Gestione del rischio globale del

diabetico di tipo 2:

un ruolo per i DPP4?

Quali obiettivi perseguire nel diabete in prevenzione primaria?

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Milano| 9 Novembre 2019

Il Prof Marco Giorgio Baroni dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

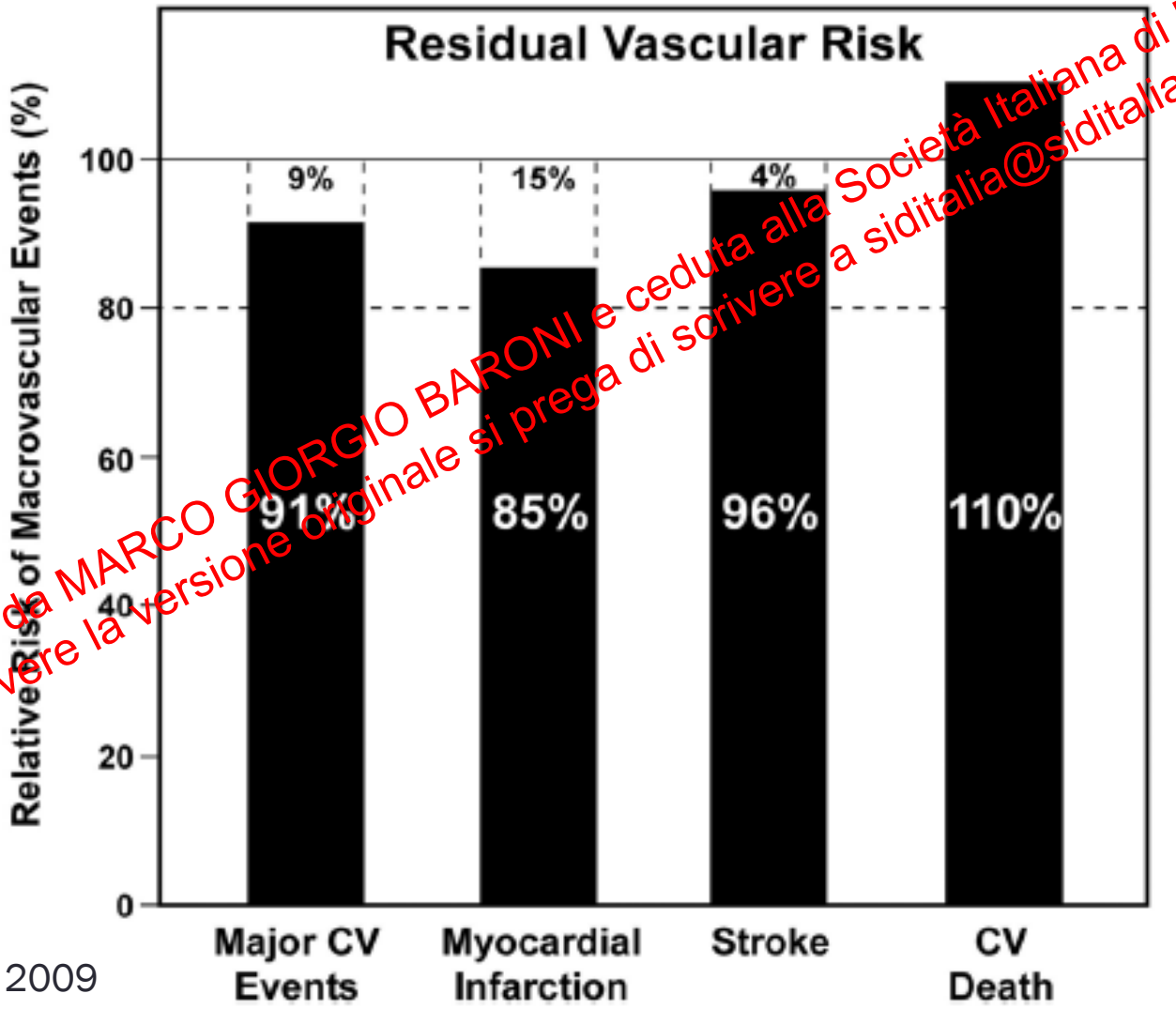
- Novo Nordisk
- Sanofi
- Abbott
- MSD
- Mundipharma
- Astra Zeneca

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.).

Quale riduzione del rischio cardiovascolare è stata ottenuta con il trattamento intensivo della glicemia?

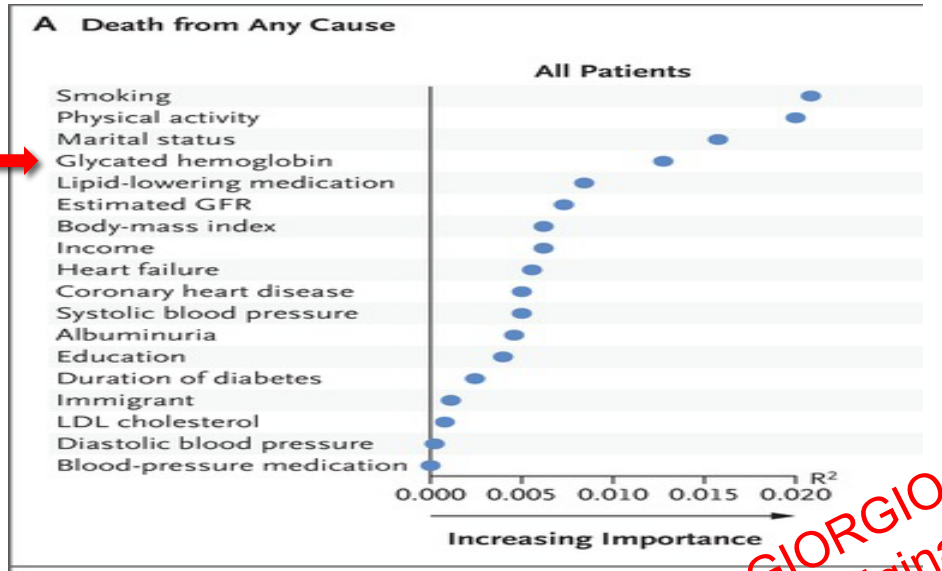
A. >30%
B. >50%
C. <10%
D. 2%

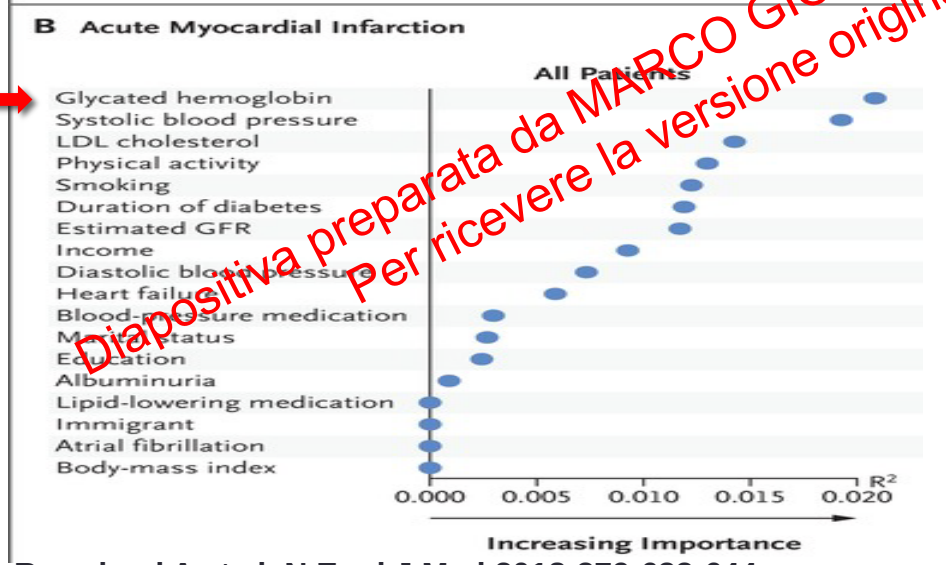
Residual vascular risk for macrovascolar complications in type 2 diabetic patients, as reported in randomized controlled trials that compared more intensive glucose control vs less intensive glucose control.

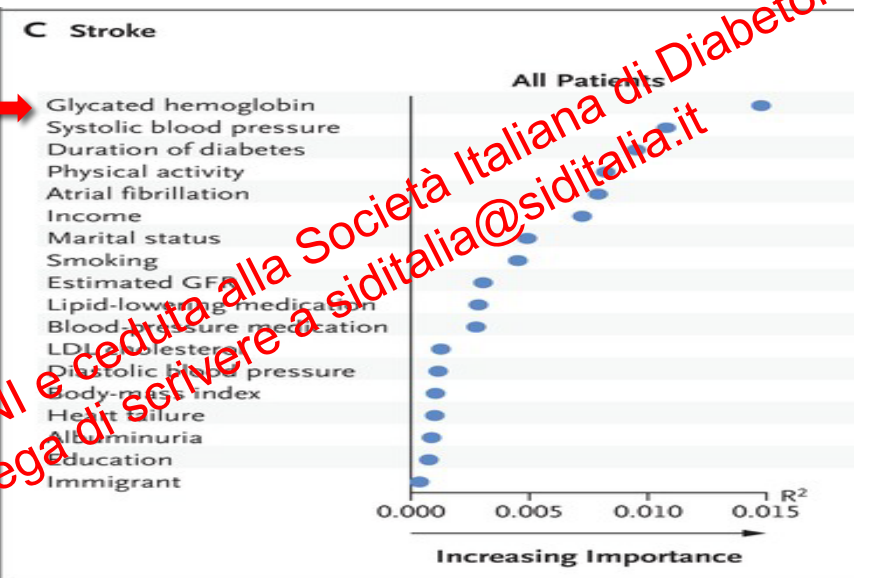


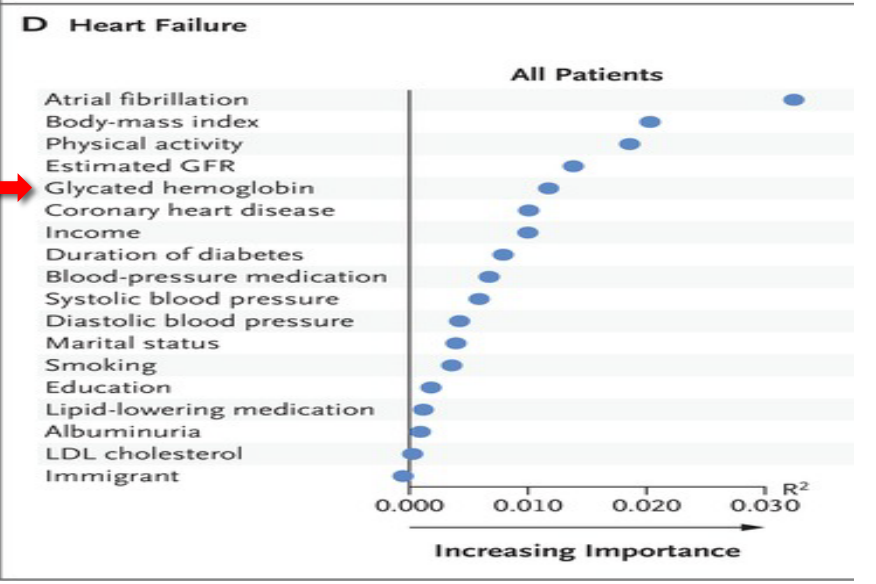
Turnbull FM et al Diabetologia 2009
Giugliano D et al. Endocrine 2018

Relative Importance of Risk Factors for Predicting Death from Any Cause, Acute Myocardial Infarction, Stroke, and Hospitalization for Heart Failure among Patients with Type 2 Diabetes, with or without Preexisting Conditions



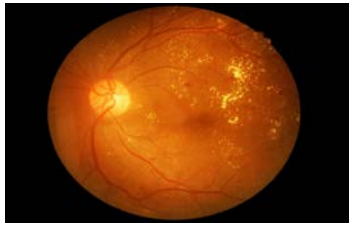






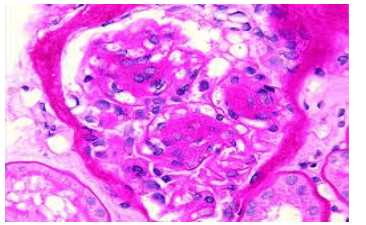
Rawshani A et al. N Engl J Med 2018;379:633-644

Factors influencing diabetes complications



Blood pressure
Smoking
Dyslipidemia
Mediterranean diet and high fruit, vegetable and fish intake

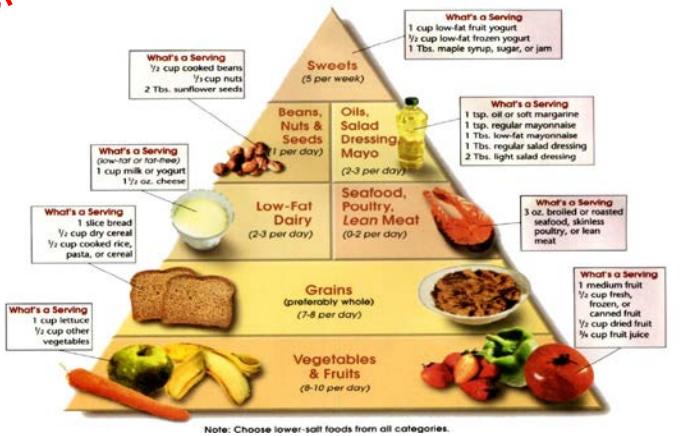
Blood pressure
Smoking
Dyslipidemia
Diet?



