IL CROSS-TALK
cuore-rene
FISIOPATOLOGIA
ED ASPETTI CLINICI

ROMA 15 MAGGIO 2019

Importanza del trattamento di altri fattori di rischio non convenzionali (trigliceridi, iperuricemia, infiammazione) nella riduzione della morbidità e mortalità cardiovascolare

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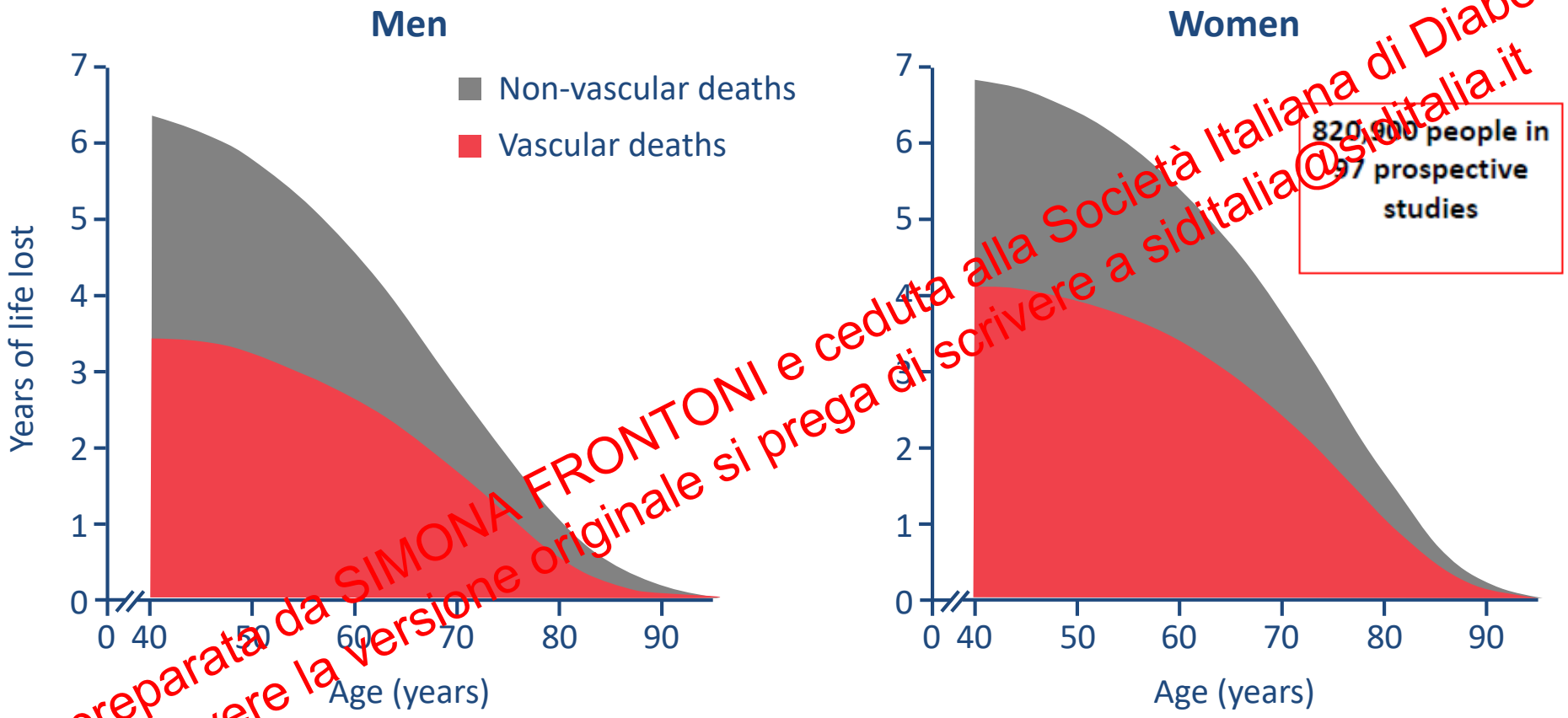
Dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Novo-Nordisk
- Eli-Lilly
- Sanofi-Aventis
- Mundipharma

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

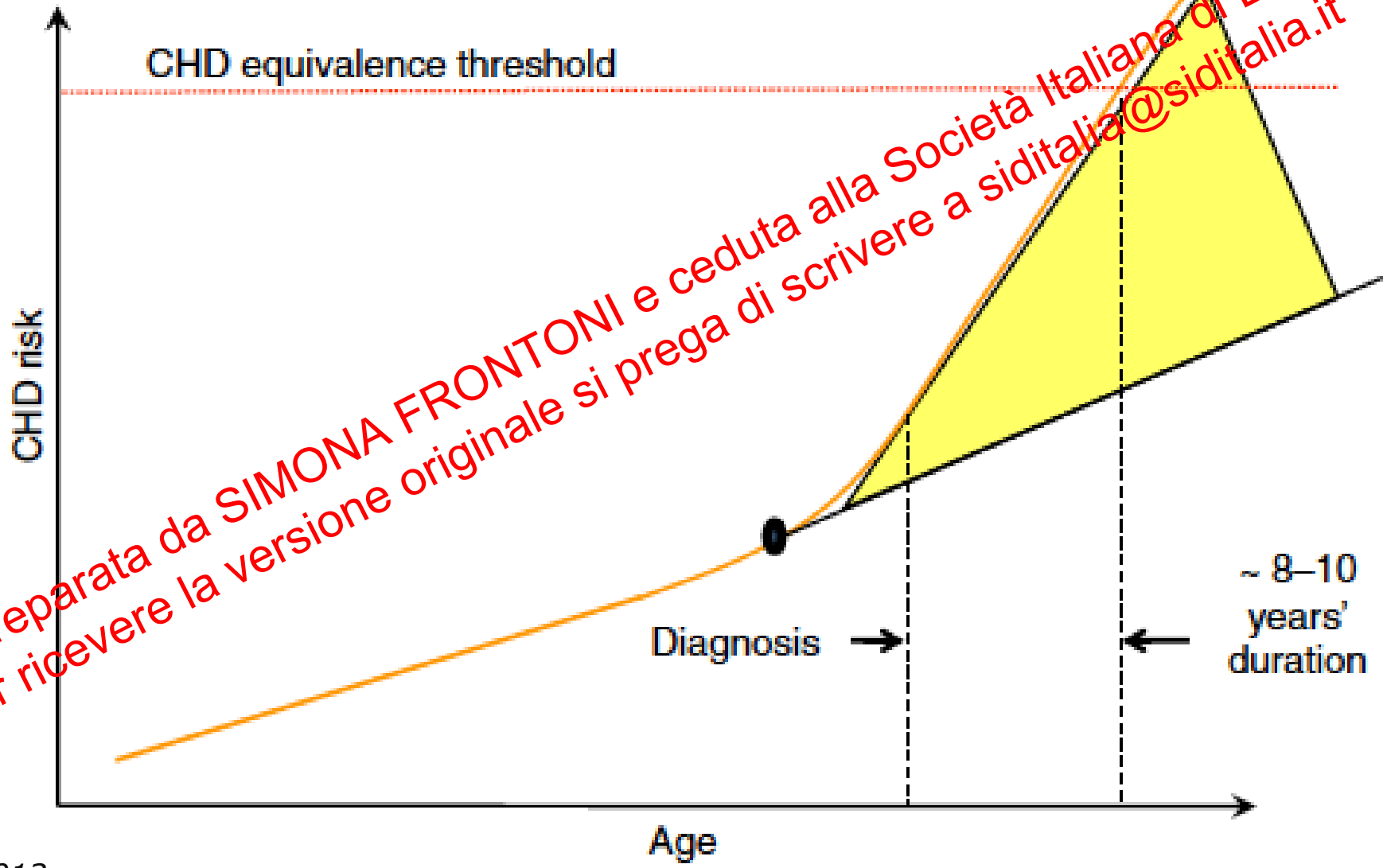
Diabetes is associated with significant loss of life years



In media una persona di 50 anni con diabete in assenza di storia di malattia cardio-vascolare ha una aspettativa di vita inferiore di 6 anni rispetto alle persone senza diabete

Seshasai et al. N Engl J Med 2011;364:829-41

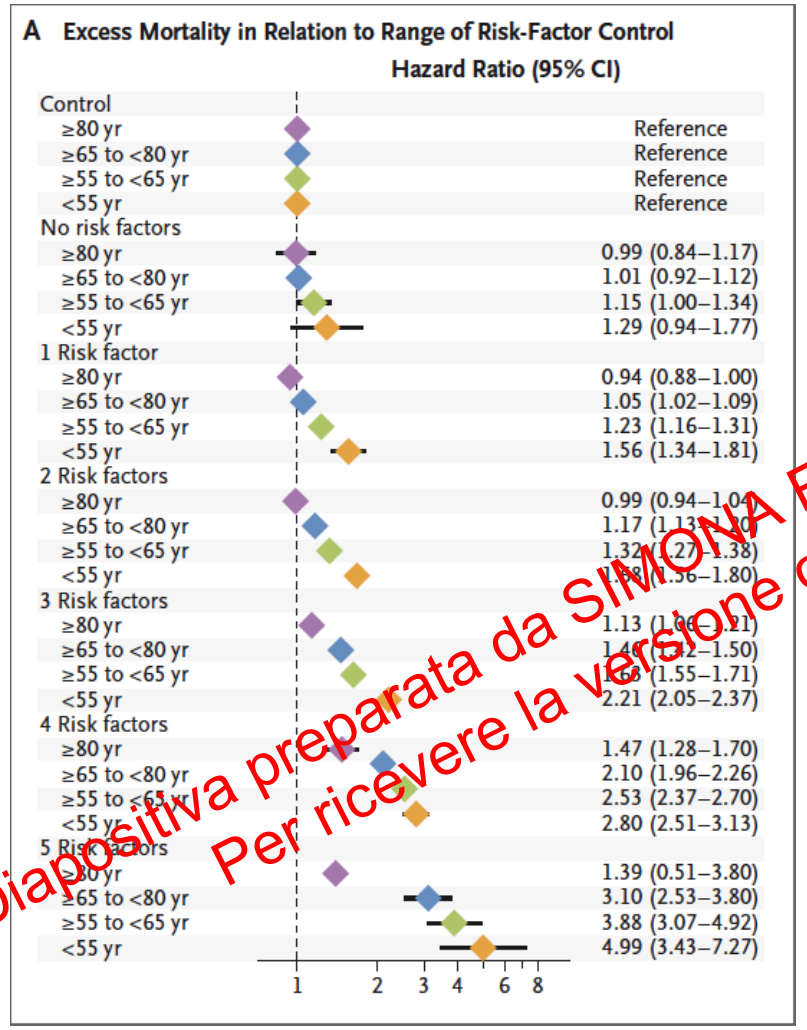
A conceptual look at vascular risk and its determinants before and during the course of type 2 diabetes

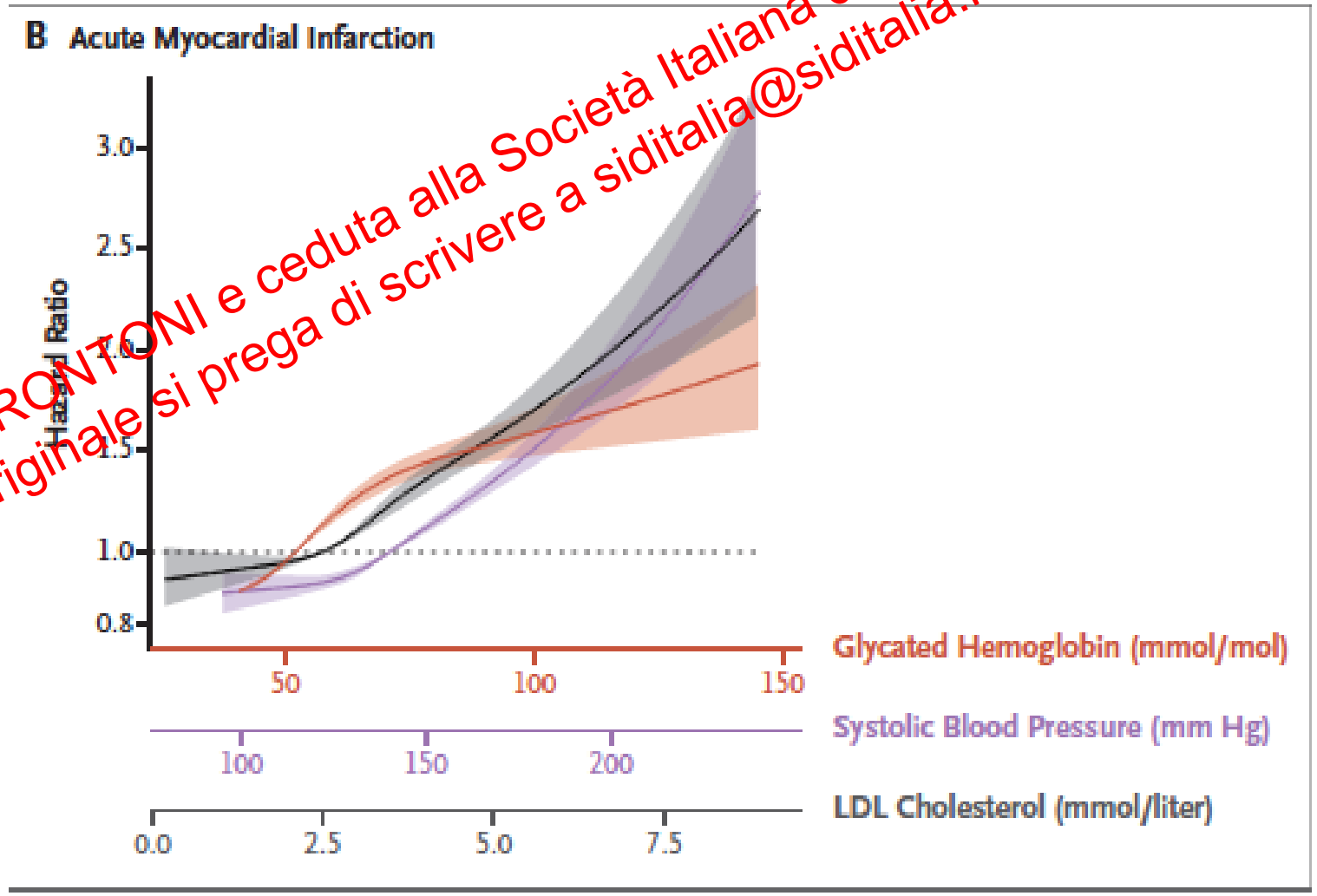


Sattar N, Diabetologia 2013

Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes

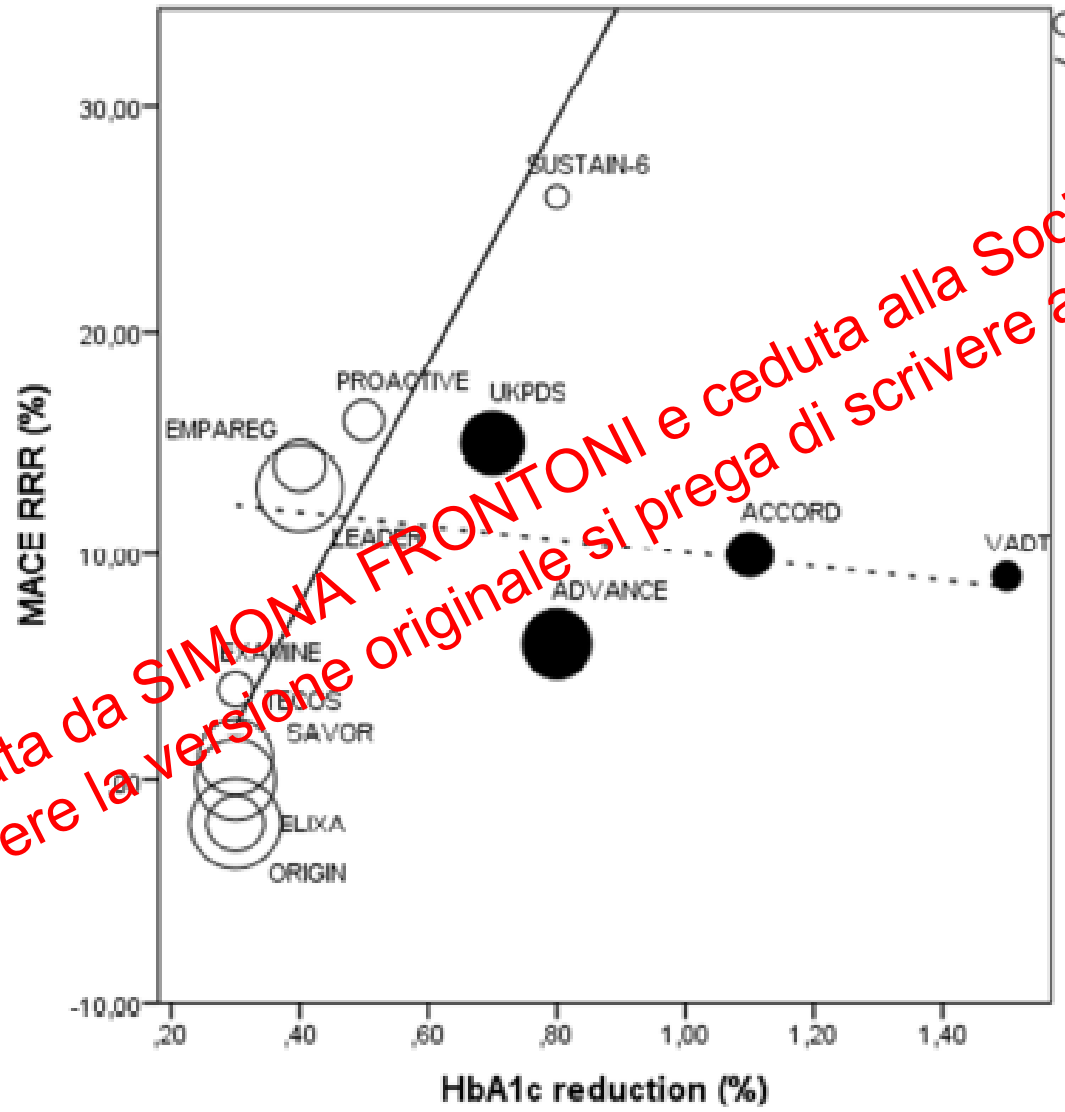
Acute myocardial infarction





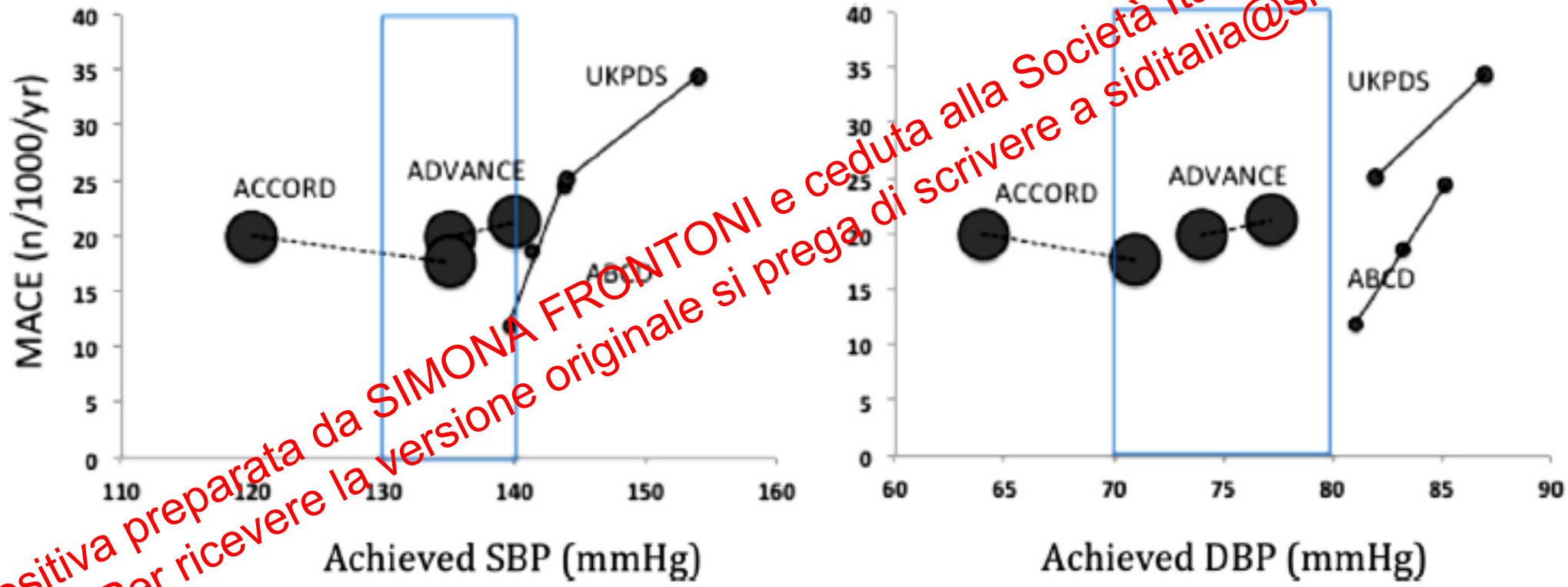
Rawshani A et al. N Engl J Med 2018; 379: 633-644

