Patients with Protocol-Defined Pre-Diabetes at Trial Entry

Infiammazione: target terapeutico nella prevenzione? Evidenze cliniche

CANTOS
Canakinumab Anti-inflammatory Thrombosis Outcomes Study



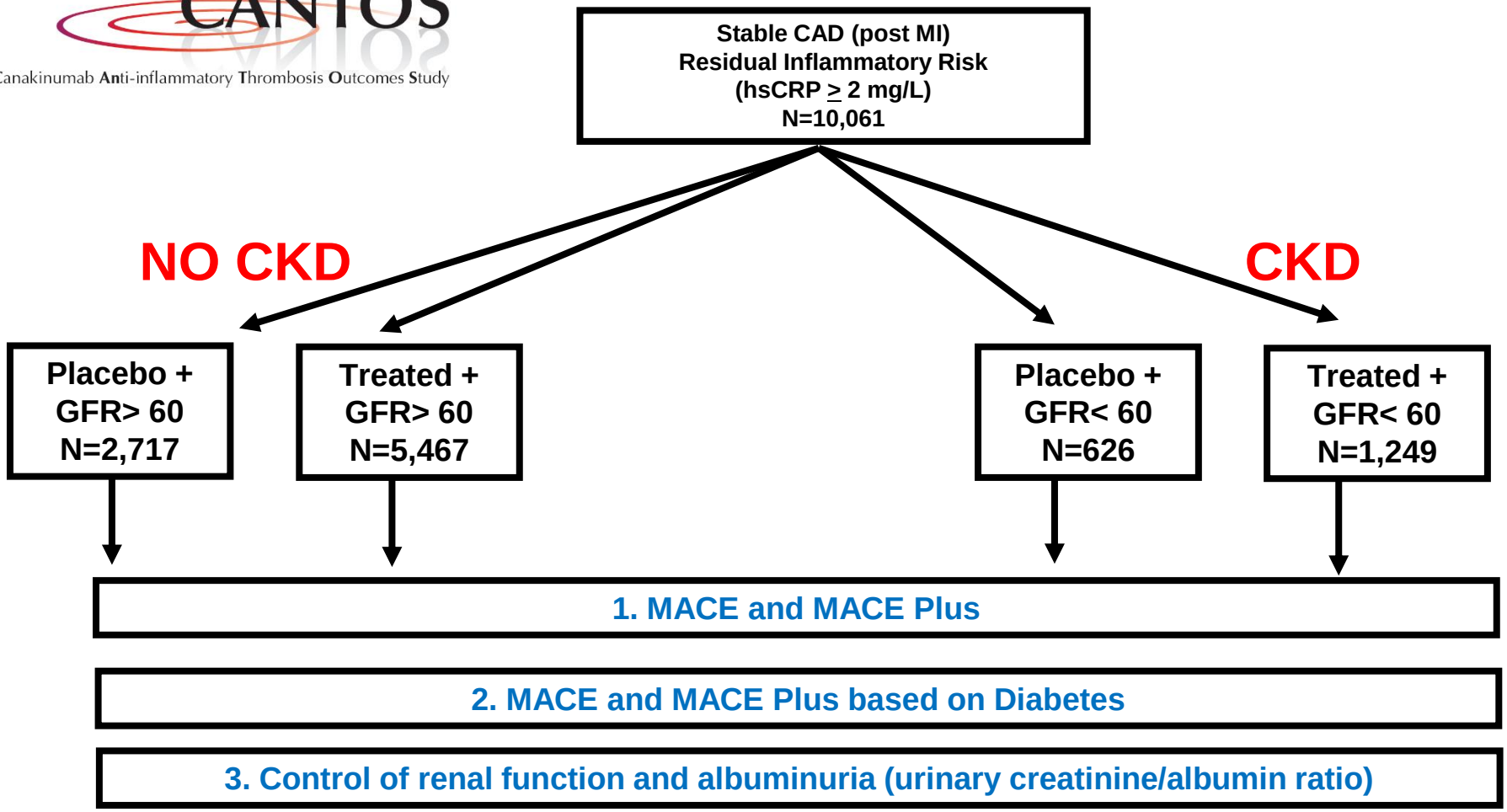
PAZIENTI AD ELEVATO RISCHIO CVD, IN TERAPIA IPOLIPEMIZZANTE AGGRESSIVA, BENEFICIANO DI ULTERIORE -15% NELL'INCIDENZA DI EVENTI CVD CON CANAKINUMAB

Pre-Specified Secondary Endpoint: New Onset Diabetes among Patients with Protocol-Defined Pre-Diabetes at Trial Entry

Infiammazione: target terapeutico nella prevenzione? Evidenze cliniche nel paziente nefropatico