Blood pressure
Smoking
Dyslipidemia
DASH Diet

Blood pressure
Smoking
Dyslipidemia
DASH diet

Blood pressure
Smoking
Dyslipidemia
Healthy diet



Rawshani A et al. N Engl J Med 2018;379:633-644; Dow C et al. EUR J EPIDEMIOL 2018 Feb;33(2):141-156.

AGENDA

- Colesterolo LDL/fibrati
- Pressione
- Fumo
- Peso e Nutrizione

LDL-Colesterolo

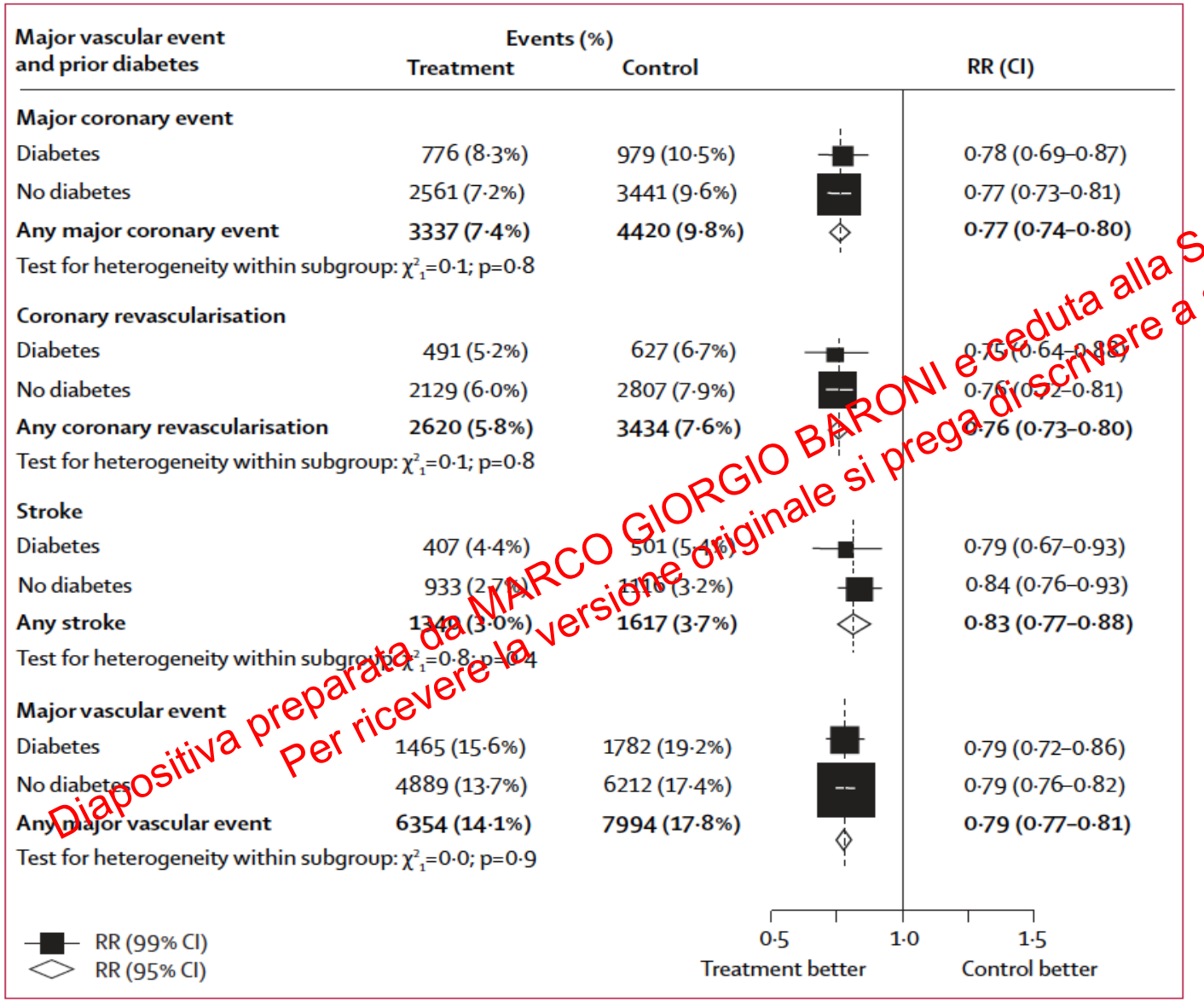
Standard italiani per la cura del diabete mellito 2018

Tabella 5.A1 Obiettivi terapeutici per il trattamento della dislipidemia in pazienti con diabete

Parametro	Obiettivo	
Colesterolo LDL	<100 mg/dl	<70 mg/dl in pazienti con pregressi eventi CV o fattori di rischio multipli
Colesterolo non HDL	<130 mg/dl	< 100 mg/dL per pazienti con pregressi eventi CV o fattori di rischio multipli
Trigliceridi	< 150 mg/dL	

Obiettivo (soglia) implica che esista una concentrazione di LDLc “sicura”?

-1.0 mM LDL: diabete vs no diabete



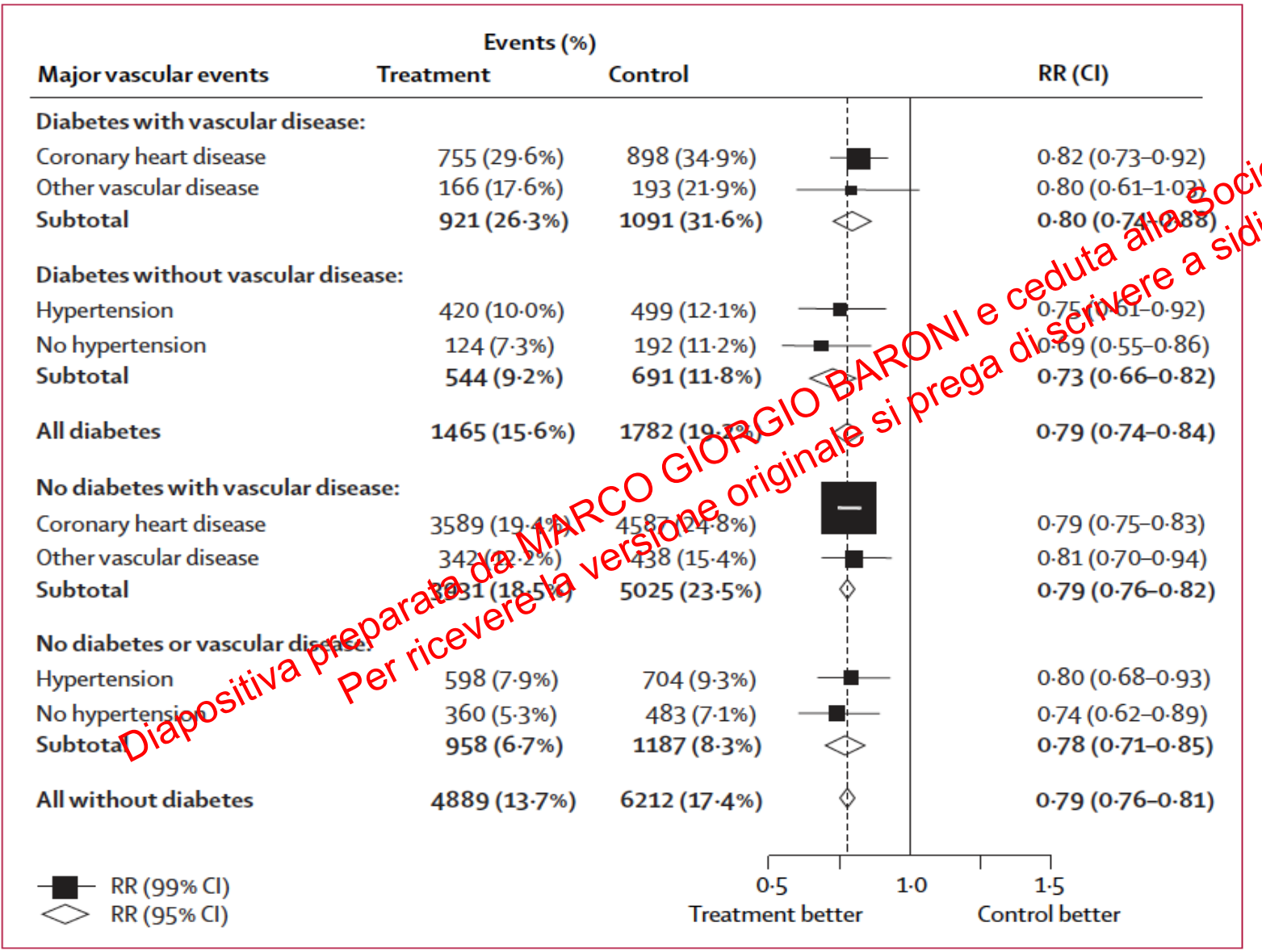
Major vascular event and prior diabetes	Events (%) Treatment	Control	RR (CI)
Major coronary event			
Diabetes	776 (8·3%)	979 (10·5%)	0·78 (0·69–0·87)
No diabetes	2561 (7·2%)	3441 (9·6%)	0·77 (0·73–0·81)
Any major coronary event	**3337 (7·4%)**	**4420 (9·8%)**	**0·77 (0·74–0·80)**
Test for heterogeneity within subgroup: χ^2_1=0·1; p=0·8			
Coronary revascularisation			
Diabetes	491 (5·2%)	627 (6·7%)	0·76 (0·64–0·88)
No diabetes	2129 (6·0%)	2807 (7·9%)	0·76 (0·72–0·81)
Any coronary revascularisation	**2620 (5·8%)**	**3434 (7·6%)**	**0·76 (0·73–0·80)**
Test for heterogeneity within subgroup: χ^2_1=0·1; p=0·8			
Stroke			
Diabetes	407 (4·4%)	501 (5·4%)	0·79 (0·67–0·93)
No diabetes	933 (2·7%)	1116 (3·2%)	0·84 (0·76–0·93)
Any stroke	**1340 (3·0%)**	**1617 (3·7%)**	**0·83 (0·77–0·88)**
Test for heterogeneity within subgroup: χ^2_1=0·8; p=0·4			
Major vascular event			
Diabetes	1465 (15·6%)	1782 (19·2%)	0·79 (0·72–0·86)
No diabetes	4889 (13·7%)	6212 (17·4%)	0·79 (0·76–0·82)
Any major vascular event	**6354 (14·1%)**	**7994 (17·8%)**	**0·79 (0·77–0·81)**
Test for heterogeneity within subgroup: χ^2_1=0·0; p=0·9			

LDL
-40 mg/dl = -20%
(-0.5% /mg)