Glycemic control for CV risk reduction



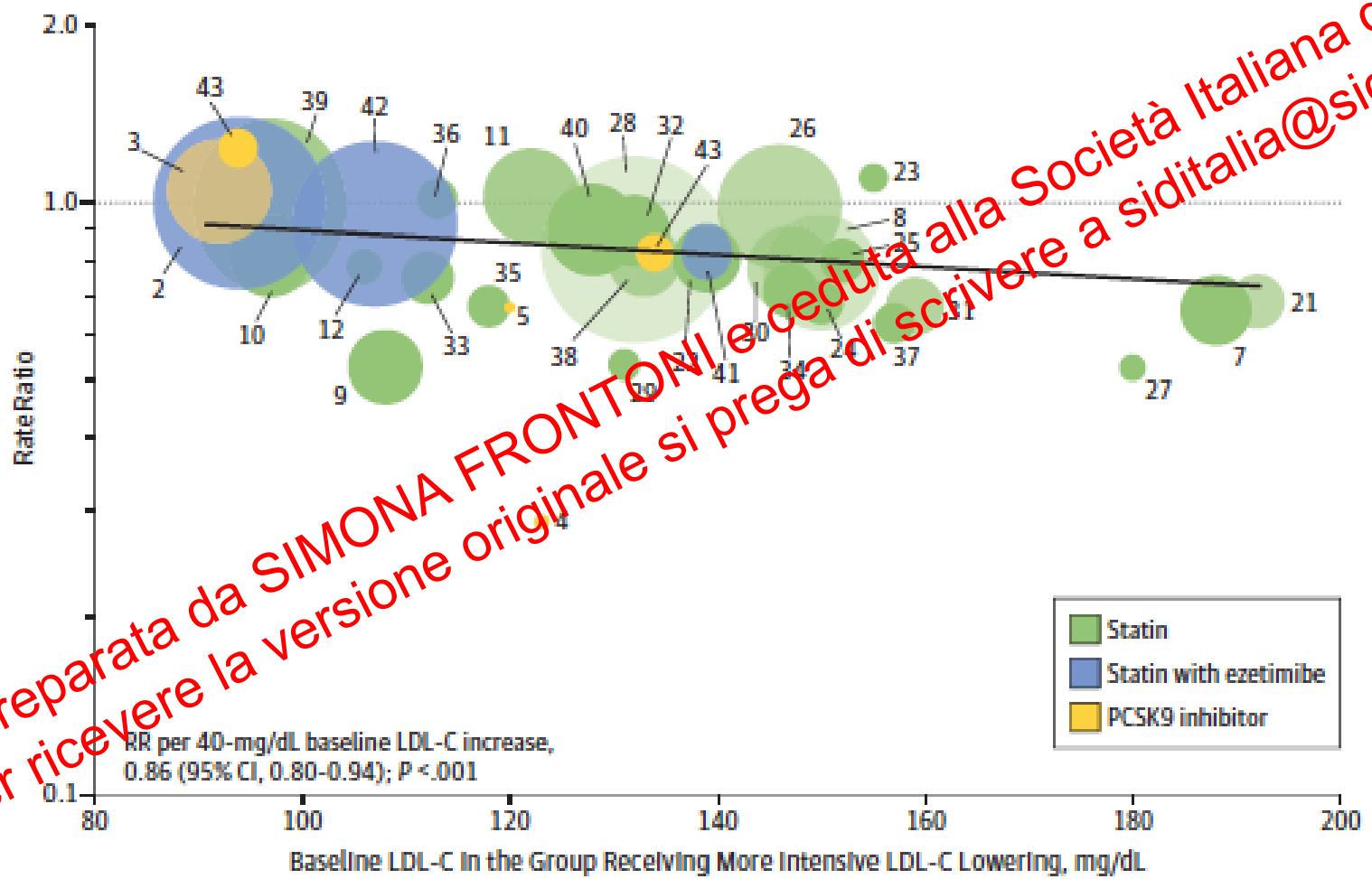
Mannucci E et al. NMCD 2017

Blood pressure control for CV risk reduction



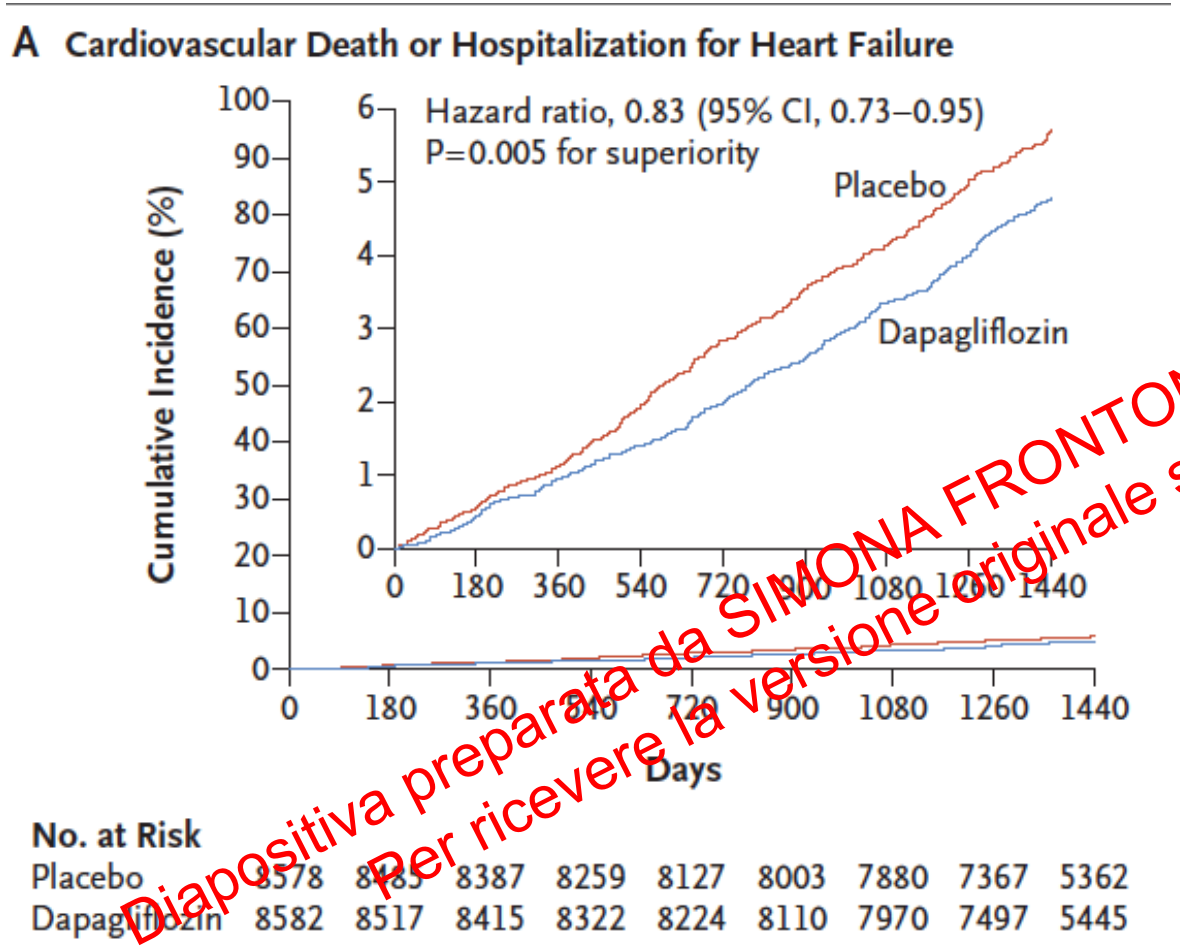
Frontoni S et al. NMCD 2014

Meta-regression analysis of cardiovascular mortality by baseline LDL-C level (34 trials: 136 299 pts more intensive, 133 989 less intensive LDL-C lowering)

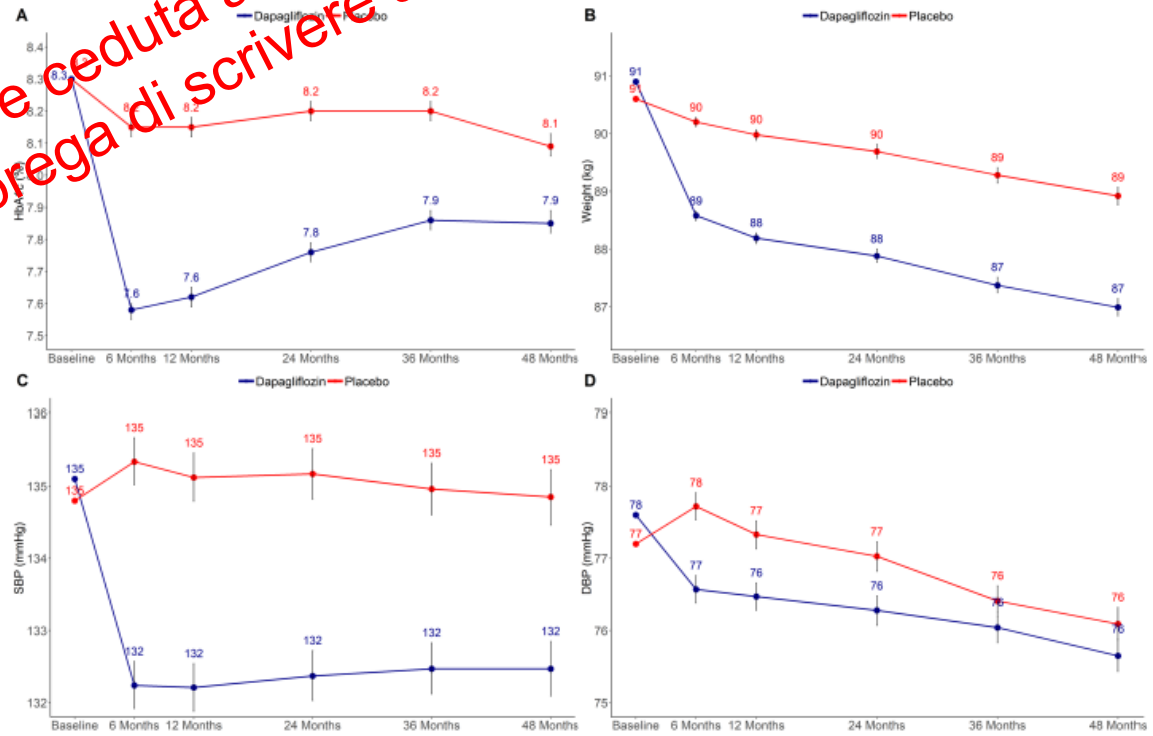


Navarese EP et al. JAMA 2018

Dapagliflozin and Cardiovascular Outcomes in Type 2 diabetes



Supplemental Figure 2: Adjusted Mean HbA1c, weight, systolic blood pressure (SBP), and diastolic blood pressure (DBP) over time by randomized treatment group. Expressed are values for HbA1c (%), weight in kg, SBP and DBP in mm/Hg.

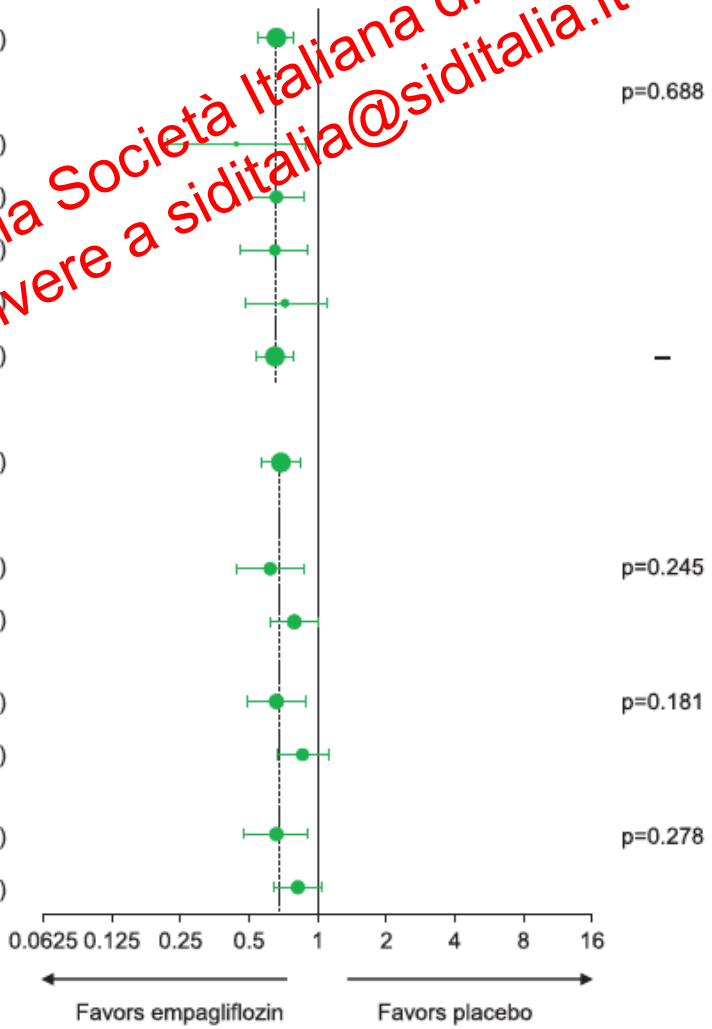


Wiviott SD et al. NEJM 2019

Improvement in Cardiovascular Outcomes with Empagliflozin is independent of glycemic control

C Heart failure hospitalization or cardiovascular death

All events				
All patients	265/4687 (5.7)	198/2333 (8.5)	0.66 (0.55, 0.79)	
HbA1c at baseline				p=0.688
<7%	16/297 (5.4)	15/127 (11.8)	0.44 (0.22, 0.89)	
7% to <8%	114/2042 (5.6)	86/1029 (8.4)	0.66 (0.50, 0.87)	
8% to <9%	77/1534 (5.0)	60/795 (7.5)	0.65 (0.46, 0.91)	
≥9%	57/812 (7.0)	37/382 (9.7)	0.72 (0.48, 1.10)	
All patients, adjusted for time-dependent HbA1c control (HbA1c <7.5%)	264/4685 (5.6)	198/2333 (8.5)	0.64 (0.54, 0.78)	–
Events after week 12				
All patients	255/4656 (5.5)	180/2308 (7.8)	0.69 (0.57, 0.84)	
Change from baseline in HbA1c at week 12				
Reduction of ≥0.5%	119/2550 (4.7)	43/562 (7.7)	0.62 (0.44, 0.88)	p=0.245
Reduction of <0.5% or increase	135/2104 (6.4)	137/1741 (7.9)	0.79 (0.62, 1.01)	
Reduction of ≥0.3%	143/3140 (4.6)	60/843 (7.1)	0.66 (0.49, 0.89)	p=0.181
Reduction of <0.3% or increase	111/1514 (7.3)	120/1460 (8.2)	0.86 (0.66, 1.12)	
Reduction ≥median (0.4%)	130/2846 (4.6)	50/705 (7.1)	0.66 (0.47, 0.91)	p=0.278
Reduction <median (0.4%)	124/1808 (6.9)	130/1598 (8.1)	0.82 (0.64, 1.05)	



Inzucchi SE et al. Circulation 2018

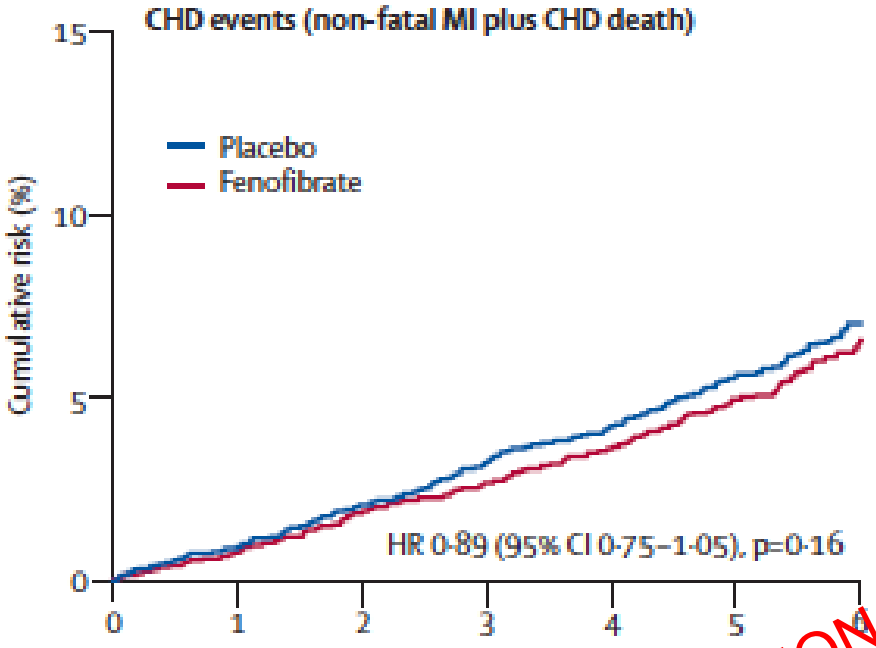
Altri meccanismi

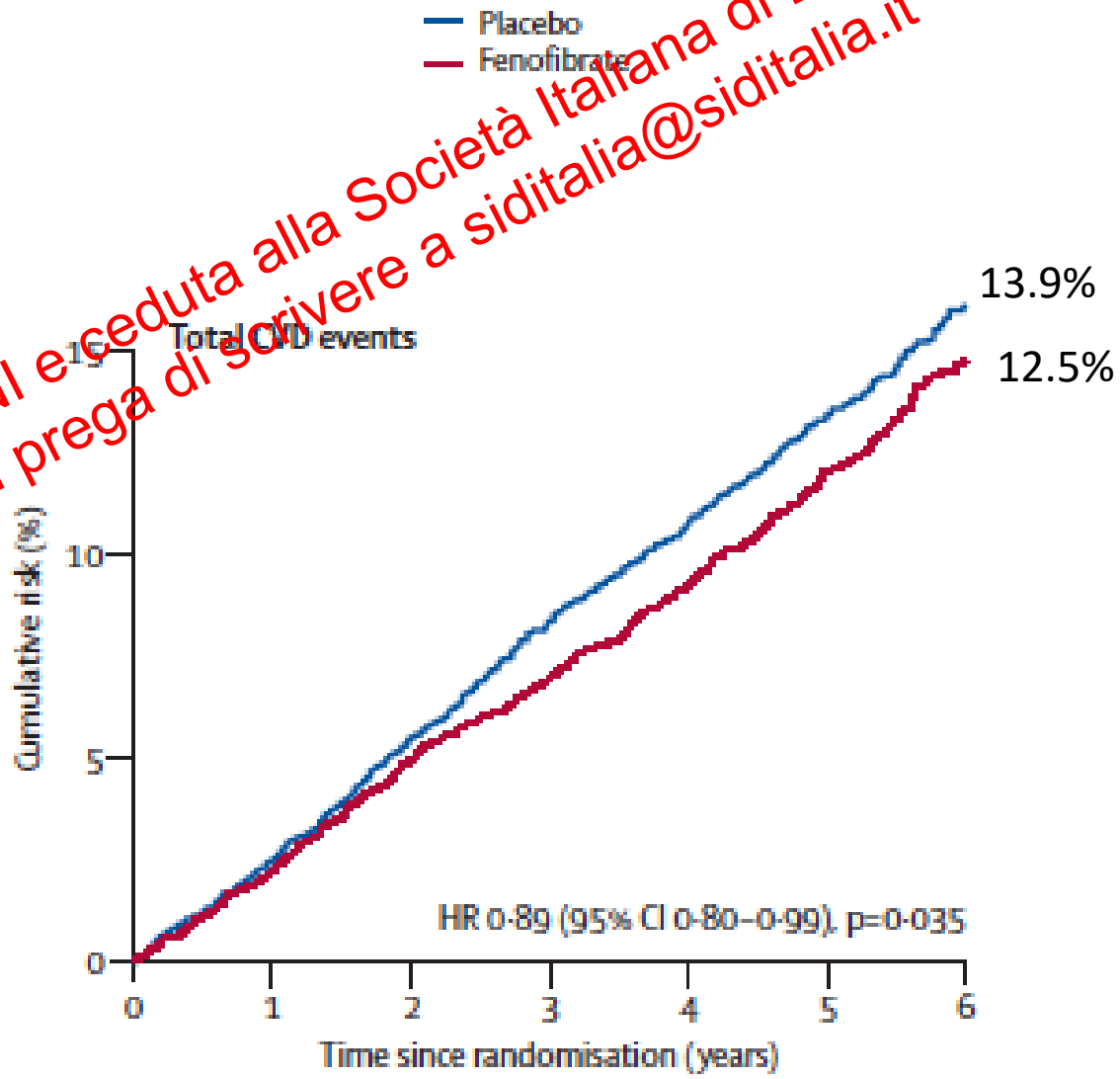
- Trigliceridi
- Acido urico
- Infiammazione