CANTOS

Canakinumab Anti-inflammatory Thrombosis Outcomes Study



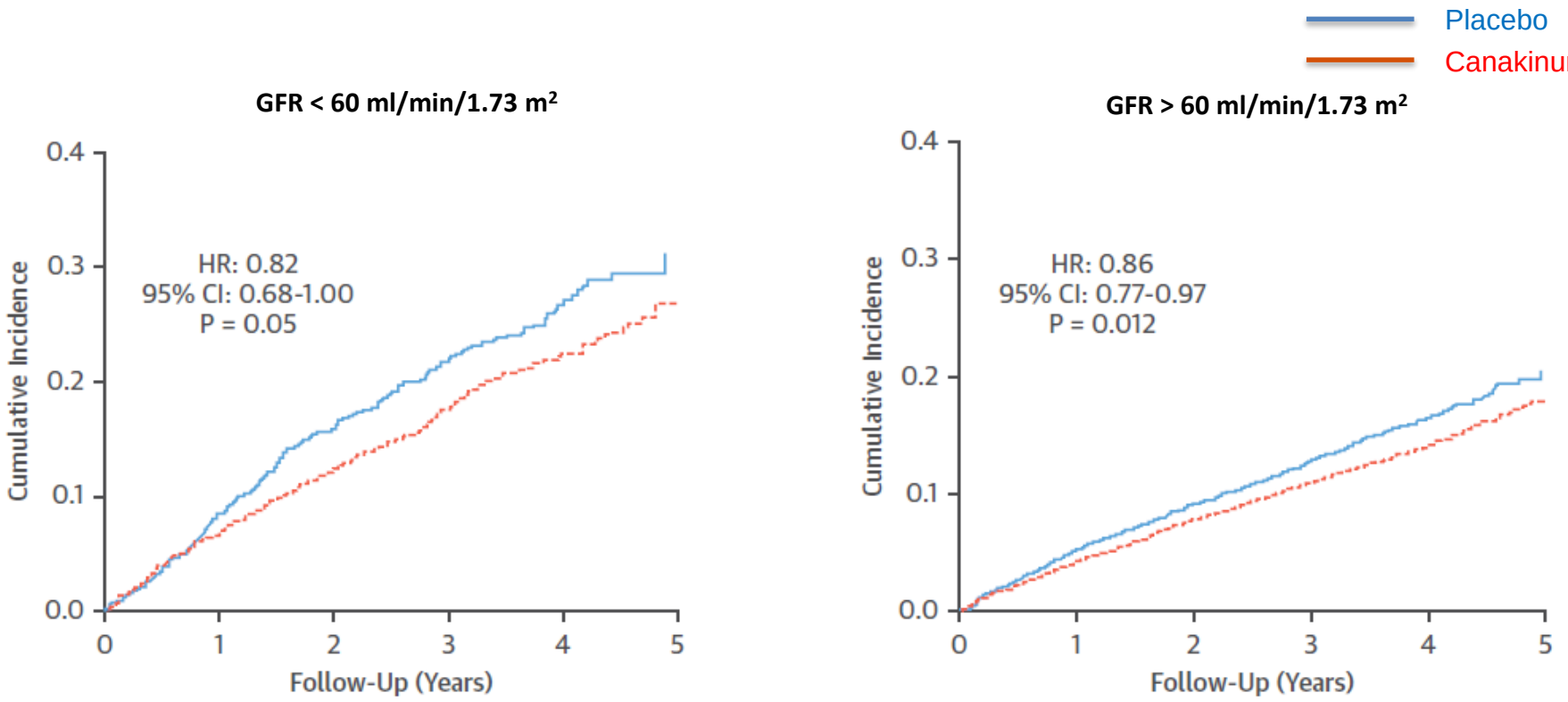
Ridker P et al. JACC 2018

Infiammazione: target terapeutico nella prevenzione? Evidenze cliniche nel paziente nefropatico

CANTOS

Canakinumab Anti-inflammatory Thrombosis Outcomes Study

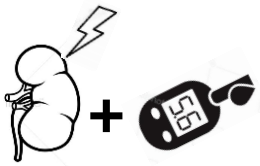
Canakinumab riduce l'incidenza di eventi CVD in pazienti CKD



Ridker P et al. JACC 2018

Infiammazione: target terapeutico nella prevenzione? Evidenze cliniche nel paziente nefropatico

Canakinumab non riduce eventi CVD in pazienti con nefropatia diabetica



	Placebo	Canakinumab hsCRP > 2 mg/L (after 3 months)	Canakinumab hsCRP < 2 mg/L (after 3 months)	P
CKD + T2D	281	265	269	
MACE; incidence (n)	9,13 (81)	7,95 (6,9)	6,94 (63)	0,13
CVD mortality; incidence (n)	4,047 (40)	4,04 (38)	3,13 (31)	0,30
Total mortality incidence (n)	6,42 (63)	6,07 (57)	5,06 (50)	0,22
CKD - T2D	311	284	347	
MACE; incidence (n)	6,86 (70)	5,26 (51)	4,19 (52)	0,0053
CVD mortality; incidence (n)	3,12 (35)	2,75 (28)	1,45 (19)	0,0079
Total mortality; incidence (n)	4,63 (52)	4,82 (49)	3,21 (42)	0,065

Ridker P et al. JACC 2018

Lezioni dagli studi pre-clinici e trials: effetti immunometabolici delle terapie reumatologiche e oncologiche