N= 18.686 people
with diabetes

Cholesterol Treatment Trialists' (CTT) Collaboration- Lancet 2008

-1.0 mM LDL: sia in prev primaria che secondaria



-20%

Cholesterol Treatment Trialists' (CTT) Collaboration- Lancet 2008

-1.0 mM LDL: a prescindere dalle comorbidità

Groups	Events (%) Treatment	Control	RR (CI)	Test for heterogenity or trend
Type of diabetes:				
Type 1 diabetes	147 (20·5%)	196 (26·2%)	0·79 (0·62–1·01)	χ^2_1=0·0; p=1·0
Type 2 diabetes	1318 (15·2%)	1586 (18·5%)	0·79 (0·72–0·87)	
Sex:				
Men	1082 (17·2%)	1332 (21·4%)	0·78 (0·71–0·86)	χ^2_1=0·1; p=0·7
Women	383 (12·4%)	450 (14·6%)	0·81 (0·67–0·97)	
Age (years):				
≤65	701 (13·1%)	898 (17·1%)	0·77 (0·68–0·87)	χ^2_1=0·5; p=0·5
>65	764 (18·9%)	884 (21·8%)	0·81 (0·71–0·92)	
Currently treated hypertension:				
Yes	1030 (16·3%)	1196 (19·1%)	0·82 (0·74–0·91)	χ^2_1=2·7; p=0·1
No	435 (14·2%)	586 (19·3%)	0·73 (0·63–0·85)	
Body-mass index:				
<25·0	276 (15·7%)	362 (20·4%)	0·78 (0·64–0·95)	χ^2_1=0·5; p=0·5
≥25·0–<30·0	639 (15·9%)	774 (19·8%)	0·77 (0·66–0·88)	
≥30·0	532 (15·1%)	628 (17·6%)	0·82 (0·71–0·95)	
Systolic blood pressure (mm Hg):				
<160	993 (15·0%)	1276 (19·1%)	0·76 (0·69–0·85)	χ^2_1=1·3; p=0·3
≥160	472 (17·1%)	505 (19·2%)	0·83 (0·71–0·96)	
Diastolic blood pressure (mm Hg):				
≤90	1176 (16·5%)	1417 (19·8%)	0·81 (0·73–0·89)	χ^2_1=1·7; p=0·2
>90	288 (12·9%)	364 (17·1%)	0·73 (0·61–0·87)	
Smoking status:				
Current smokers	266 (17·5%)	347 (22·5%)	0·78 (0·64–0·96)	χ^2_1=0·0; p=0·9
Non-smokers	1199 (15·2%)	1435 (18·5%)	0·79 (0·72–0·87)	
Estimated GFR (mL/min/1·73m²):				
<60	415 (20·6%)	477 (24·0%)	0·83 (0·71–0·97)	χ^2_1=2·9; p=0·09
≥60–<90	816 (15·5%)	961 (18·4%)	0·81 (0·72–0·91)	
≥90	194 (12·5%)	286 (18·7%)	0·65 (0·50–0·84)	
Predicted risk of major vascular event (per year):				
<4·5%	474 (8·4%)	631 (11·2%)	0·74 (0·64–0·85)	χ^2_1=1·8; p=0·2
≥4·5–<8·0%	472 (23·2%)	540 (27·3%)	0·80 (0·66–0·96)	
≥8·0%	519 (30·5%)	611 (35·8%)	0·82 (0·70–0·95)	
All diabetes	**1465 (15·6%)**	**1782 (19·2%)**	**0·79 (0·74–0·84)**	

Global test for heterogeneity within subtotals: χ^2_{13}=13·9: p=0·4

RR (99% CI)

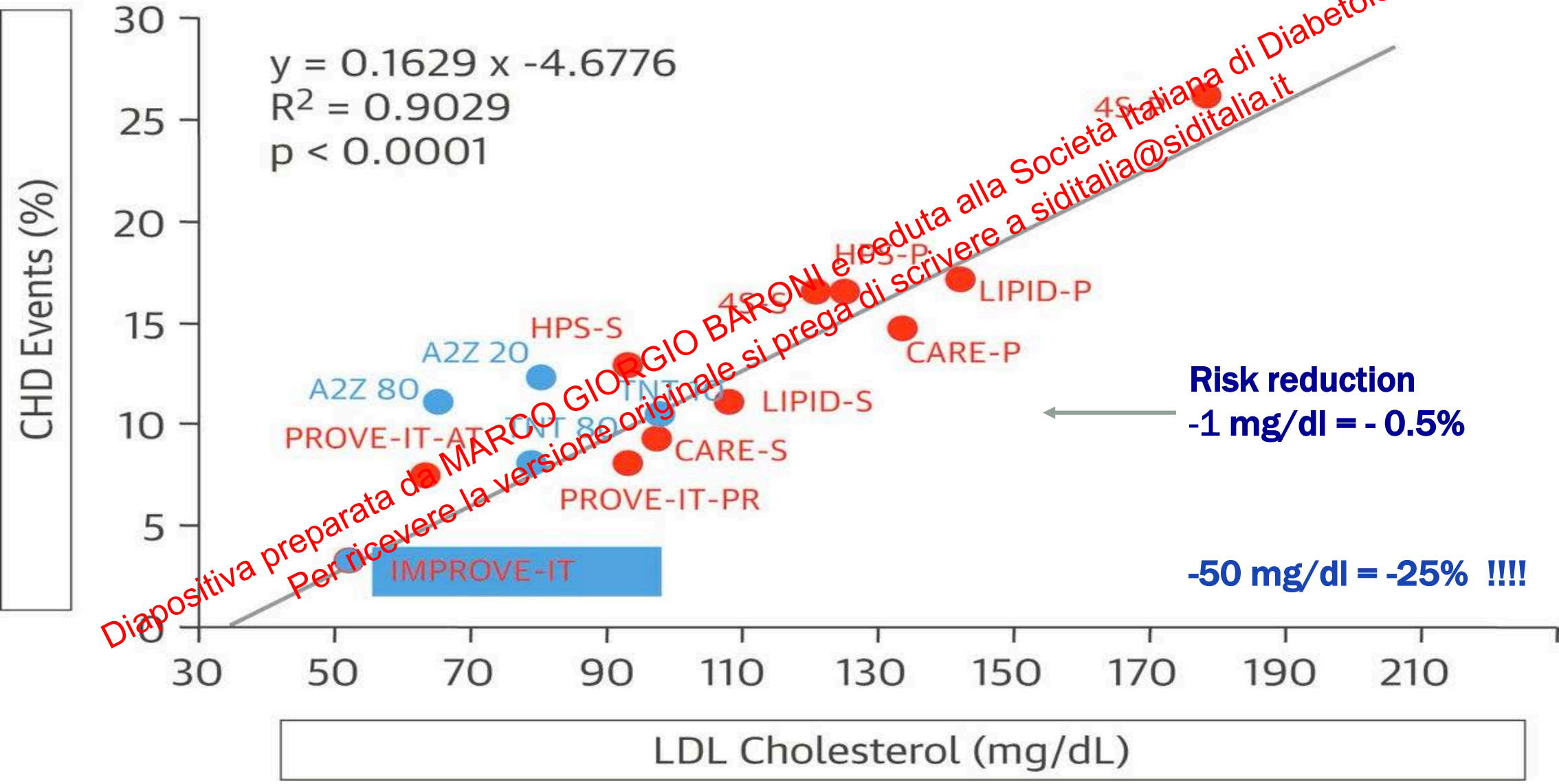
RR (95% CI)

0·5 Treatment better — 1·0 — 1·5 Control better

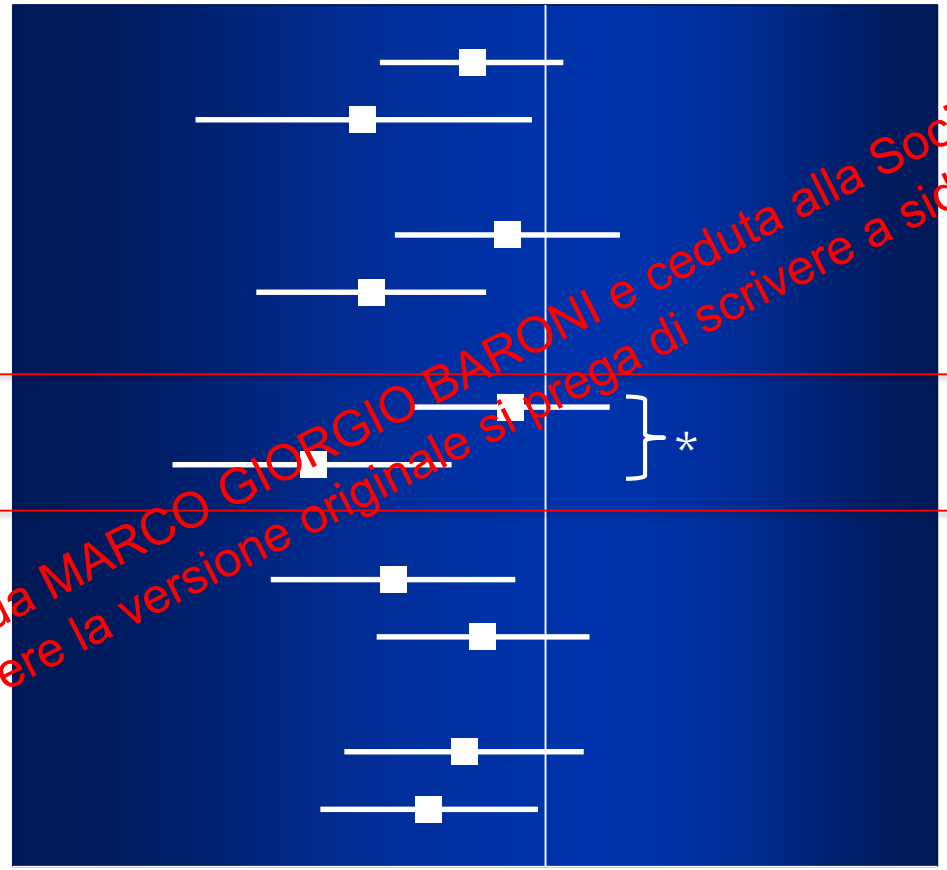
-20%

Cholesterol Treatment Trialists' (CTT) Collaboration- Lancet 2008

On-Treatment LDL Predicts Clinical Event Rates



Improve-IT
Major Pre-specified Subgroups

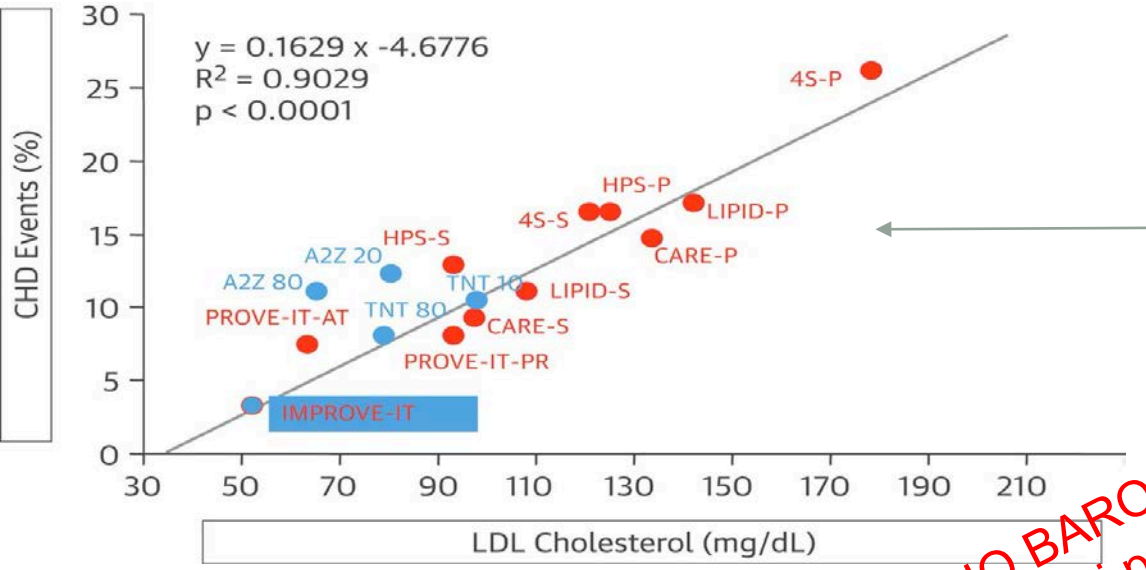


	Simva†	EZ/Simva†
Male	34.9	33.3
Female	34.0	31.0
Age < 65 years	30.8	29.9
Age ≥ 65 years	39.9	36.4
No diabetes	30.8	30.2
Diabetes	45.5	40.0
Prior LLT	43.4	40.7
No prior LLT	30.0	28.6
LDL-C > 95 mg/dl	31.2	29.6
LDL-C ≤ 95	38.4	36.0

