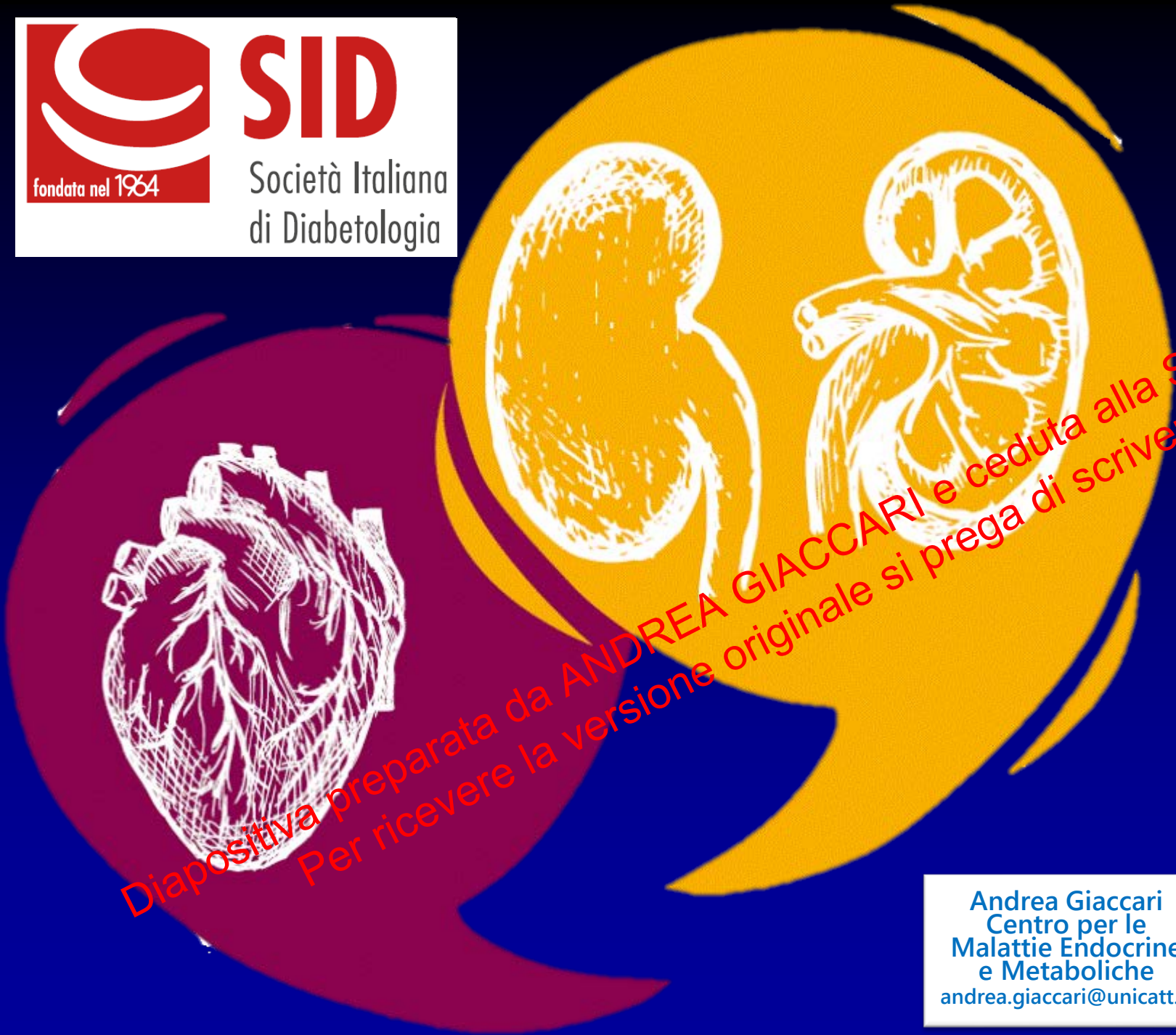
SID
Società Italiana di Diabetologia
fondata nel 1964



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

IL CROSS-TALK
cuore-rene
FISIOPATOLOGIA
ED ASPETTI CLINICI

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Catania
4 novembre 2019

TEAM DIABETE
Gemelli

disclosure

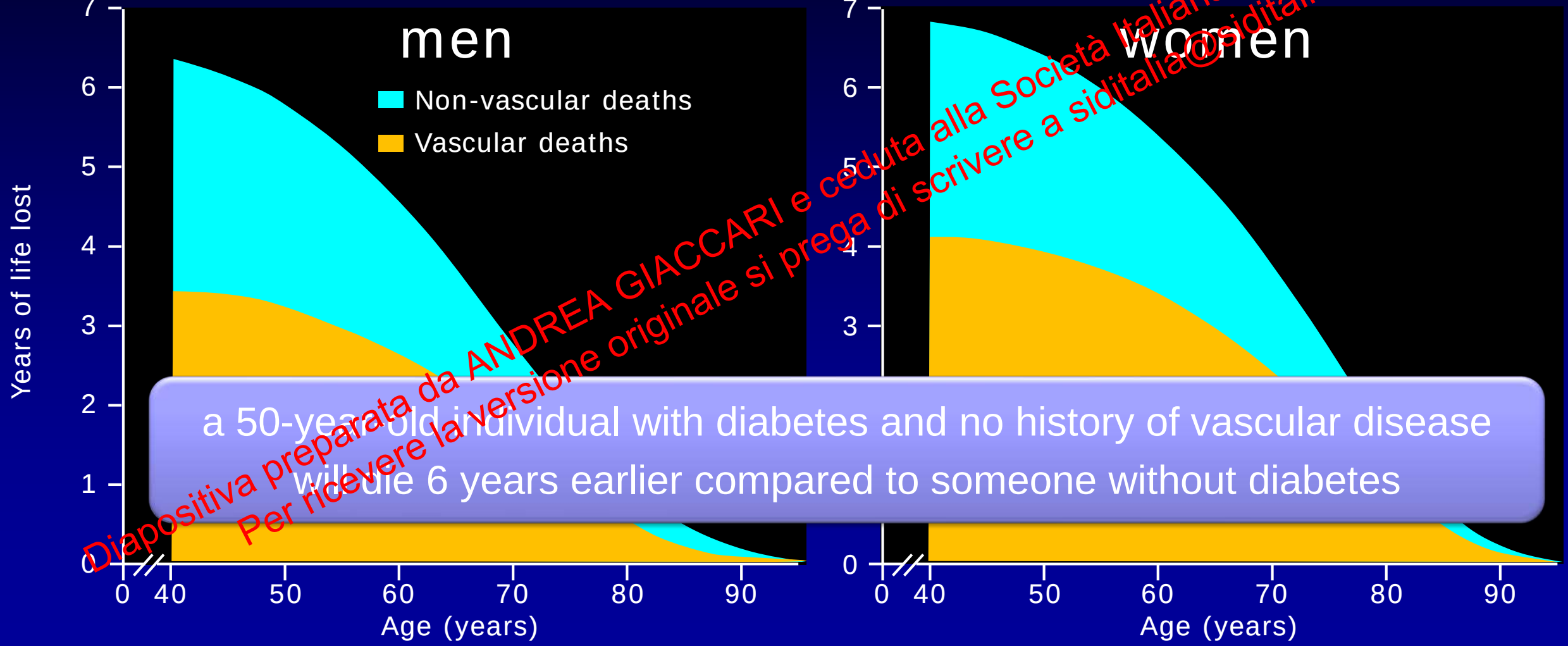
Il dr. Andrea Giaccari dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Amgen
- Astra Zeneca
- Boehringer Ingelheim
- Eli-Lilly
- MSD
- Sanofi

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

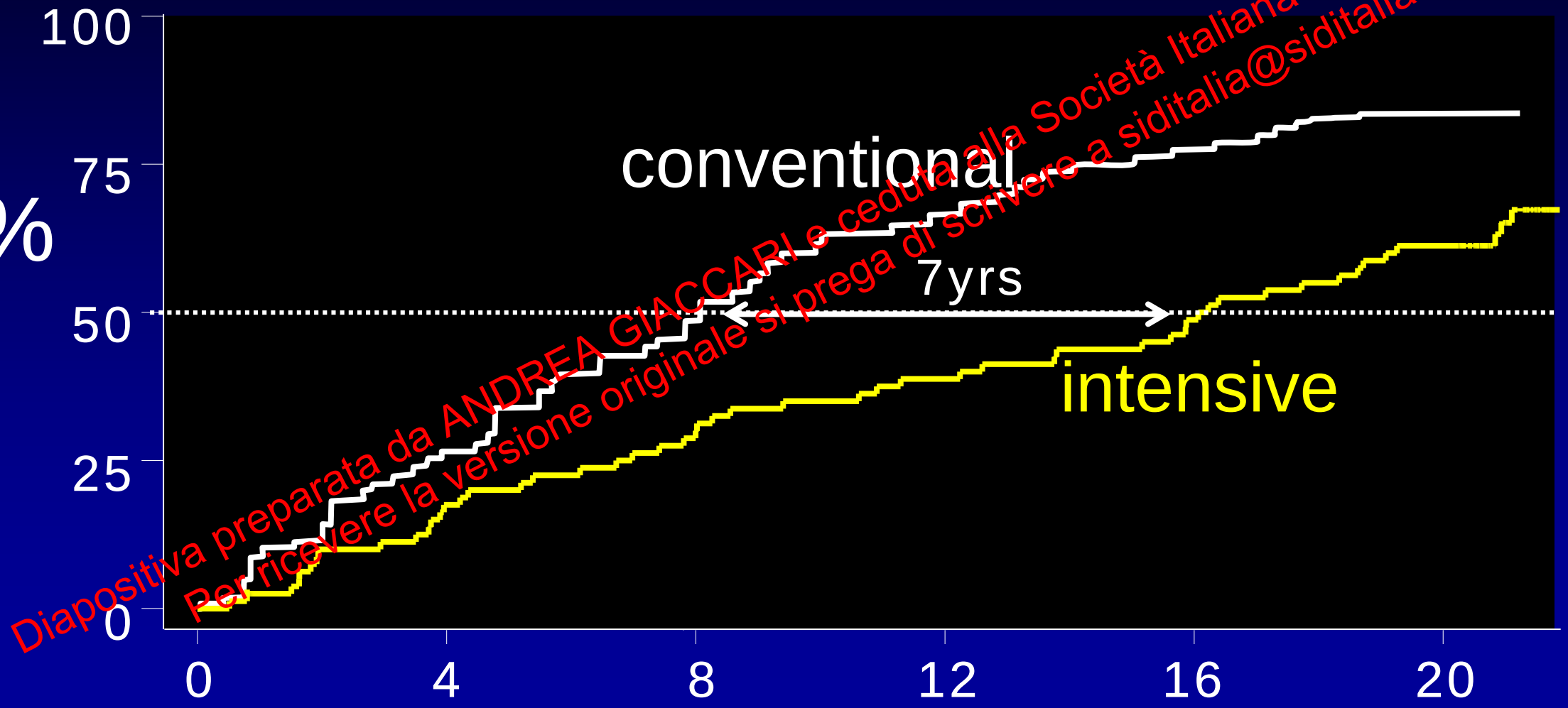
820,900 people in 97 prospective studies



a 50-year-old individual with diabetes and no history of vascular disease will die 6 years earlier compared to someone without diabetes

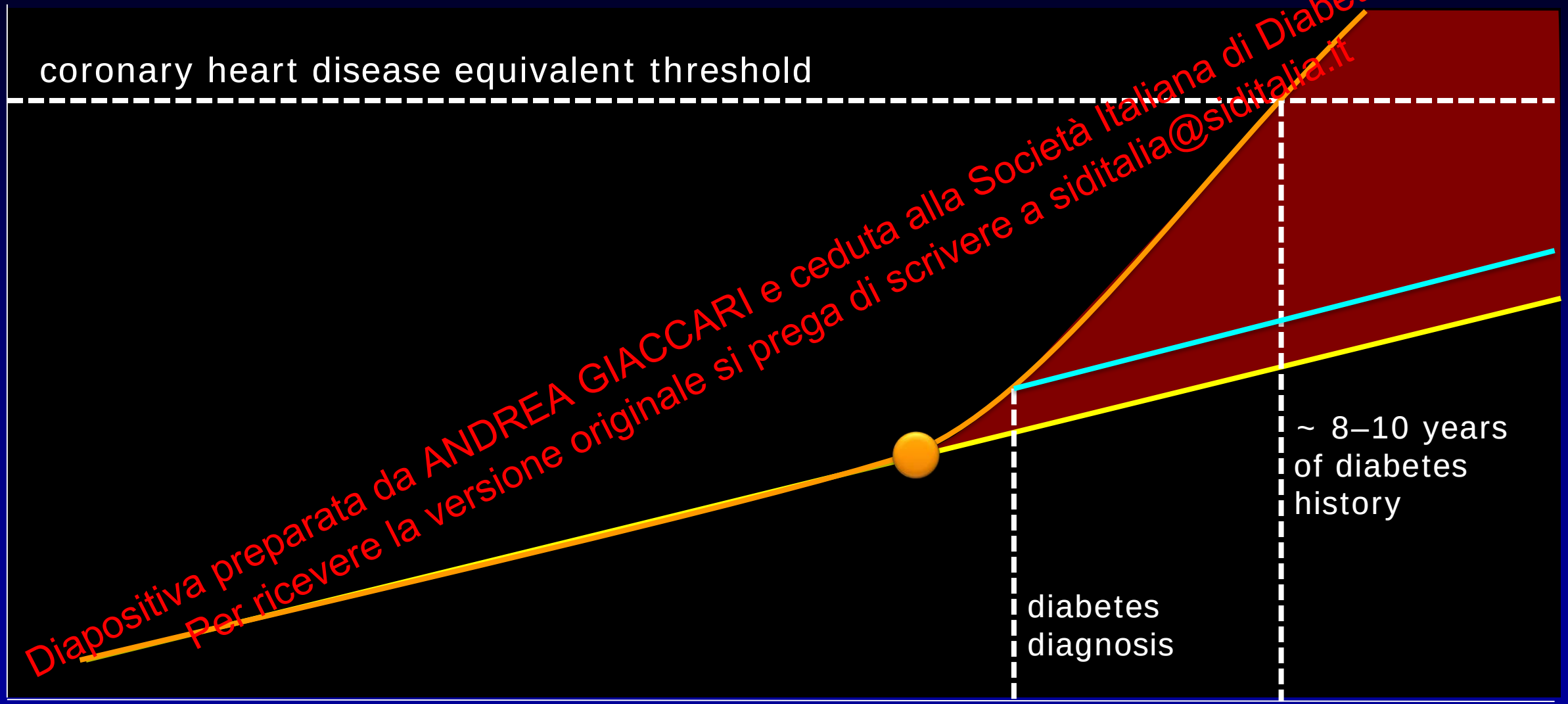
Seshasai SR et al. NEJM 364:829, 2011

STENO 2: 21 years of follow up: cumulative CV event or death



Gaede P.et al.: Diabetologia 59:2298, 2016

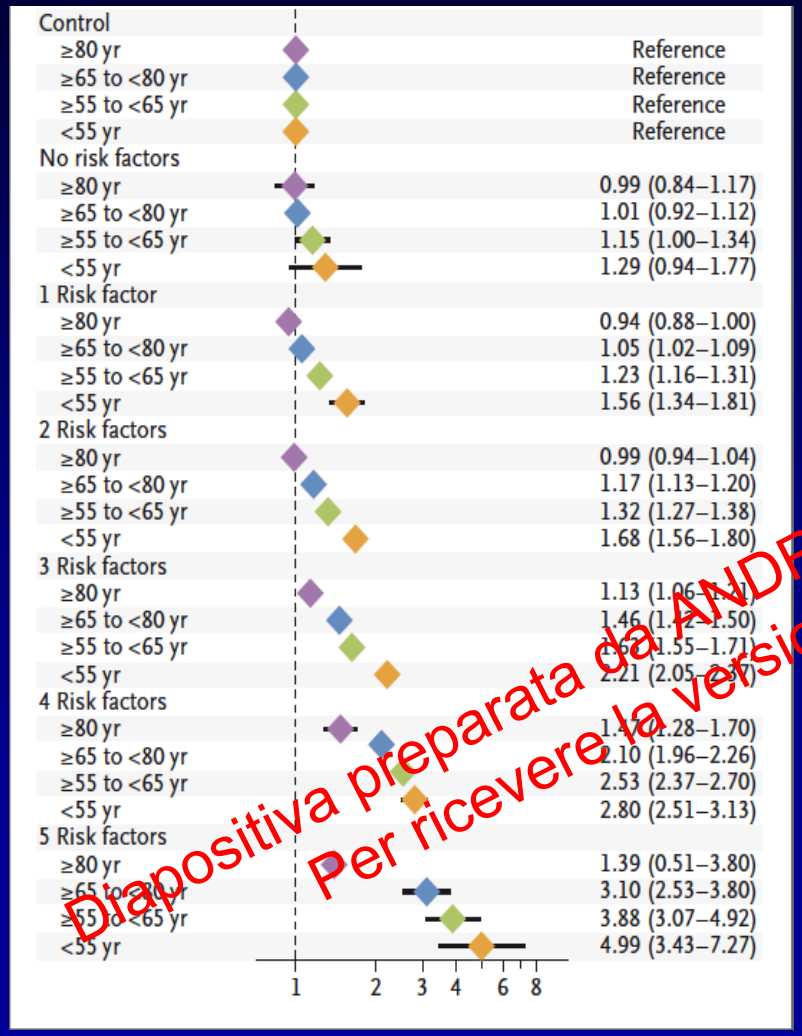
A conceptual look at vascular risk and its determinants before and during the course of type 2 diabetes