Drug	Mechanism of action			
Canakinumab	Anti IL-1beta antibody	-↓ CRP --↓ IL-6 -reduces vascular inflammation	-no effect on new-onset diabetes reduction -no effect on HB1Ac neither in prediabetes nor in T2D	-no effects on renal outcomes
Atezolizumab And Nivolumab	Anti-PD and Anti-PDL-1 (programmed death and ligand-1)	-controls T lymphocytes with malignant cells to prevent their de-activation	-↑ HB1Ac	-associates with acute kidney injuries in pre-clinical models
Tocilizumab	IL-6 receptor inhibitor	-↓ CRP ↑ T cells responsivness and T regulatory activity	- ↓HB1Ac in rheumatoid arthritis patients	-Stabilizes Renal Function in Kidney Transplant Recipients
Etanercept	Chimeric antibody TNF-alpha antagonist	-↓ TNF-alpha -↓ CRP -↑ reglatory T cells activity	-↓ glucose levels -↓insulin levels	- Possible glomerulonephritis in RA patients

Effetto positivo

Effetto negativo

Nessun effetto

“Rischio infiammatorio residuo” nel paziente CKD: Una strada ancora molto lunga da percorrere

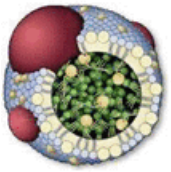
Lezioni dagli studi pre-clinici e trials: effetti immunometabolici delle attuali terapie farmacologiche

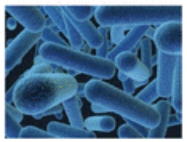
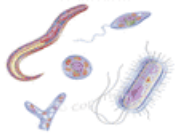
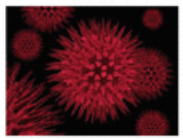
Drug	Mechanism of action			
Glibenclamide	Inhibits ATP-sensitive K^+ channel in beta cells	- ↑ insulin secretion by beta cells in pancreas - ↓ insulin resistance	- Preserve kidney function in rats ↓ innate response against infection in advanced renal disease	-↓ IL-1beta secretion by pancreas
Metformin	AMPK agonist	- ↑ insulin secretion by beta cells in pancreas -↓ insulin resistance	X	-↑ cellular energetic homeostasis -↓ mTOR → ↓ glycolysis
Pioglitazone	PPAR-gamma agonist	-↓ insulin resistance -↓ glycated hemoglobin	-↓ albuminuria	-↓ cytokines secretion by monocytes mmunomodulatory activity of visceral adipose tissue-resident Tregs -↓ CRP
Canagliflozin	SGLT2 Inhibitor	-↑ Glucose urinary secretion -modest effect on insulin secretion	-↓ albuminuria -↓ CKD progression to end-stage renal disease -↓ CV mortality in CKD	-↓ 6-Phosphofructokinase -↑ autophagy (↑ AMPK, p62)
Empagliflozin	SGLT2 Inhibitor	-↑ Glucose urinary secretion -↑ insulin sensitivity	-↓ albuminuria -↓ CV mortality in CKD	-↑ anti-inflammatory M2 macrophages -↓ TNF-alpha
Linagliptin, Sitagliptin and Saxagliptin	Dipeptidyl peptidase-4 (DPP4) inhibitor	-↓ glucagone secretion -↑ insulin secretion by beta cells in pancreas -↓ glycated hemoglobin	-↓ albuminuria -↓microvascular complications in CKD patients	-↓ NF-kB activity in rat insulinoma -↓ NLRP3 inflammasome -↓ Caspase activity -↓ IL-1beta secretion -↓ CRP
Exenatide	GLP-1 receptor agonist	-↓ insulin resistance -↓ glycated hemoglobin	X	-↓ CRP
Sacubitril / Valsartan	Neprylisin inhibitor + angiotensin-II receptor blocker	-↓ blood pressure -↑ hepatic and muscle glucose sensitivity -not clear effects on pancreatic homeostasis	- ↓ glomerular pressure - glomerual oxidative stress	-↓ cardiac oxidative stress and inflammation -attenuates renal tubular injury
Low Protein Diet	A part of the «Nutritional Therapy» aaccording to ADA	- Beneficial effect on glucose metabolism - To be understood in ESRD	-control the intra-glomerular pressure and afferent/efferent tone	-Reduces fibrosis by reducing mesangial TGF-beta production -↓↑ low-grade inflammation

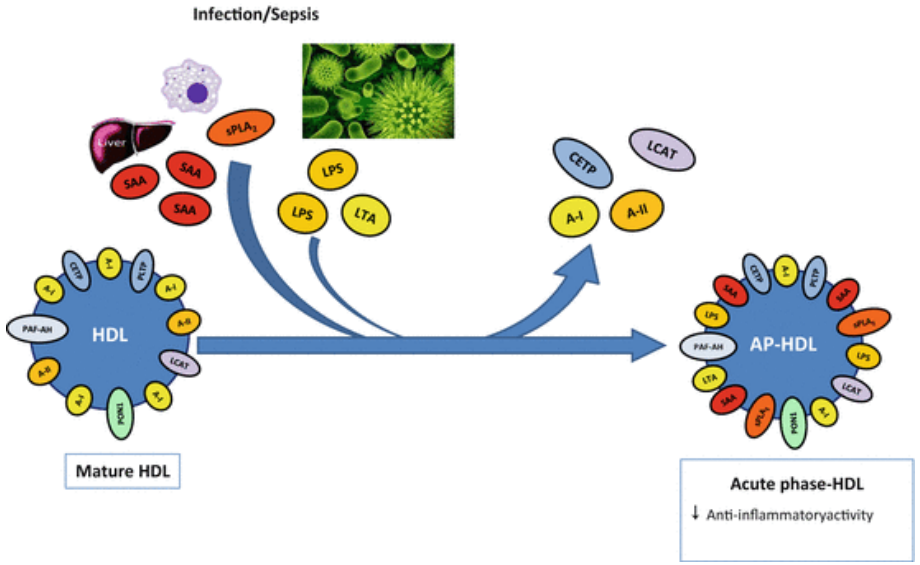
HDL : tra metabolismo del colesterolo e immuno-infiammazione