Altri meccanismi

- Trigliceridi
- Acido urico
- Infiammazione

The FIELD Study (n: 9795 T2DM)
Total cardiovascular events





The Field Study Investigators, Lancet 2005

The FIELD Study (n: 9795 T2DM)
Plasma concentration of lipids

	Plasma concentrations at baseline (mean [SD])		Absolute (mmol/L) and relative (%) differences between treatment groups in plasma lipid concentrations after randomisation*				Plasma concentrations at study close (mean [SD])	
	Placebo	Fenofibrate	4 months	1 year	2 years	Study close	Placebo	Fenofibrate
Full cohort (fenofibrate n=4895, placebo n=4900)								
Total cholesterol	5·03 (0·71)	5·04 (0·69)	−0·58 (−11·4%)	−0·58 (−11·6%)	−0·56 (−11·1%)	−0·33 (−6·9%)	4·56 (0·90)	4·23 (0·78)
LDL cholesterol	3·07 (0·66)	3·07 (0·64)	−0·39 (−12·0%)	−0·38 (−11·9%)	−0·36 (−11·7%)	−0·17 (−5·8%)	2·60 (0·78)	2·43 (0·65)
HDL cholesterol	1·10 (0·26)	1·10 (0·26)	0·05 (5·1%)	0·05 (4·5%)	0·04 (3·5%)	0·01 (1·2%)	1·12 (0·29)	1·13 (0·30)
Triglycerides	1·93 (0·88)	1·95 (0·87)	−0·56 (−28·6%)	−0·58 (−30·9%)	−0·52 (−27·4%)	−0·41 (−21·9%)	1·87 (0·96)	1·47 (0·78)
Started other lipid-lowering therapy (fenofibrate n=944, placebo n=1776)								
Total cholesterol	5·2 (0·67)	5·25 (0·69)	−0·42 (−8·0%)	−0·39 (−7·6%)	−0·33 (−6·5%)	−0·08 (−1·6%)	4·12 (0·88)	3·98 (0·85)
LDL cholesterol	3·31 (0·63)	3·23 (0·64)	−0·24 (−6·6%)	−0·19 (−5·5%)	−0·15 (−4·6%)	0·02 (0·7%)	2·18 (0·74)	2·13 (0·66)
HDL cholesterol	1·08 (0·25)	1·03 (0·24)	0·05 (4·6%)	0·03 (2·8%)	0·01 (1·7%)	−0·01 (−0·5%)	1·12 (0·28)	1·05 (0·29)
Triglycerides	2·08 (0·99)	2·22 (0·99)	−0·54 (−24·6%)	−0·55 (−24·8%)	−0·45 (−21·0%)	−0·24 (−10·9%)	1·84 (0·97)	1·74 (0·96)
Did not start other lipid-lowering therapy (fenofibrate n=3951, placebo n=3124)								
Total cholesterol	4·87 (0·68)	4·92 (0·69)	−0·63 (−12·5%)	−0·66 (−13·1%)	−0·68 (−13·4%)	−0·66 (−13·1%)	4·82 (0·80)	4·29 (0·74)
LDL cholesterol	2·93 (0·64)	3·03 (0·64)	−0·44 (−13·6%)	−0·45 (−14·3%)	−0·48 (−15·3%)	−0·46 (−14·7%)	2·84 (0·70)	2·50 (0·63)
HDL cholesterol	1·11 (0·27)	1·11 (0·26)	0·05 (5·1%)	0·05 (4·8%)	0·04 (4·0%)	0·02 (2·1%)	1·13 (0·29)	1·15 (0·30)
Triglycerides	1·85 (0·87)	1·89 (0·83)	−0·57 (−29·6%)	−0·60 (−31·6%)	−0·55 (−29·1%)	−0·51 (−27·3%)	1·88 (0·95)	1·41 (0·72)

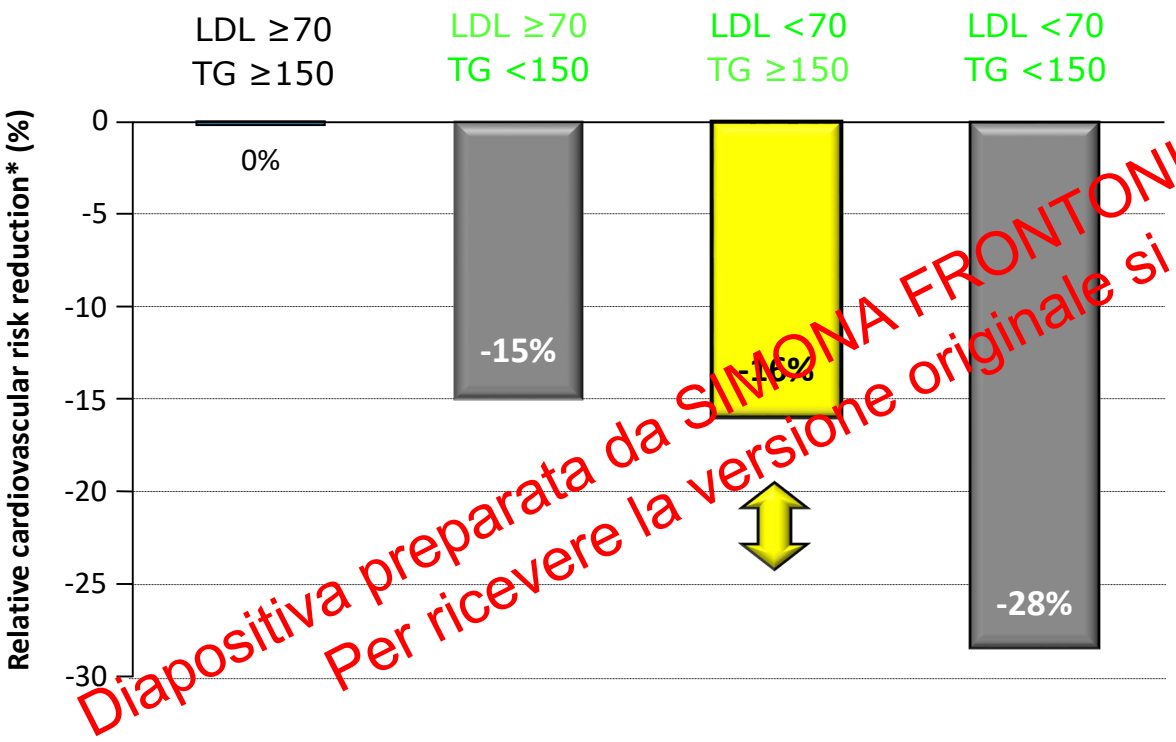
*Fenofibrate minus placebo. p≤0·05 for all differences between groups at every timepoint shown, except in patients who started other lipid-lowering therapy, for HDL cholesterol and LDL cholesterol at study close.

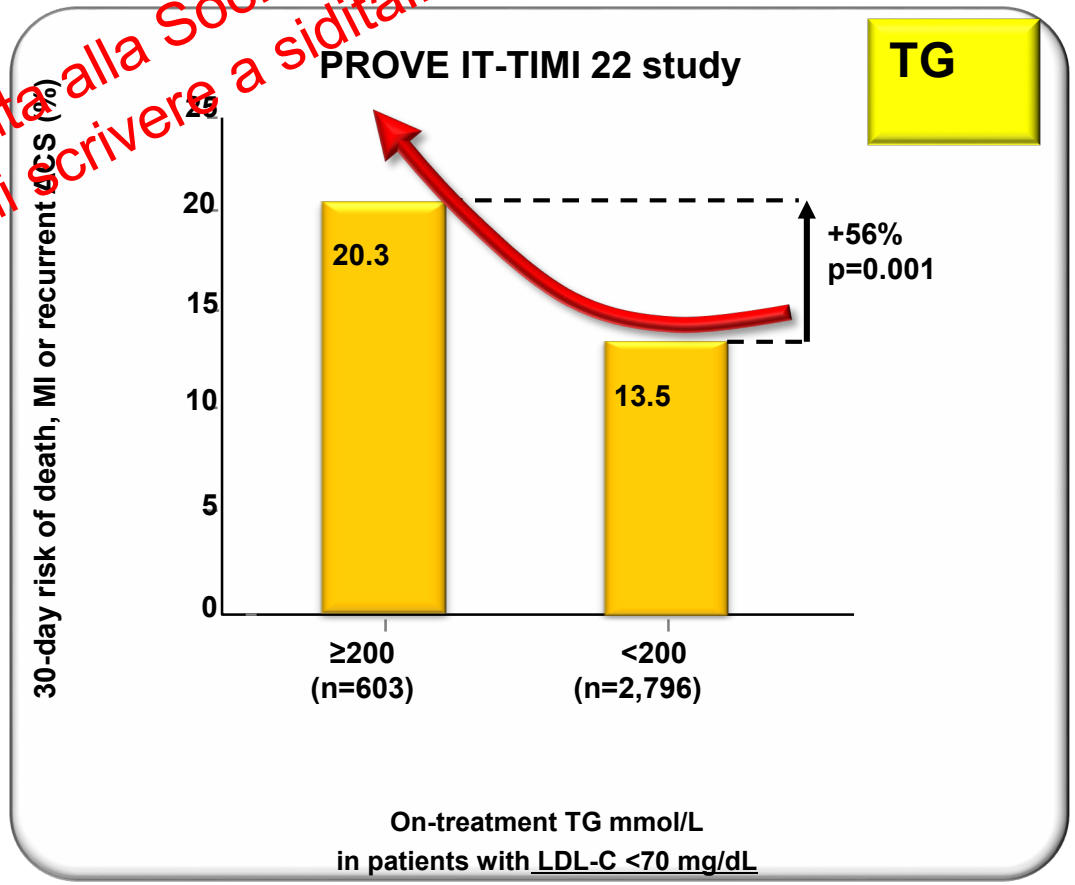
The Field Study Investigators, Lancet 2005

PROVE IT-TIMI 22

reaching target LDL alone with statin therapy does not achieve maximal CV risk reduction if TGs are raised

For people at target LDL, those with low TGs have an additional 12% reduction in cardiovascular risk versus those with raised TGs





Miller A et al. J Am Coll Cardiol 2008

The REDUCE-IT Study

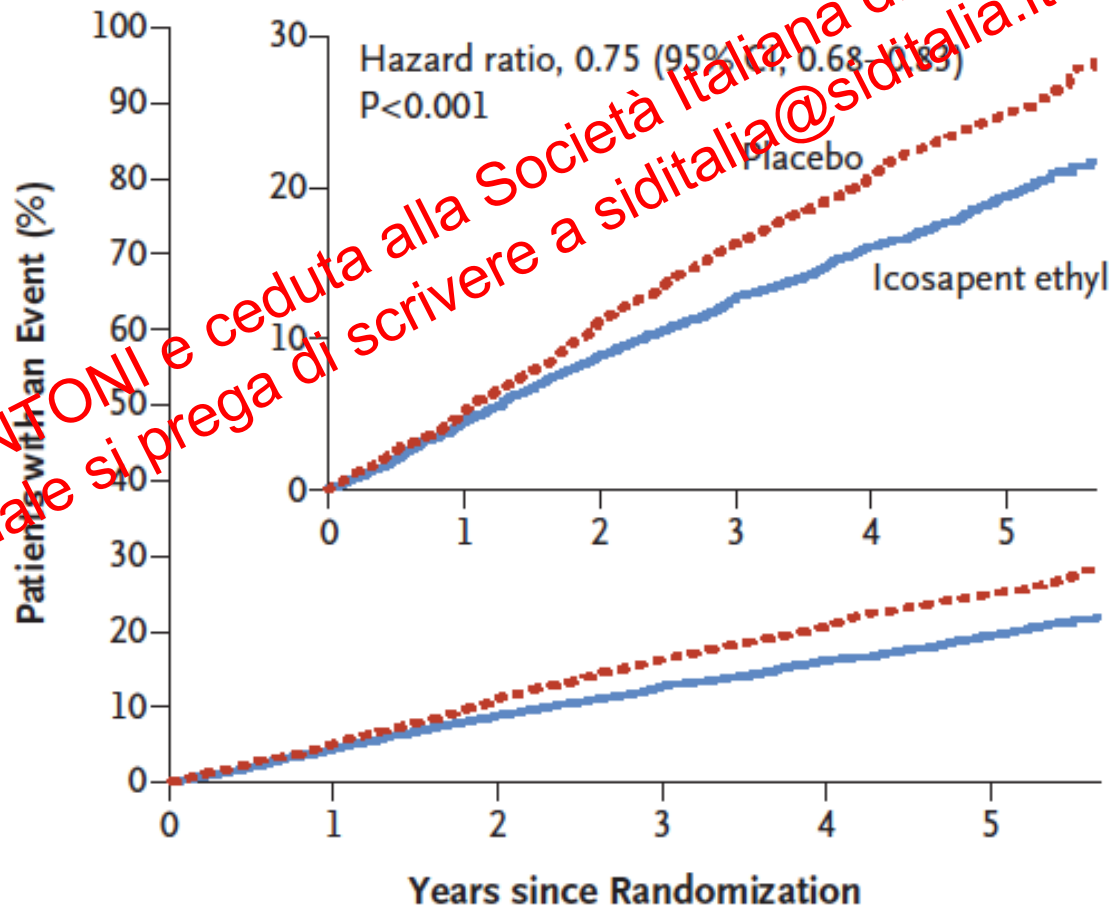
Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Primary end-point: composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina

patients with established CVD or with diabetes and other risk factors:

- *who had been receiving statin therapy, and*
- *who had a fasting triglyceride level of 135 to 499 mg/dl and a LDL cholesterol level of 41 to 100 mg/dl*

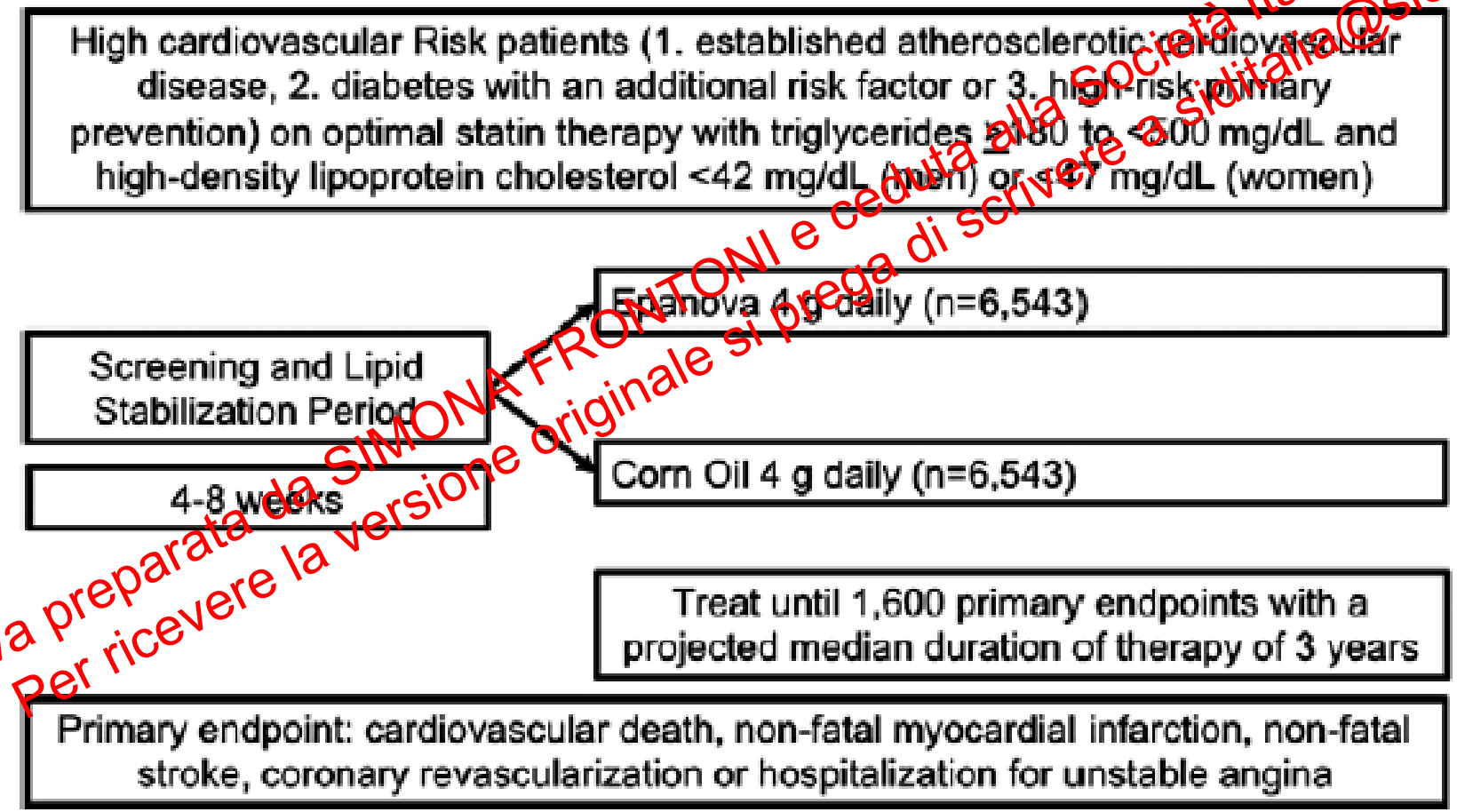
- *The patients were randomly assigned to receive 2 g of icosapent ethyl twice daily or placebo*