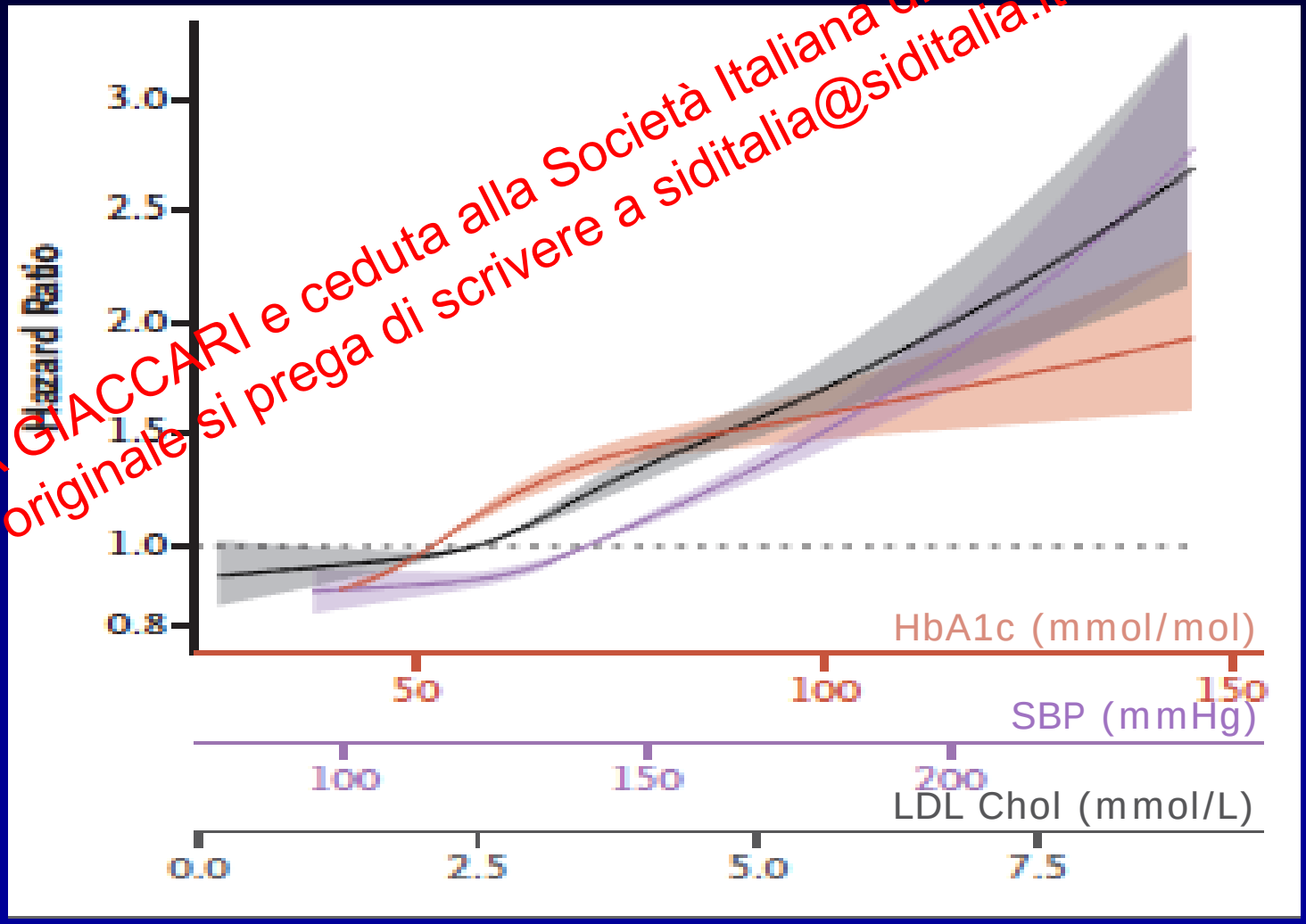
Sattar N, Diabetologia 2013

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

Excess Mortality and risk factors

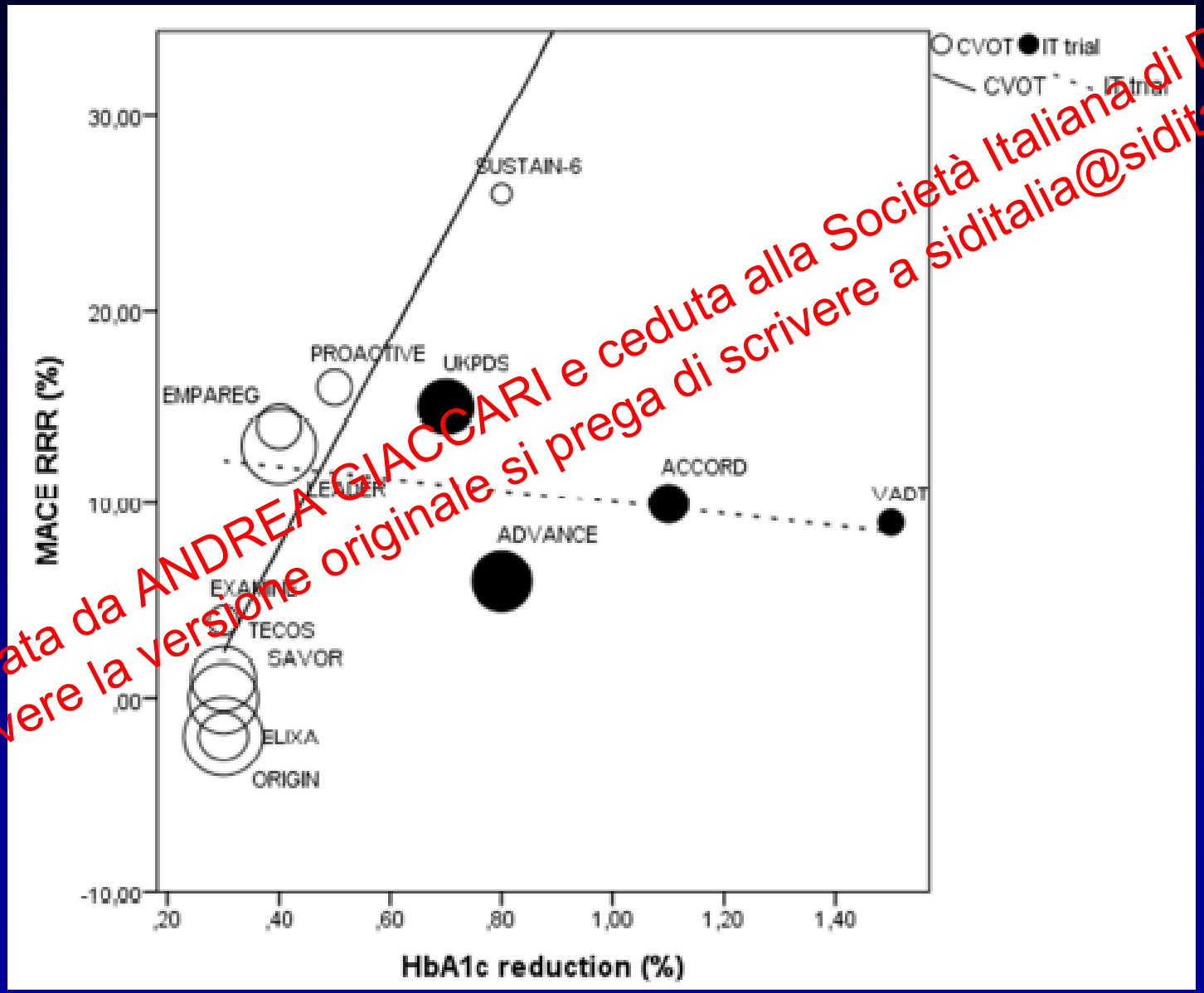


Acute myocardial infarction



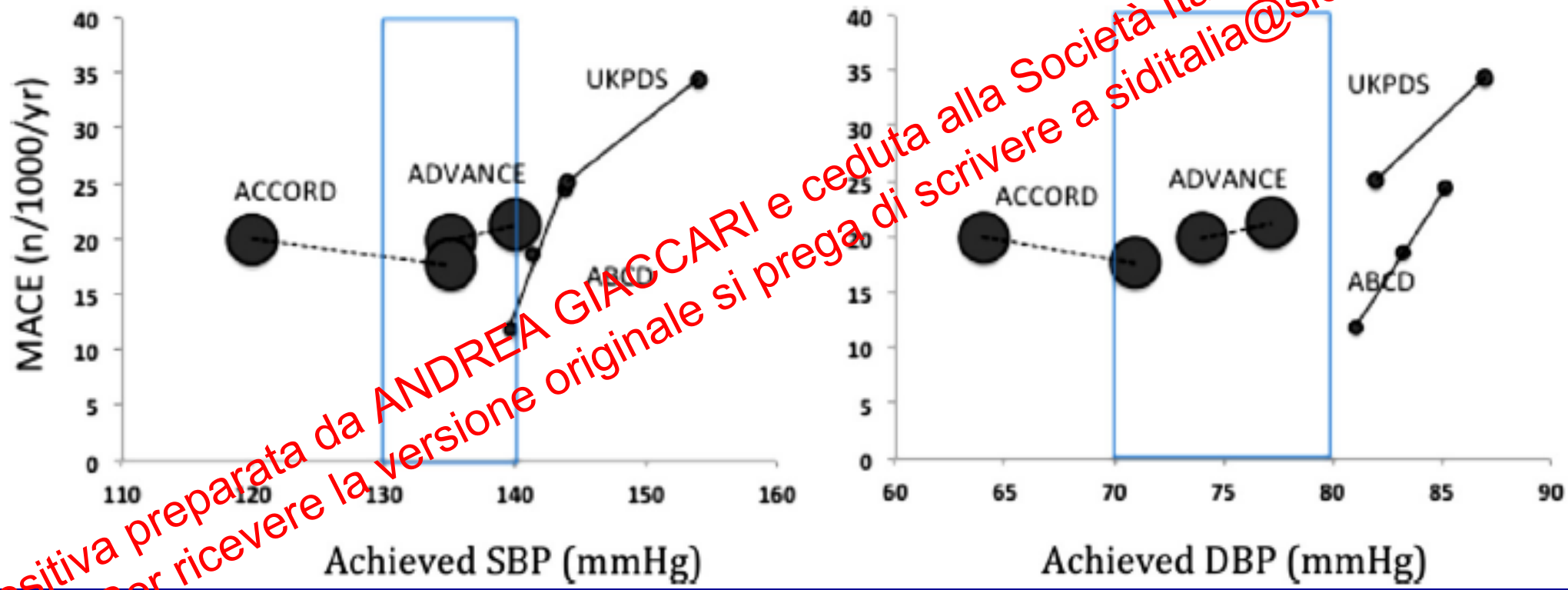
Rawshani A et al. N Engl J Med 2018; 379: 633-644

Glycemic control for CV risk reduction



Mannucci E et al. NMCD 2017

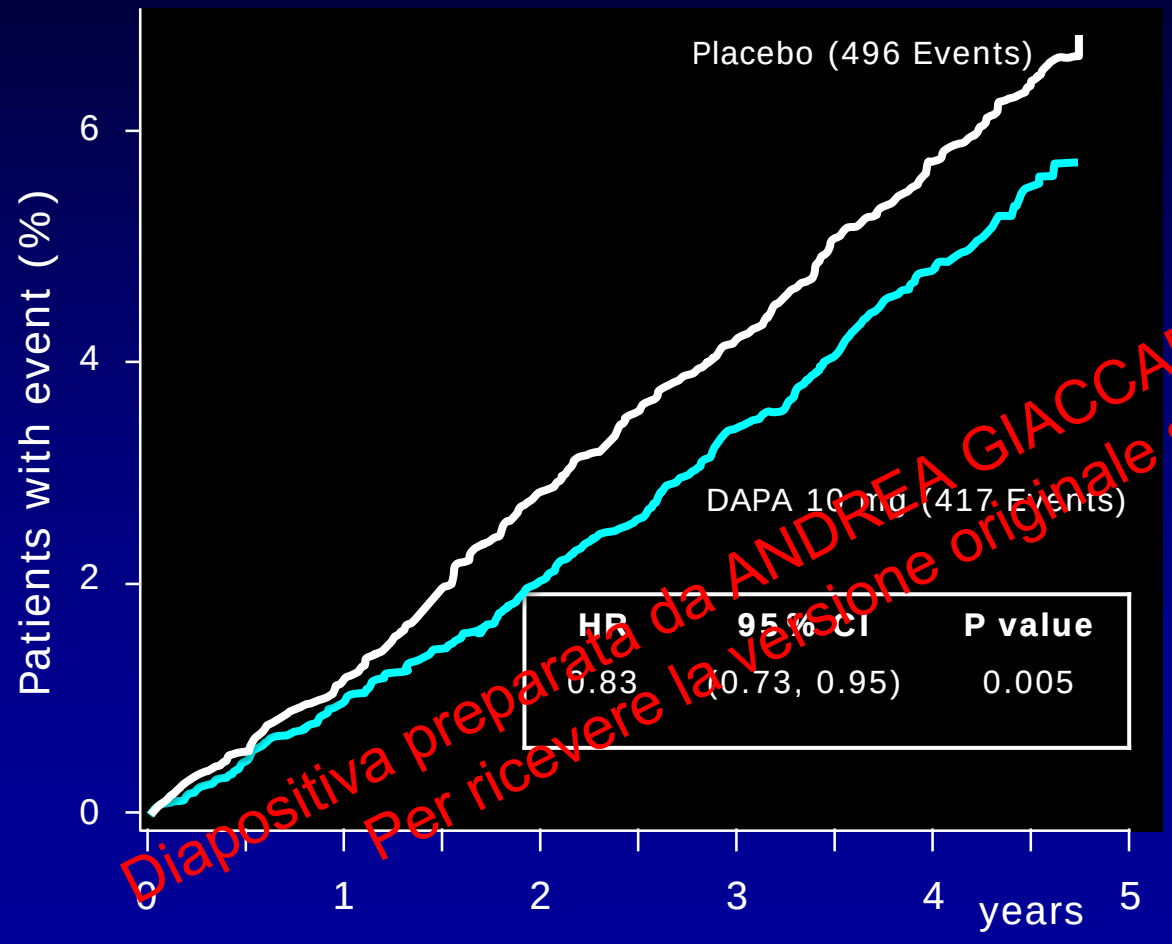
Blood pressure control for CV risk reduction