Lipoproteine HDL e ruolo nelle infezioni

HDL

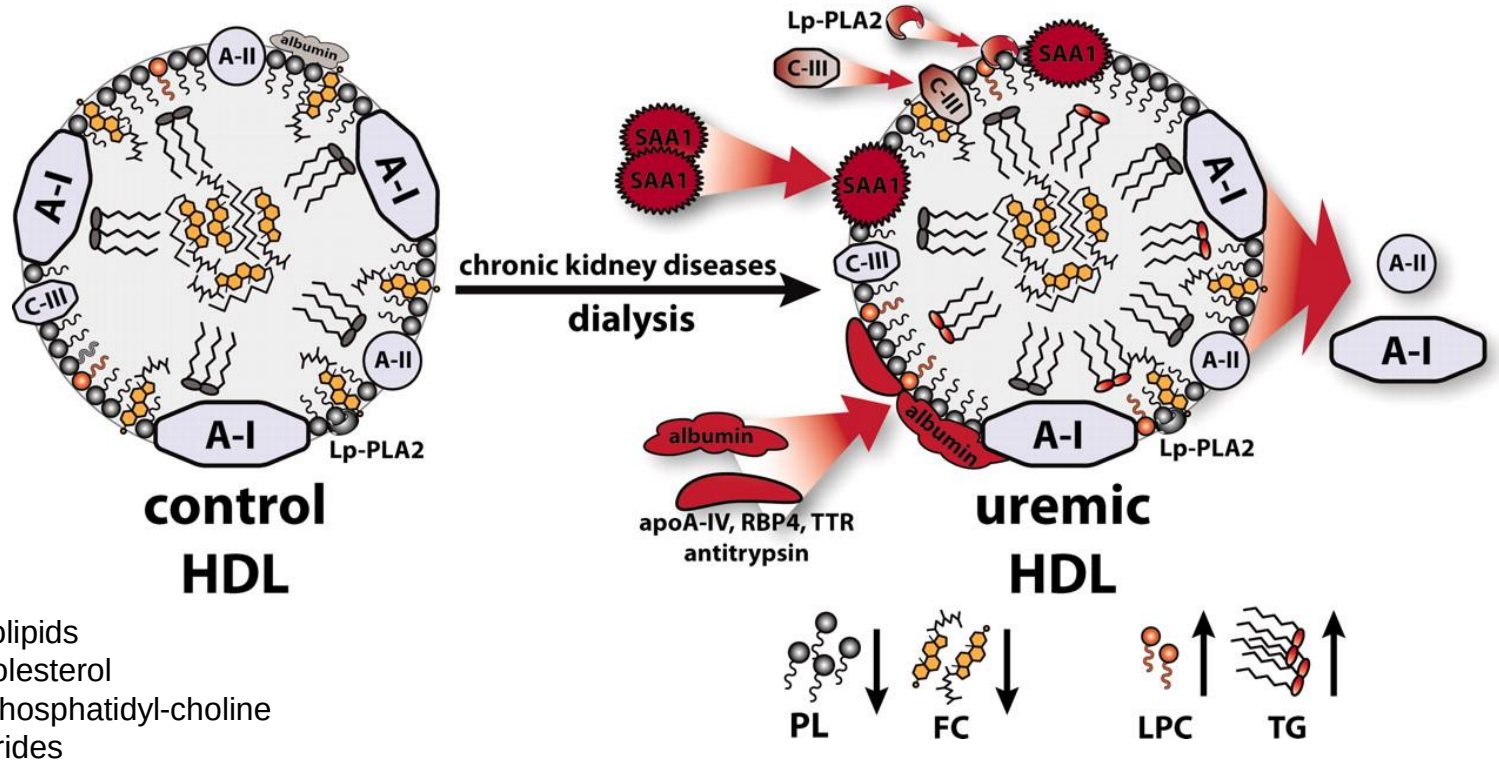


TYPE OF INFECTION	HDL-MEDIATED EFFECT
Bacteria 	• Favor LPS/LTA binding and neutralization. • Favor LPS/LTA clearance • Inhibit LPS (LTA)-induced cytokine release • Inhibit of LPS (LTA)-induced cell activation • Induce an early inflammatory response
Parasites 	• Support ApoL1, Apo-AI and HRP interaction to form the trypanosoma lytic factor-1 (TLF-1). complex. ApoL1 then traffics to the trypanosomal lysosome, where causes swelling which kills the trypanosome.
Virus 	• Dampen (ApoA-1 mimetic peptides) the ABCA-1 impairment induced by the HIV-1 Nef protein. • Inhibit cell fusion, both in HIV-1-infected T cells and in recombinant vaccinia-virus-infected CD4+ HeLa cells. • Compete with Hepatitis C virus on SRBI interaction to dampen virus entry?