Bhatt DL et al, NEJM 2018

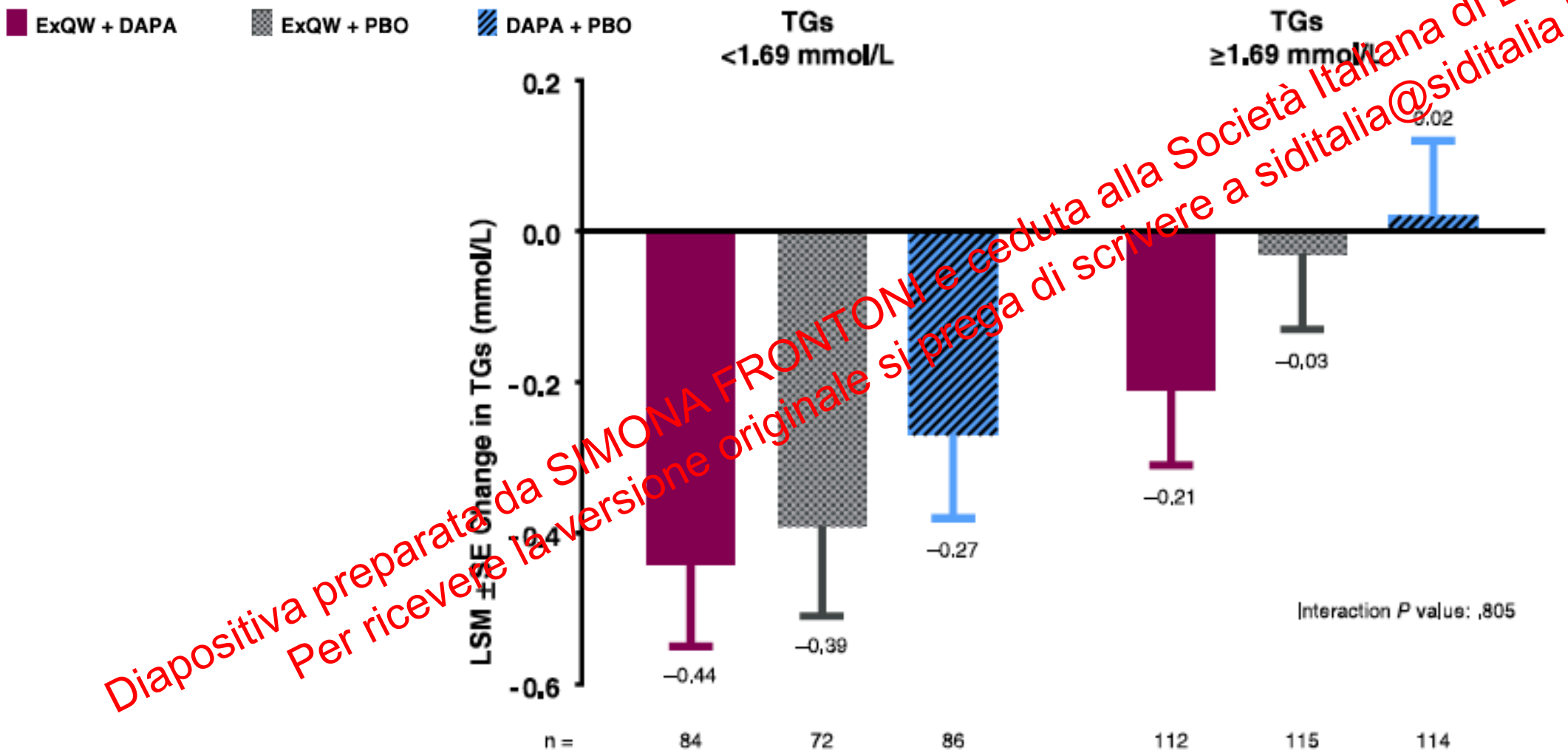
The STRENGTH Trial

Assessment of omega-3 carboxylic acids in statin-treated patients with high levels of triglycerides and low levels of high-density lipoprotein cholesterol



Nicholls SJ et al, Clinical Cardiology 2018

The DURATION 8 Study



Jabbour SA et al, DOM 2018

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Effects of the SGLT2 inhibitor dapagliflozin on HDL chol, particle size, and chol efflux capacity, in T2DM

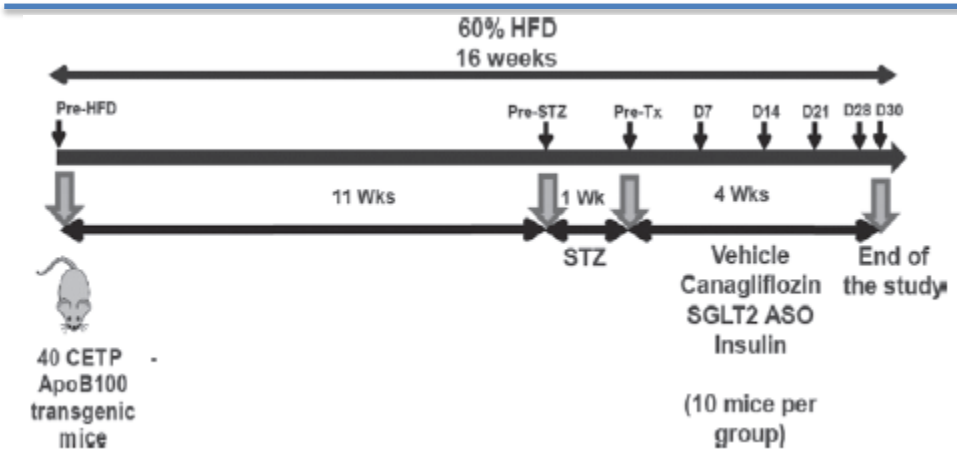
Variable	Placebo (n = 16)			Dapagliflozin (n = 15)		
	Baseline	12 weeks	Change	Baseline	12 weeks	Change
Lipid profile						
Total cholesterol	150.6 ± 9.8	151.7 ± 6.2	1.1 ± 6.4	162.2 ± 5.8	169.9 ± 11.7	7.7 ± 9.2
HDL cholesterol	46.3 ± 3.0	47.4 ± 3.5	1.0 ± 1.1	48.1 ± 3.4	46.8 ± 3.9	−1.4 ± 2.3
LDL cholesterol (direct method)	75.8 ± 8.1	76.5 ± 5.4	0.9 ± 5.4	86.3 ± 4.1	92.5 ± 9.5	6.2 ± 8.2
LDL cholesterol (Friedewald formula)	76.4 ± 8.1	76.5 ± 5.4	0.1 ± 6.1	85.9 ± 5.2	95.0 ± 9.7	9.1 ± 9.5
Triglycerides	139.1 ± 13.9	138.9 ± 14.5	−0.1 ± 14.1	141.1 ± 19.8	140.9 ± 18.5	−0.1 ± 17.9
HDL subfractions, %						
Large	27.8 ± 2.2	27.8 ± 2.1	0.0 ± 1.7	24.8 ± 2.8	23.9 ± 2.6	−0.9 ± 1.3
Intermediate	51.5 ± 1.2	51.3 ± 0.9	−0.3 ± 1.1	54.2 ± 1.9	53.5 ± 1.6	−0.7 ± 1.1
Small	20.3 ± 2.8	21.0 ± 2.3	0.7 ± 1.7	20.7 ± 2.1	22.6 ± 1.9	1.9 ± 1.0
HDL subfractions, mg/dl						
Large	13.6 ± 1.5	13.5 ± 1.7	−0.1 ± 1.0	11.7 ± 1.7	11.7 ± 1.6	0.0 ± 0.6
Intermediate	24.9 ± 1.9	23.9 ± 1.9	−1.1 ± 1.2	25.2 ± 2.1	25.3 ± 2.1	0.0 ± 0.7
Small	9.3 ± 1.2	9.5 ± 1.1	0.0 ± 0.8	9.4 ± 0.9	10.5 ± 1.0	1.2 ± 0.6
Enzymatic activity						
PON1, U/ml	46.1 ± 6.4	50.3 ± 7.6	4.2 ± 4.9	40.8 ± 3.9	41.5 ± 2.9	0.7 ± 2.7
ARE, kU/ml	138.8 ± 22.1	138.9 ± 17.0	0.1 ± 24.8	156.3 ± 21.1	149.4 ± 17.2	−7.0 ± 30.9
CESD, mU/ml	1.4 ± 0.1	1.3 ± 0.1	0.0 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	0.0 ± 0.1
Cholesterol efflux capacity, %	35.6 ± 2.7	35.3 ± 2.2	−0.3 ± 1.8	40.8 ± 2.8	34.2 ± 2.2*#	−6.7 ± 2.4*

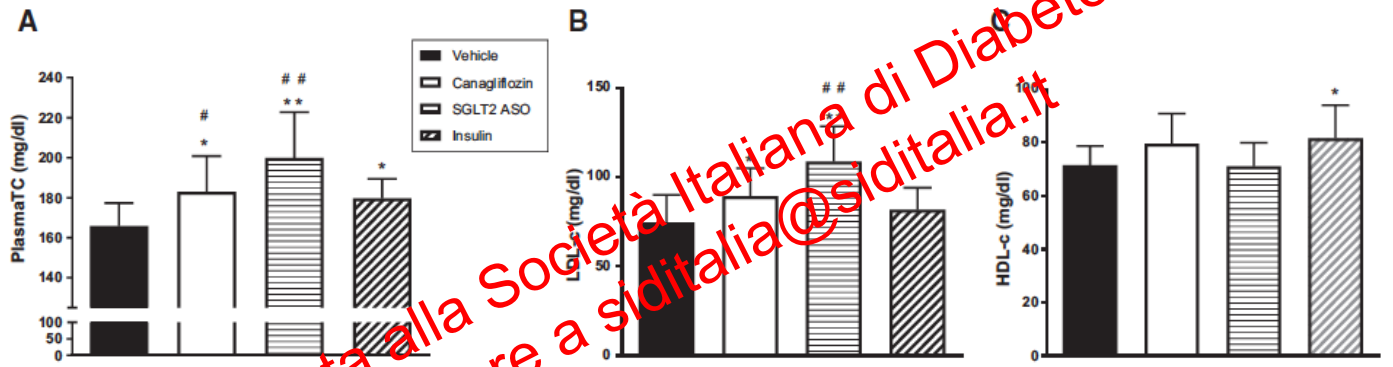
* $p < 0.05$ versus placebo

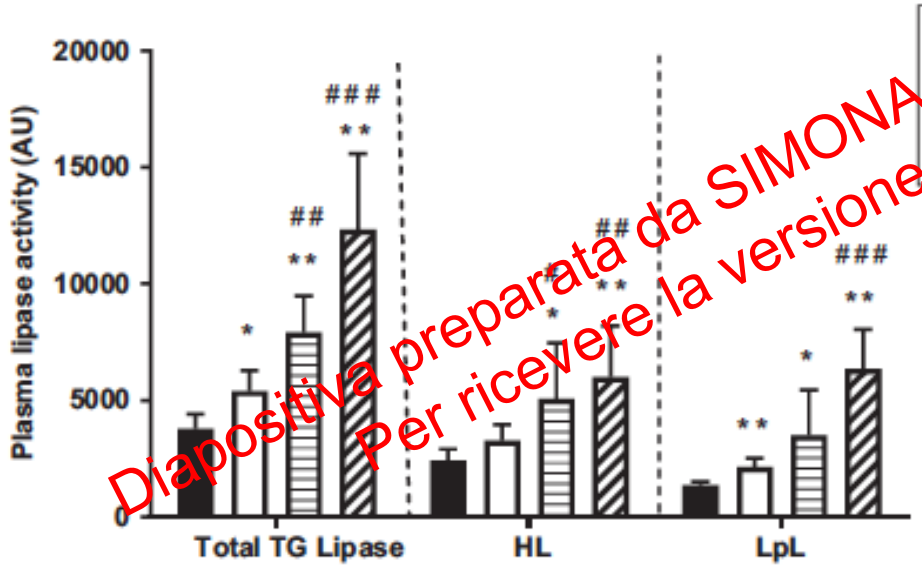
# $p < 0.05$ versus baseline

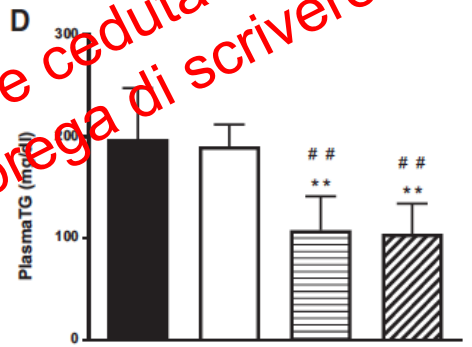
Fadini GP et al, Cardiovasc Diabetol 2017

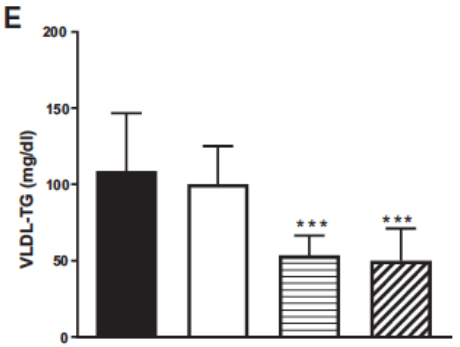
Mechanism of increased LDL and decreased triglycerides with SGLT2 inhibition











Basu D et al, Arterioscler Thromb Vasc Biol. 2018

Altri meccanismi

- Trigliceridi
- Acido urico
- Infiammazione

Uric acid is an independent risk factor for decline in kidney function, CV events and mortality in T1DM

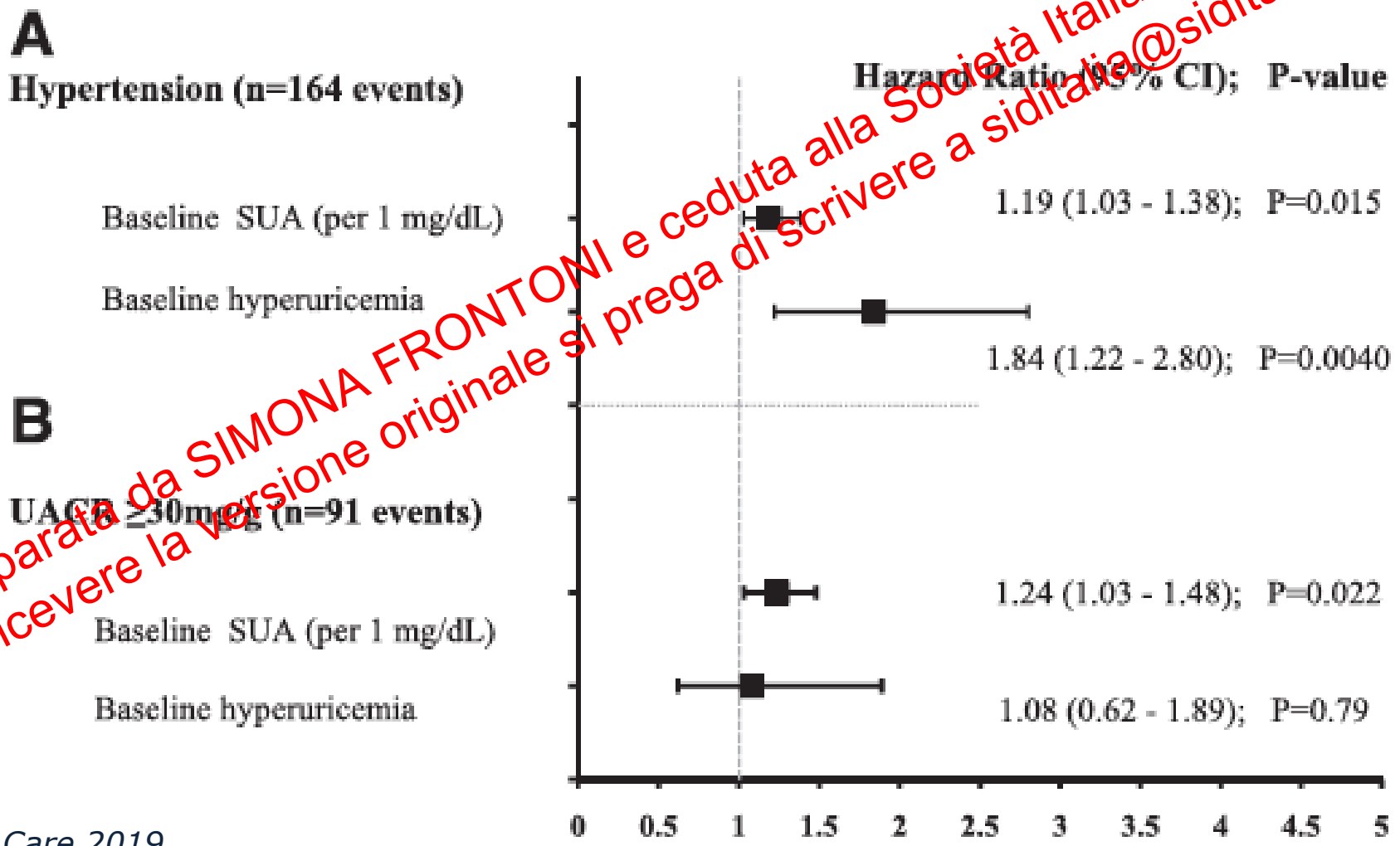
Hr per doubling of uric acid

	Total mortality		CVE		Decline in eGFR ≥30%		Albumin progression		ESRD	
Number of participants included	667		667		669		667		665	
Events, *n* (%)	58 (8.7)		94 (14.0)		89 (13.3)		36 (5.4)		21 (3.2)	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Unadjusted	3.74 (2.23–6.28)	<0.001	4.16 (2.76–6.28)	<0.001	5.25 (3.47–7.95)	<0.001	1.28 (0.66–2.51)	0.47	18.2 (5.36–61.8)	<0.001
Adjusted*	2.58 (1.12–5.90)	0.025	2.25 (1.20–4.21)	0.011	3.18 (1.71–5.93)	<0.001	0.95 (0.37–2.46)	0.91	2.23 (0.41–12.1)	0.35
rIDI (%)	11.8	0.003	6.5	0.010	12.6	<0.001	1.4	0.93	—	—

Pyleman-Lyberg S et al, Diabetes Care 2019

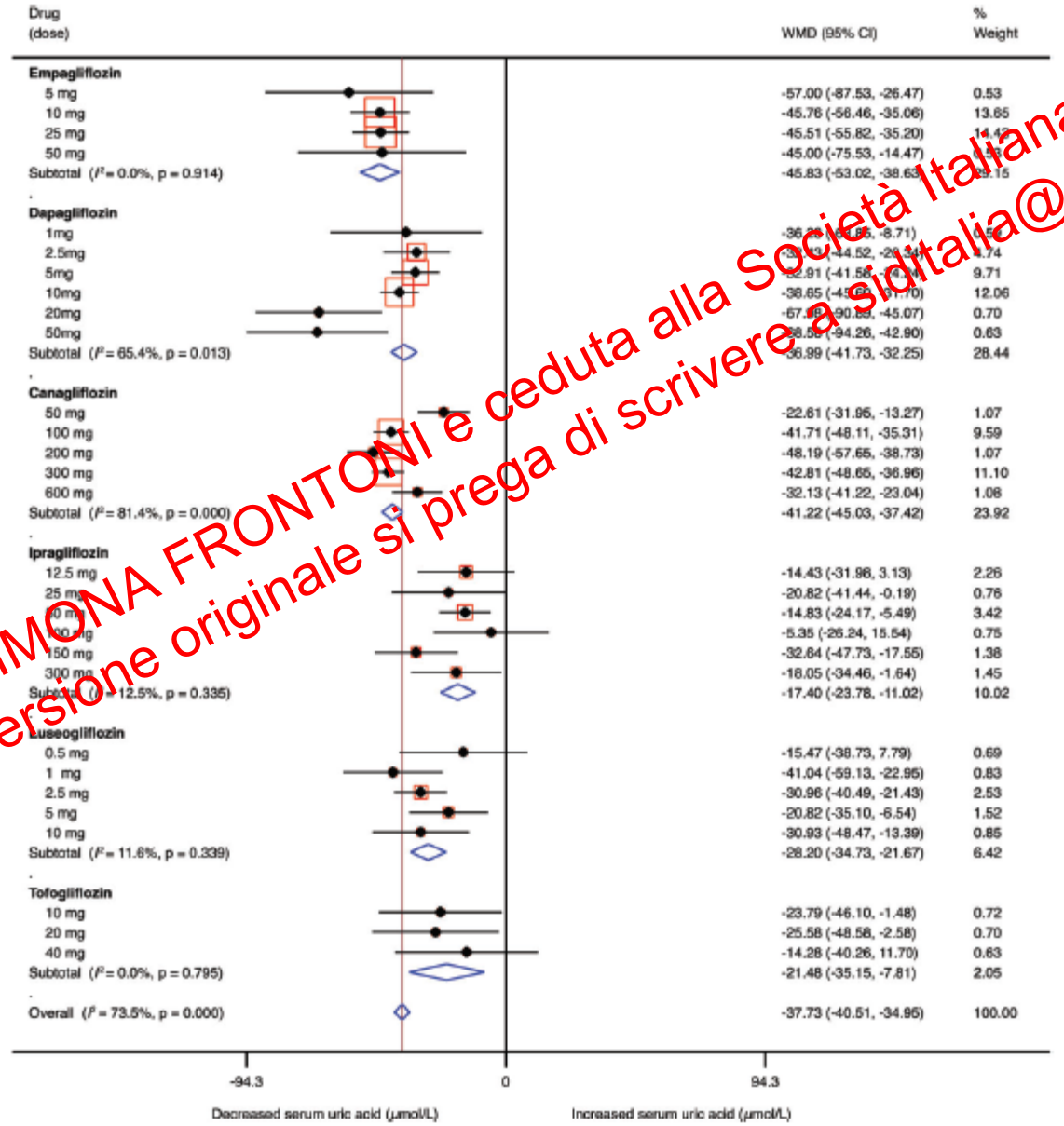
Elevated serum uric acid is associated with greater risk for hypertension and diabetic kidney disease, in obese adolescents with type 2 diabetes, duration <2 yrs (n: 539)