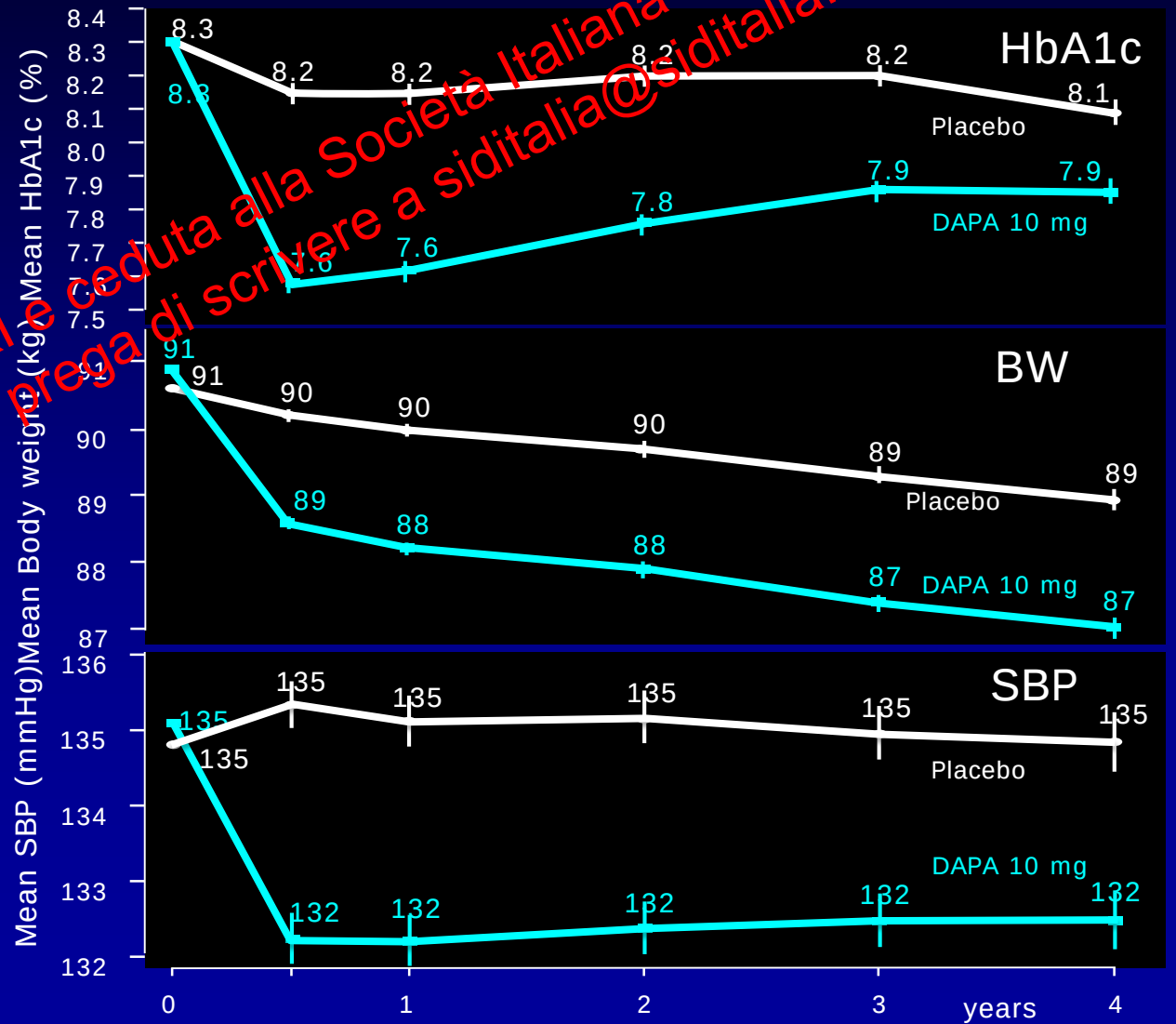


Frontoni S et al. NMCD 2014

DECLARE: hHF/CVD co-primary endpoint and risk factors

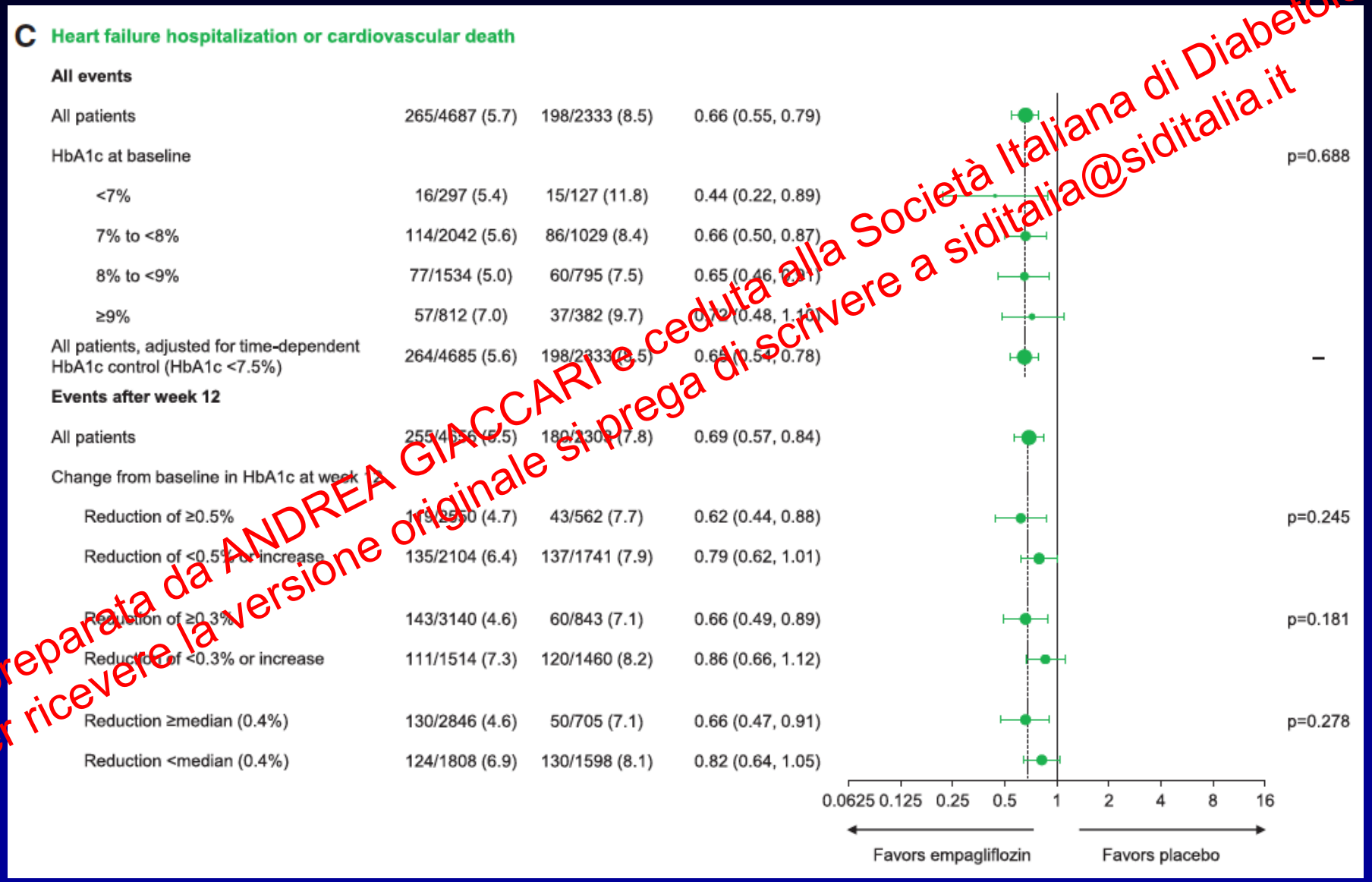
hHF/CVD





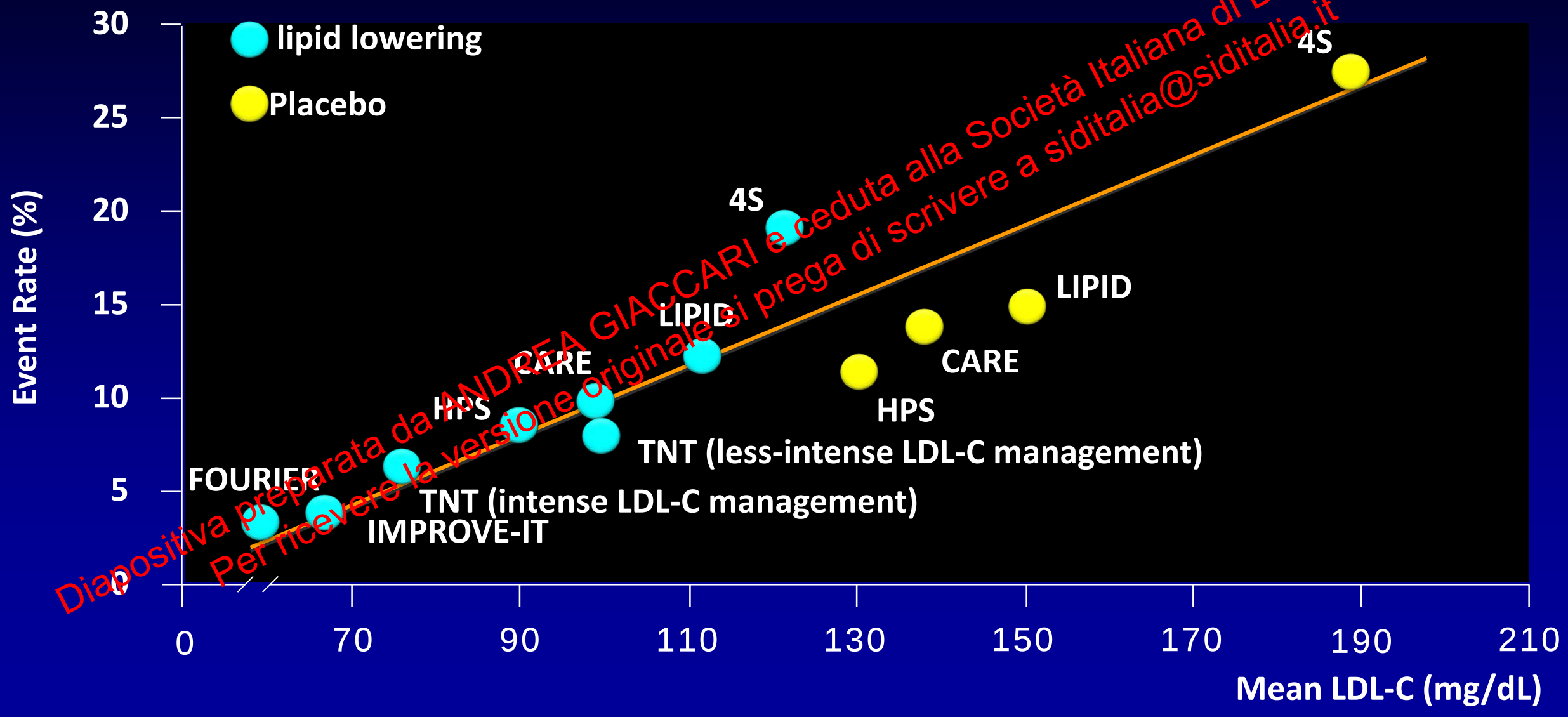
Wiviott SD et al. Online ahead of print. N Engl J Med. 2018

Improvement in Cardiovascular Outcomes with Empagliflozin is independent of glycemic control



Inzucchi SE et al. Circulation 2018

LDL-C and CV events in interventional trials



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 ± 11.2	7.7 ± 9.2
HDL cholesterol	46.3 ± 3.0	47.4 ± 3.5	1.0 ± 1.1	48.1 ± 3.4	46.8 ± 4.0	−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 ± 10.3	141.0 ± 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	51.5 ± 0.9	0.0 ± 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	13.0 ± 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 ± 1.7	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

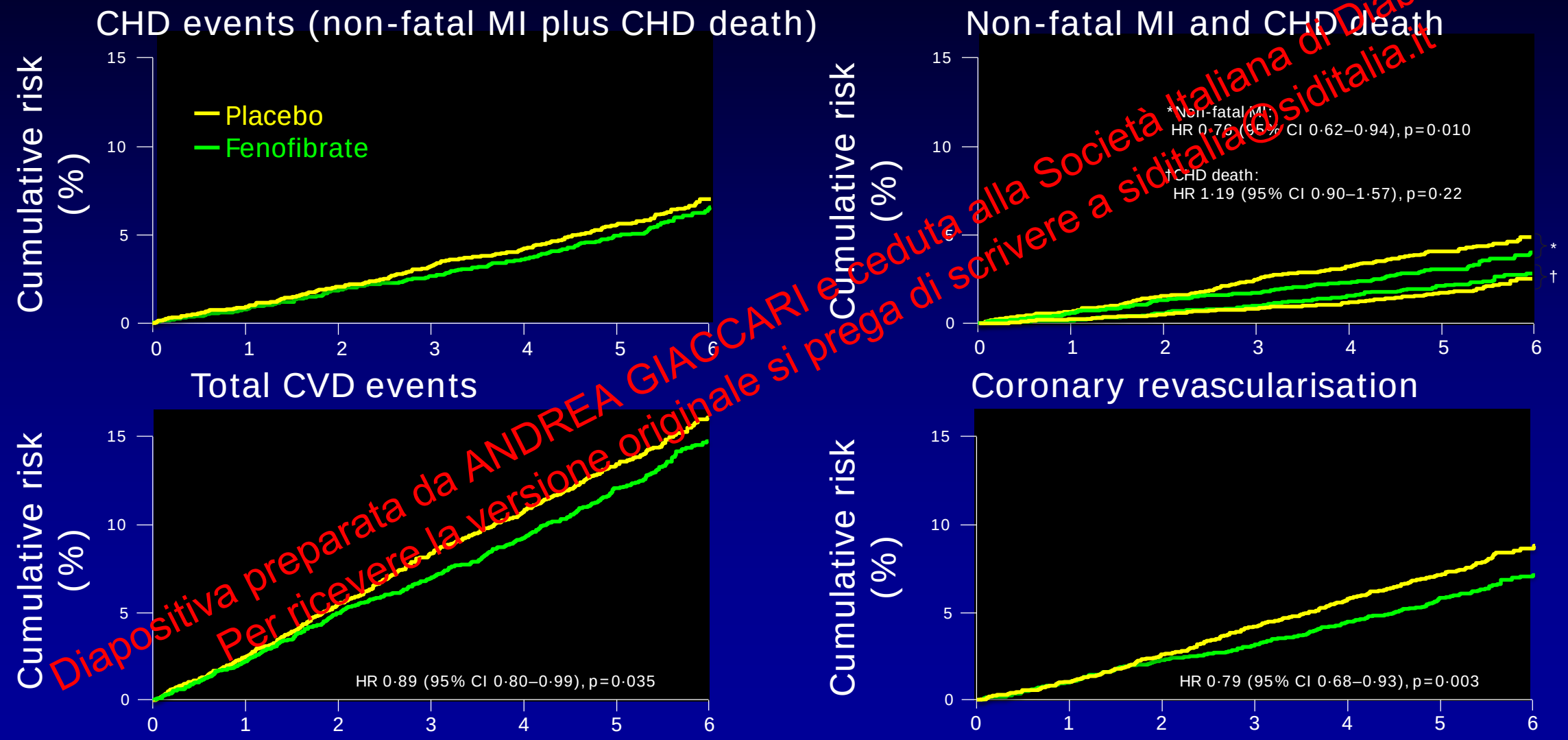
\# $p < 0.05$ versus baseline

Fadini GP et al, Cardiovasc Diabetol 2017

altri meccanismi

- trigliceridi
- acido urico
- infiammazione

FIELD: no effect of fenfibrate (?)



Keech A. et al. for the FIELD Investigators: Lancet 366(9500):1849, 2005

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

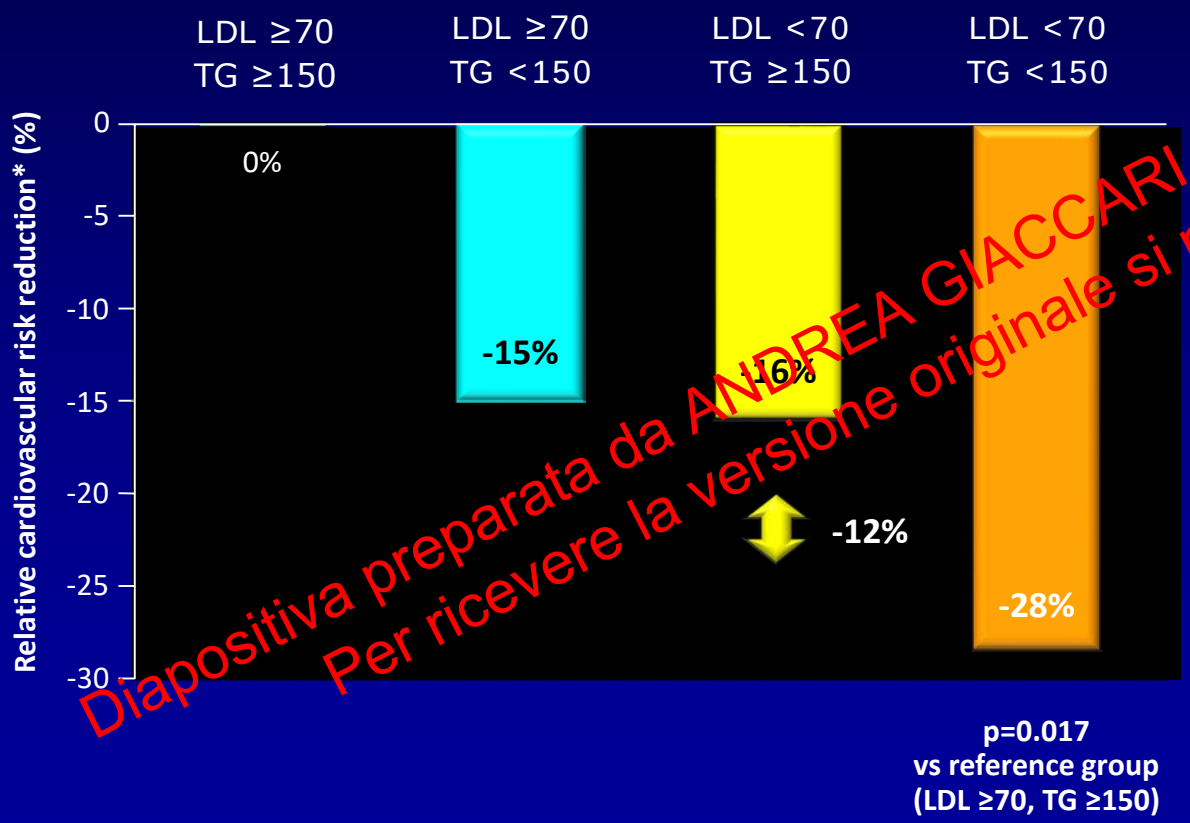
	Plasma concentrations at baseline (mean [SD])			Plasma concentrations at study close (mean [SD])	
	Placebo	Fenofibrate	Study close	Placebo	Fenofibrate
Full cohort (fenofibrate n=4895, placebo n=4900)					
Total cholesterol	5·03 (0·71)	5·04 (0·69)	−0·33 (−6·9%)	4·56 (0·90)	4·23 (0·78)
LDL cholesterol	3·07 (0·66)	3·07 (0·64)	−0·17 (−5·8%)	2·60 (0·78)	2·43 (0·65)
HDL cholesterol	1·10 (0·26)	1·10 (0·26)	0·01 (1·2%)	1·12 (0·29)	1·13 (0·30)
Triglycerides	1·93 (0·88)	1·95 (0·87)	−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)	−0·08 (−1·6%)	4·12 (0·88)	3·98 (0·85)
LDL cholesterol	3·31 (0·63)	3·23 (0·64)	0·02 (0·7%)	2·18 (0·74)	2·13 (0·66)
HDL cholesterol	1·08 (0·28)	1·03 (0·24)	−0·01 (−0·5%)	1·12 (0·28)	1·05 (0·29)
Triglycerides	2·08 (0·99)	2·22 (0·99)	−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)	4·99 (0·69)	−0·66 (−13·1%)	4·82 (0·80)	4·29 (0·74)
LDL cholesterol	2·93 (0·64)	3·03 (0·64)	−0·46 (−14·7%)	2·84 (0·70)	2·50 (0·63)
HDL cholesterol	1·11 (0·27)	1·11 (0·26)	0·02 (2·1%)	1·13 (0·29)	1·15 (0·30)
Triglycerides	1·85 (0·81)	1·89 (0·83)	−0·51 (−27·3%)	1·88 (0·95)	1·41 (0·72)

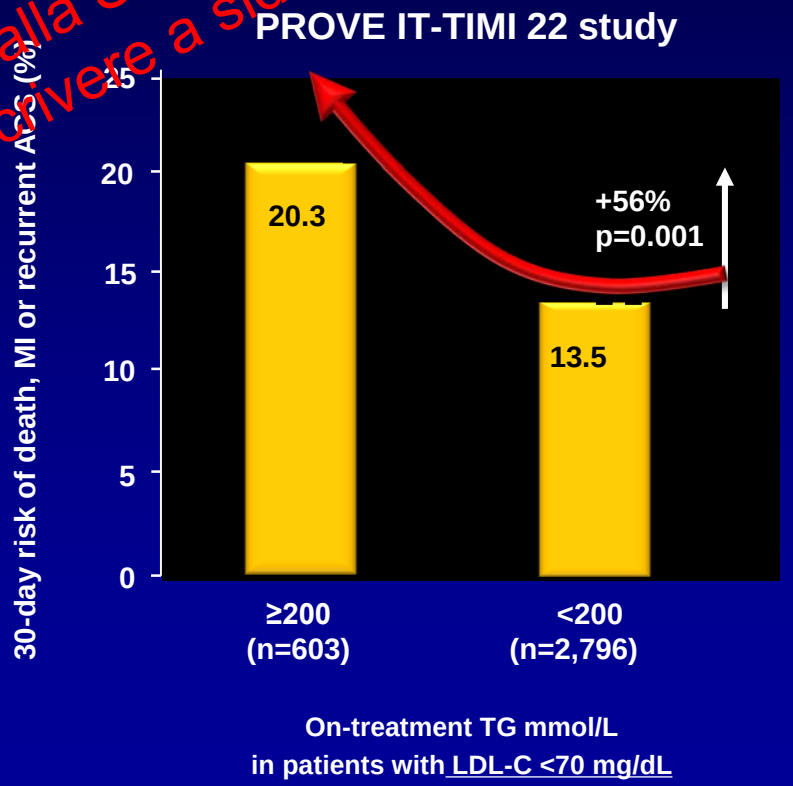
Keech A. et al. for the FIELD Investigators: Lancet 366(9500):1849, 2005

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

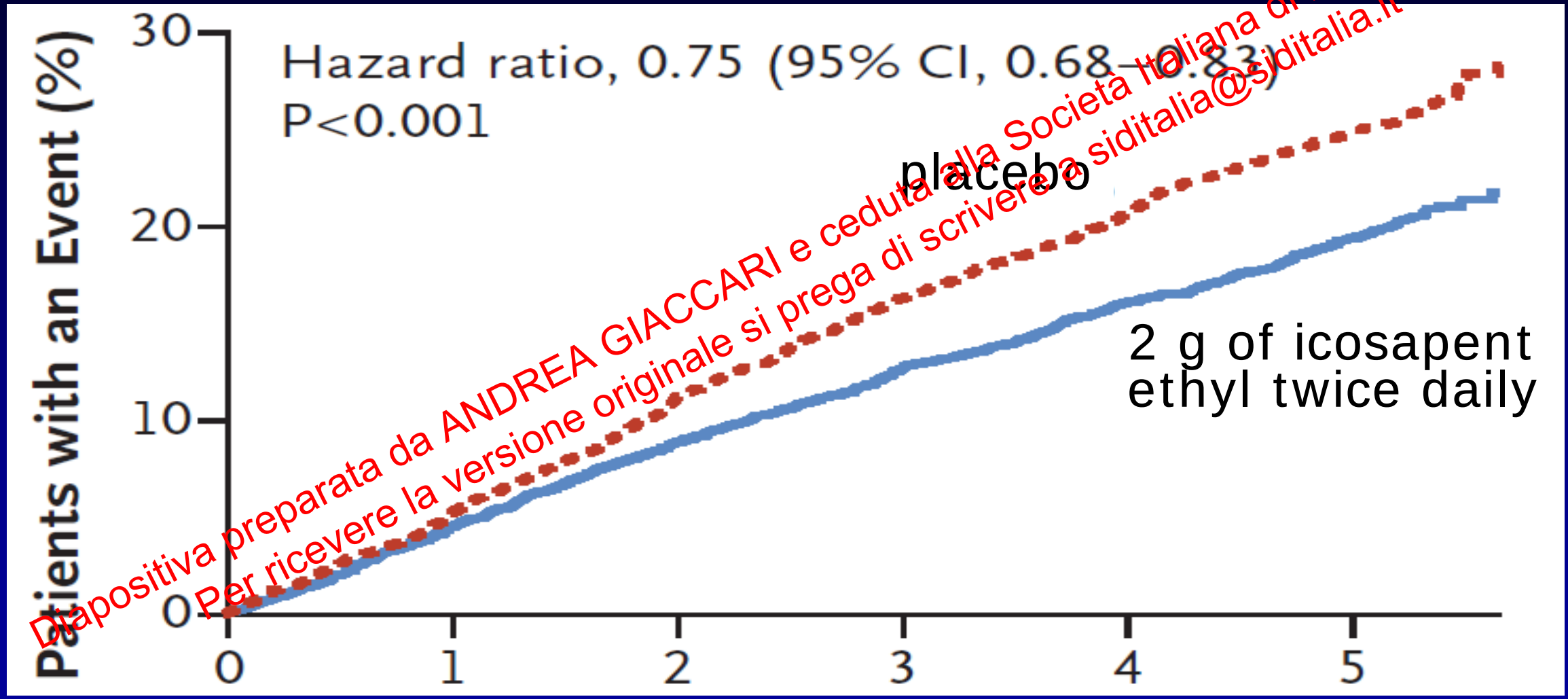




Miller A et al. J Am Coll Cardiol 2008

REDUCE-IT: primary endpoint (MACE-3)