†*7-year event rates*

**p-interaction = 0.023, otherwise > 0.05*

Riduzione del rischio con statine e ezetimibe



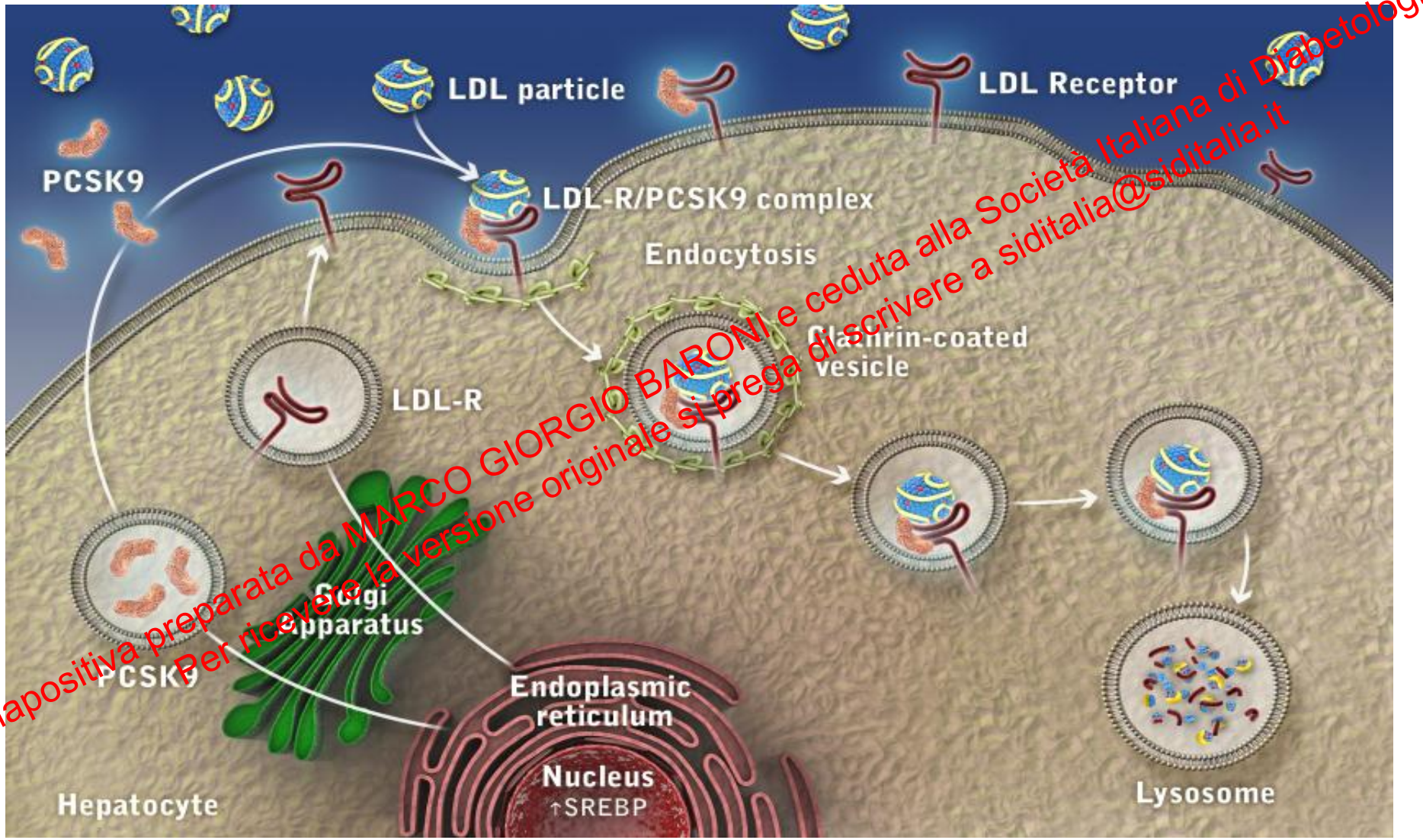
Risk reduction
-1 mg/dl = -0.5%

-50 mg/dl = -25% !!!!

Low-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	High-Intensity Statin Therapy
LDLc reduction <30%	*LDLc reduction 30 - 50%*	*LDLc reduction >50%*
Simvastatin 10 mg	Atorvastatin 10 (20) mg	Atorvastatin (40†)–80 mg
Pravastatin 10–20 mg	Rosuvastatin (5) 10 mg	Rosuvastatin 20 (40) mg
Fluvastatin 20–40 mg	Simvastatin 20–40 mg‡	
	Pravastatin 40 (80) mg	
	Fluvastatin XL 80 mg mg	
	Fluvastatin 40 mg bid	

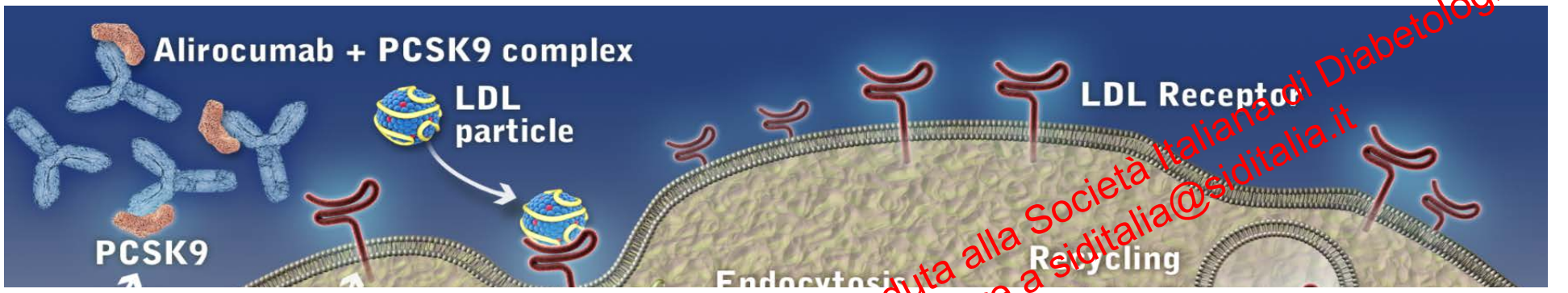
Ezetimibe
Ulteriore -20/25%

The Role of PCSK-9 in the Regulation of LDL Receptor Expression



Lambert G et al. *J Lipid Res.* 2012. 53: 2515–2524.

Impact of anti-PCSK9 MAb on LDL Receptor Expression



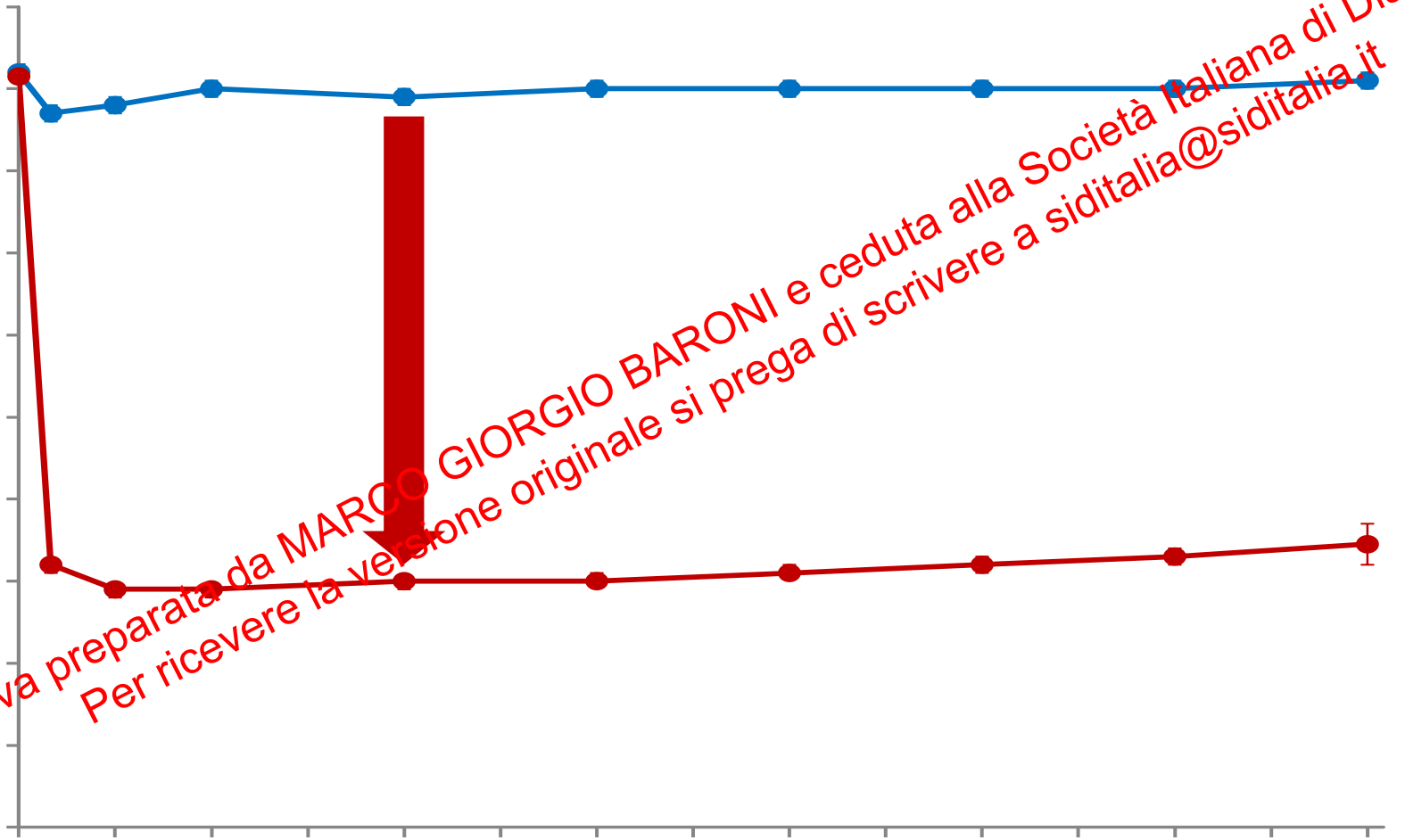
Blocking PCSK9 binding of LDLR with a PCSK9 monoclonal antibody may lead to increased expression of LDLR, increased clearance of LDL and lower LDL levels

L’efficacia degli inibitori di PCSK9 nel ridurre i livelli di LDL-C nel paziente diabetico:

A. E’ uguale al paziente non diabetico
B. E’ superiore al paziente non diabetico
C. E’ inferiore al paziente non diabetico
D. E’ significativa solo sui trigliceridi

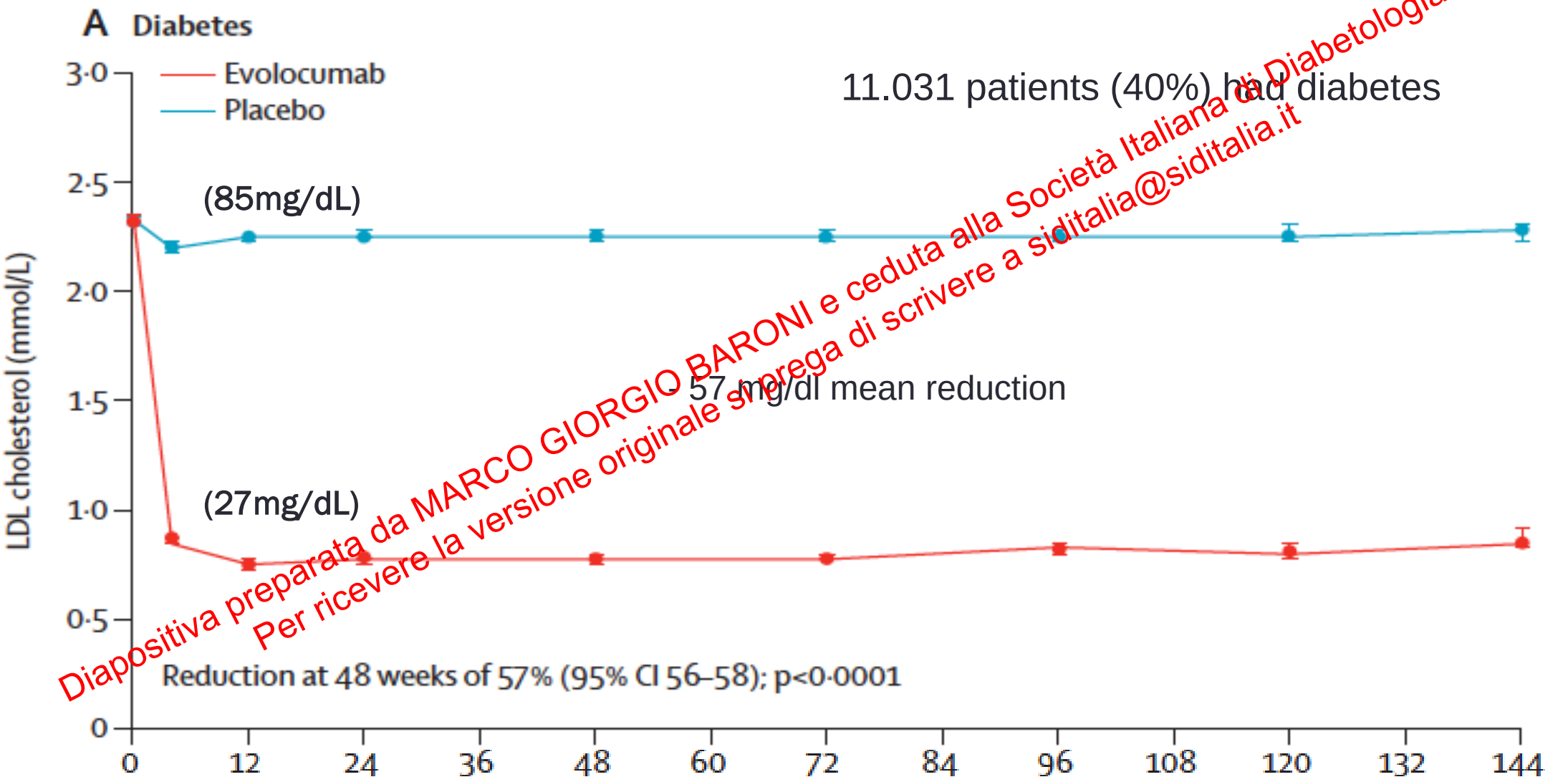
Fourier trial: LDL cholesterol concentrations over time