TODAY study (average FU 5.7 yrs)



Bjornstad P et al, Diabetes Care 2019

Effects of sodium-glucose co-transporter 2 (SGLT2) inhibitors on serum uric acid level: A meta-analysis of randomized controlled trials



Zhao Y et al, Diabetes Obes Metab 2018

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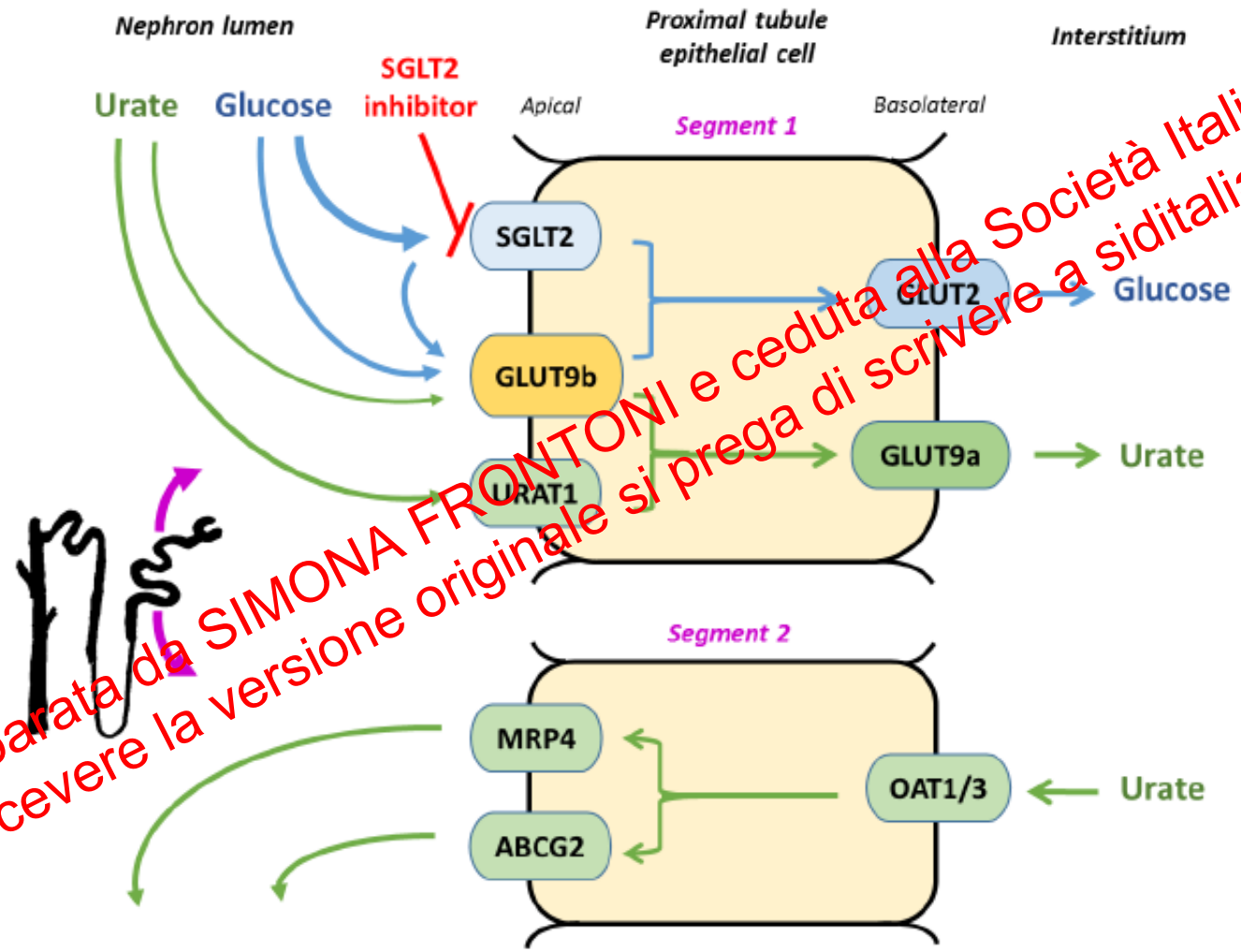
Uric acid and the cardio-renal effects of SGLT2 inhibitors



Bailey CJ et al, Diabetes Obes Metab 2019

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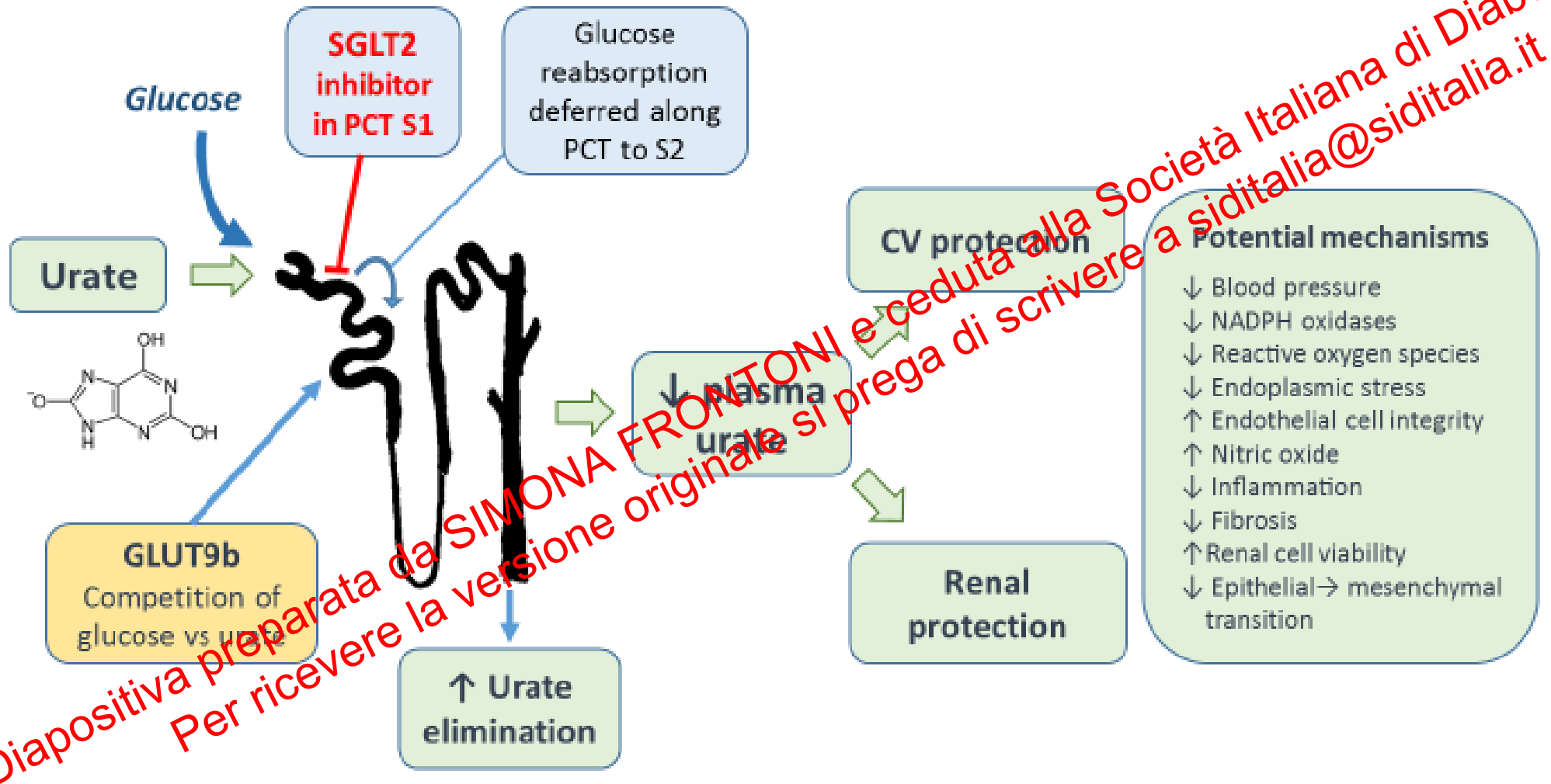


Bailey CJ et al, Diabetes Obes Metab 2019

Altri meccanismi

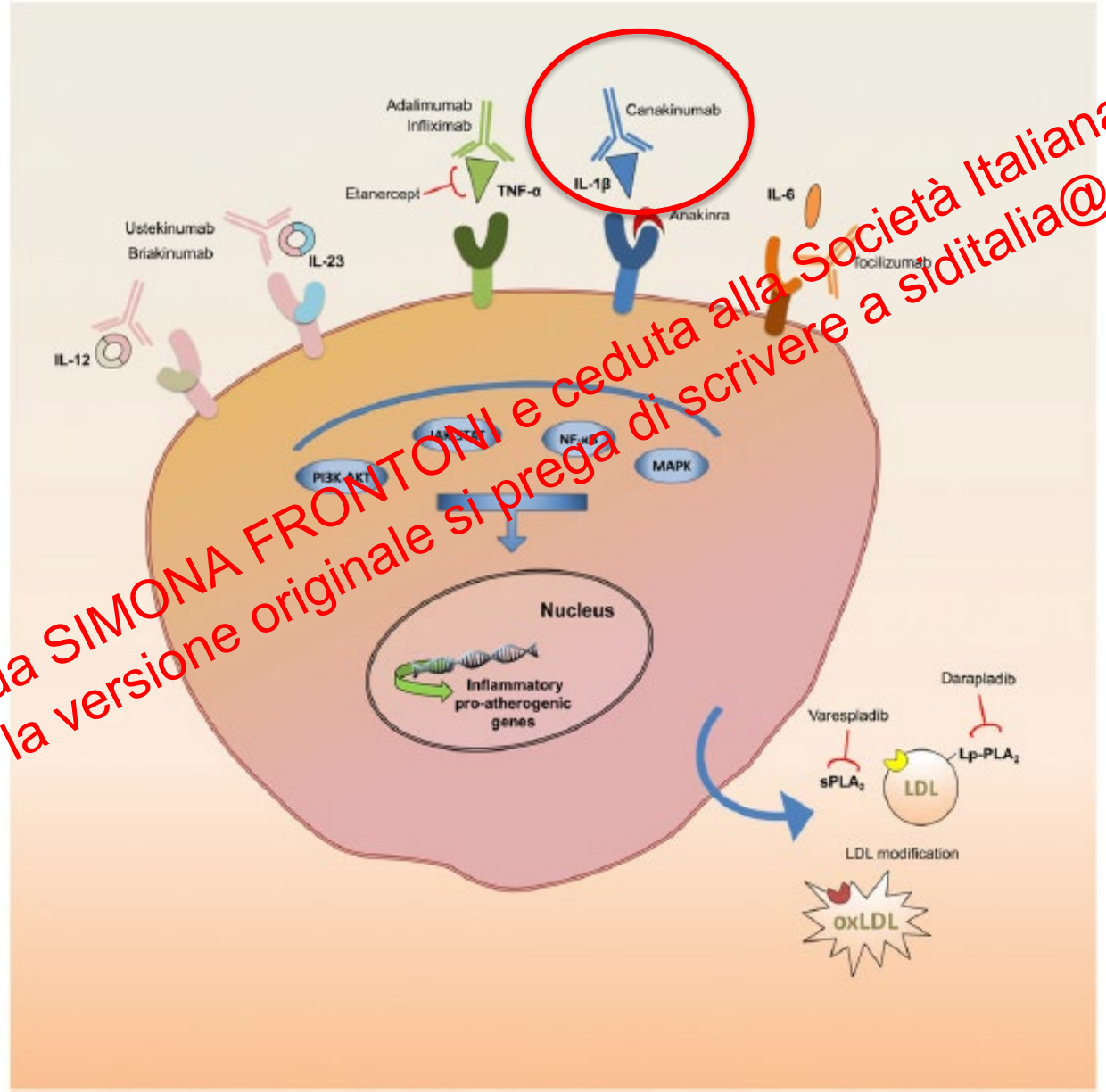
- Trigliceridi
- Acido urico
- Infiammazione

Targeting inflammation to reduce CV disease risk: a realistic prospect?

Target	Intervention	Observational studies (low weighted evidence of causal inference)	Mendelian randomization studies (intermediate weighted evidence of causal inference)	Randomized trials (strong weighted evidence of causal inference)
TNF-α	Adalimumab Infliximab Etanercept	↑ Circulating TNF-α ↑ CVD risk Biological use ↓risk of CVD (Greenberg *et al.*, 2011) Biological use ↓NT-proBNP (Peters *et al.*, 2010)	NA	↑Infections (Singh *et al.*, 2011) **? CVD risk**
IL-6R	Tocilizumab	↑ Circulating IL-6 ↑CVD risk (Sarwar *et al.*, 2012; Interleukin-6 Receptor Mendelian Randomisation Analysis (IL6R MR) Consortium, 2012)	IL6R SNPs rs7529229 and rs2228145 (Sarwar *et al.*, 2012) ↓CRP **↓risk of CHD**	↑LDL-C, ↓lipoprotein(a), ↓fibrinogen, ↓D-dimer; ↔ small LDL, ↔ oxidized LDL, (McInnes *et al.*, 2015) **? CVD risk**
IL-12/23 p40	Ustekinumab Briakinumab	NA	NA	↓CRP (Toedter *et al.*, 2009) **↑CVD** (Tzellos *et al.*, 2013)
IL-1β	Canakinumab	NA	IL-1Ra SNPs rs6743376 and rs1542176 (Interleukin 1 Genetics Consortium, 2015)	Ongoing (https://clinicaltrials.gov/ct2/show/NCT01327846)
IL-1R	Anakinra (rIL-1RA)		↓IL-6; ↓CRP; **↑risk of CHD**	
Lp-PLA_2	Darapladib	↑Lp-PLA_2 mass and activity ↑CVD risk (Thompson *et al.*, 2010)	Several SNPs including rs1051931 (Casas *et al.*, 2010) ↔ **risk of CVD**	↓IL-6; ↓CRP (Mohler *et al.*, 2008) ↔ **risk of CVD** (O'Donoghue *et al.*, 2014; White *et al.*, 2014)
sPLA_2	Varespladib	↑sPLA_2 circulating concentration ↑CVD risk (Boekholdt *et al.*, 2005)	SNP rs11573156 (Holmes *et al.*, 2013) ↔ **risk of CVD**	↑**risk of CVD** (Nicholls *et al.*, 2014)
Multiple	Methotrexate	Methotrexate use ↓risk of CVD (Micha *et al.*, 2011)	NA	Ongoing (https://clinicaltrials.gov/ct2/show/NCT01594333)

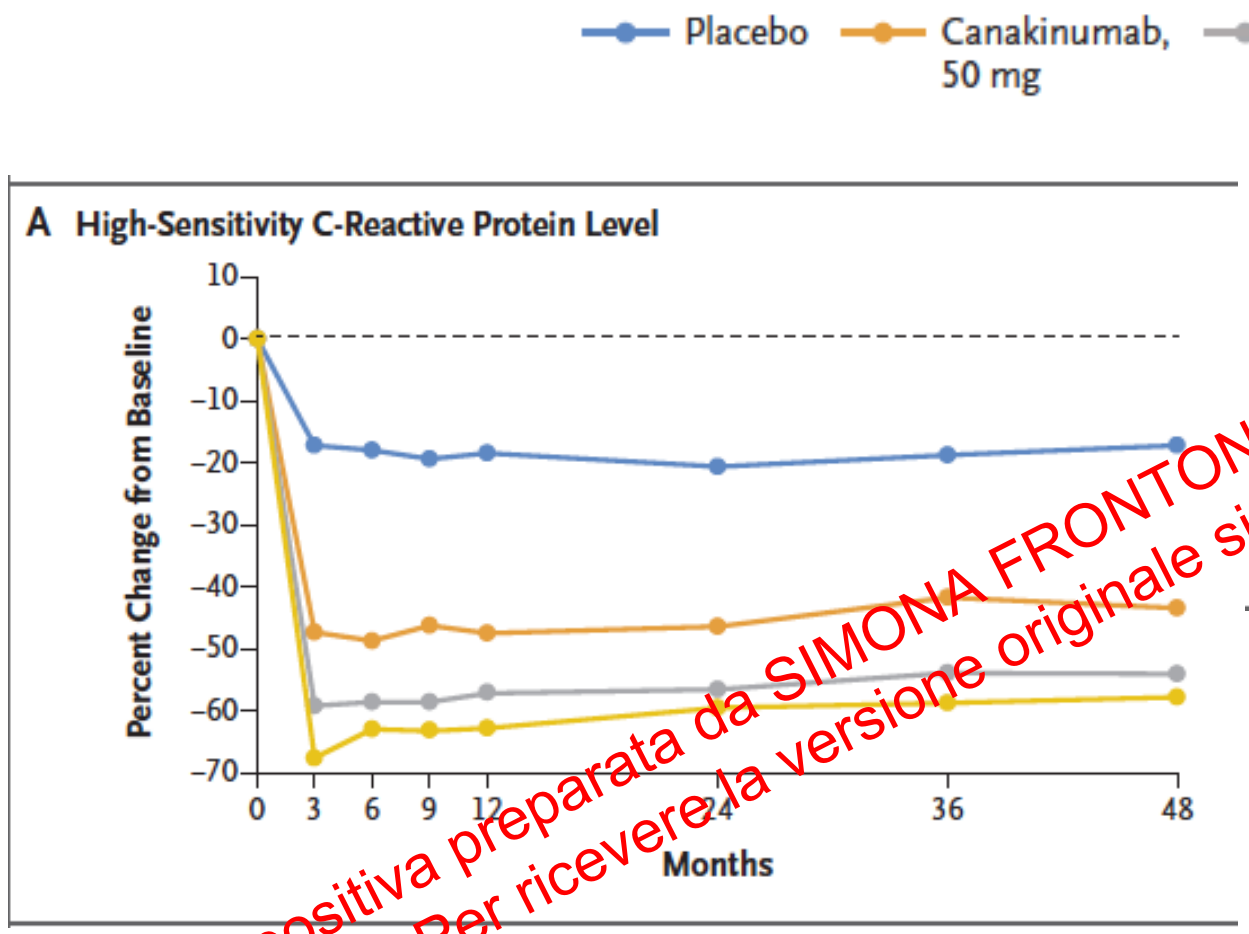
Welsh P, Br J Pharmacol 2017

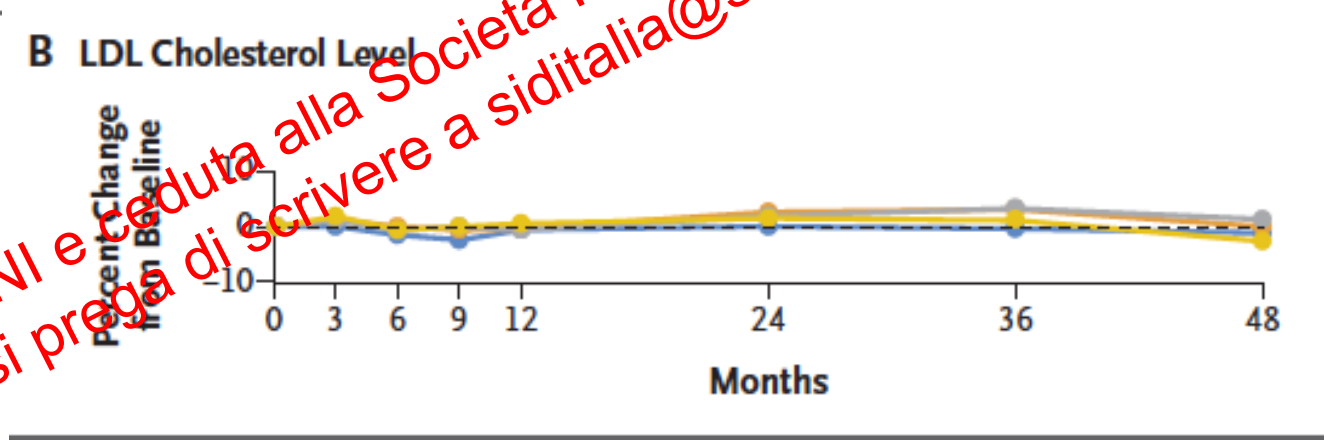
Pro-atherogenic and inflammatory pathways targeted by prospective anti-atherosclerotic antibodies and inhibitors