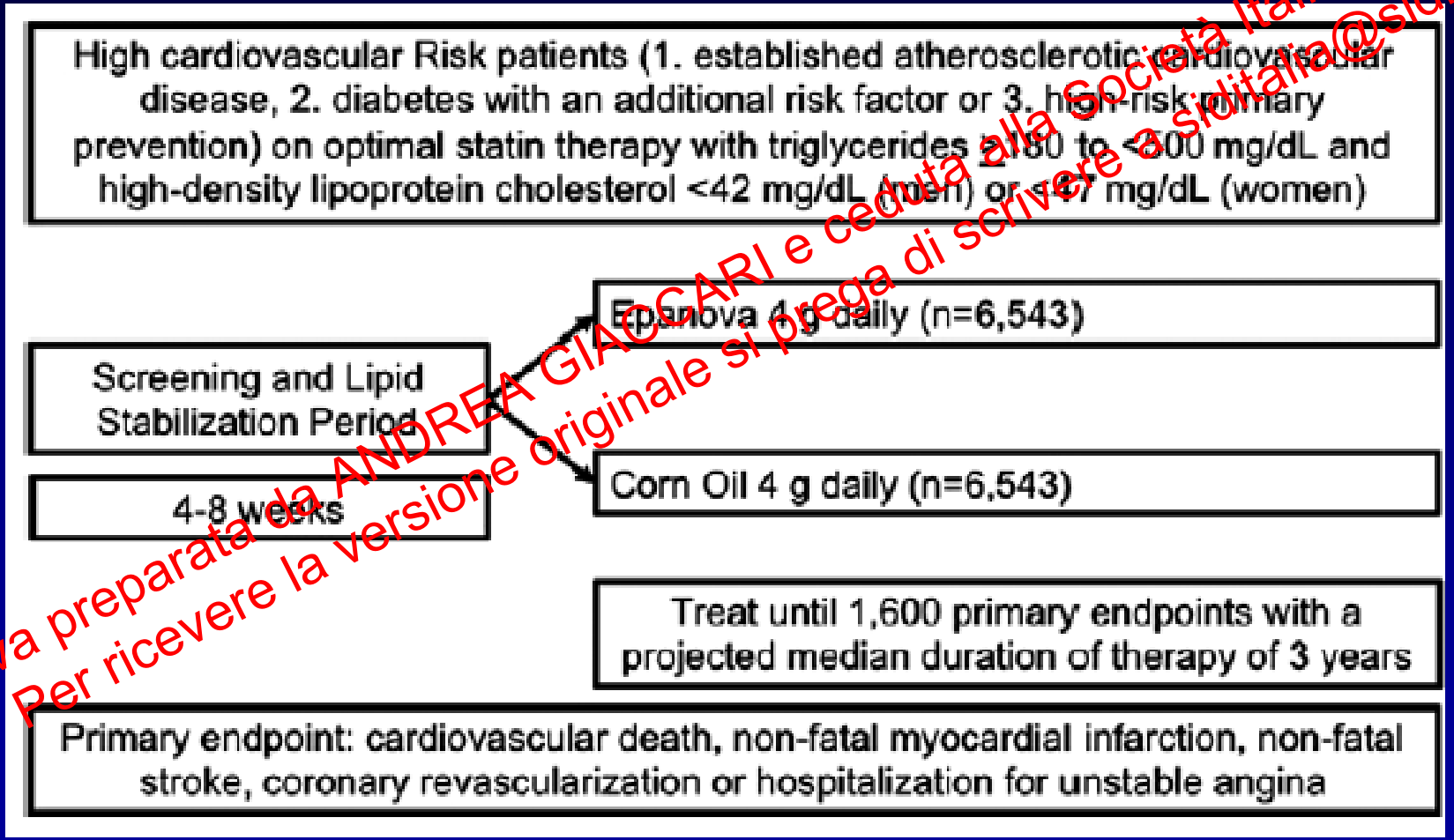
patients with established CVD or with diabetes and other risk factors, receiving statin and triglyceride level of 135 to 499 mg/dl and a LDL cholesterol level of 41 to 100 mg/dl



N Engl J Med. 2018 Nov 10. doi: 10.1056/NEJMoa1812792

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

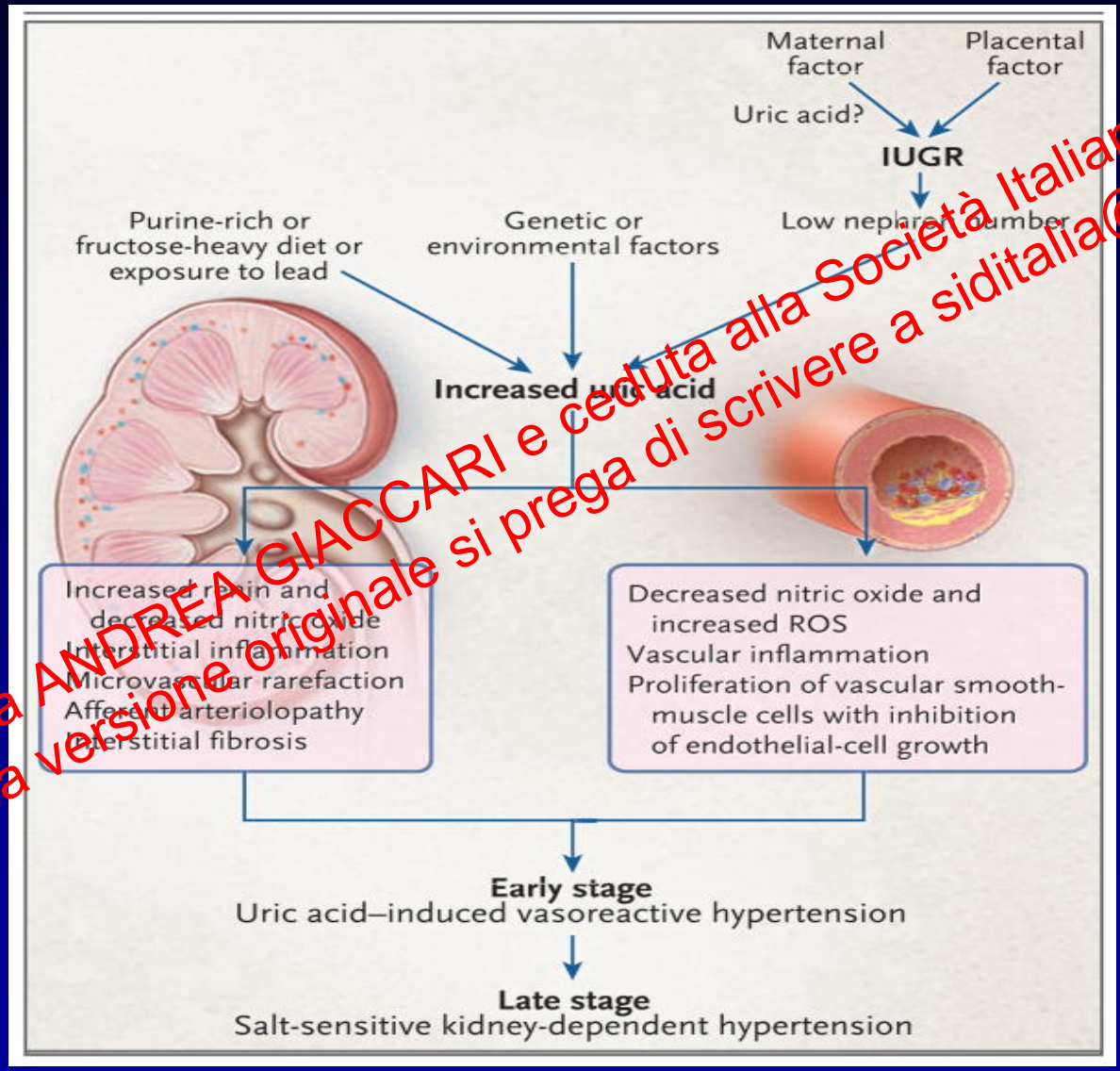


Nicholls SJ et al, Clinical Cardiology 2018

altri meccanismi

- trigliceridi
- acido urico
- infiammazione

uric acid and cardiovascular risk



Feig DI et al.: NEJM 359:1811, 2008 doi: 10.1056/NEJMra0800885

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

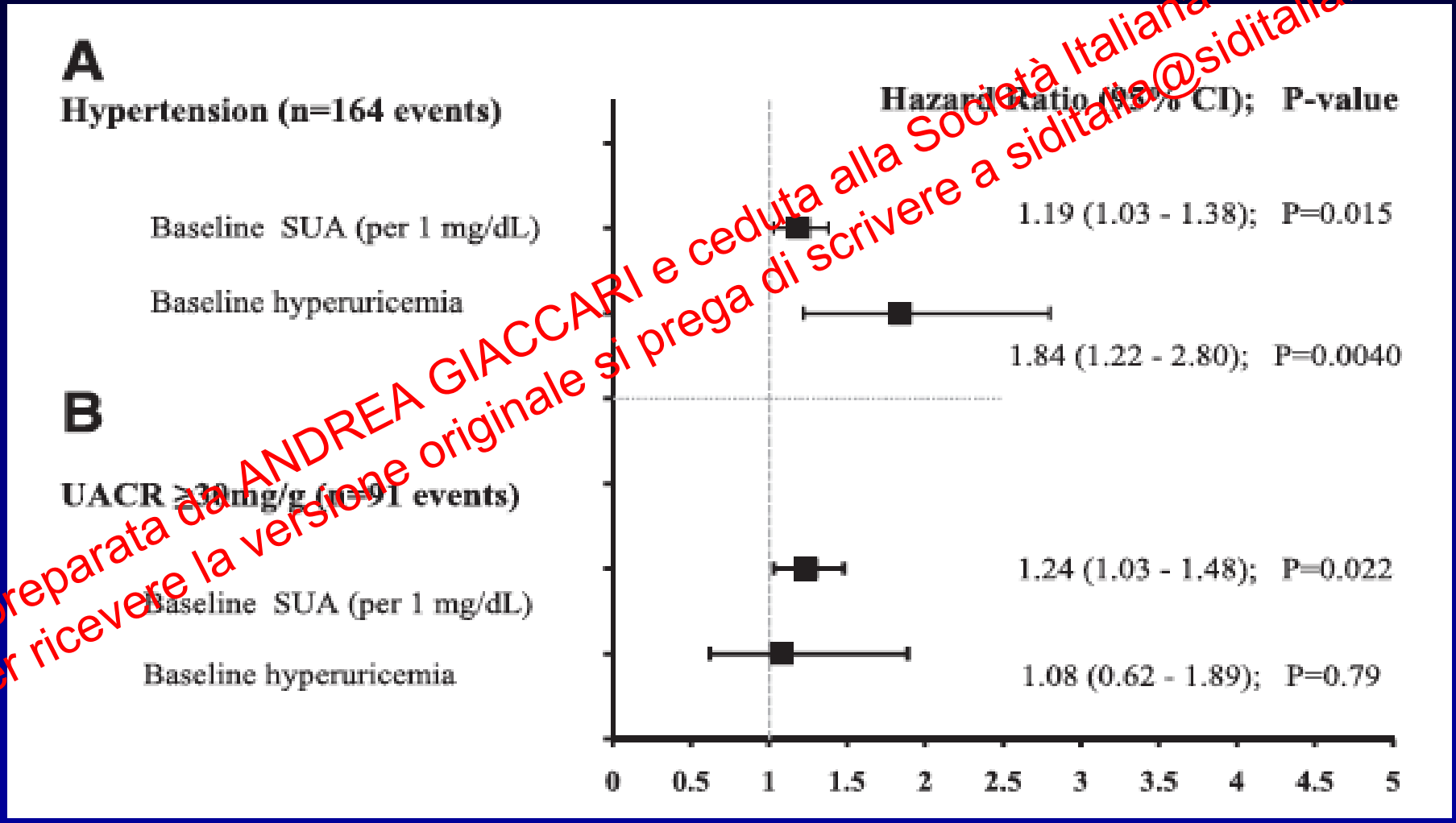
HR per doubling of uric acid

	Total mortality		CVE		Decline in eGFR ≥30%		Albuminuria 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
eGFR (%)	11.8	0.003	6.5	0.010	12.6	<0.001	1.4	0.93	—	—

Pyleman-Lyberg S et al, Diabetes Care 2019

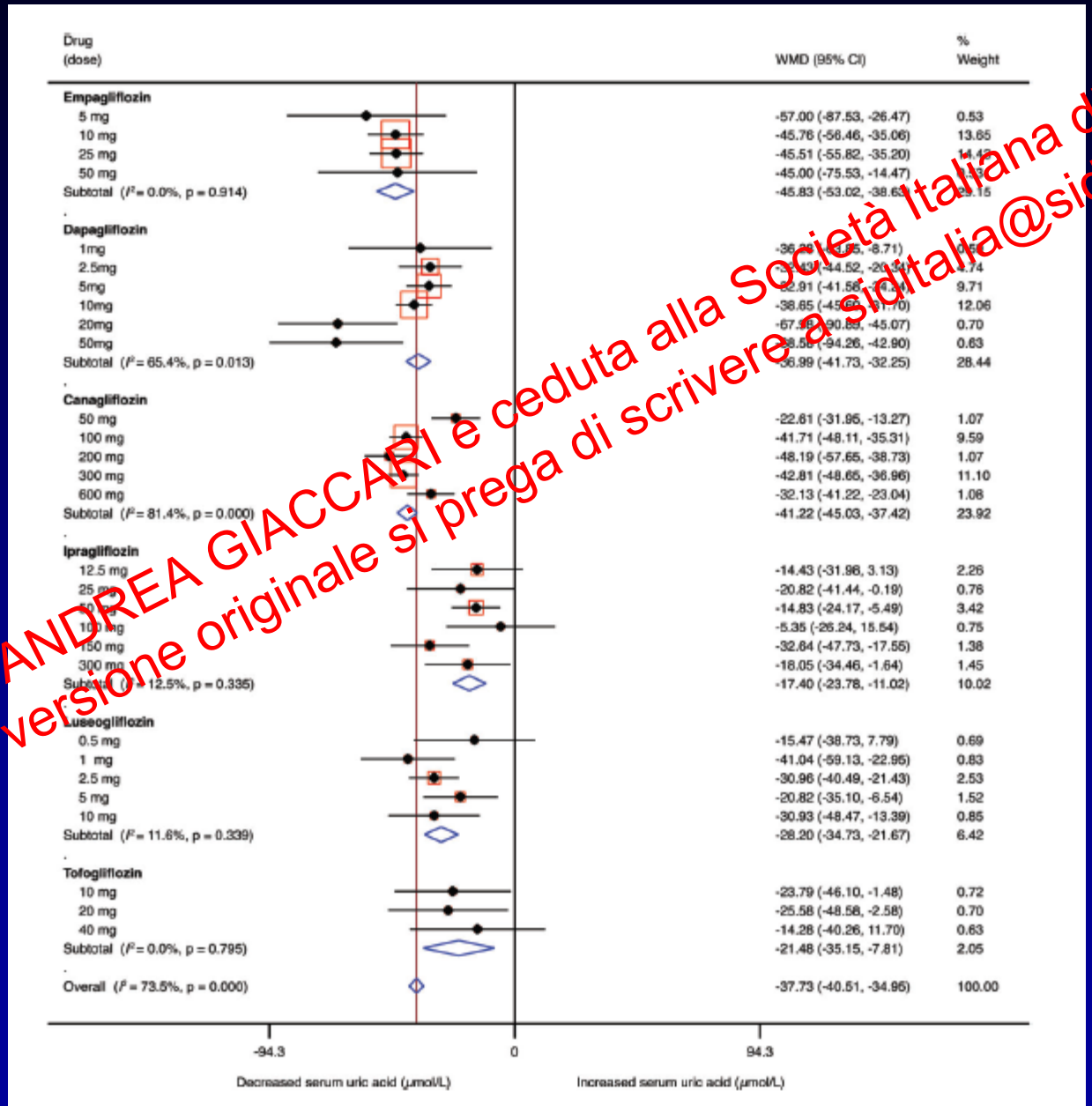
Elevated serum uric acid is associated with greater risk for hypertension and diabetic kidney disease, in obese adolescents with type 2 diabetes, duration <2 yrs (n: 539)

TODAY study (average FU 5.7 yrs)