11.031 patients (40%) had diabetes



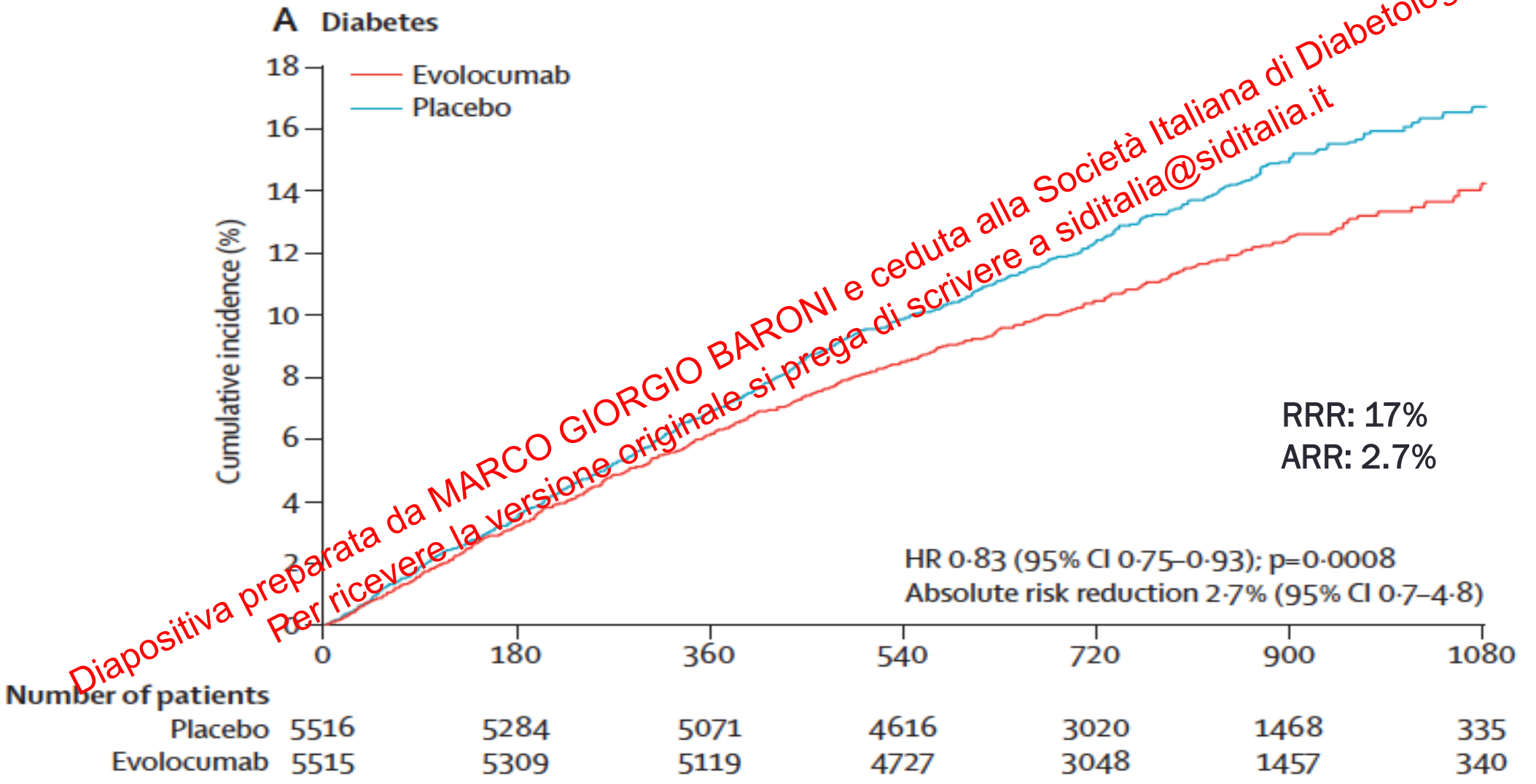
Sabatine MS et al: NEJM 2017

Fourier trial: LDL cholesterol concentrations over time in T2D



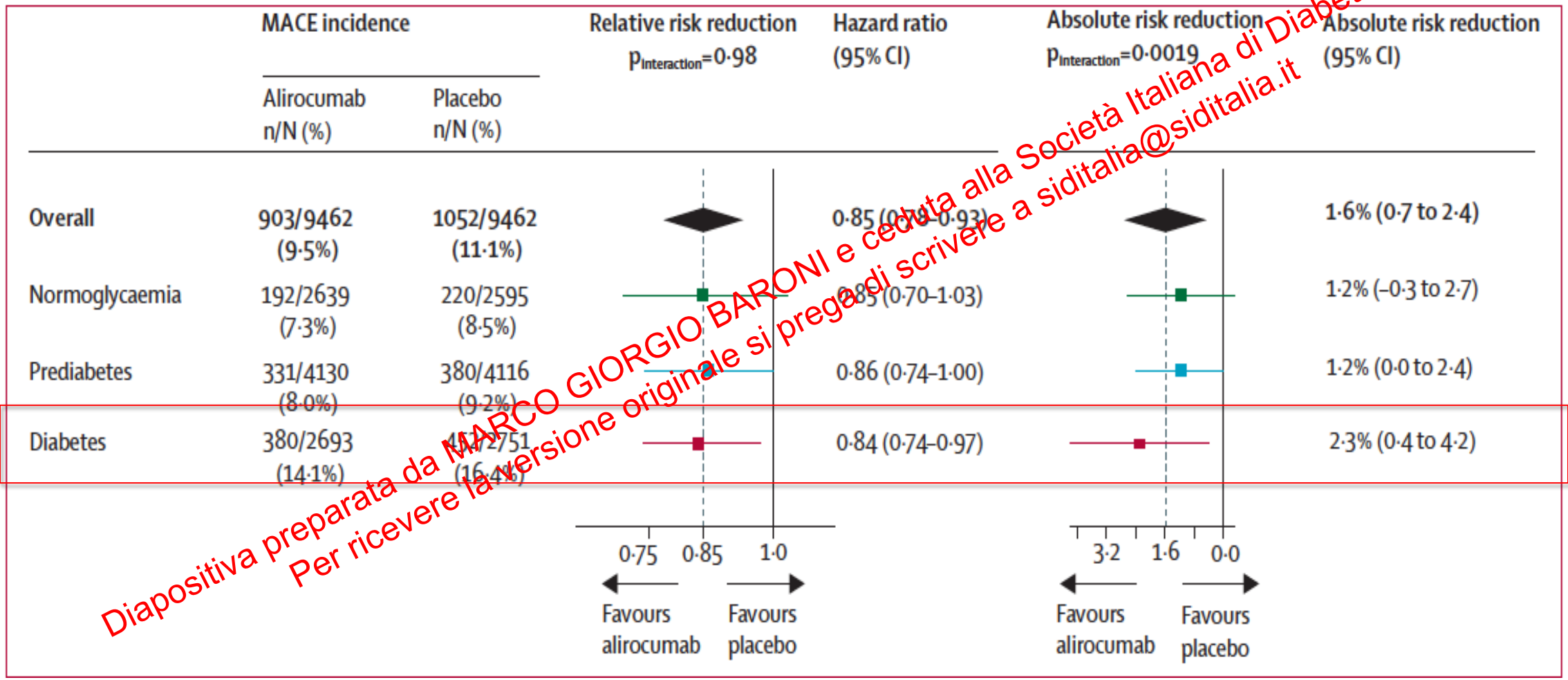
Sabatine MS et al: Lancet Diab Endocr 2017

Fourier trial: primary endpoint (CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularisation) in patients with diabetes at baseline



Sabatine MS et al: Lancet Diab Endocr 2017

Relative and Absolute Risk Reduction with Alirocumab By Glucometabolic Status



Ray KK et al. Lancet Diab Endocr, July 1, 2019

PCSK9 Rimborsabilità

1) **Prevenzione secondaria= CAD, CVD, PAD, DMc, DM+fumo, DM+HT**

   - età≤80aa, no ipercolest. secondaria, no GFR<30ml/min, no insuff.epatica

2) **Ipercolesterolemia (familiare e non) *oppure* dislipidemia mista**

4) LDLc ≥ 100 mg/dl dopo 6 mesi di terapia alla dose massima tollerata di statina (anche 0 mg°) + ezetimibe 10 mg/die

° Intolleranza alle statine = almeno 2 statine, 1 alla dose bassa e l'altra a qualsiasi dose oppure CK>x10