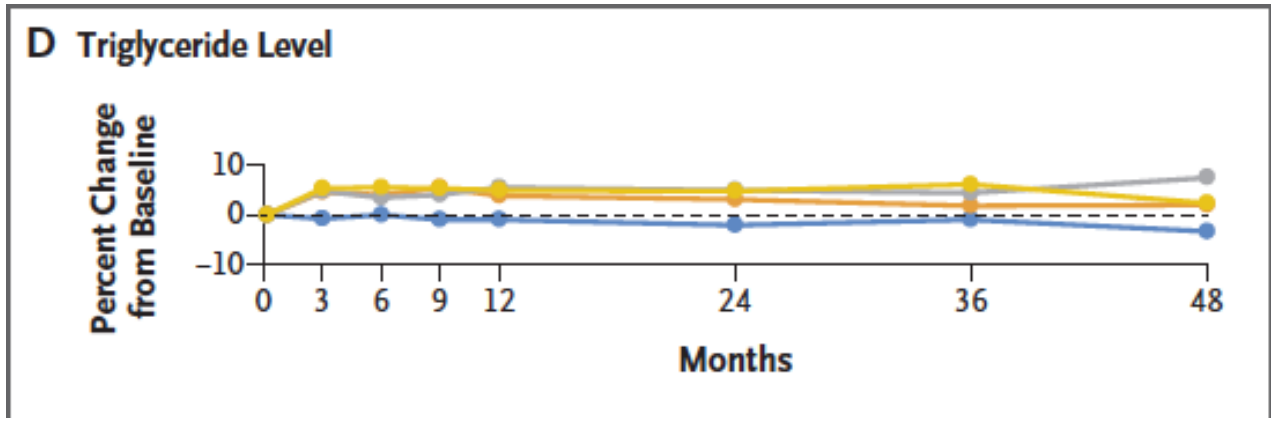


Welsh P, Br J Pharmacol 2017

Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease (the CANTOS trial)



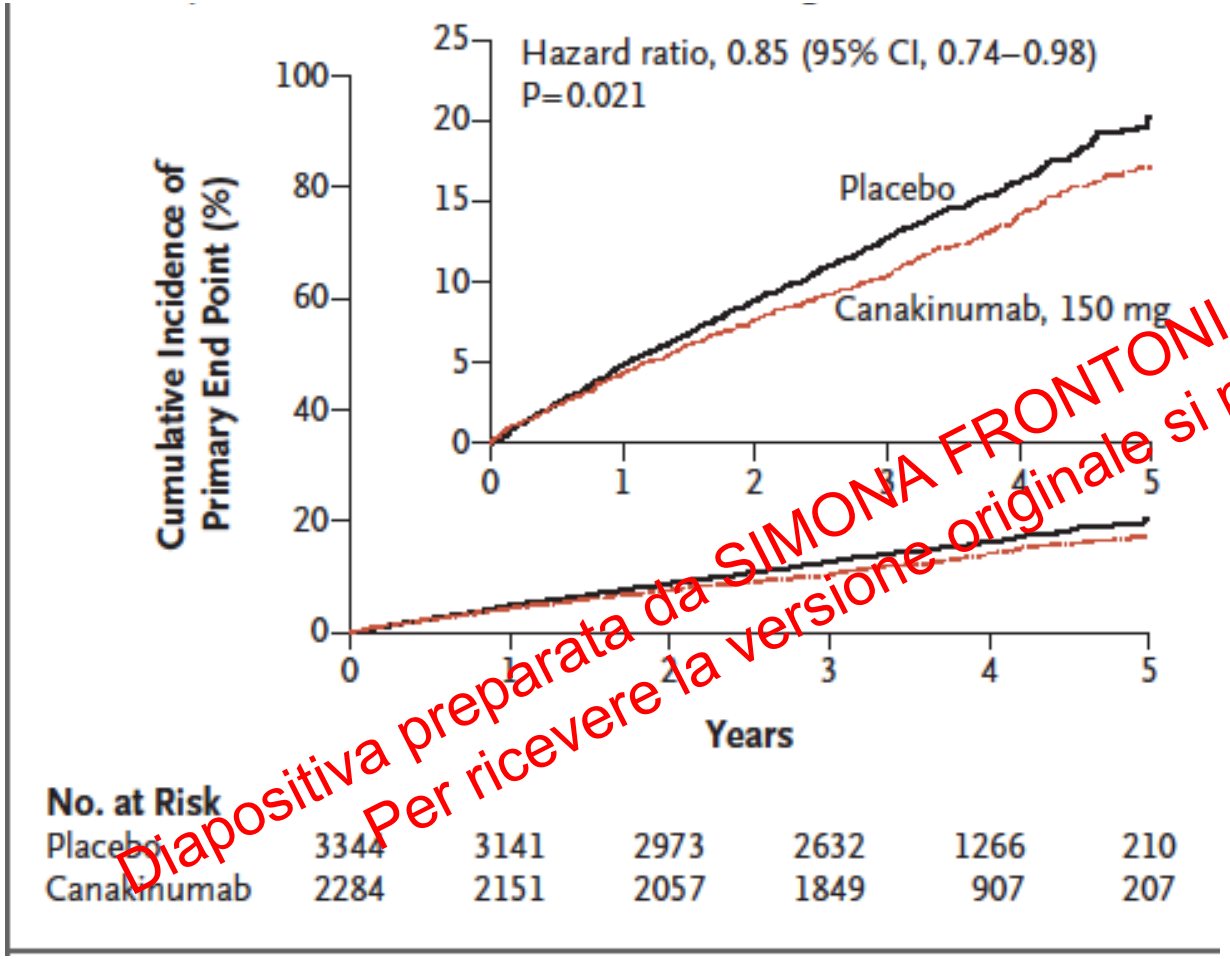




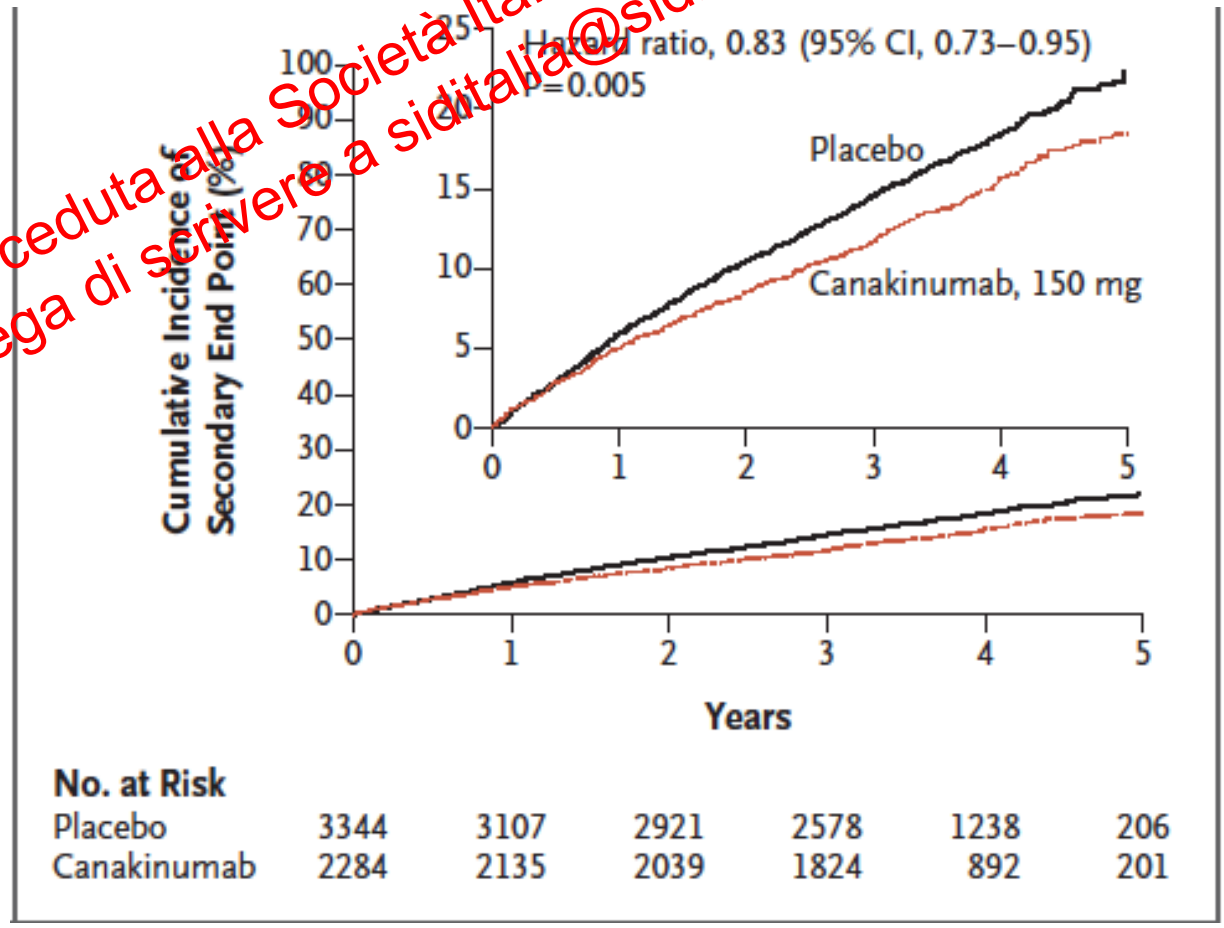
Ridker PM, et al. N Engl J Med 2017

Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease (the CANTOS trial)

Primary End Point with Canakinumab, 150 mg, vs. Placebo
non fatal myocardial infarction, nonfatal stroke, or cardiovascular death

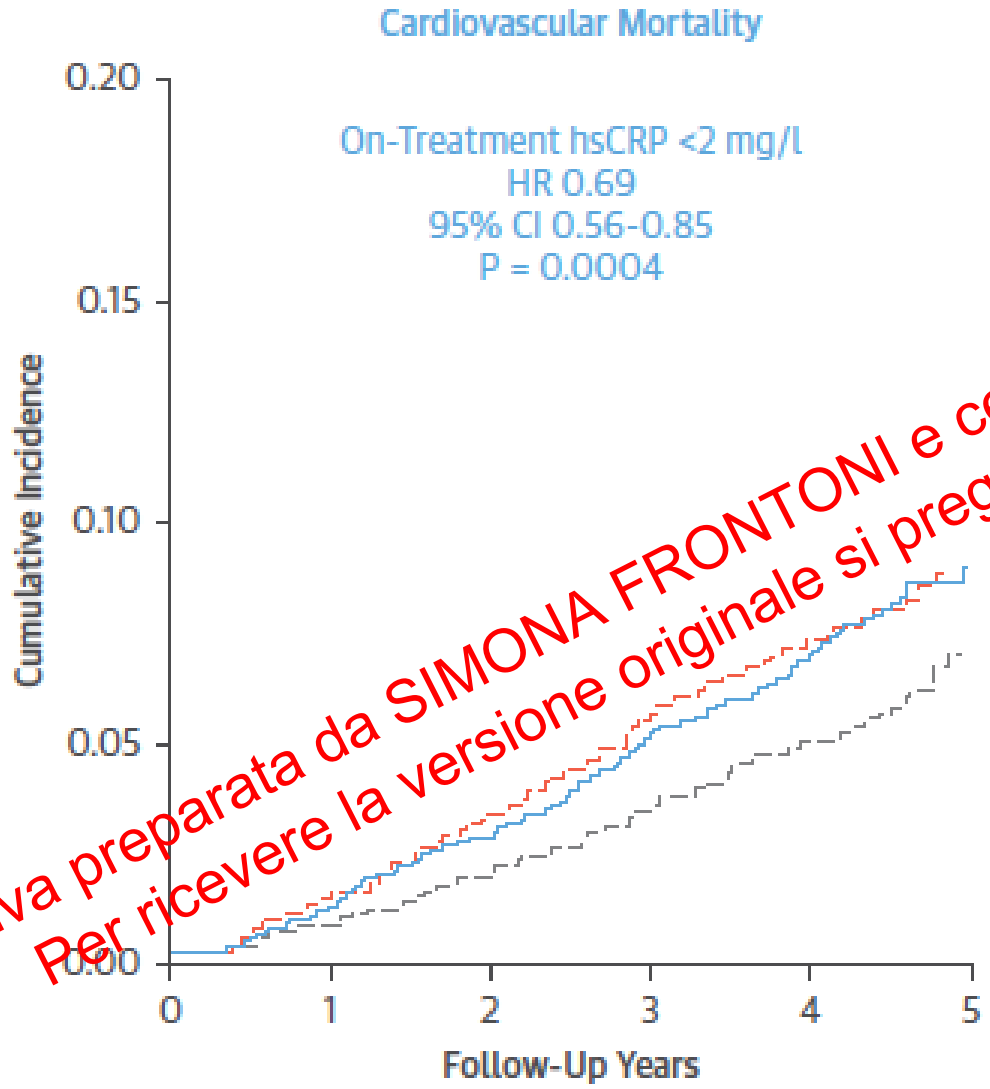


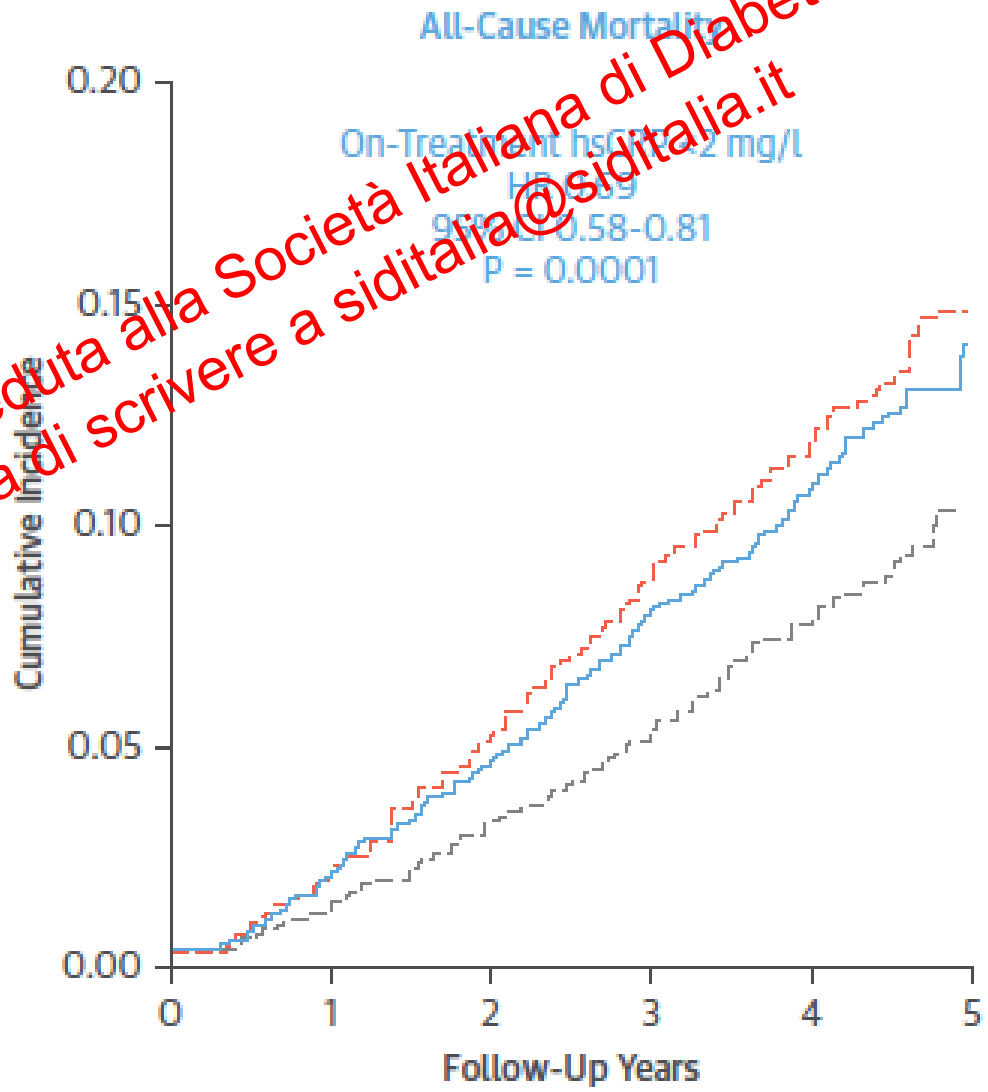
Key Secondary End Point with Canakinumab, 150 mg, vs. Placebo
additionally included hospitalization for unstable angina that led to urgent revascularization



Ridker PM, et al. N Engl J Med 2017

Greater risk reduction with greater hsCRP reduction (the CANTOS trial)