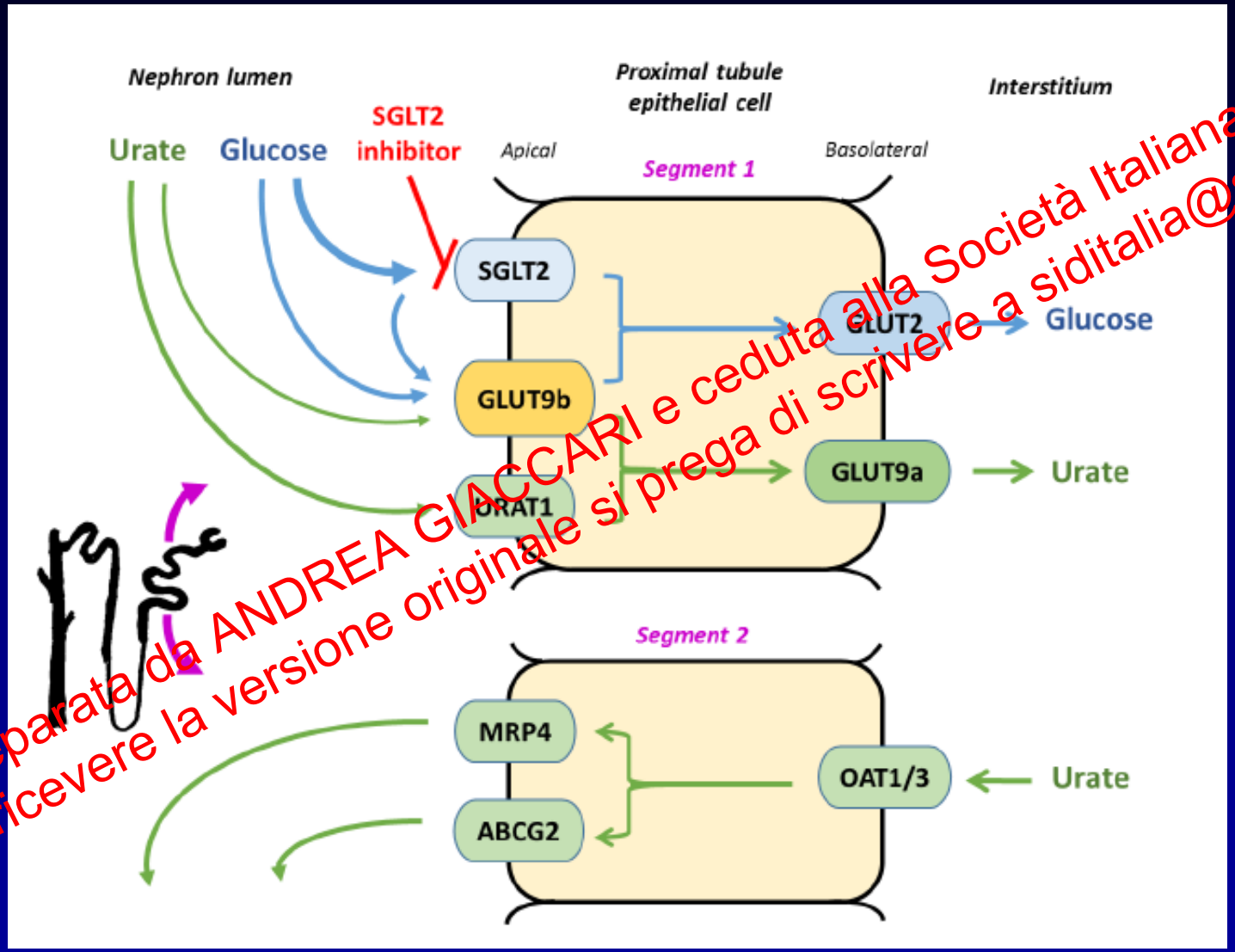
Bjornstad P et al, Diabetes Care 2019

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



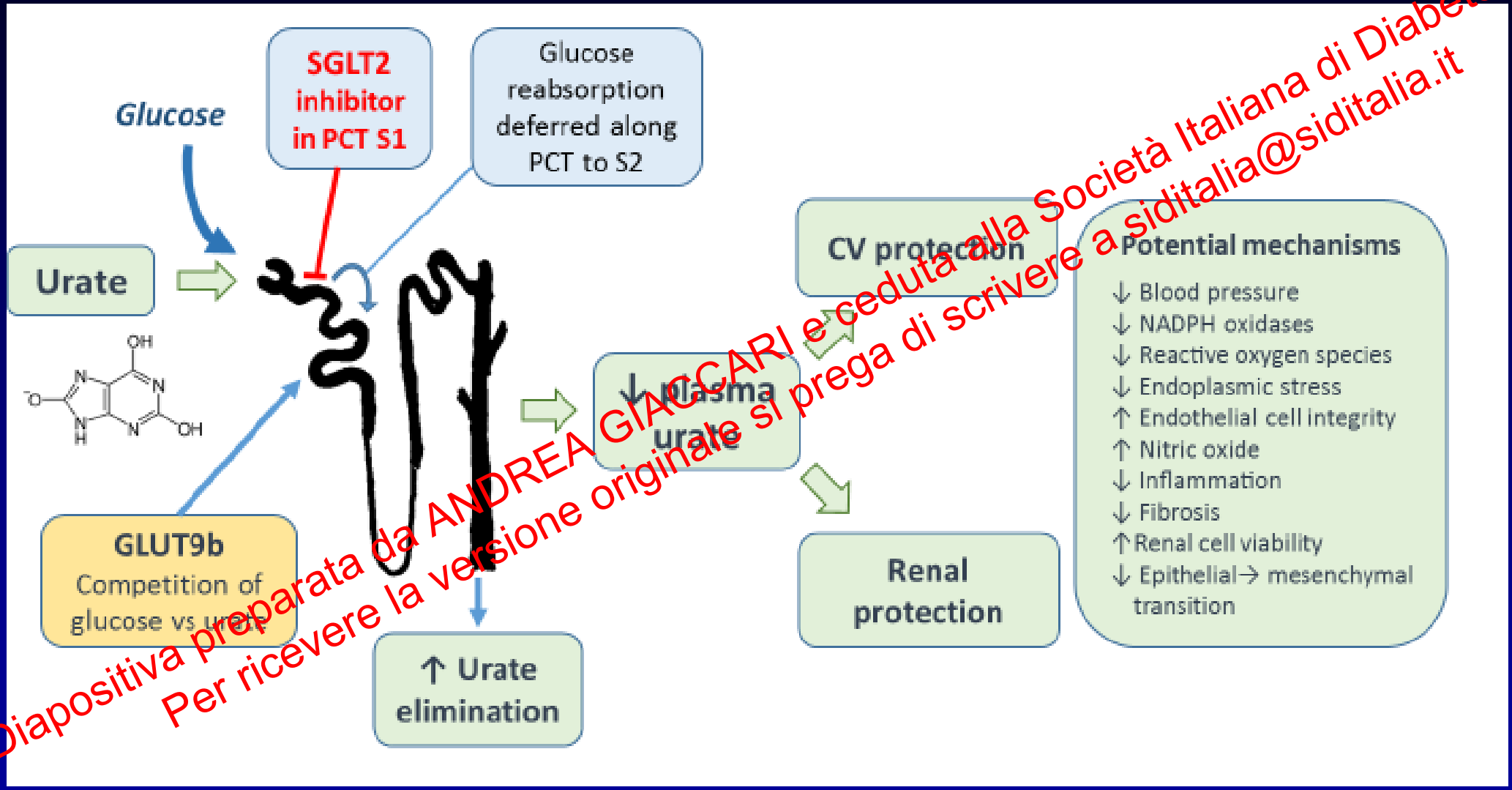
Zhao Y et al, DOM 2018

Uric acid and the cardio-renal effects of SGLT2 inhibitors



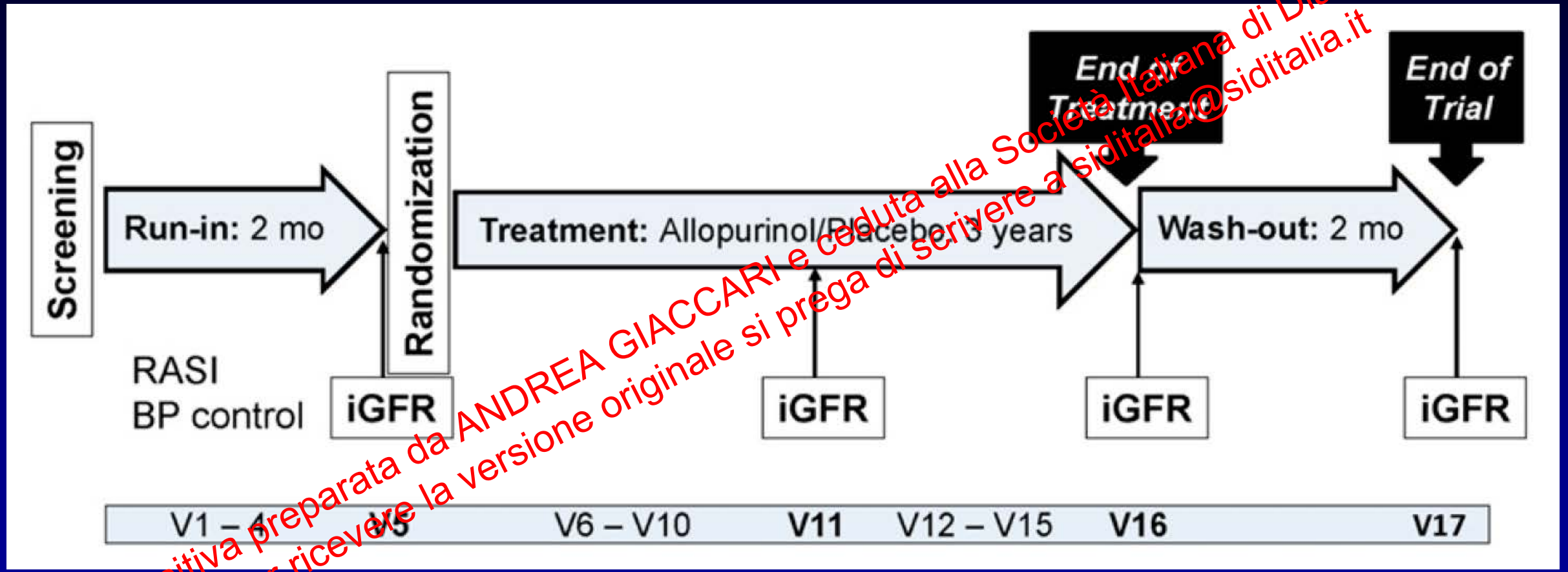
Bailey CJ et al, Diabetes Obes Metab 2019

Uric acid and the cardio-renal effects of SGLT2 inhibitors



Bailey CJ et al, Diabetes Obes Metab 2019

Preventing Early Renal Loss in type 1 diabetes (PERL): A Randomized Double-Blinded Trial of Allopurinol



NCT02017171: double-blind, placebo-controlled, multicenter trial randomized 530 participants with T1D, estimated GFR (eGFR) of 40–99.9 mL/min/1.73 m2, SUA ≥4.5 m/dL, and micro- to macroalbuminuric DKD or normoalbuminuria with declining kidney function (NDKF) (defined as historical eGFR decline ‡3 mL/min/1.73 m2/year) to allopurinol or placebo. The primary outcome is baseline-adjusted iohexol GFR (iGFR) after 3 years of treatment plus a 2-month washout period.; iGFR: iohexol GFR;

Afkarian M, … and Doria A; Diabetes Care 42:1454, 2019 doi: 10.2337/dc19-0342

altri meccanismi

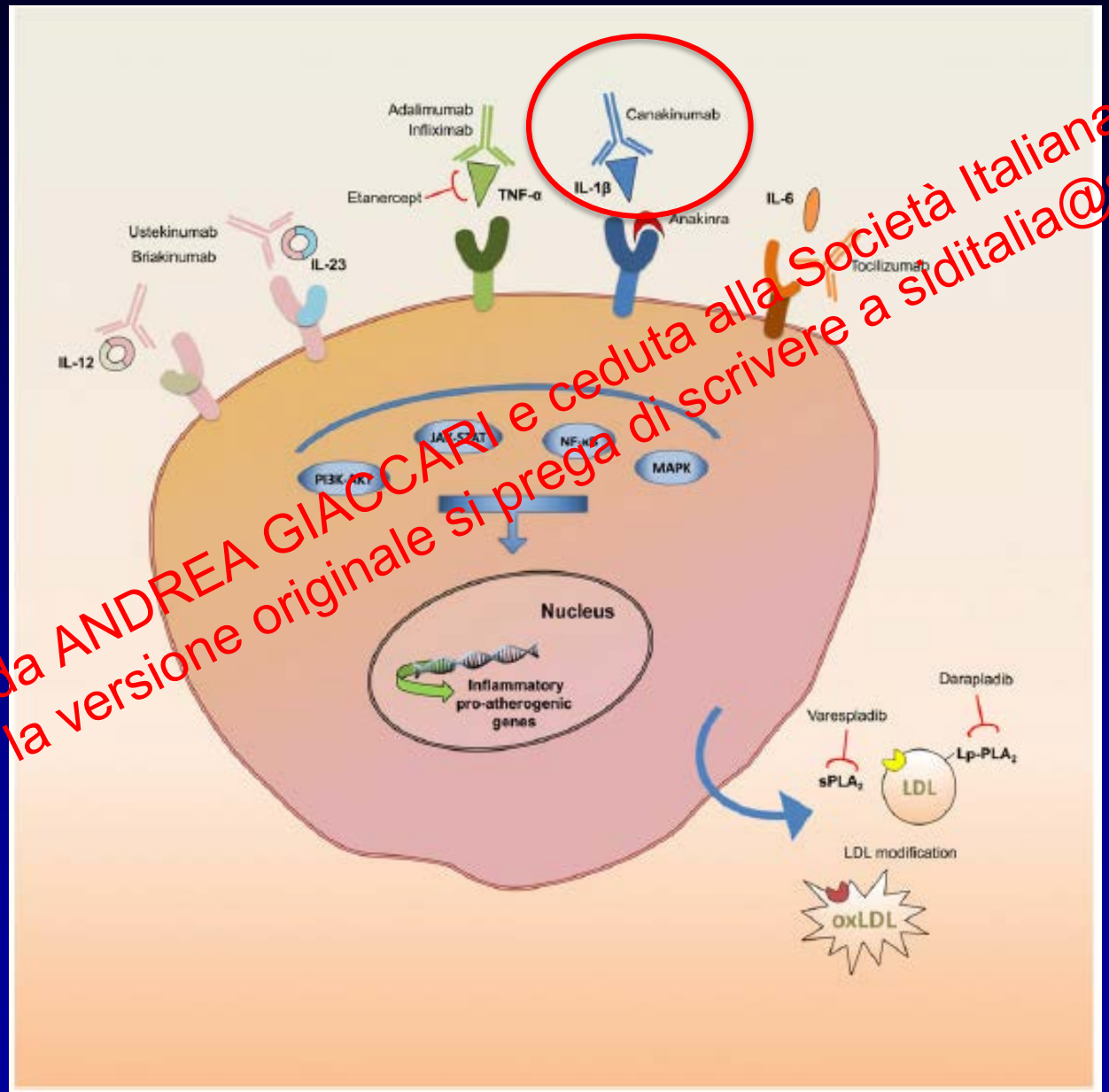
- trigliceridi
- acido urico
- infiammazione

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)	IL-6R 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 (rhIL1RA)		↓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)

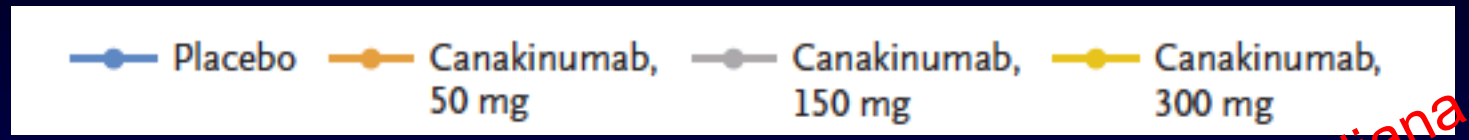
Welsh P, Br J Pharmacol 2017

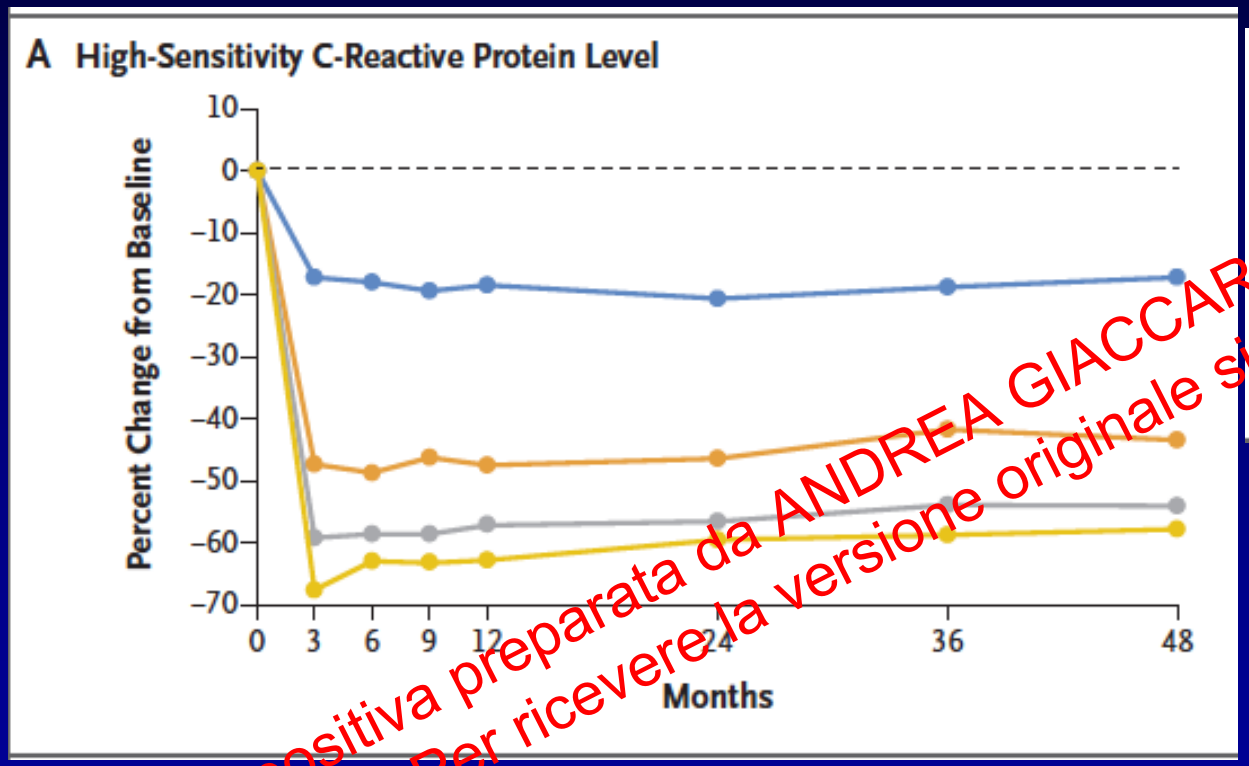
Pro-atherogenic and inflammatory pathways targeted by prospective anti-atherosclerotic antibodies and inhibitors