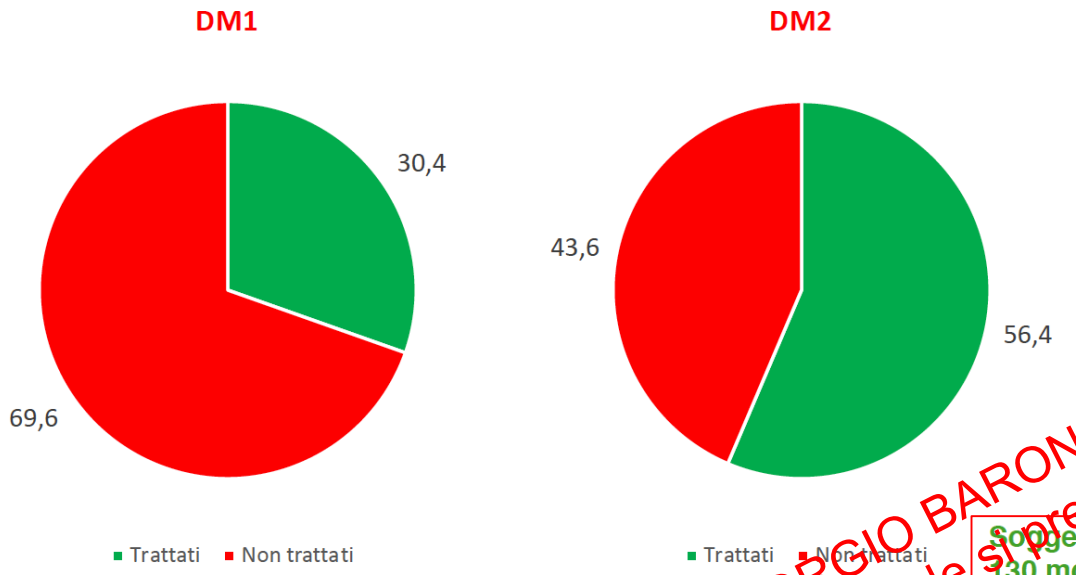
Esempio

Risk reduction
- 0.5% per -1 mg/dl

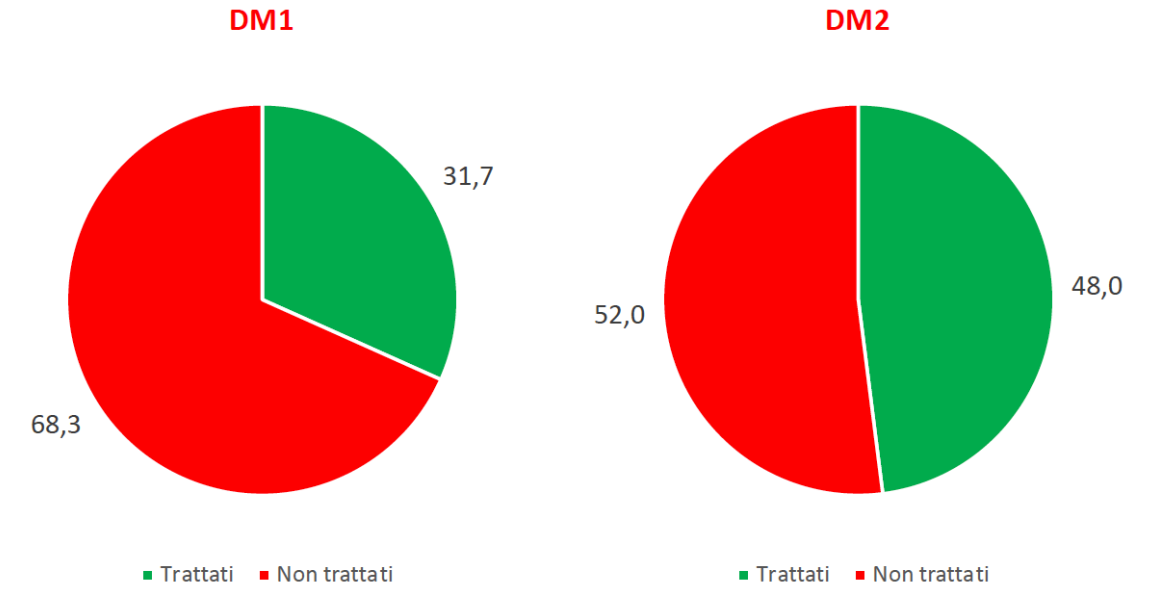
	Arturo **58 aa, HT, T2D, fumo** **Colesterolo LDL 100** **RCV = 20%**	**Alberto** **58 aa, HT, T2D** **Colesterolo LDL 200** **RCV = 20%**
Atorvastatina 10 (-30%)	LDL = 70 ∂LDL = 30 ∂RCV = 15% **RCV = 17%**	LDL = 140 ∂LDL = 60 ∂RCV = 30% **RCV = 14%**
Ros/Ezet 20/10 (-50%)	LDL = 50 ∂LDL = 50 ∂RCV = 25% **RCV = 15%**	LDL = 100 ∂LDL = 100 ∂RCV = 50% **RCV = 10%**
Ros/Ezet 20/10 +PCSK9 (ulteriore -50%)	LDL = 25 ∂LDL = 75 ∂RCV = 32% **RCV = 13%**	LDL = 50 ∂LDL = 150 ∂RCV = 75% **RCV = 5%**

Ipolipemizzanti «real life»

Soggetti trattati con ipolipemizzanti (%)

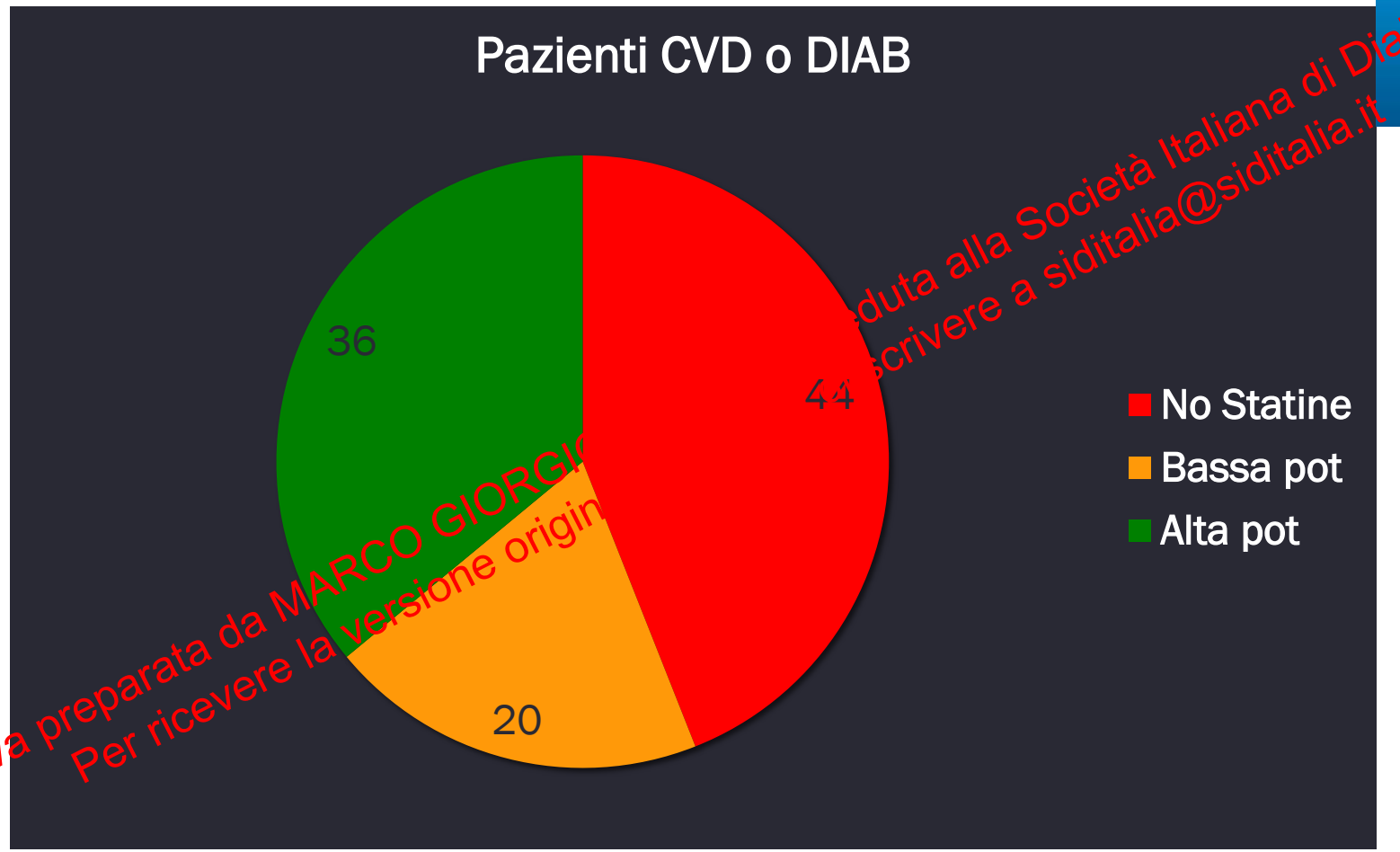


Soggetti non trattati con ipolipemizzanti nonostante valori di colesterolo LDL ≥ 130 mg/dl (%)



ANNALI AMD 2018

Altri dati «real life»



Aderenza (>290 gg/a) alla terapia con statine = 50%

TOSCA (2013-2017)

	Metformin plus pioglitazone (n=1535)	Metformin plus sulfonylurea (n=1493)	Overall (n=3028)
Age (years)	62·4 (6·4)	62·2 (6·5)	62·3 (6·5)
Sex			
Men	909 (59%)	865 (58%)	1774 (59%)
Women	626 (41%)	628 (42%)	1254 (41%)
BMI (kg/m²)	30·2 (4·4)	30·4 (4·5)	30·3 (4·5)
Cardiovascular risk factors			
Smokers	281 (18%)	252 (17%)	533 (18%)
LDL cholesterol (mmol/L)	2·67 (0·81)	2·66 (0·82)	2·67 (0·81)
HDL cholesterol (mmol/L)	1·20 (0·34)	1·20 (0·33)	1·20 (0·34)
Triglycerides (mmol/L)	1·72 (1·04)	1·73 (0·93)	1·73 (1·00)
Systolic blood pressure (mm Hg)	134·3 (15·1)	133·7 (14·2)	134·0 (14·7)
Diastolic blood pressure (mm Hg)	79·6 (8·7)	79·6 (8·1)	79·6 (8·4)
Microalbuminuria	321 (21%)	312 (21%)	633 (21%)
Diabetes characteristics			
Duration of diabetes (years)	8·4 (5·6)	8·5 (5·8)	8·5 (5·7)
HbA_{1c} (%)	7·67 (0·50)	7·69 (0·51)	7·68 (0·50)
HbA_{1c} (mmol/mol)	60·3 (5·4)	60·5 (5·6)	60·4 (5·5)
Previous cardiovascular history			
Previous cardiovascular disease*	187 (12%)	148 (10%)	335 (11%)
Previous acute myocardial infarction	109 (7%)	86 (6%)	195 (6%)
Previous stroke	28 (2%)	13 (1%)	41 (1%)
Previous acute coronary syndrome	39 (3%)	40 (3%)	79 (3%)
Carotid artery revascularisation	14 (1%)	12 (1%)	26 (1%)
Coronary artery revascularisation	105 (7%)	101 (7%)	206 (7%)
Use of cardiovascular drugs			
Antihypertensive drugs	1072 (70%)	1049 (70%)	2121 (70%)
Lipid-lowering drugs	888 (58%)	847 (57%)	1735 (57%)
Antiplatelet drugs	644 (42%)	574 (38%)	1218 (40%)

Data are mean (SD) or n (%). *Some patients had more than one condition.

Table 1: **Baseline characteristics**

102 mg/dl

50% LDLc>100 mg/dl
43% nessuna terapia !!!!

57 %

Fibrati e Omega-3

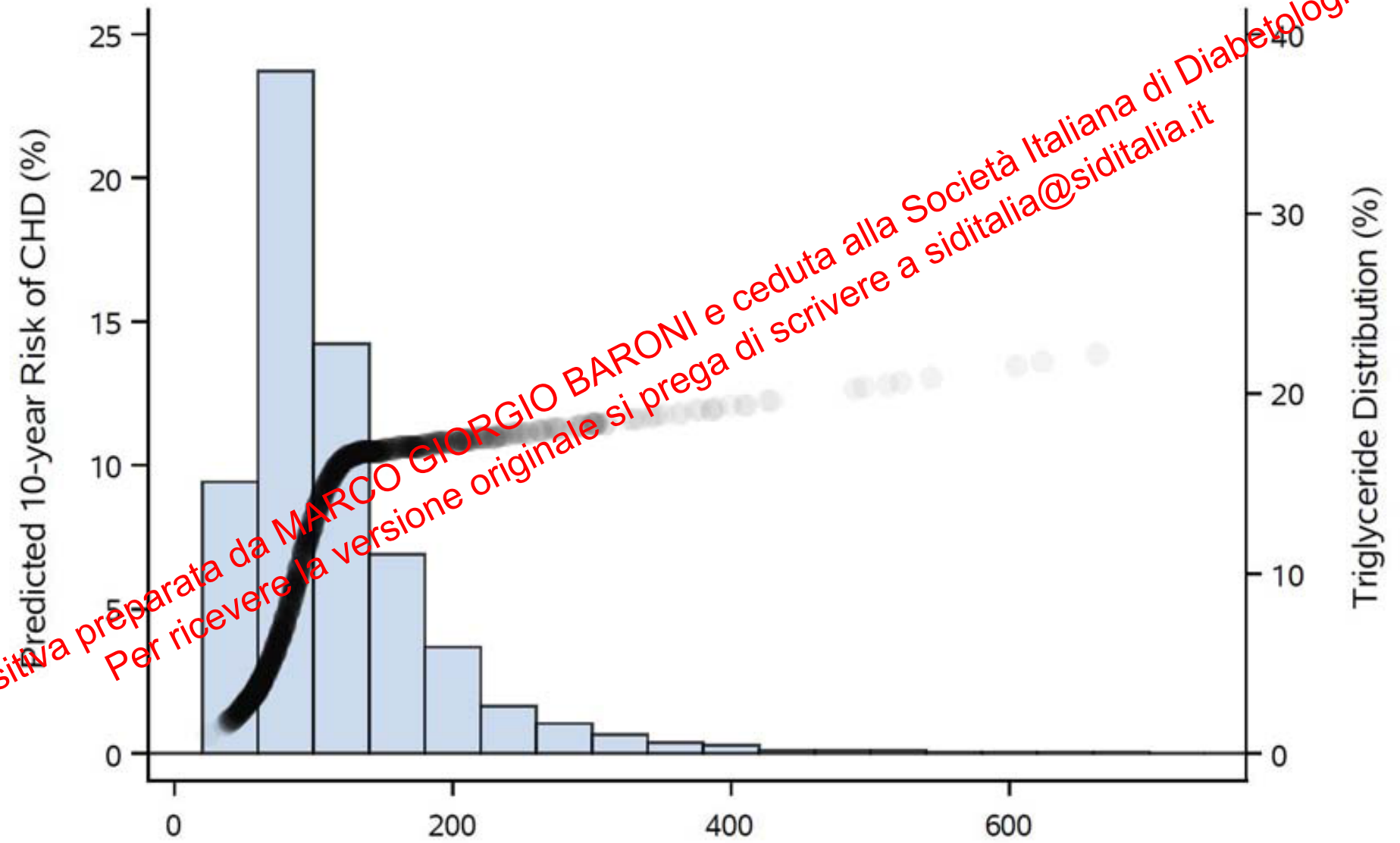
Alterazioni lipidiche nel Diabete mellito tipo 2