HDL-C e HDL nel paziente nefropatico: quali evidenze?

Le lipoproteine HDL sono sensibili al milieu uremico



PL = Phospholipids
FC = Free cholesterol
LPC = Lyso-phosphatidyl-choline
TG = Triglycerides
SAA1 = Serum Amyloid A 1
Lp-PLA2 = Lipoprotein-associated phopholipase A2

Holzer et al. JASN 2011

HDL-C e HDL nel paziente nefropatico: quali evidenze?

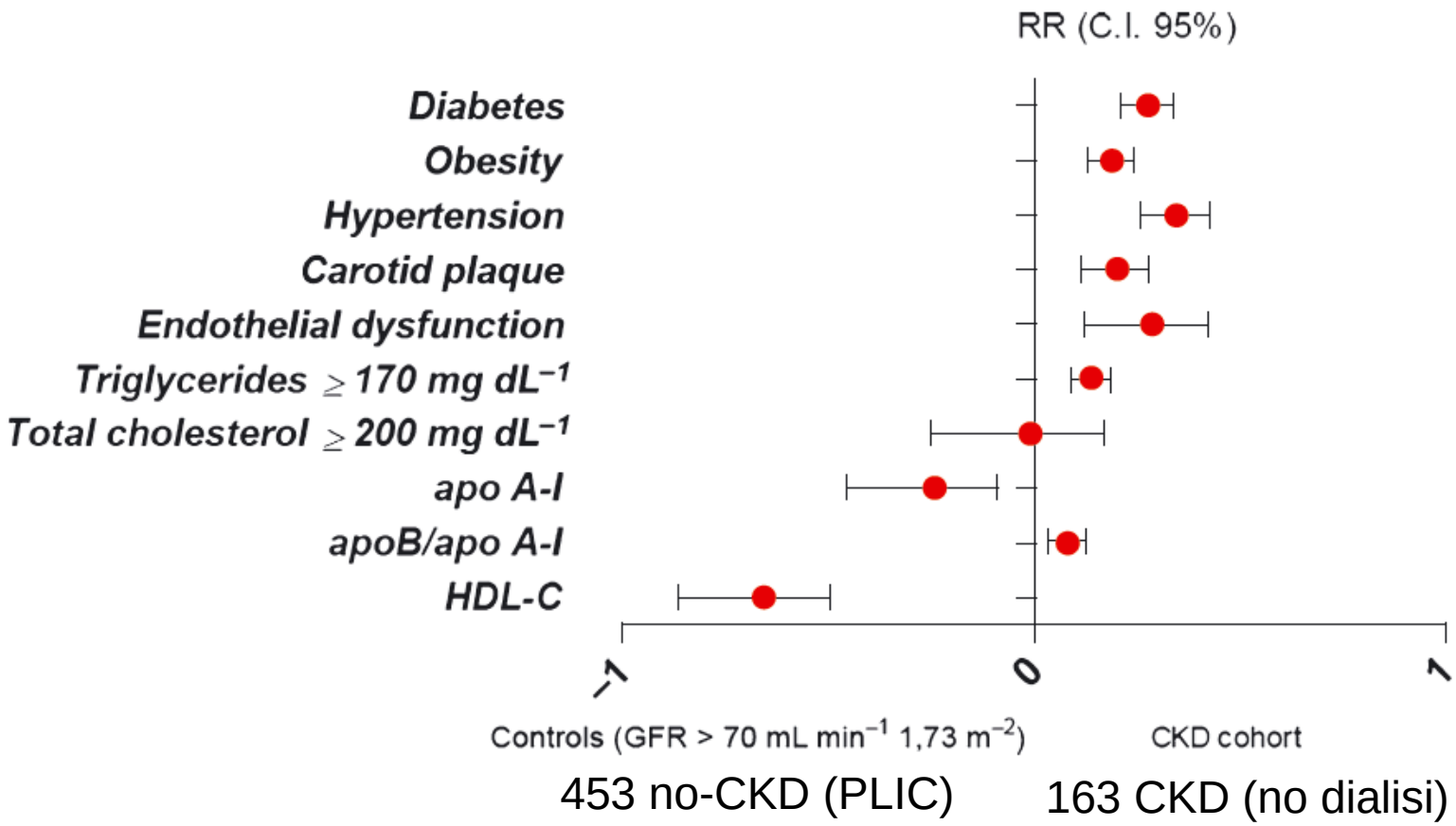
Ridotta esterificazione del colesterolo e ridotta quantità di LCAT nel paziente CKD e nel paziente in dialisi