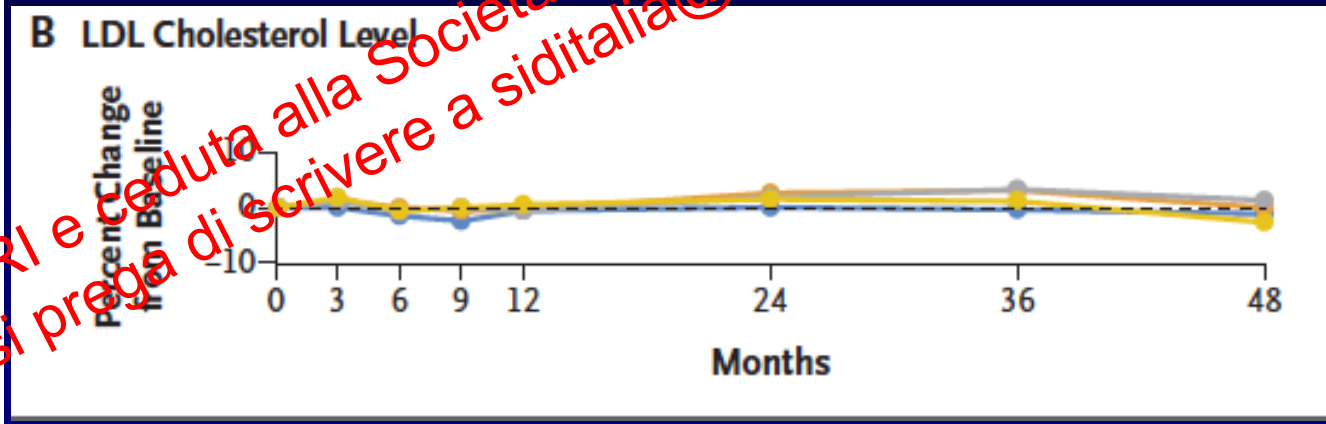


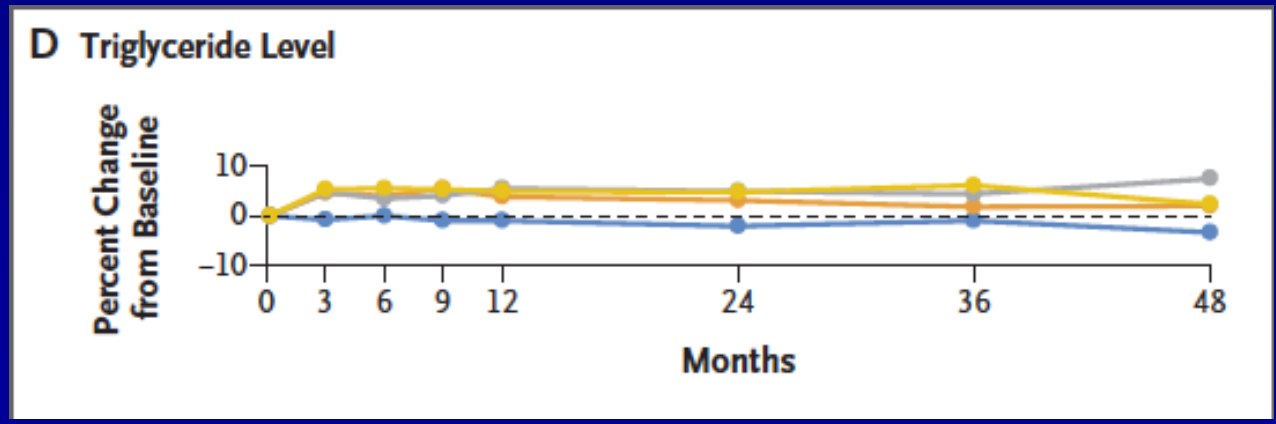
Welsh P, Br J Pharmacol 2017

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





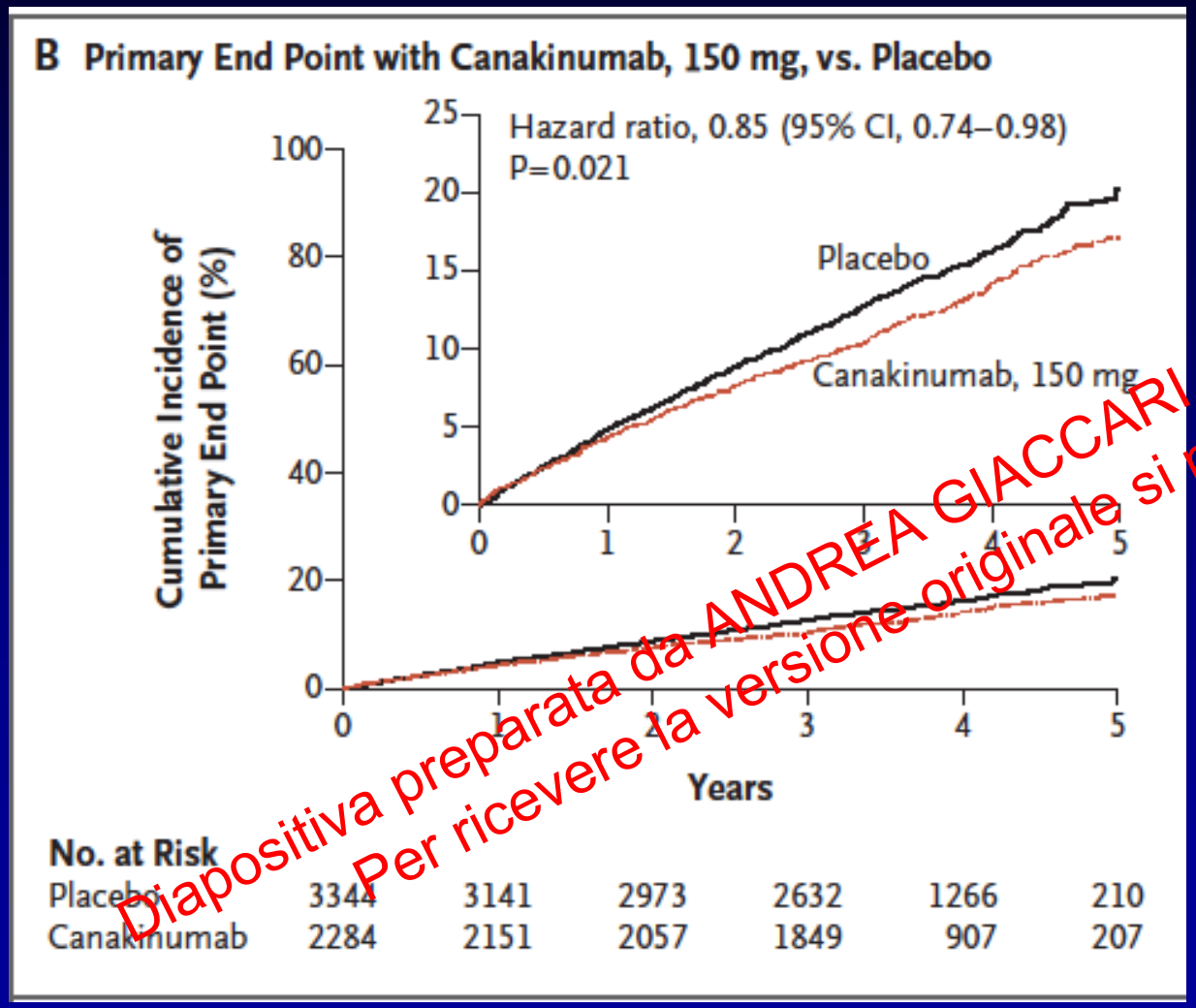




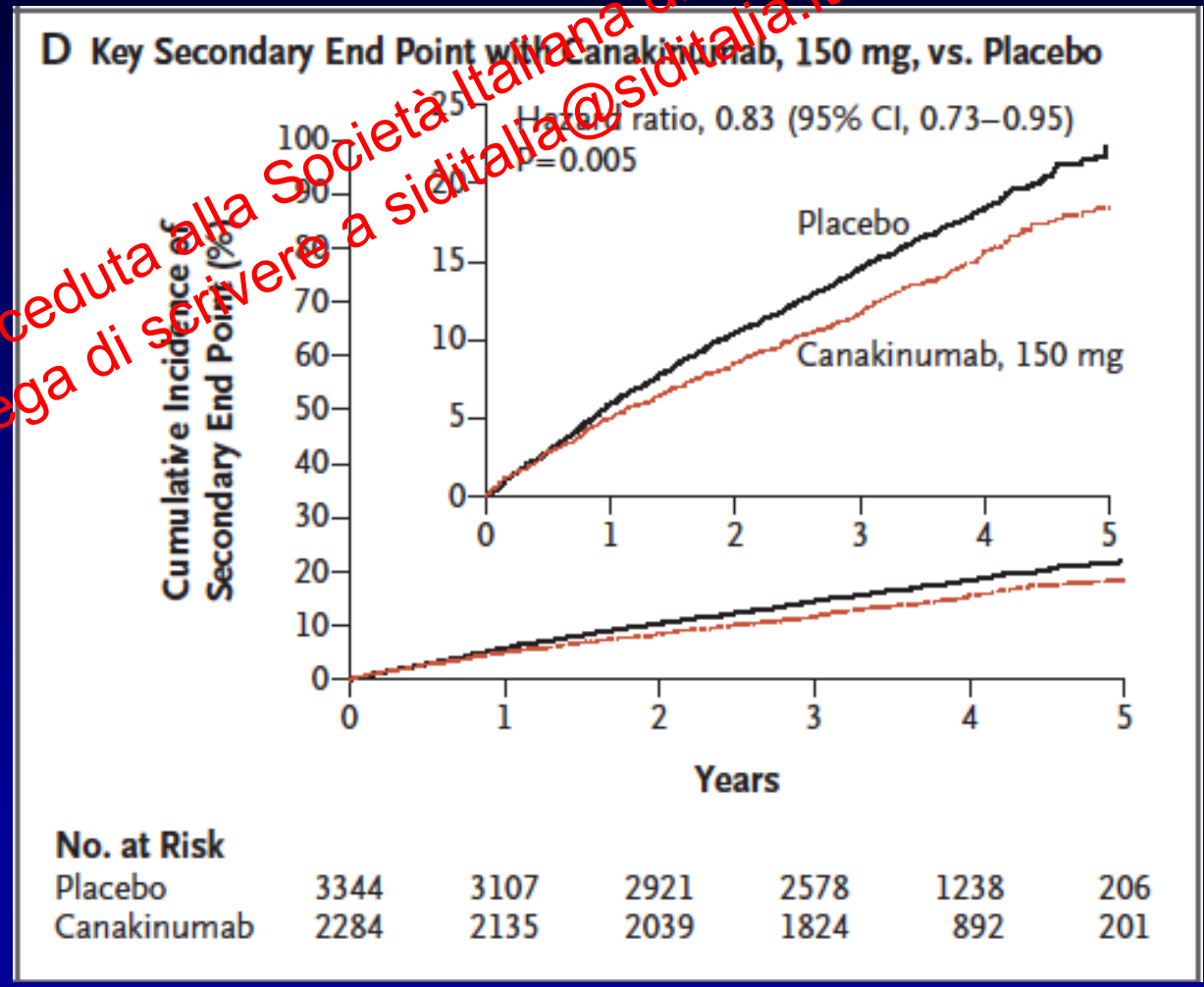
Ridker PM, et al. N Engl J Med 2017

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

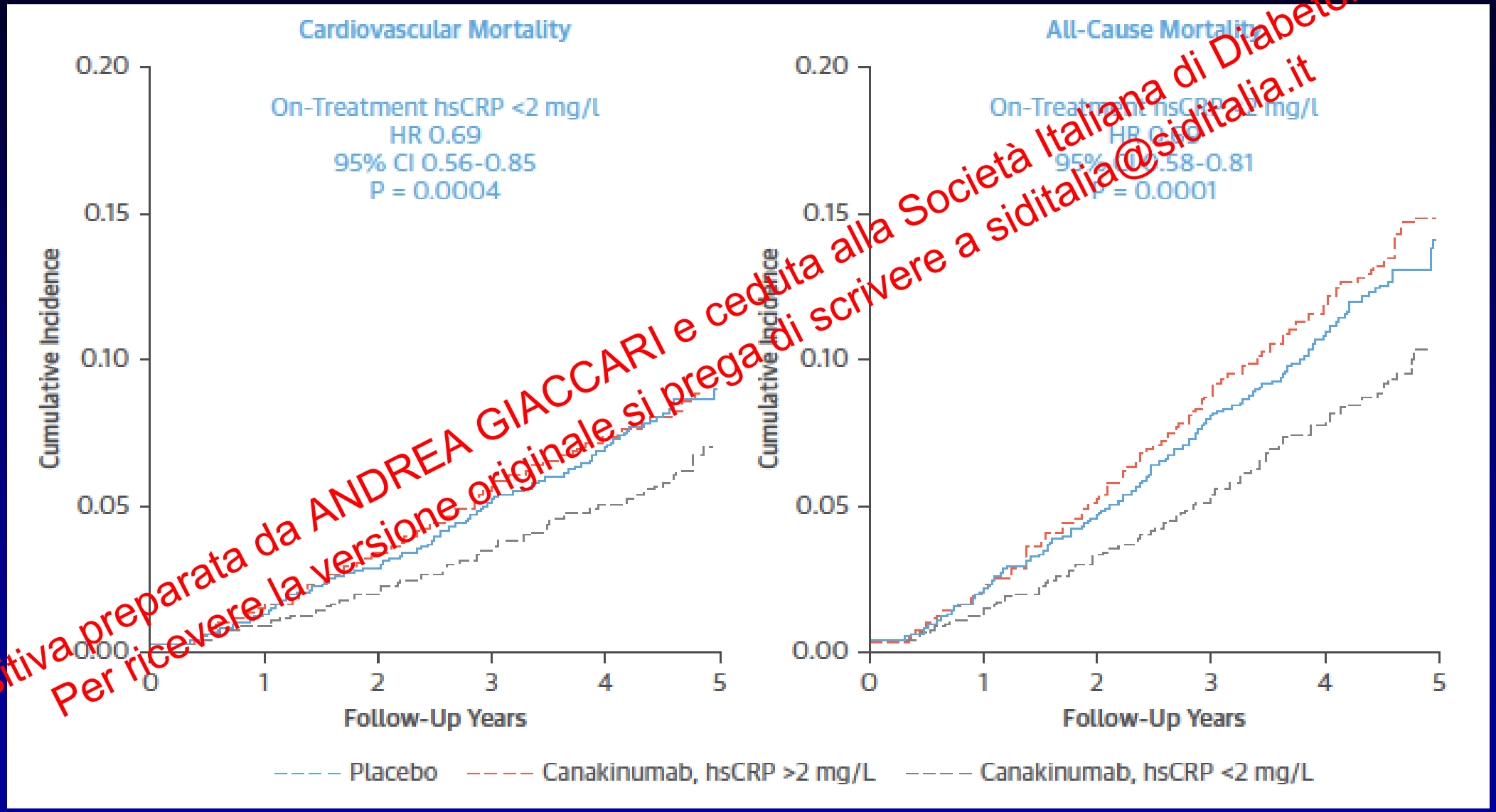


Key Secondary End Point with Canakinumab, 150 mg, vs. Placebo
additionally included hospitalization for unstable angina that led to urgent revascularization



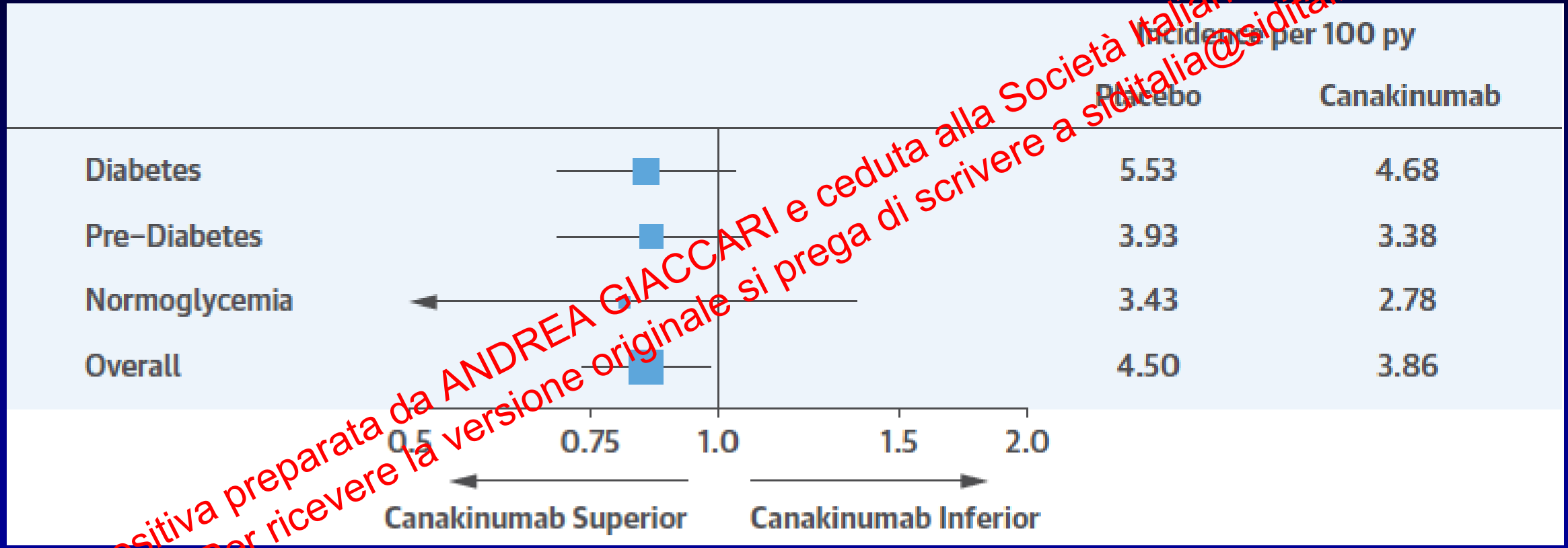
Ridker PM, et al. N Engl J Med 2017

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



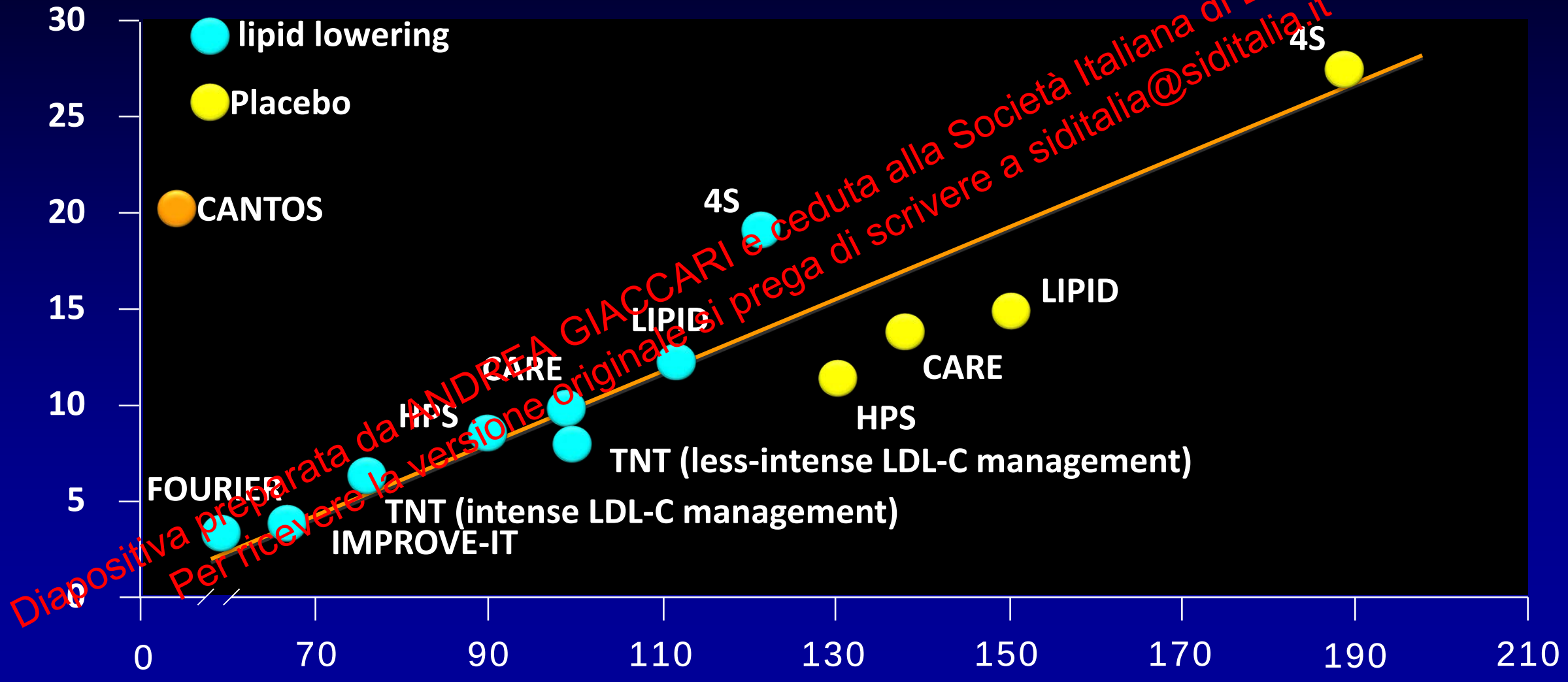
Ridker PM, et al. Circulation 2018

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



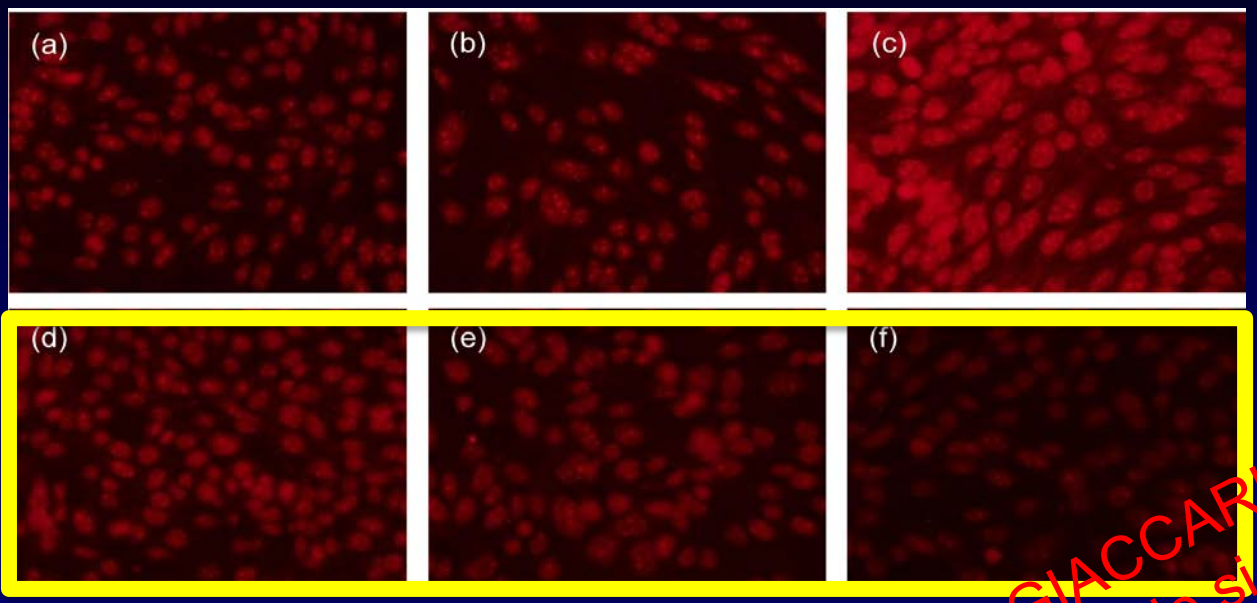
Everett BM, et al. J Am Coll Cardiol 2018