- ***QUANTITATIVE***
  - ↑ ↑ Trigliceridi VLDL
  - ↓ HDL Colesterolo
  - ↑ Colesterolo totale e LDL

3 - 6 volte aumento rischio CAD

- ***QUALITATIVE***
  - LDL piccole e dense (-Colest, +TG)
  - VLDL ricche di colesterolo
  - HDL ricche di trigliceridi
  - Apoproteine glicosilate

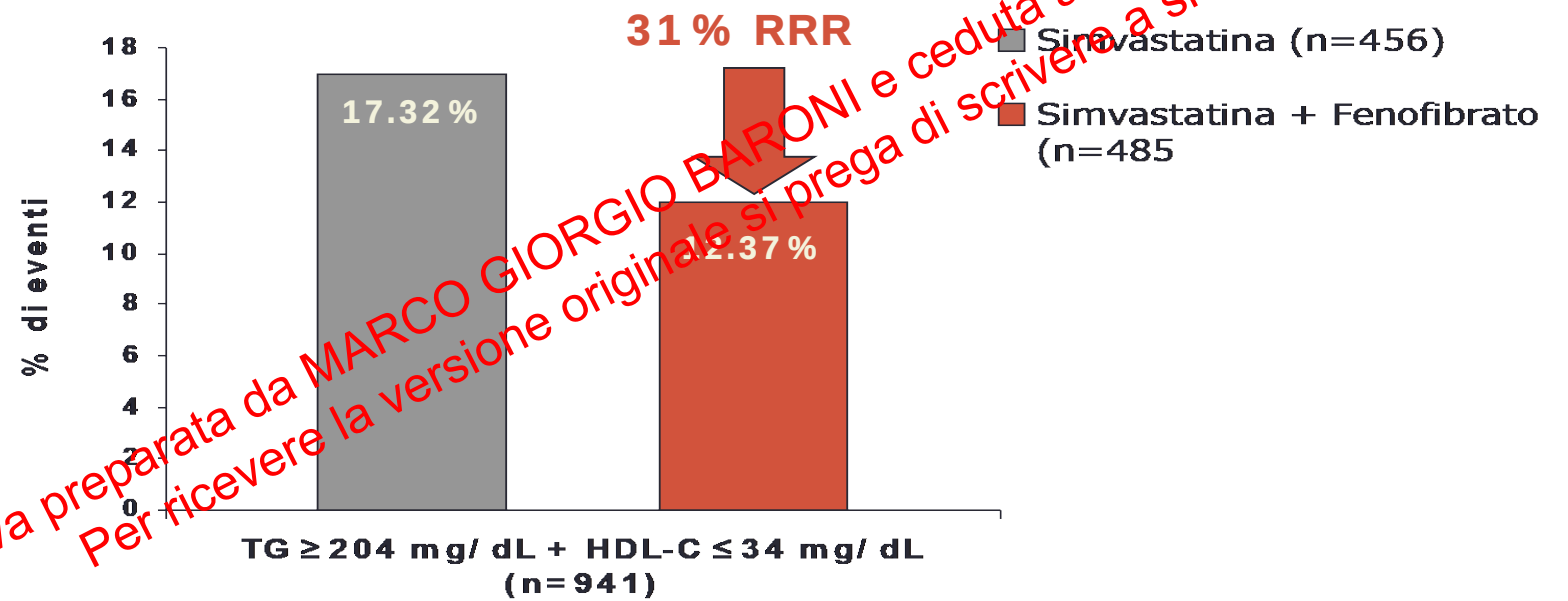
TRIGLYCERIDES AS A RISK FACTOR FOR CORONARY HEART DISEASE



JACC March 12, 2019 Volume 73, Issue 9

Effetto del fenofibrato sugli eventi CV maggiori nei pazienti dislipidemici

- Il trattamento con Fenofibrato è associato ad una riduzione del numero di eventi cardiovascolari maggiori* nel sottogruppo dei pazienti dislipidemici (TG ≥204 mg/dl e HDL-C ≤34 mg/dl)



RRR: riduzione del rischio relativo

*Eventi CV maggiori definiti con morte CV, IMA non fatale, ictus non fatale (endpoint primario)

ACCORD Study Group. N Engl J Med 2010

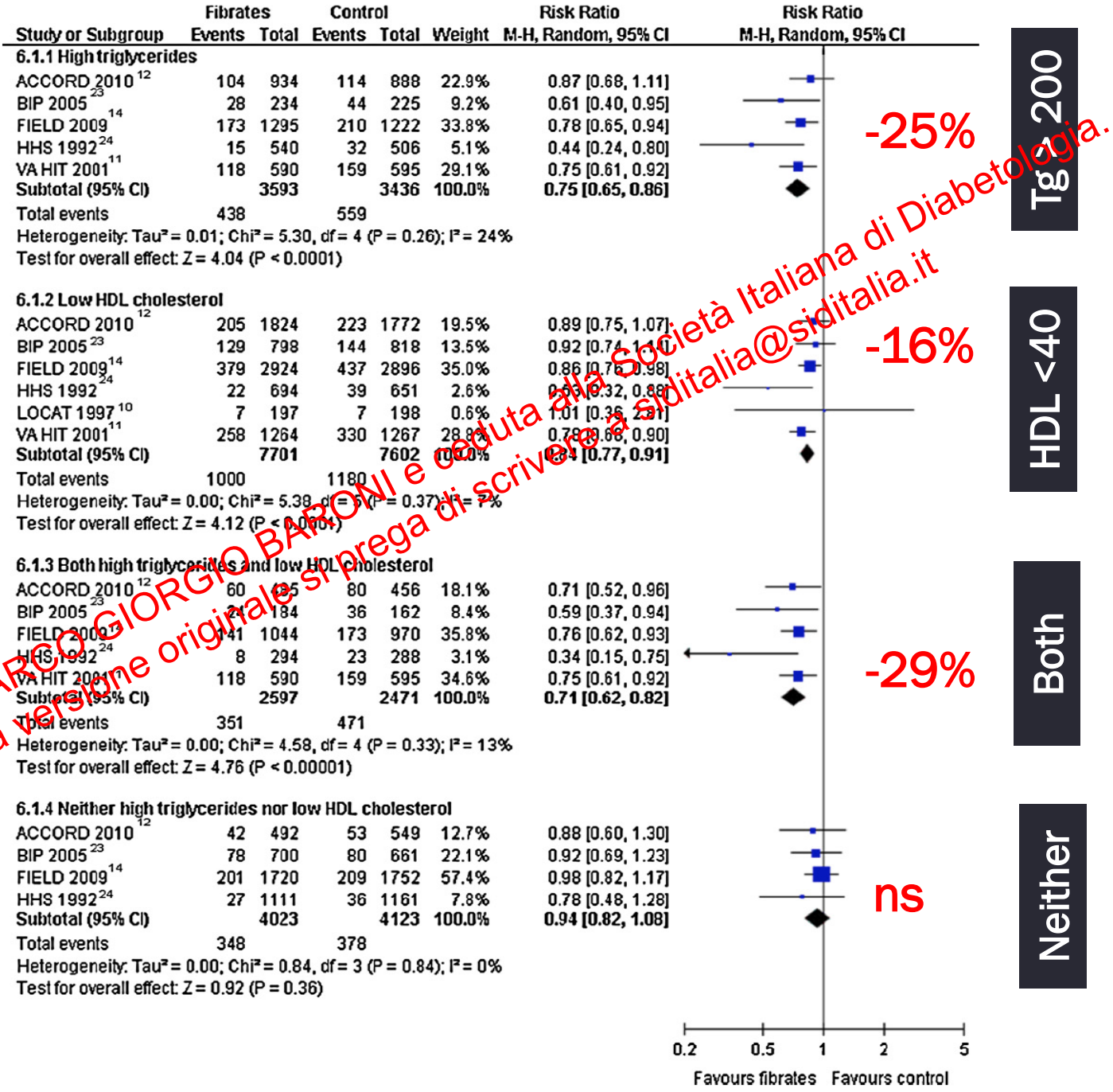
The effect of fenofibrate treatment on cardiovascular disease risk in 9795 people with type 2 diabetes and various components of the metabolic syndrome: the FIELD study

- Nei pazienti con **dislipidemia aterogena** marcata (TG>200mg/dl e HDL< 40 negli U e < 50 nelle D) **la riduzione del rischio cardiovascolare è stata del** 27% (p< 0.005)

- NNT = 23 (per ogni 23 pazienti trattati si evita un evento CVD)
- Durante lo studio era **possibile aggiungere una statina**, se necessaria (19% nel gruppo fenofibrato vs 36% nel gruppo placebo, p<0.0001)
- Anche con aggiunta di statina il **Fenofibrato ha dimostrato di ridurre il rischio residuo del paziente diabetico con dislipidemia aterogena**

FIELD Study Investigators, Diabetes Care 2009

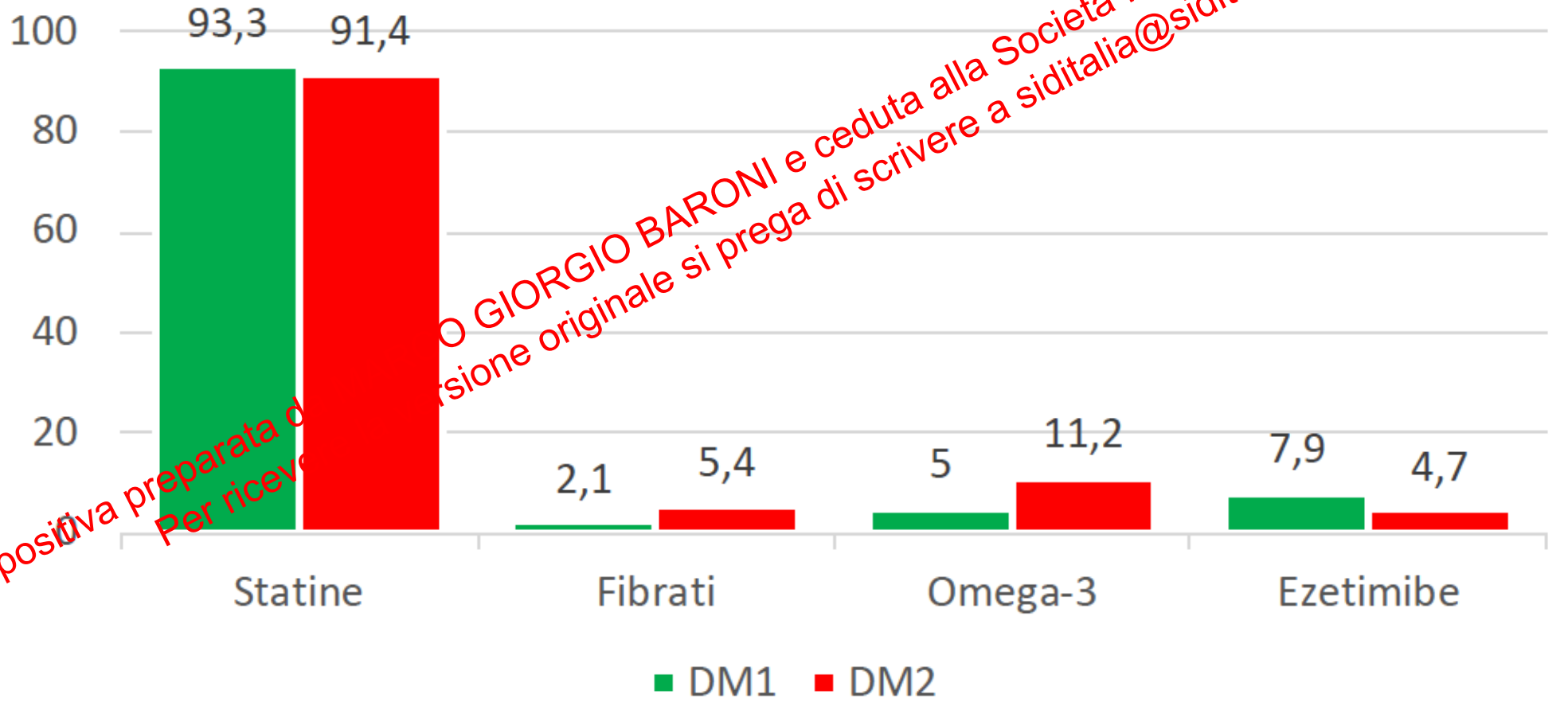
Fibrati e CVD



Lee M, Atherosclerosis 2011

Fibrati

Distribuzione dei pazienti per classe di farmaco ipolipemizzante (%)