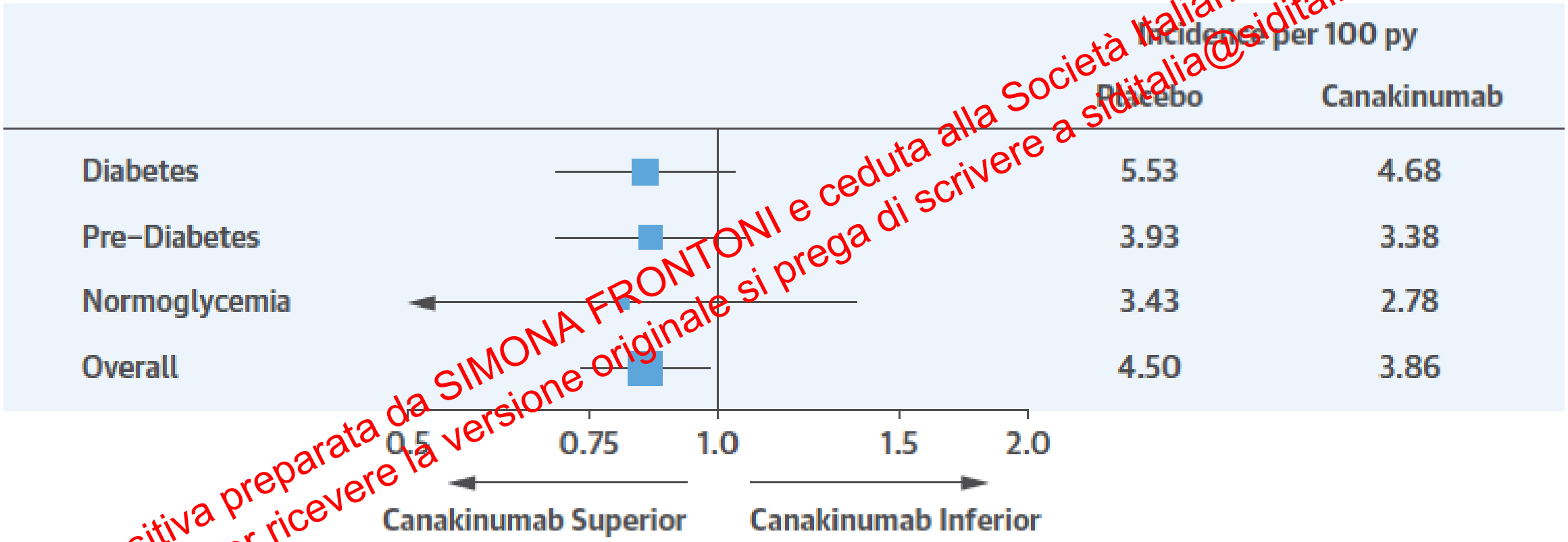




Placebo — Canakinumab, hsCRP >2 mg/L — Canakinumab, hsCRP <2 mg/L

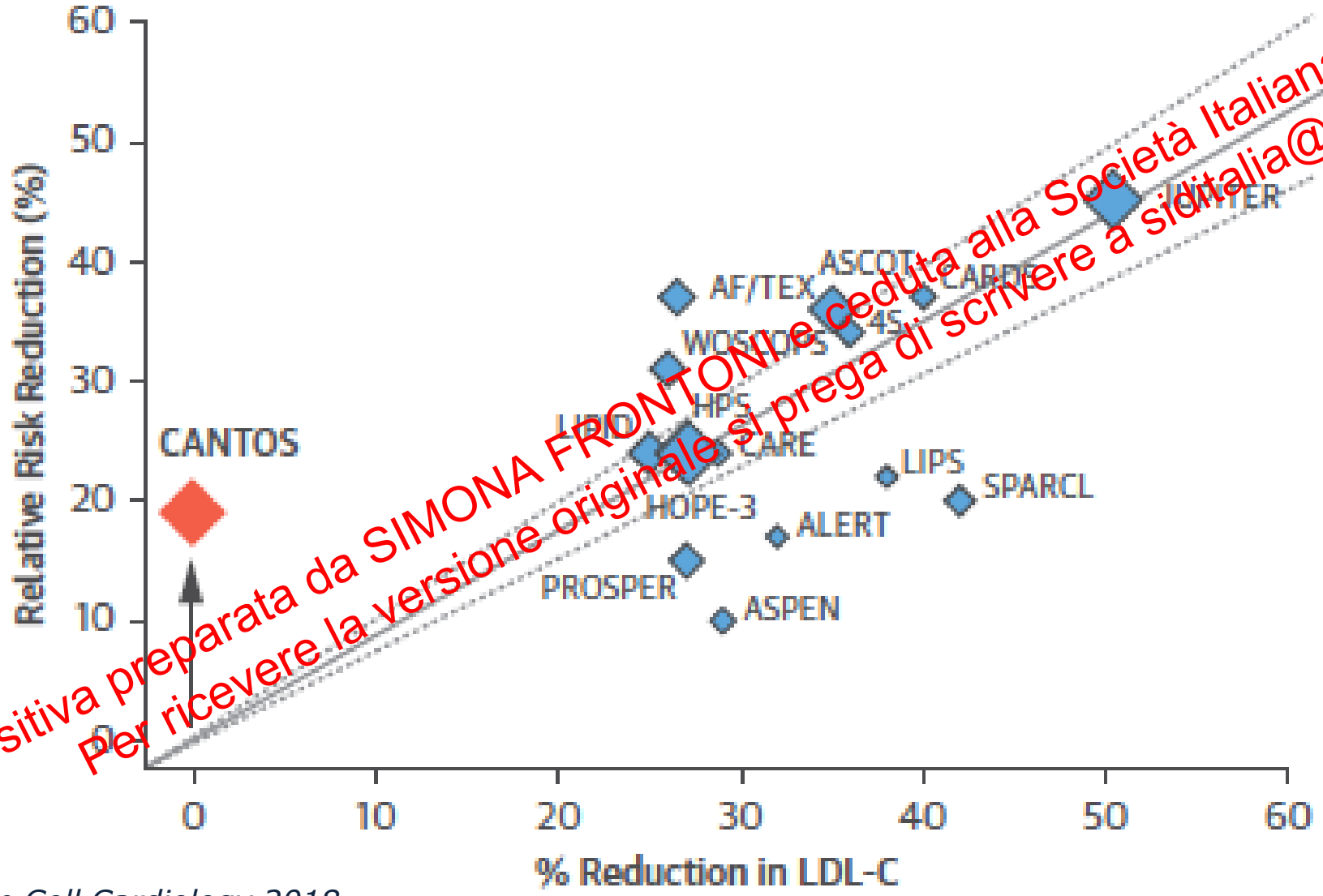
Ridker PM, et al. Circulation 2018

Canakinumab was equally effective in preventing major cardiovascular events in patients with diabetes, pre-diabetes and normoglycemia at study enter



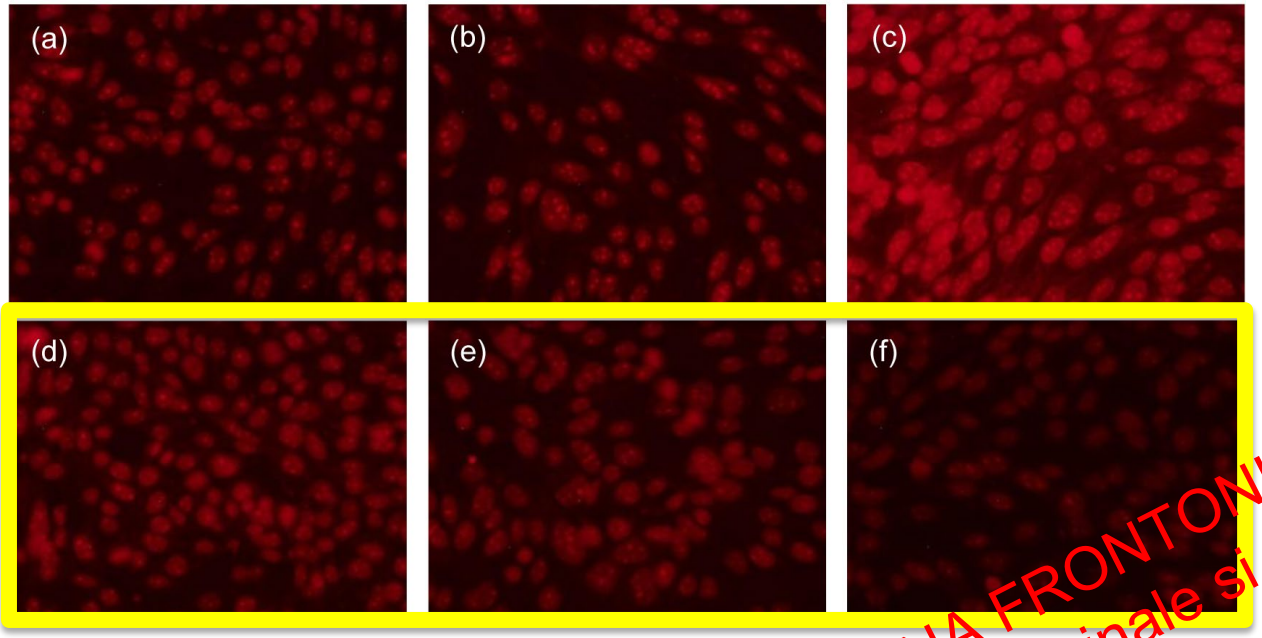
Everett BM, et al. J Am Coll Cardiol 2018

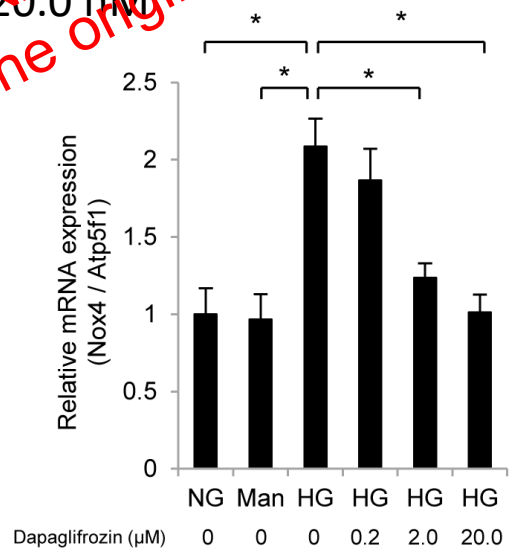
Cardiovascular event reduction with no change in LDLC: additive effects of inflammation inhibition to lipid lowering

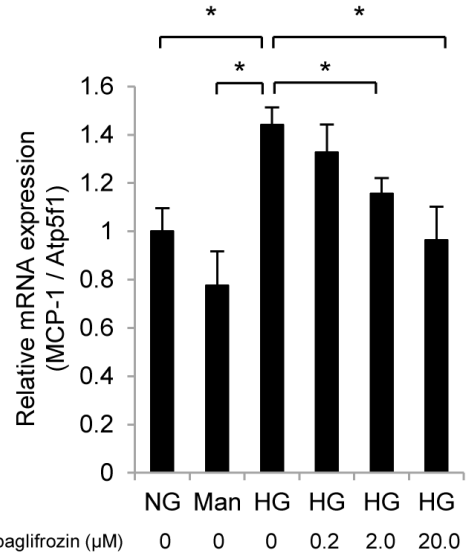


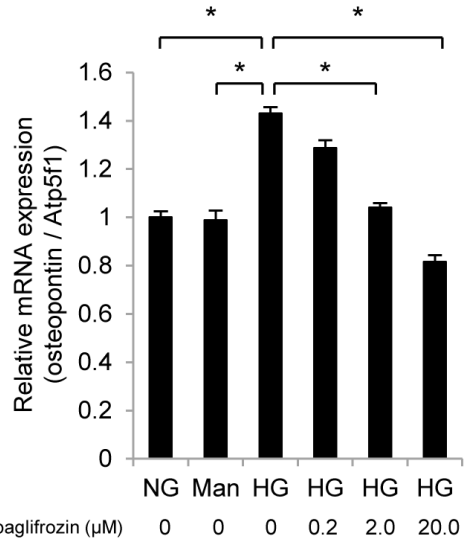
Ridker PM, J Am Coll Cardiology 2018

Dapagliflozin suppresses oxidative stress and inflammatory gene expression in cultured proximal tubular epithelial cells



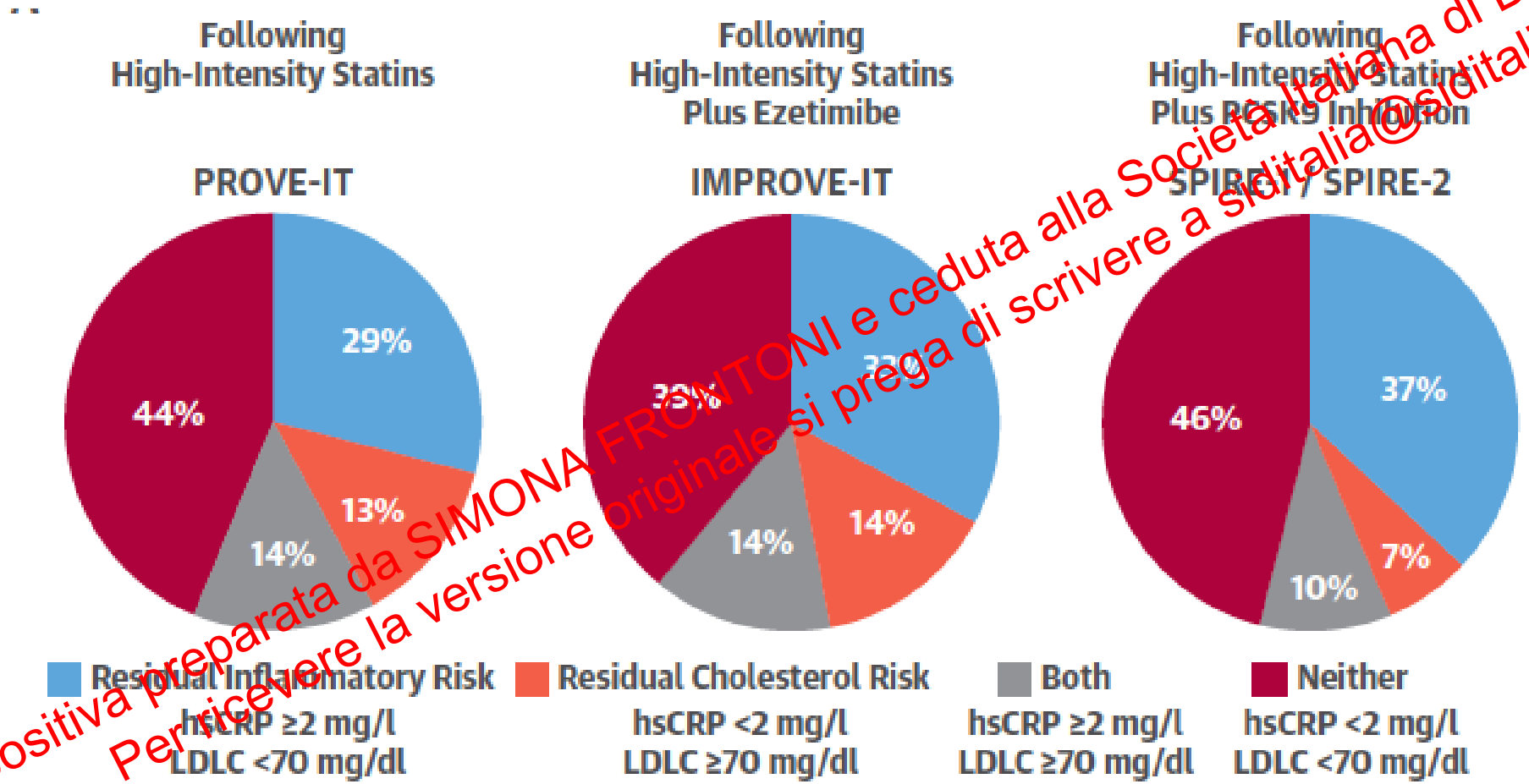






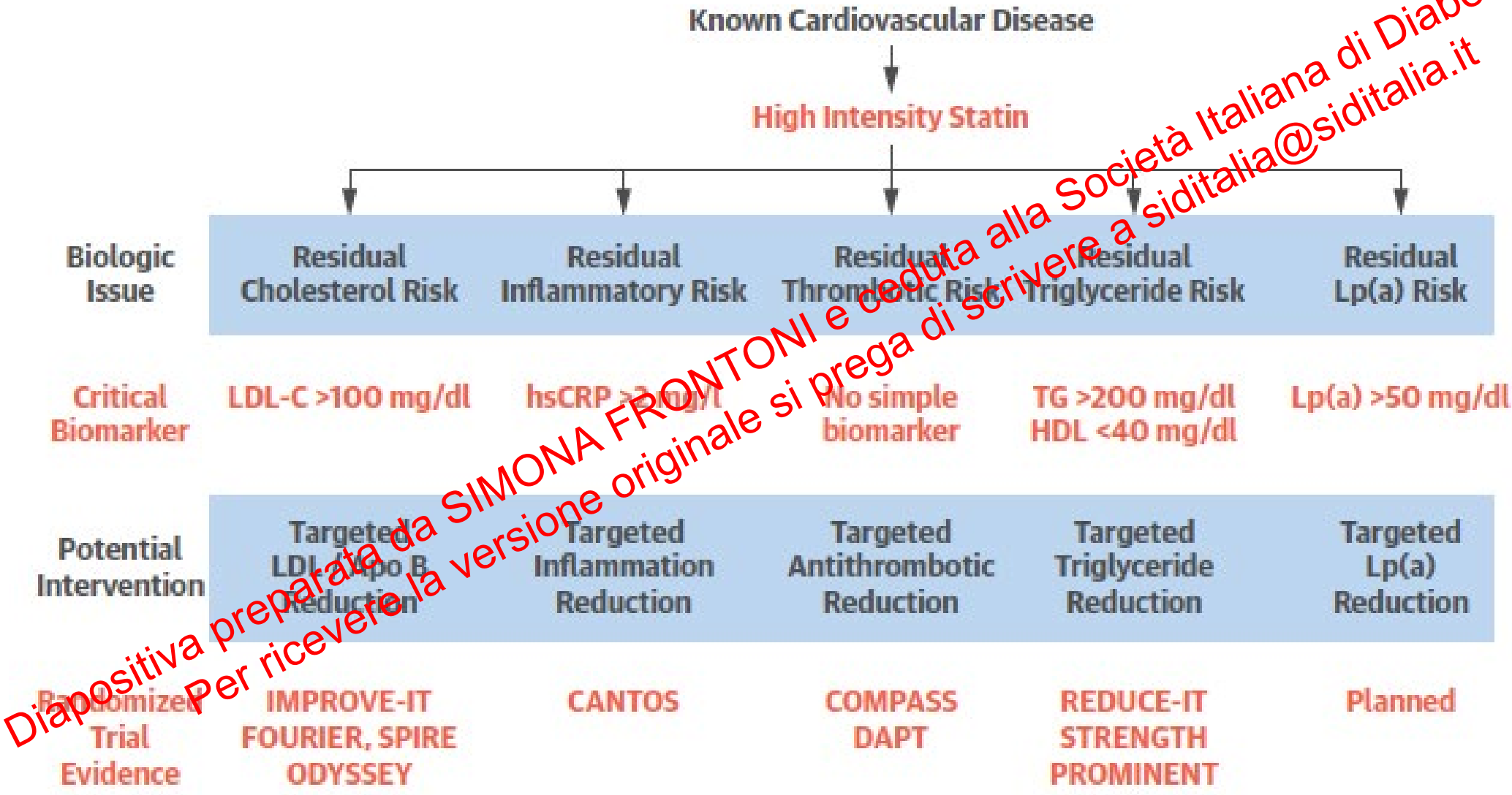
Terami N, PLOS ONE 2014

Atherosclerosis patients with "residual inflammatory risk" are more common that patients with "residual cholesterol risk"