	CKD-HD	CKD	Controls	*P**
LpA-I, mg dL^{-1}	43.1 ± 12.8	55.2 ± 15.9	50.1 ± 13.2	<0.0001
LpA-I:A-II, mg dL^{-1}	49.2 ± 13.6	64.0 ± 14.4	84.6 ± 12.7	<0.0001
Pre-β HDL, %	17.1 ± 4.7	15.8 ± 4.7	13.1 ± 3.2	<0.0001
HDL_2 size, nm	11.2 ± 0.4	11.1 ± 0.2	11.2 ± 0.3	0.267
HDL_3 size, nm	8.8 ± 0.4	8.9 ± 0.2	8.8 ± 0.3	0.372
Unesterified/total cholesterol	0.34 ± 0.05	0.29 ± 0.04	0.27 ± 0.02	<0.0001
CER, nmol mL^{-1} h^{-1}	30.2 ± 11.2	28.9 ± 10.7	38.5 ± 8.5	0.0001
LCAT activity, nmol mL^{-1} h^{-1}	26.1 ± 9.9	30.0 ± 8.8	36.0 ± 6.4	<0.0001
LCAT concentration, μg mL^{-1}	4.01 ± 0.92	4.64 ± 0.75	5.05 ± 0.73	<0.0001
CETP concentration, μg mL^{-1}	1.36 ± 0.35	1.61 ± 0.36	1.57 ± 0.34	<0.0001

Calabresi L et al. J Intern Med 2014

HDL-C e HDL nel paziente nefropatico: quali evidenze?

Ridotto HDL-C emerge come prominente marcatore associato a CKD

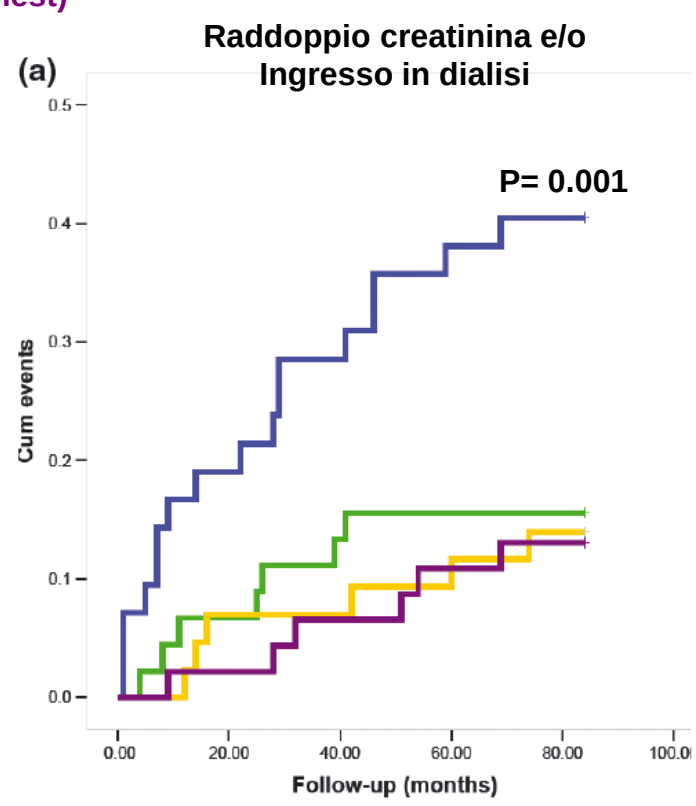


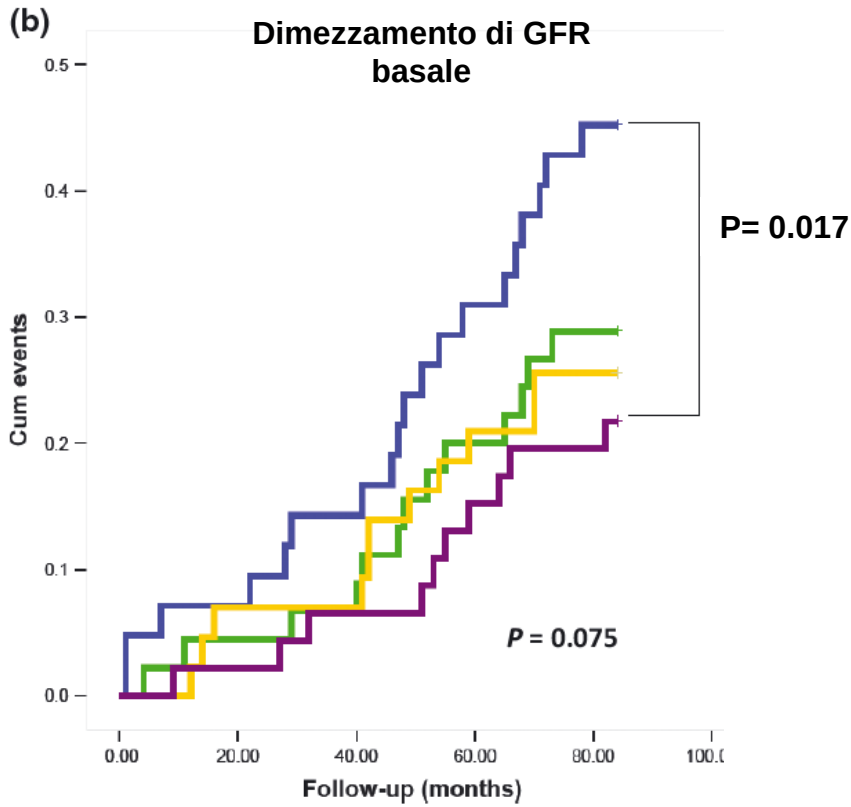
Baragetti A et al. J Intern Med 2013
Baragetti I et al. PlosOne 2013
Norata GD et al. Stroke 2007

HDL-C e HDL nel paziente nefropatico: quali evidenze?