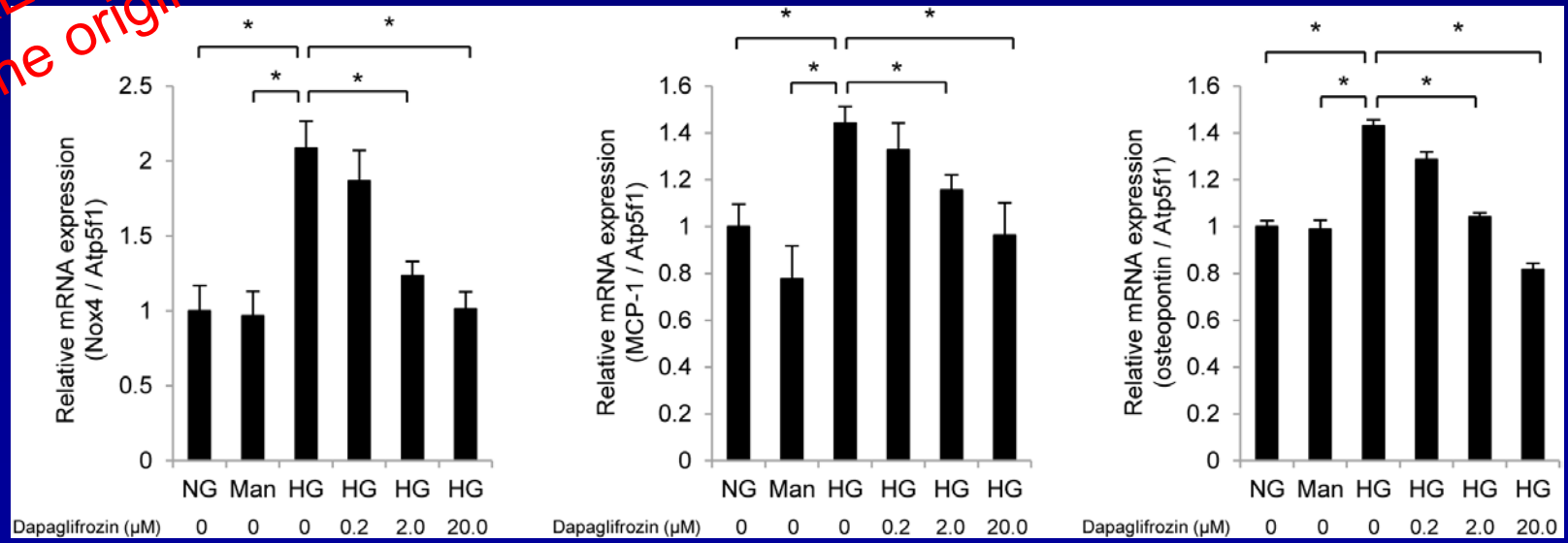
Cardiovascular event reduction with no change in LDLC: additive effects of inflammation inhibition to lipid lowering



Ridker PM, J Am Coll Cardiology 2018

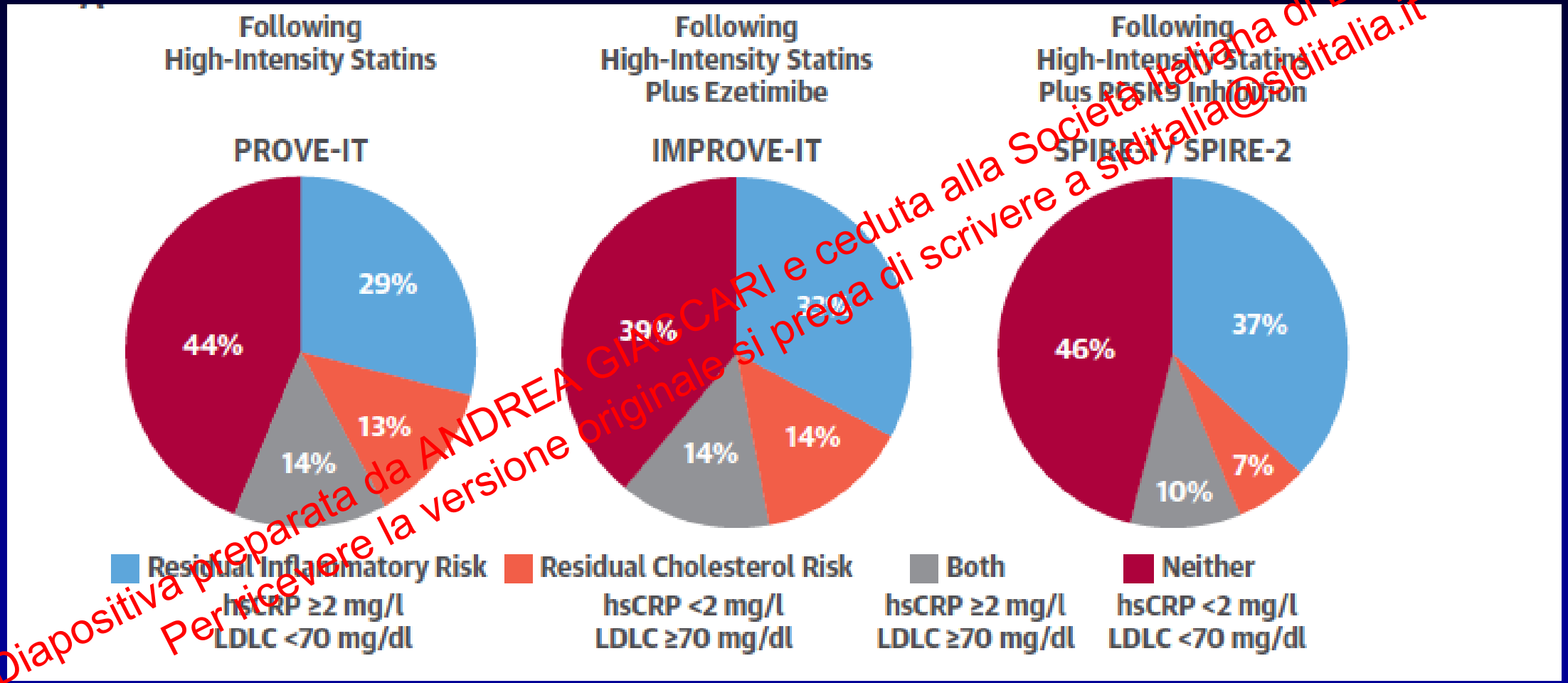
Dapagliflozin suppresses oxidative stress and inflammatory gene expression in cultured proximal tubular epithelial cells





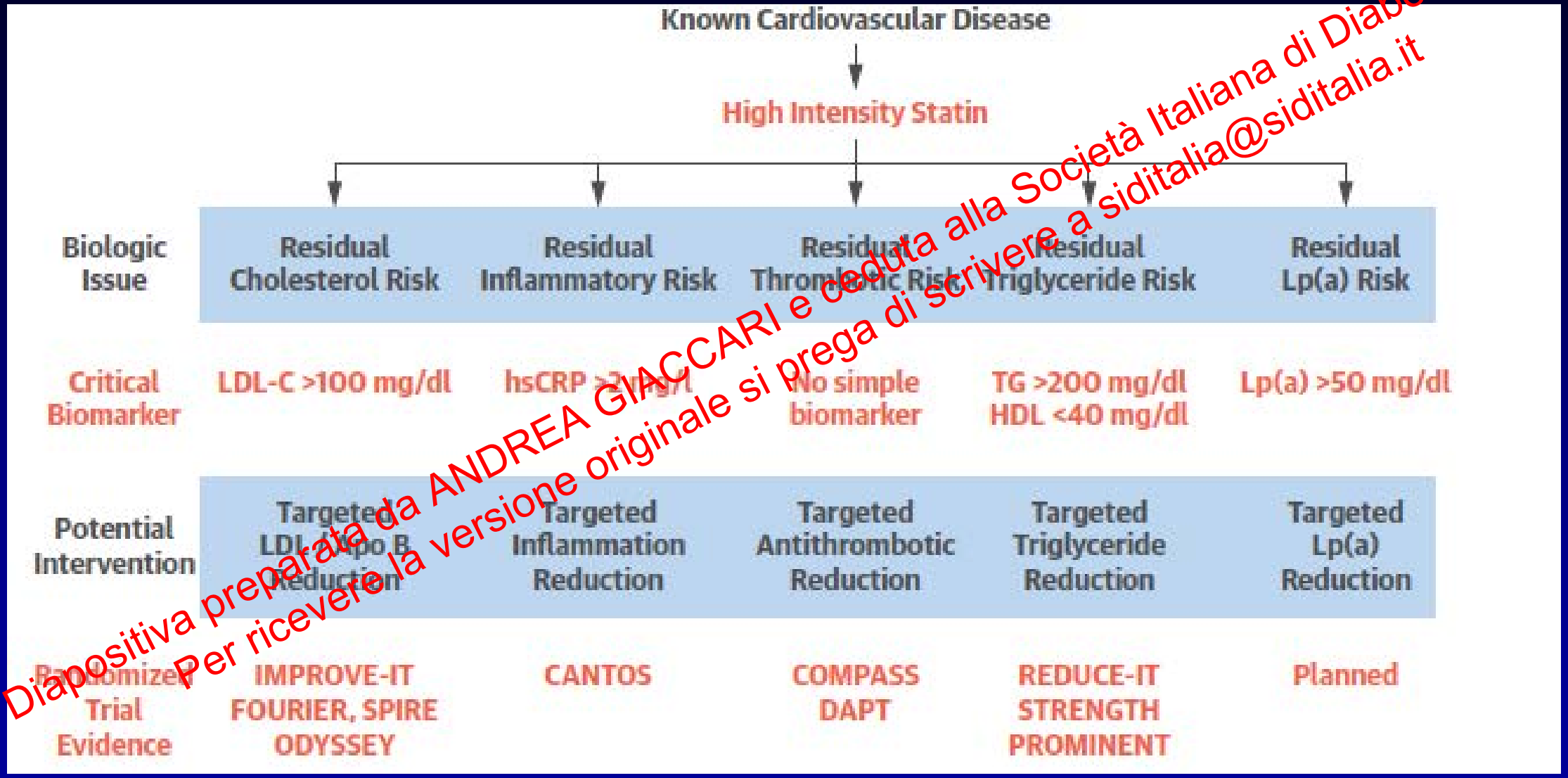
Terami N, PLOS ONE 2014

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

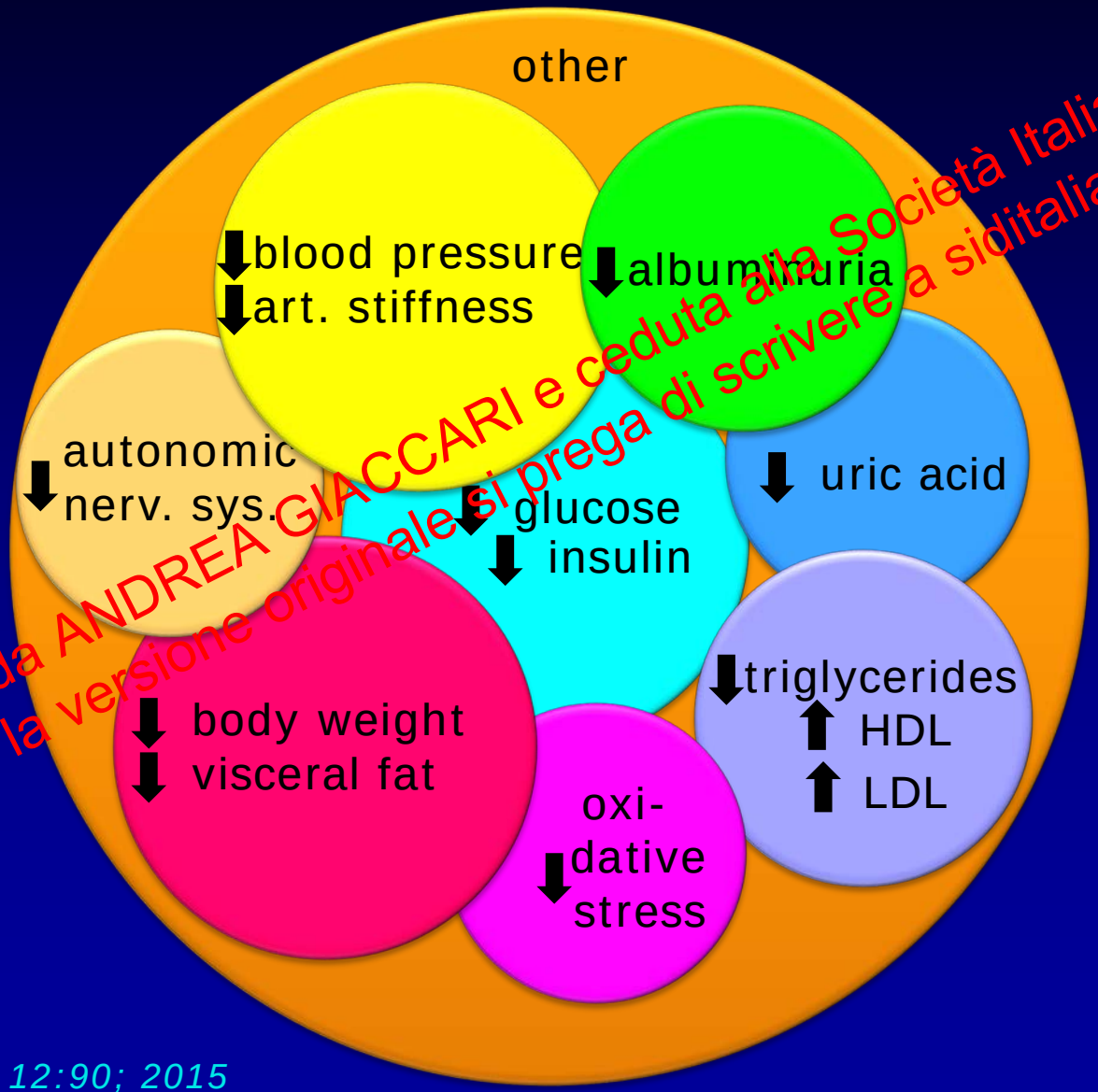


Ridker PM, et al. J Am Coll Cardiology 2018

altri meccanismi

- trigliceridi
- acido urico
- infiammazione
- altro?

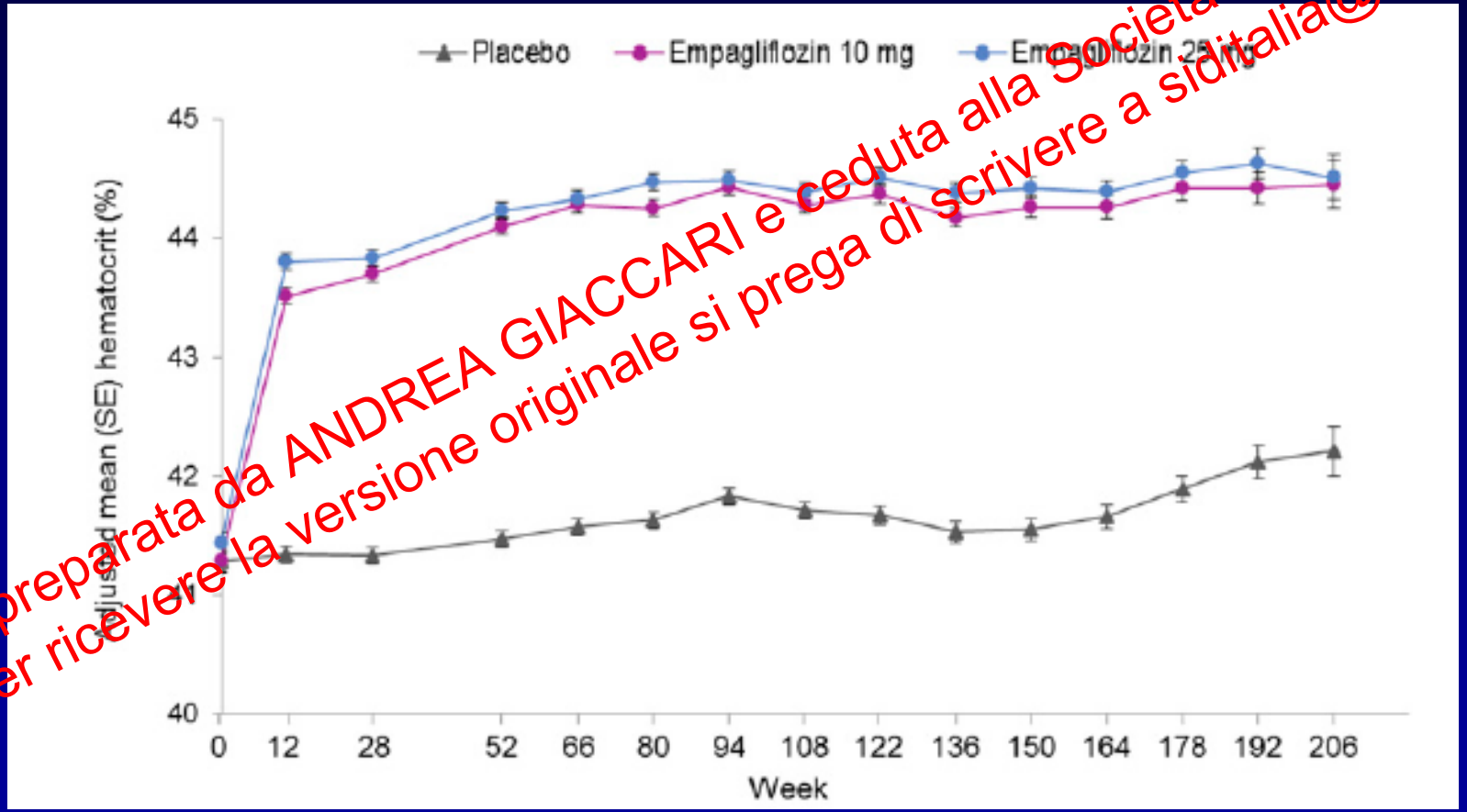
potential and novel pathways associated with CV effects of SGLT2-i



Inzucchi SE, et al. Diab Vasc Dis Res 12:90; 2015

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

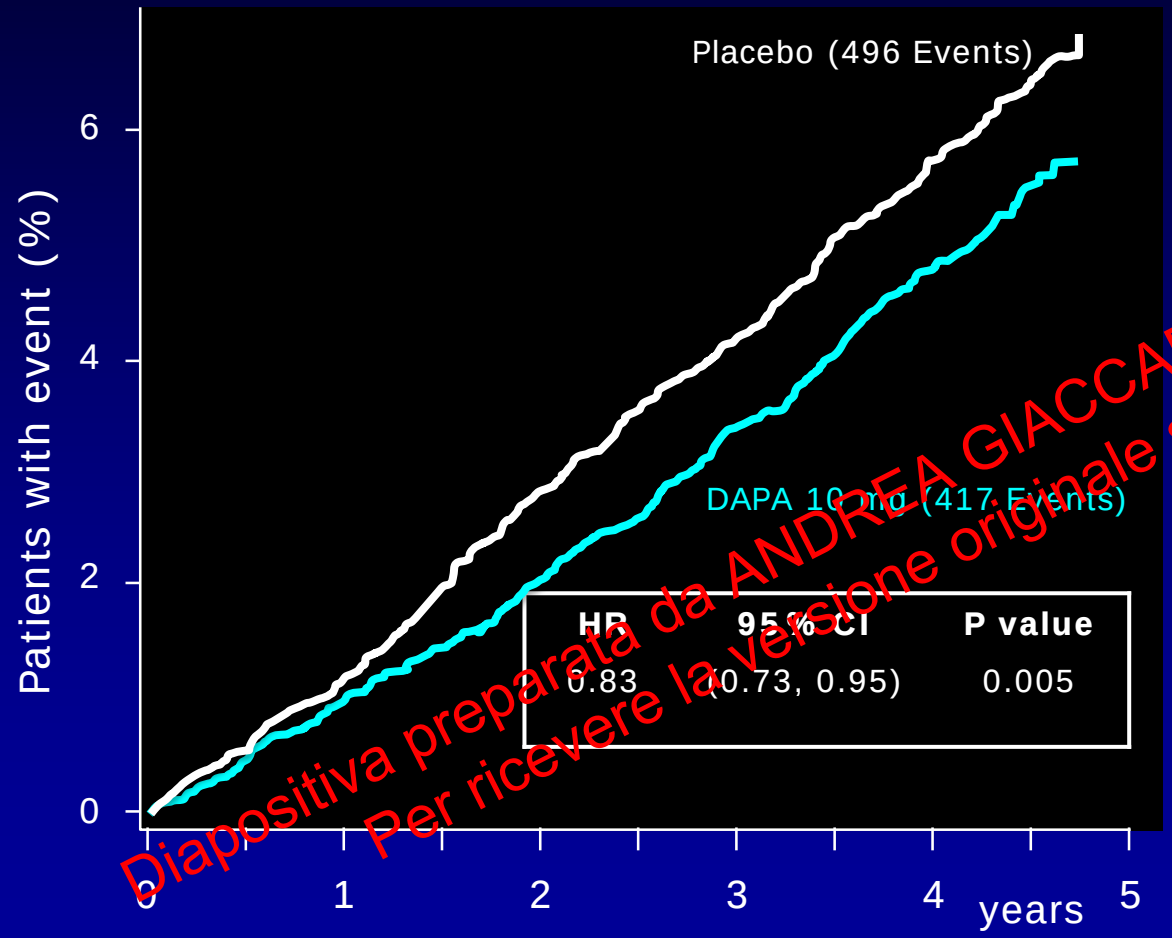
Univariate mediation analysis of risk of CV death with empagliflozin vs. placebo: time-dependent covariate analysis adjusting for the updated mean of each variable