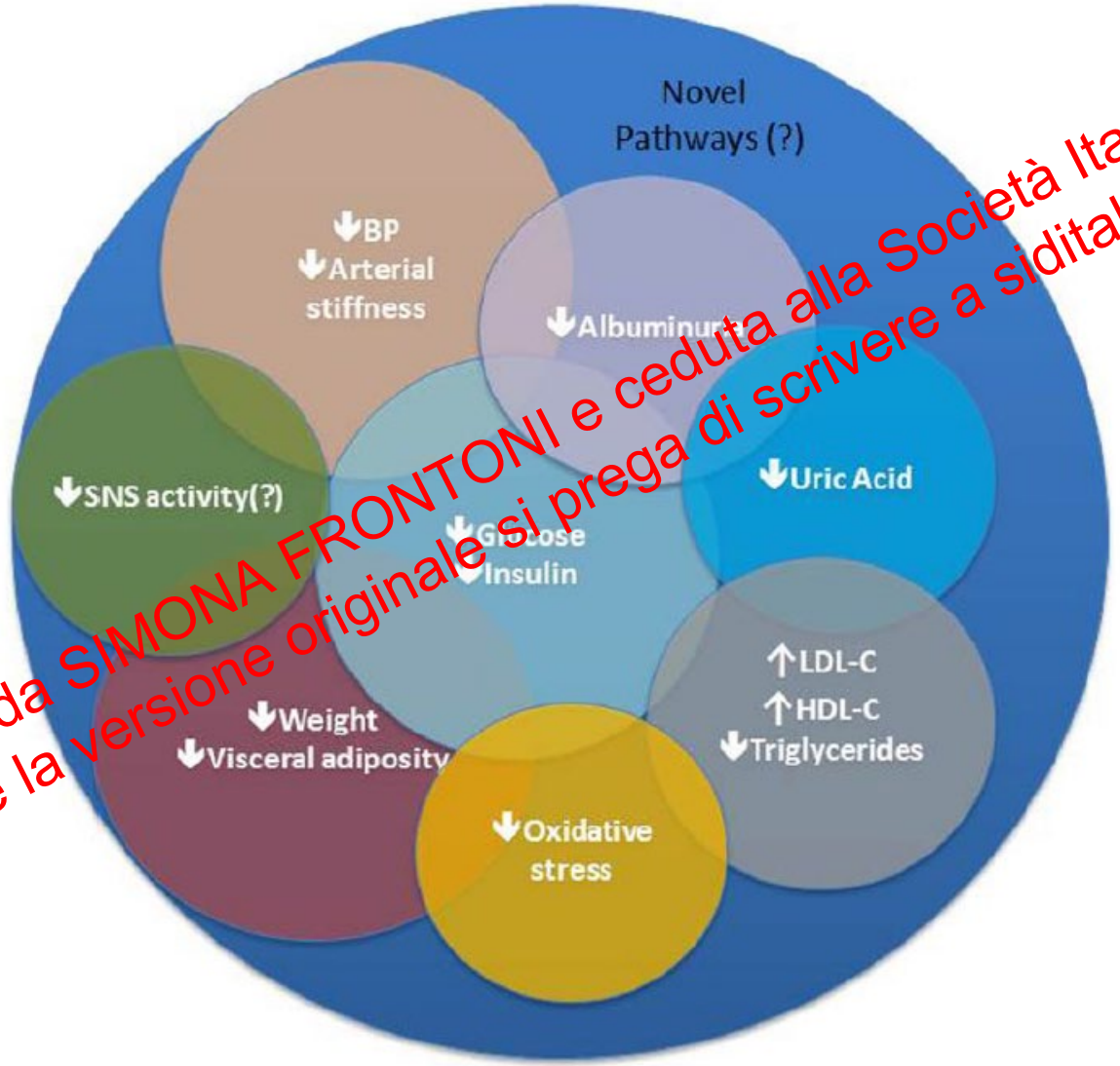
Ridker PM, et al. Circulation Res 2017
Pradhan A, et al. Circulation 2018

Redefining residual risk: moving toward personalized medicine



Ridker PM, et al. J Am Coll Cardiology 2018

Identified potential and novel pathways associated with CV effects of SGLT2-i



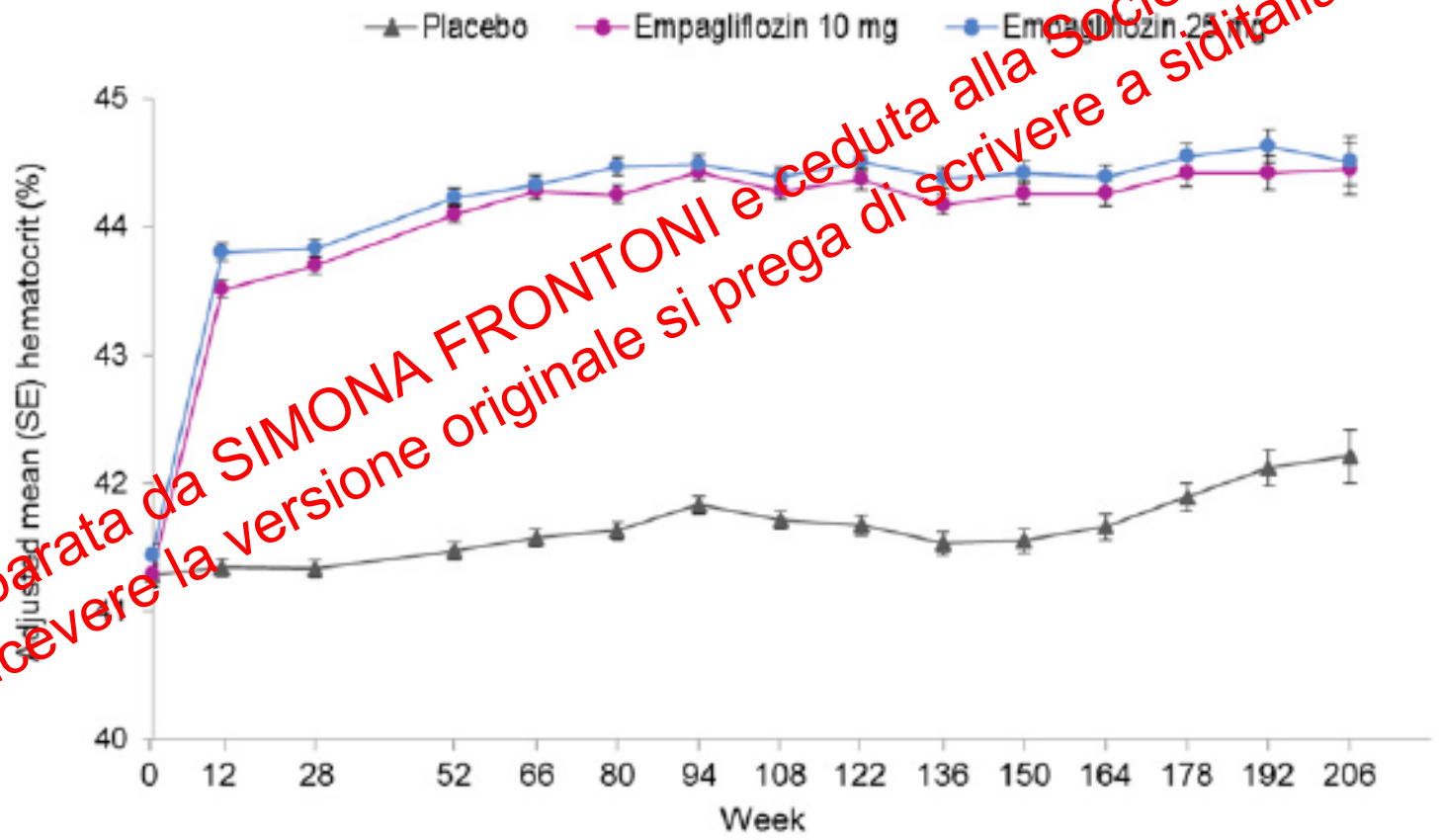
Inzucchi SE et al. Diab and Vasc Dis Res 2015

Altri meccanismi

- Trigliceridi
- Acido urico
- Infiammazione
- che altro?

Hematocrit over time in patients treated with empagliflozin and placebo.

Mixed-model repeated-measures analysis using all data up to individual trial completion in patients treated with one or more doses of study drug who had a baseline and post-baseline measurement



Inzucchi SE et al. Diabetes Care 2018

EMPA-REG outcome trial

changes in markers of plasma volume are the most important mediators of the reduction in risk of CV death with empagliflozin versus placebo

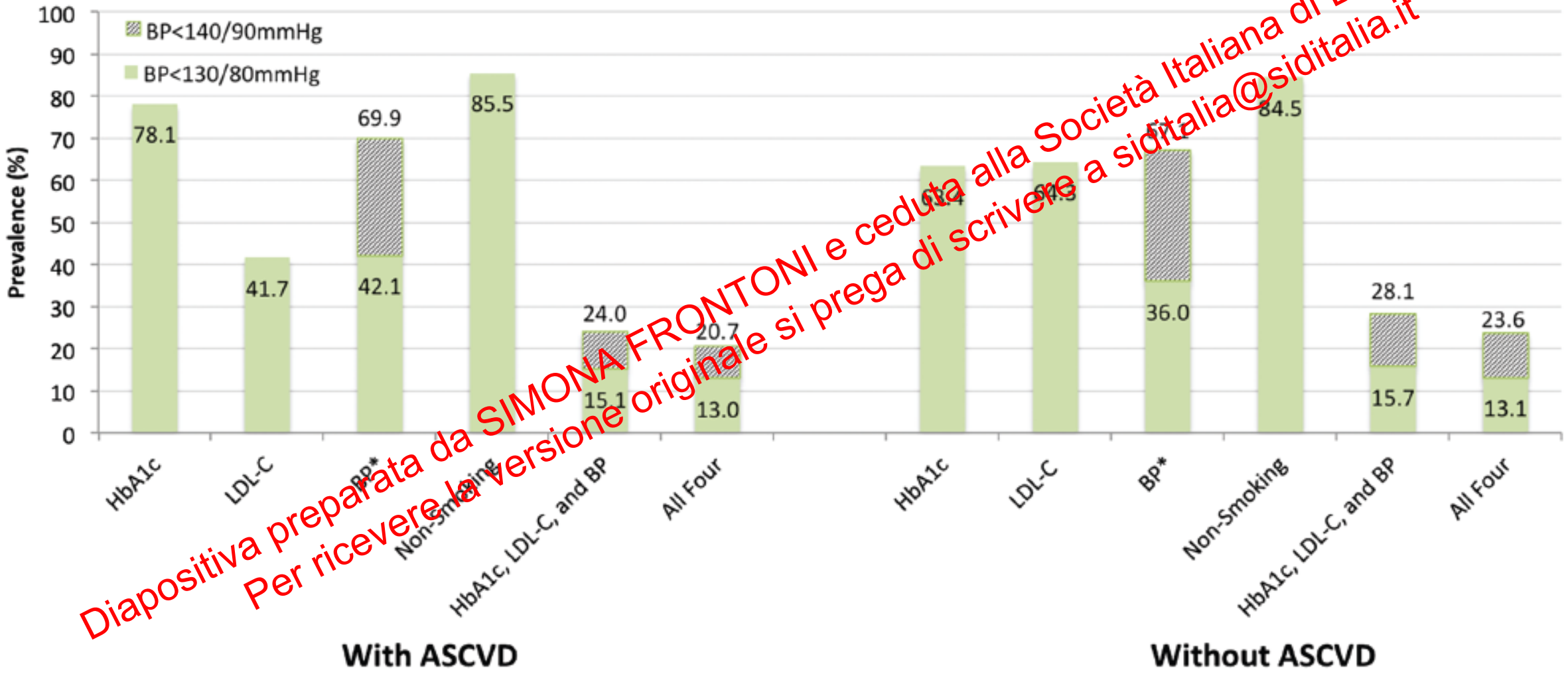
Univariate mediation analysis of risk of CV death with empagliflozin vs. placebo: time-dependent covariate analysis adjusting for the updated mean of each variable

	HR for CV death with empagliflozin vs. placebo (95% CI)	Percentage mediation
Unadjusted	0.615 (0.491, 0.770)	
Adjusted for		
HbA_{1c}	0.687 (0.543, 0.868)	22.8
FPG	0.709 (0.559, 0.898)	29.3
SBP	0.610 (0.486, 0.766)	−1.7
DBP	0.618 (0.493, 0.774)	1.0
Heart rate	0.623 (0.495, 0.782)	2.7
LDL-C	0.591 (0.471, 0.741)	−8.2
HDL-C	0.629 (0.500, 0.789)	4.6
logTG	0.603 (0.481, 0.757)	−4.1
FFAs	0.587 (0.463, 0.743)	−9.6
logUACR	0.672 (0.536, 0.844)	18.2
eGFR (MDRD)	0.601 (0.480, 0.752)	−4.7
eGFR (CKD-EPI)	0.597 (0.477, 0.748)	−6.1
Weight	0.588 (0.466, 0.741)	−9.2
BMI	0.588 (0.466, 0.742)	−9.2
WC	0.602 (0.480, 0.755)	−4.4
Hematocrit	0.791 (0.620, 1.009)	51.8
Hemoglobin	0.768 (0.604, 0.978)	45.7
Albumin	0.717 (0.571, 0.900)	31.6
Uric acid	0.673 (0.536, 0.845)	18.5

Inzucchi SE et al. Diabetes Care 2018

Composite cardiovascular risk factor target achievement and its predictors in US adults with diabetes: The Diabetes Collaborative Registry

(n: 74 393 patients, mean age 69.0 years, 41.0% women)



Fan W et al. DOM 2019

Conclusioni

- non ci basta più ottenere soltanto il goal glicemico, quello pressorio e quello lipidico
- dobbiamo volere di più e pretendere che le molecole che utilizziamo ci garantiscano una protezione cardiovascolare globale
- dobbiamo lavorare per comprendere meglio i meccanismi implicati nel rischio cardiovascolare del diabete e sviluppare strategie terapeutiche ad hoc

…nel frattempo

- utilizziamo i farmaci giusti (e ne abbiamo!)
- arriviamo a goal con glicemia, pressione e lipidi

trigliceridi

Online version at http://www.minervamedica.it

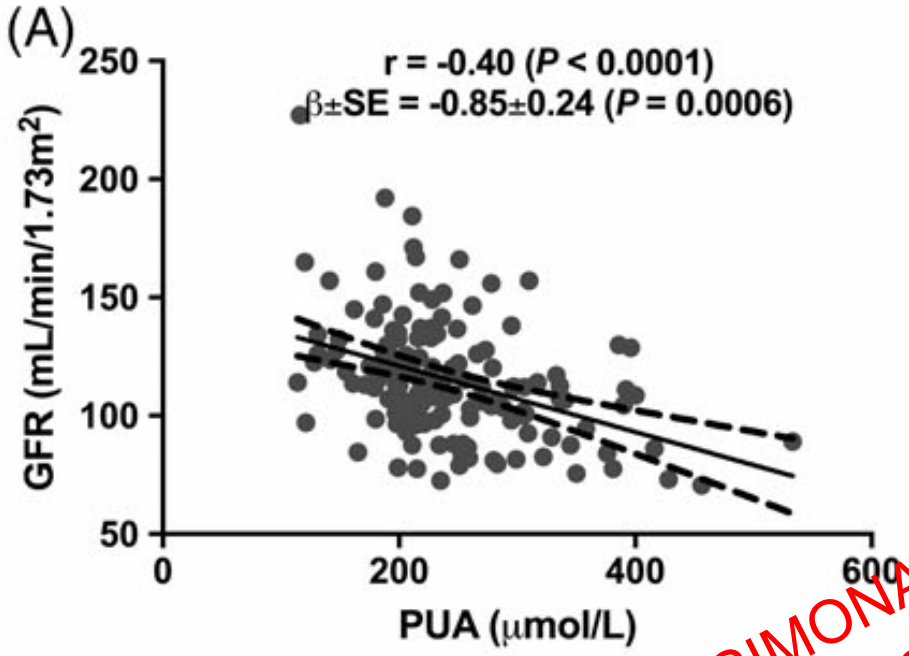
Minerva Endocrinologica 2018 September;43(3):229-35
DOI: 10.23736/S0391-1977.16.02550[illegible]

ORIGINAL ARTICLE

Effect of dapagliflozin administration on metabolic syndrome, insulin sensitivity, and insulin secretion

Manuel GONZÁLEZ-ORTIZ*, Miriam MENDEZ-del VILLAR, Esperanza MARTÍNEZ-ABUNDIS, Alejandra M. RAMÍREZ-RODRÍGUEZ

Association between uric acid, renal haemodynamics and arterial stiffness over the natural history of T1D



Received: 2 November 2018 | Revised: 3 February 2019 | Accepted: 10 February 2019
DOI: 10.1111/dom.13665

WILEY

ORIGINAL ARTICLE

Association between uric acid, renal haemodynamics and arterial stiffness over the natural history of type 1 diabetes

Yuliya Lytvyn PhD[1] | Petter Bjornstad MD[2,3] | Julie A. Lovshin PhD[4] |

Lytvyn Y et al, Diabetes Obes Metab 2019

Acido urico

Published in final edited form as:
Curr Diab Rep. 2013 August ; 13(4): 550–559. doi:10.1007/s11892-013-0381-0.

Uric Acid Lowering to Prevent Kidney Function Loss in Diabetes: The Preventing Early Renal Function Loss (PERL) Allopurinol Study

David M. Maahs, MD, PhD[1,2], M. Luiza Caramori, MD, PhD[3], David Z.I. Cherney, MD, PhD[4], Andrzej T. Galecki, MD, PhD[5], Chuanyun Gao, MD[6], Diana Jalal, MD[2], Bruce A. Perkins,

EDITORIAL

Inflammatory residual risk: An emerging target to reduce cardiovascular disease?

Infiammazione

Circulation

PERSPECTIVE

Mortality Differences Associated With Treatment Responses in CANTOS and FOURIER

Insights and Implications

iammazione

METHODS: Diabetes (D) was induced by streptozotocin (65 mg/bwkg, *ip.*) in adult, male Wistar rats. Following the onset of D, animals were treated for six weeks with dapagliflozin (D+DAPA, 1 mg/bwkg/day, *po.*). Metabolic, renal parameters and kidn fibrosis were evaluated. Hypoxia marker HIF1-α, as well as *O*-GlcNAc, OGT and OG protein levels were measured. Specific markers of tubular damage (NGAL, KIM-1), profibrotic factors (CTGF, PDGF, TGF-β, PAI-1) and proinflammatory cytokines (TNF-α, IL-1β, IL-6) were determined.

RESULTS: Development of DKD was confirmed by functional impairment, massive proteinuria and structural damage of kid
256±10.9 *vs.* D+DAPA: 333±13.9 g; p<
37±2.7 *vs.* D+DAPA: 18±5.6 mmol/L; p
nine clearance: D: 3.8±0.4 *vs.* D+DAPA:
mitigated tubular hypoxia (HIF-1α) and
O-GlcNAcylation and OGT levels. Subse
PDGF, TGF-β, PAI-1) expression and re
Renal proinflammatory cytokine (TNF-α
by DAPA.

CONCLUSIONS: Our results support th
experimental DKD. Here we identified a
tubular hypoxia and inhibition of OGT b
GlcNAcylation. These processes in turn l
renal function. *Funding: LP008/2017, OT
VKE-2017-00006, EEMOFAKT-2017*

Long-Term Treatment with the Sodium Glucose Cotransporter 2 Inhibitor, Dapagliflozin, Ameliorates Glucose Homeostasis and Diabetic Nephropathy in *db*/*db* Mice

Naoto Terami[1], Daisuke Ogawa[1,2]*, Hiromi Tachibana[1], Takashi Hatanaka[1], Jun Wada[1], Atsuko Nakatsuka[1], Jun Eguchi[1], Chikage Sato Horiguchi[1], Naoko Nishii[1], Hiroshi Yamada[3], Kohji Takei[3], Hirofumi Makino[1]

Review

Potential Drug Combinations to Reduce Cardiovascular Disease Burden in Diabetes

Sivaram Pillarisetti[1,2,*]

FP408 **NOVEL MOLECULAR MECHANISMS IN THE RENOPROTECTIVE EFFECT OF SGLT2 INHIBITORS VIA MITIGATION OF TUBULAR HYPOXIA AND PROTEIN *O*-GLCNACYLATION**

Dora Balogh[2], Judit Hodrea[2], Lilla Lenart[2], Adam Hosszu[4,2], Csenge Mesko[1], Adam Vannay[1], Laszlo Wagner[4], Attila Szabo[1,3], Andrea Fekete[1,2]

[1]*Pediatrics and Nephrology Research Group, MTA-SE, Budapest, Hungary, [2]Lendület Diabetes Research Group, MTA-SE, Budapest, Hungary, [3]1st Department of Pediatrics, Semmelweis University, Budapest, Hungary and [4]Department of Transplantation and Surgery, Semmelweis University, Budapest, Hungary*

INTRODUCTION AND AIMS: Tubular hypoxia has recently been rediscovered as a major factor in the progression of diabetic kidney disease (DKD). Hypoxia is also known to be in strong association with elevated glucose consumption and increased protein *O*-GlcNAcylation. We previously showed that enhanced *O*-GlcNAcylation (increased addition of single O‑GlcNAc moieties by O‑GlcNAc tranferase (OGT) or decreased removal by O‑GlcNAcase (OGA) induces cellular processes leading to kidney fibrosis. Growing body of clinical data support that sodium-glucose co-transporter 2 inhibitors (SGLT2i) have renoprotective effects; but the mechanism of action is still not fully clarified. Considering the major role of SGLT2 in glucose metabolism, here we investigated whether SGLT2i's renoprotection is mediated in part by the decrement of tubular hypoxia and *O*-GlcNAcylation.