Ridotti livelli di HDL-C predicono la progressione della patologia CKD nel tempo (7 anni)

1° quartile (lowest)
2° quartile
3° quartile
4° quartile (highest)



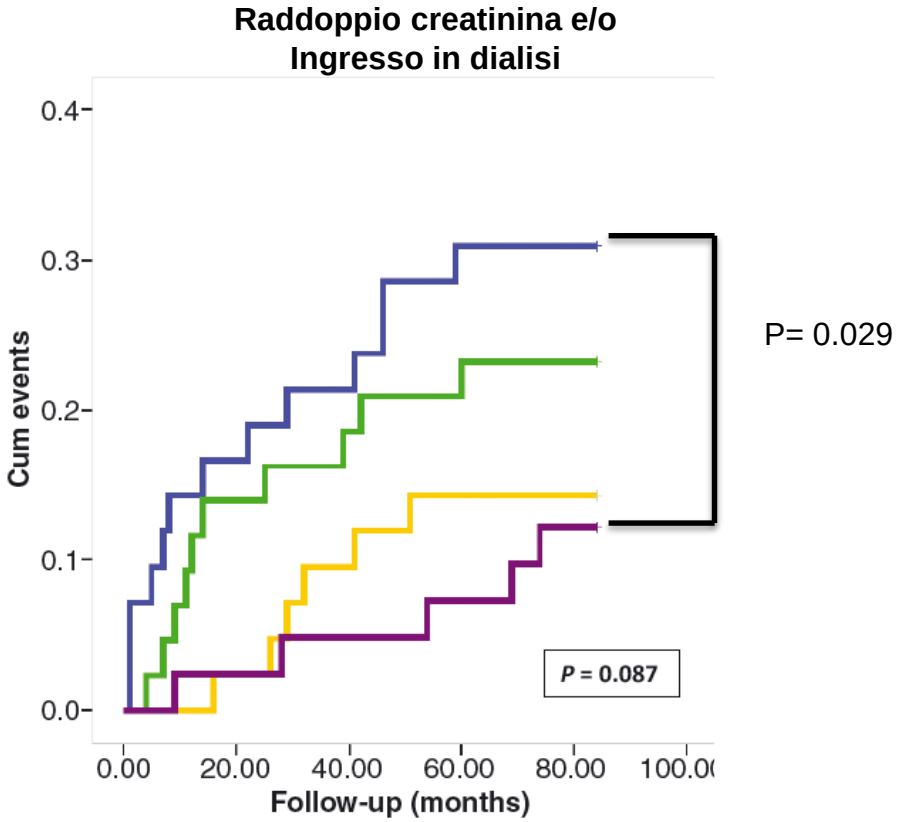


Baragetti A et al. J Intern Med 2013

HDL-C e HDL nel paziente nefropatico: quali evidenze?

Estremi livelli di ApoA-I predicono la progressione della patologia CKD nel tempo (7 anni)

1° quartile (lowest)
2° quartile
3° quartile
4° quartile (highest)