	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	0.628 (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
FFA	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

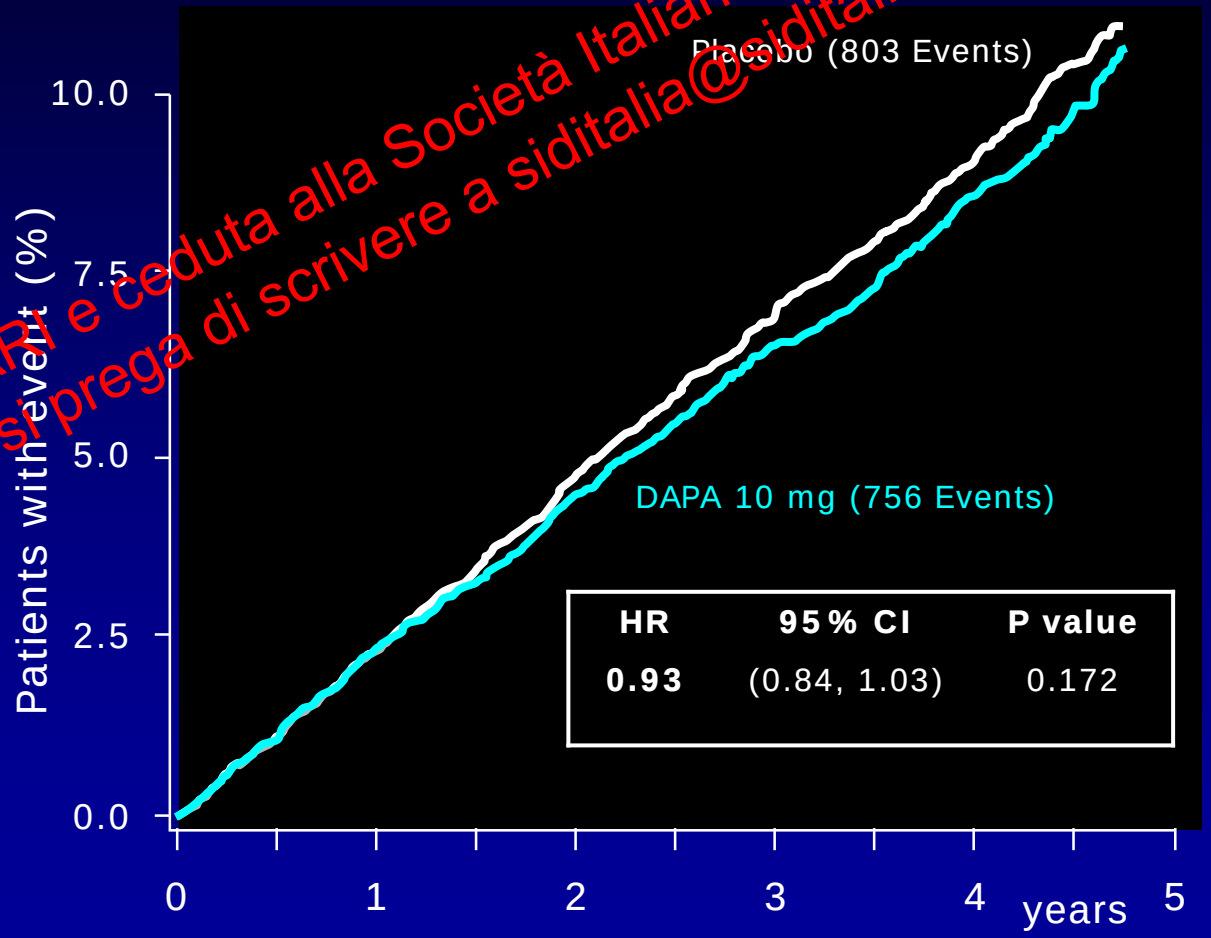
Inzucchi SE et al. Diabetes Care 2018

DECLARE: co-primary outcomes

hHF/CVD



MACE

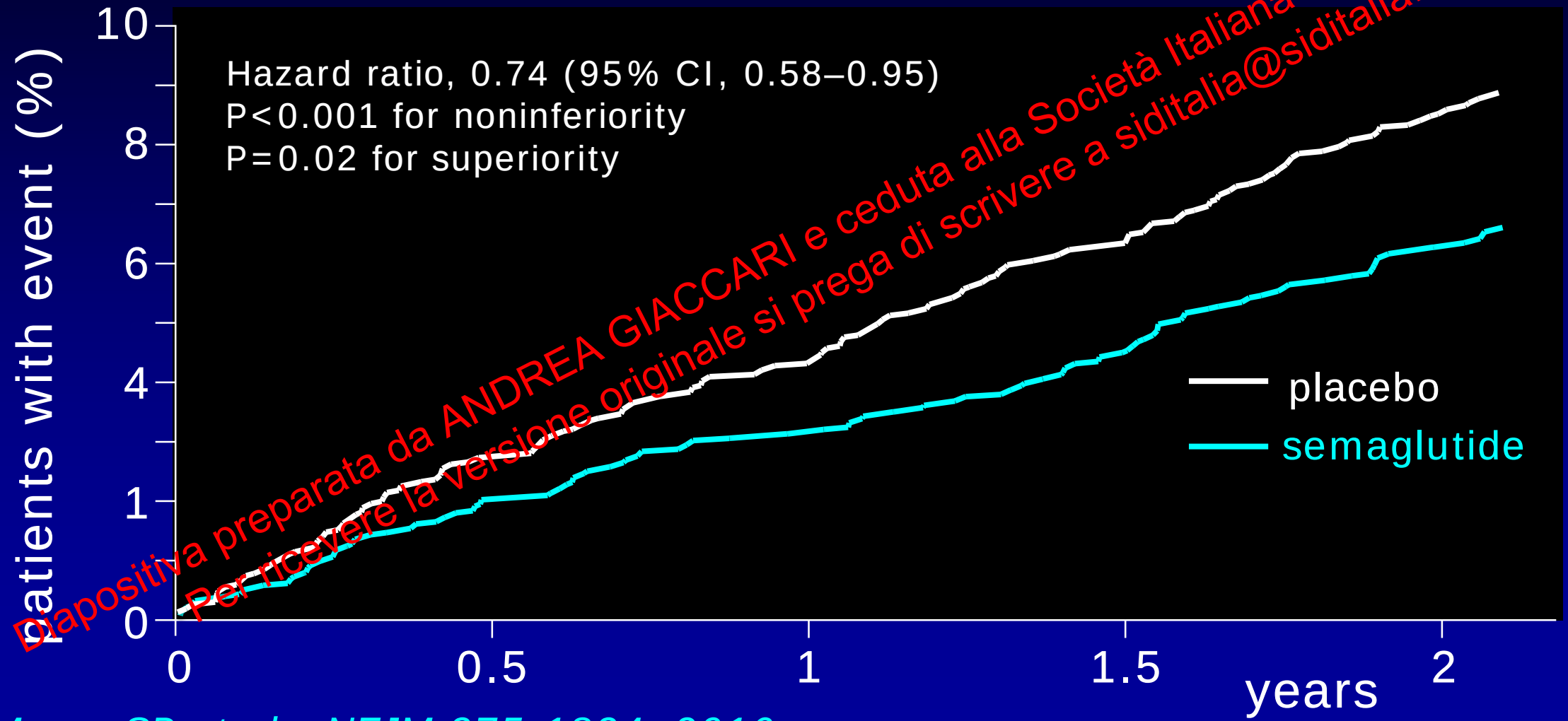


N at risk is the number of subjects at risk at the beginning of the period. 2-sided p-value is displayed; HR, CI, and p-value are from cox proportional hazard model.
CV, cardiovascular; Dapa, dapagliflozin; hHF, hospitalization for heart failure; MACE, major adverse cardiac event

Wiviott SD et al. Online ahead of print. *N Engl J Med*. 2018

SUSTAIN6: MACE (primary outcome)

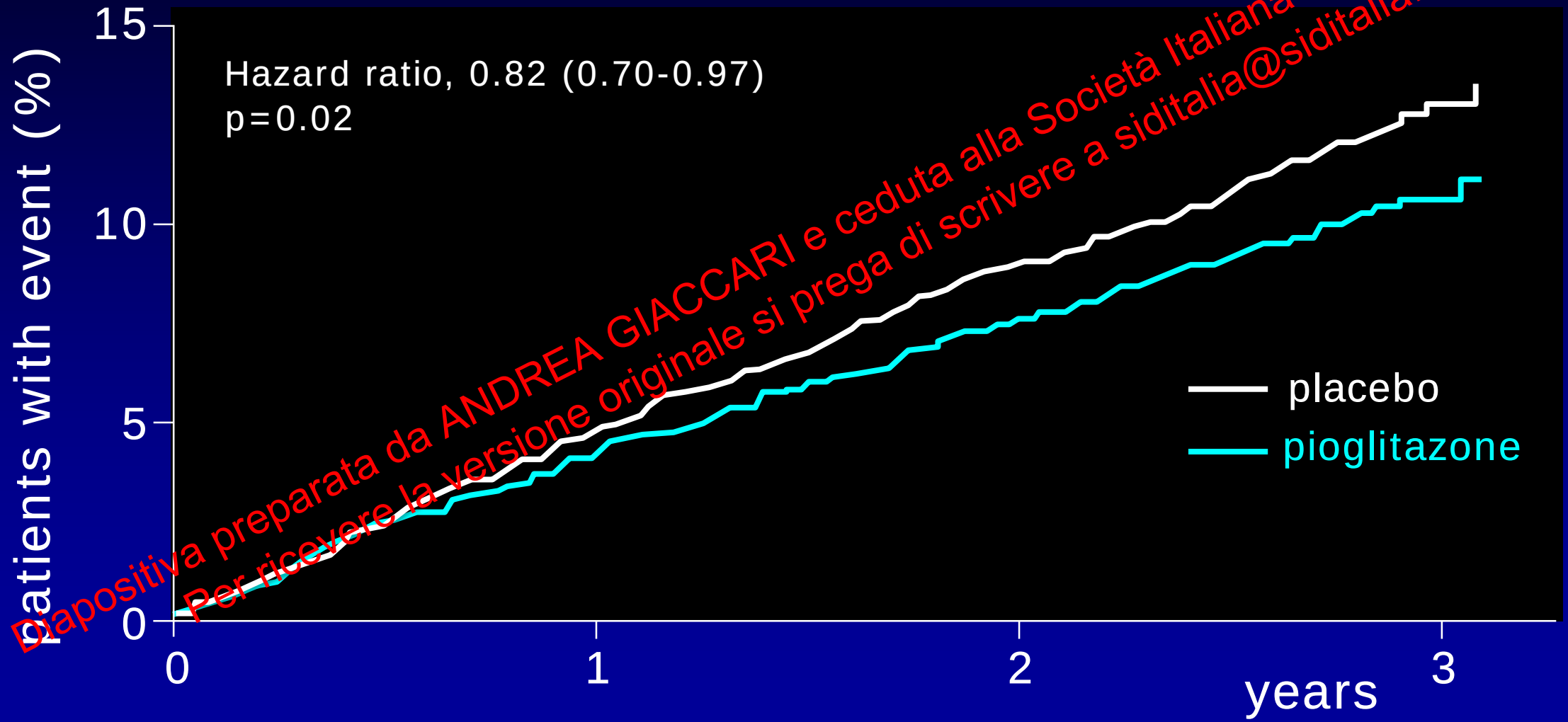
CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke



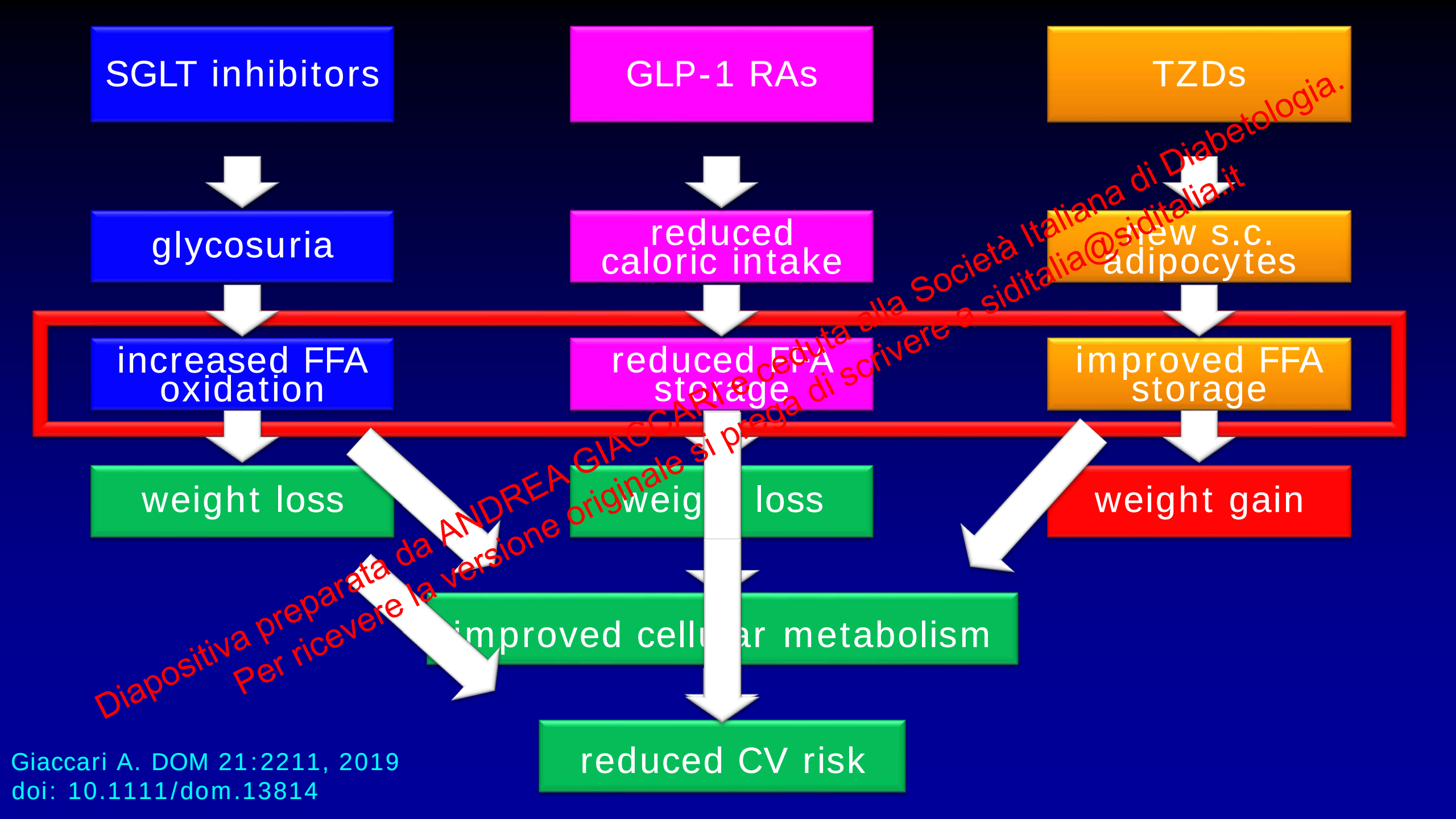
Marso SP et al.: NEJM 375:1834, 2016

PROACTIVE: MACE (primary outcome failed)

CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke



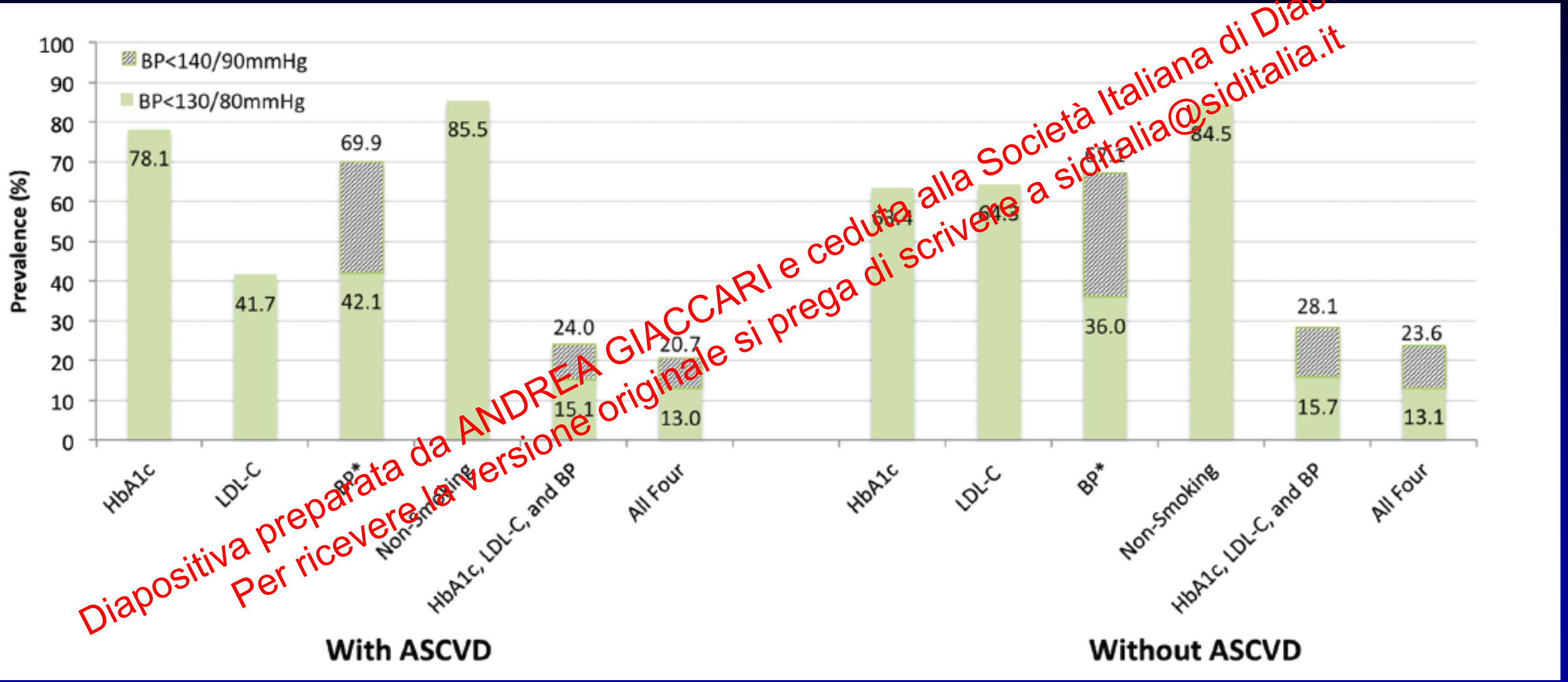
Wilcox R. et al AHJ 155:712, 2008



Giaccari A. DOM 21:2211, 2019
doi: 10.1111/dom.13814

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 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