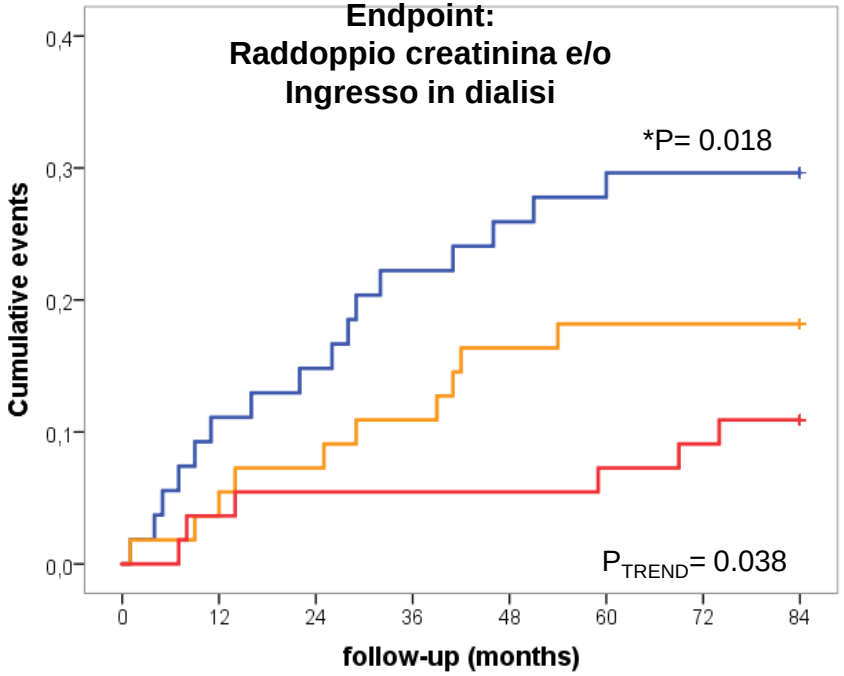


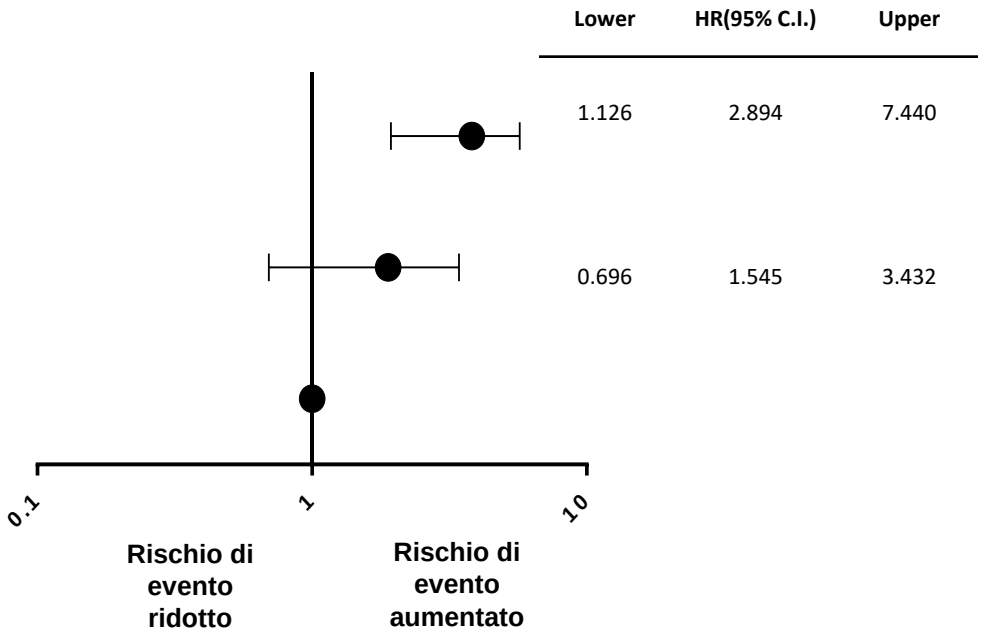
Baragetti A et al. J Intern Med 2013

HDL-C e HDL nel paziente nefropatico: quali evidenze?

Ridotta concentrazione di LCAT predice la progressione della malattia CKD

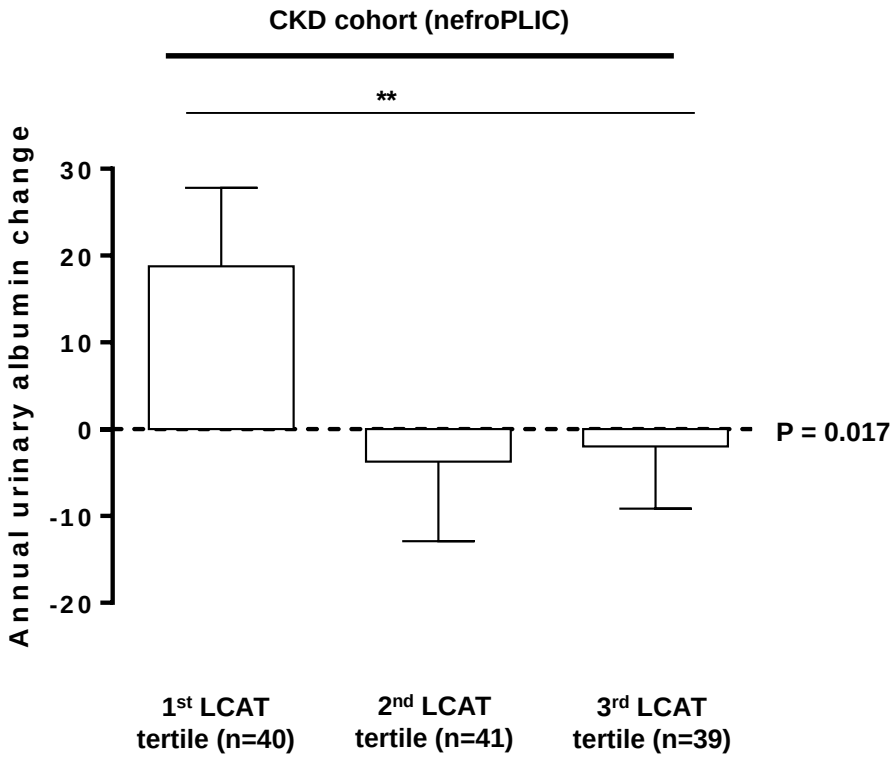
1st LCAT tertile (lowest)
2nd LCAT tertile
3rd LCAT tertile (highest)





HDL-C e HDL nel paziente nefropatico: quali evidenze?

Ridotta concentrazione di LCAT predice la variazione di GFR



Post-hoc data
In collaborazione con Prof. Calabresi L. e Alice Ossoli

HDL rilevanti nel danno renale e glomerulare del paziente nefropatico? Una strada ancora molto lunga da percorrere

UNIVERSITÀ DEGLI STUDI DI MILANO

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