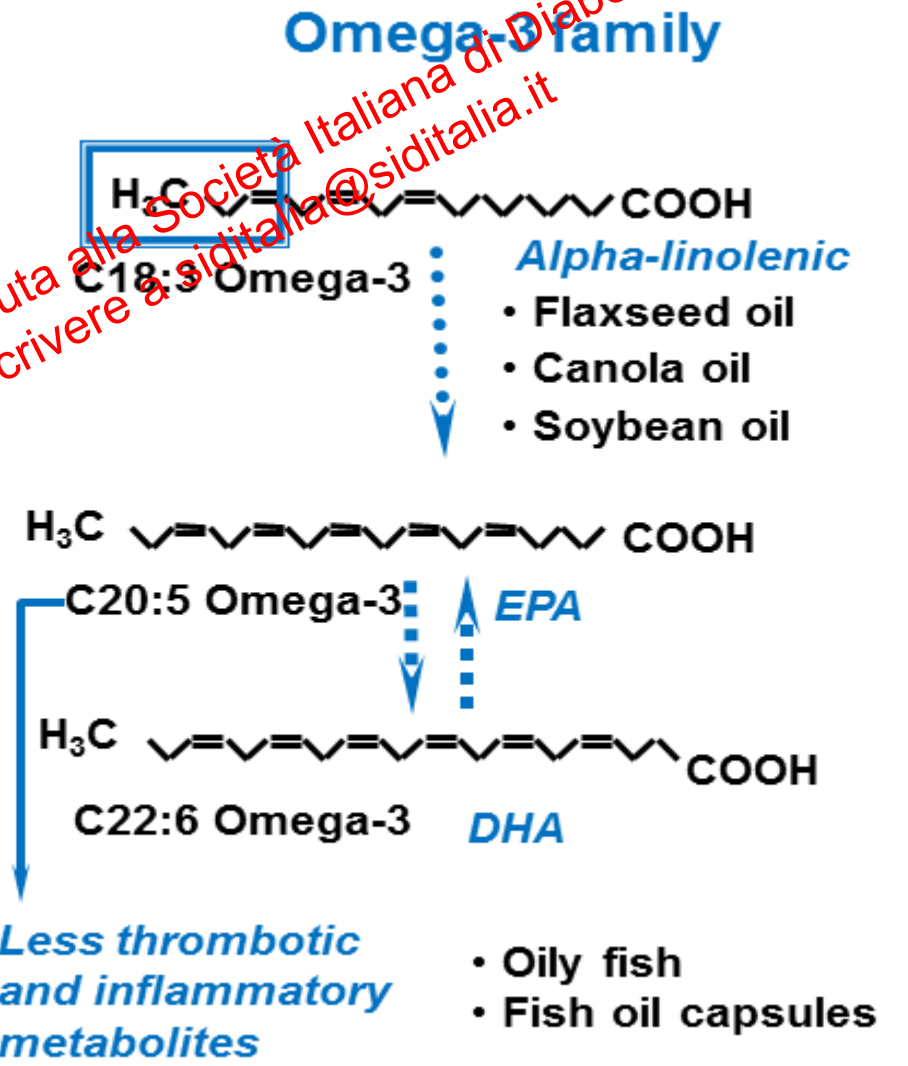


Acidi grassi OMEGA 3 poli-insaturi

- Ac.Eicosapentanoico
- Ac.Docosaesanoico

RIDUZIONE DELLE VLDL

- ↓ lipogenesi epatica attraverso la↓ della conversione enzimatica della Acetil CoA in acidi grassi (FA)
- ↑ B-ossidazione degli FA con conseguente riduzione della quantità di FA disponibili per la sintesi dei TG
- Inibiscono gli enzimi fosfatidato-fosfatasi (PAP) e diaciliglicerolo aciltransferasi (DGAT), enzimi chiave della sintesi dei TG nel fegato
- ↑ l'attività della LPL



Acidi Grassi Omega-3

Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial

THE LANCET • Vol 354 • August 7, 1999

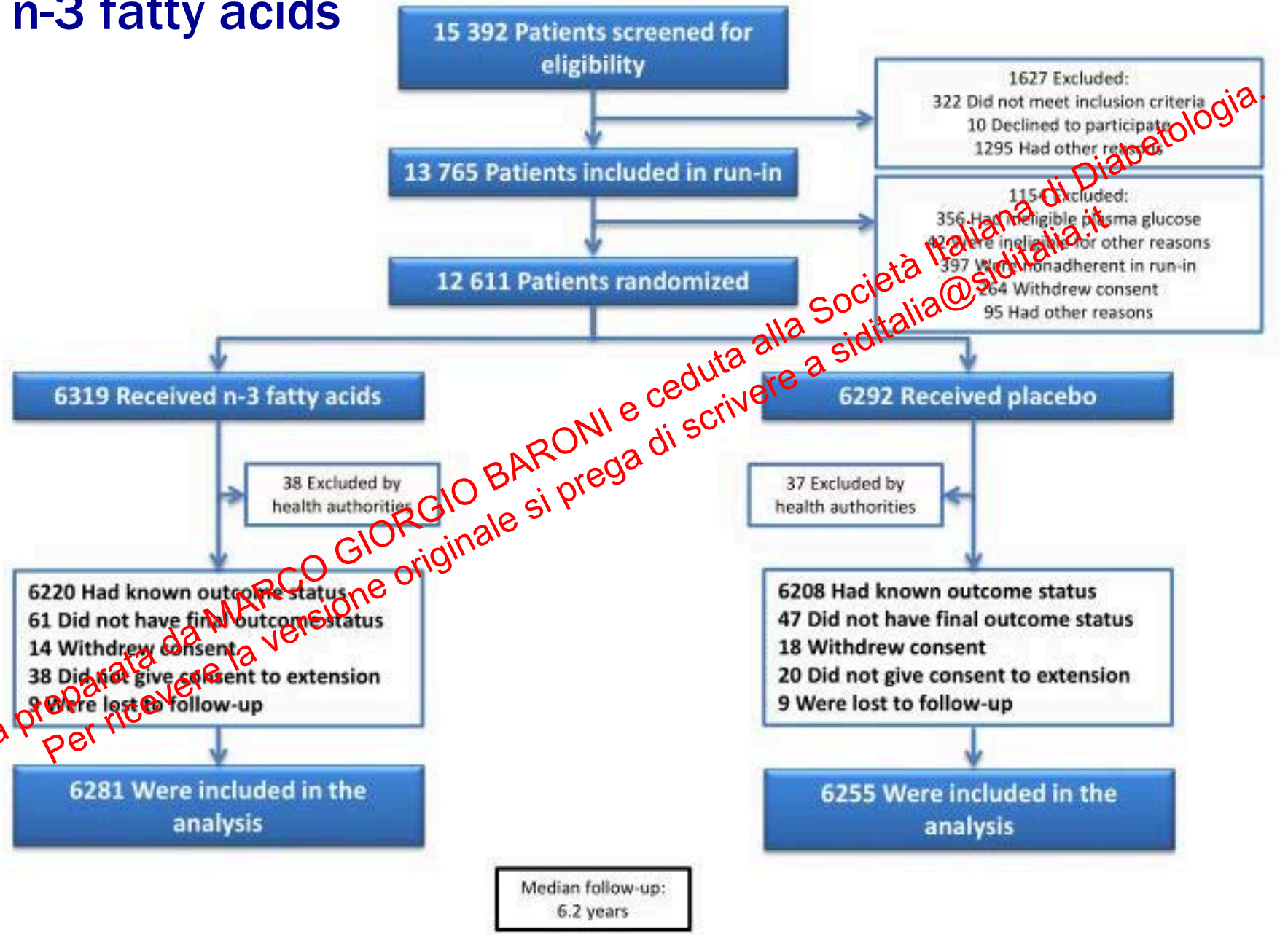
*GISSI-Prevenzione Investigators** (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico)

	All (n=11 324)	Two-way analysis		
		n-3 PUFA (n=5666)	Control (n=5668)	Relative risk (95% CI)
Main endpoints				
Death, non-fatal MI, and non-fatal stroke	1500 (13·3%)	715 (12·6%)	785 (13·9%)	0·90 (0·82–0·99)
Cardiovascular death, non-fatal MI, and non-fatal stroke	1155 (10·2%)	547 (9·7%)	608 (10·8%)	0·89 (0·80–1·01)
Secondary analyses				
All fatal events	1017 (9·0%)	472 (8·3%)	545 (9·6%)	0·86 (0·76–0·97)
Cardiovascular deaths	639 (5·6%)	291 (5·1%)	348 (6·2%)	0·83 (0·71–0·97)
Cardiac death	520 (4·6%)	228 (4·0%)	292 (5·2%)	0·78 (0·65–0·92)
Coronary death	479 (4·2%)	214 (3·8%)	265 (4·7%)	0·80 (0·67–0·96)
Sudden death	286 (2·5%)	122 (2·2%)	164 (2·9%)	0·74 (0·58–0·93)
Other deaths	378 (3·3%)	181 (3·2%)	197 (3·5%)	0·91 (0·74–1·11)
Non-fatal cardiovascular events	578 (5·1%)	287 (5·1%)	291 (5·1%)	0·98 (0·83–1·15)
Other analyses				
CHD death and non-fatal MI	909 (8·0%)	424 (7·5%)	485 (8·6%)	0·87 (0·76–0·99)
Fatal and non-fatal stroke	178 (1·6%)	98 (1·7%)	80 (1·4%)	1·21 (0·91–1·63)

L'assunzione di un grammo al giorno di ω-3 migliora significativamente la prognosi dei pazienti reduci da infarto;

il beneficio consiste in una riduzione relativa del 15% di reinfarto e ictus;

ORIGIN n-3 fatty acids



The ORIGIN Trial Investigators. N Engl J Med 2012;367:309-318.

ORIGIN n-3 fatty acids: Changes in Key Risk Factors

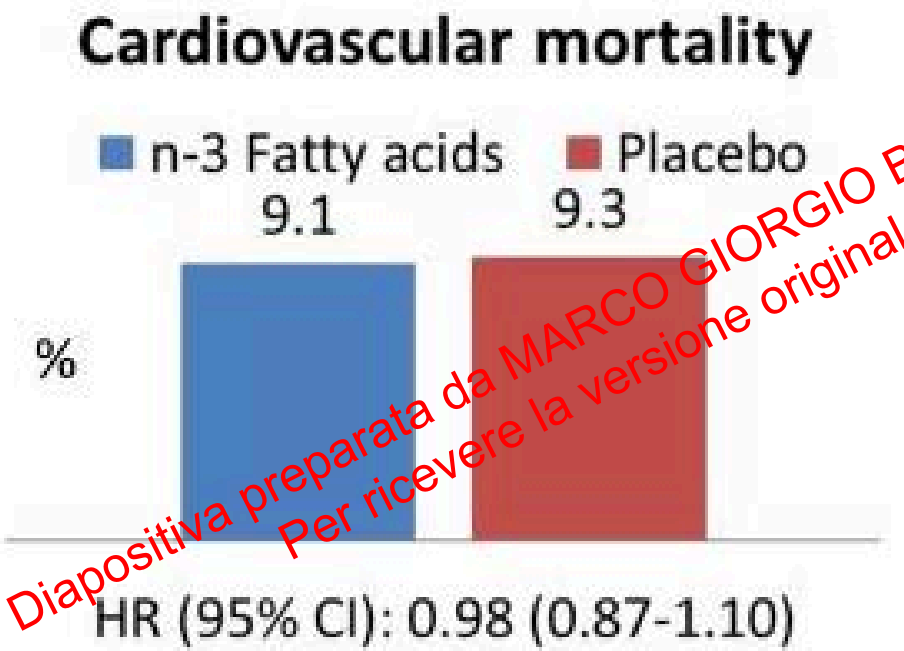
Table 3. Changes in Key Risk Factors.*

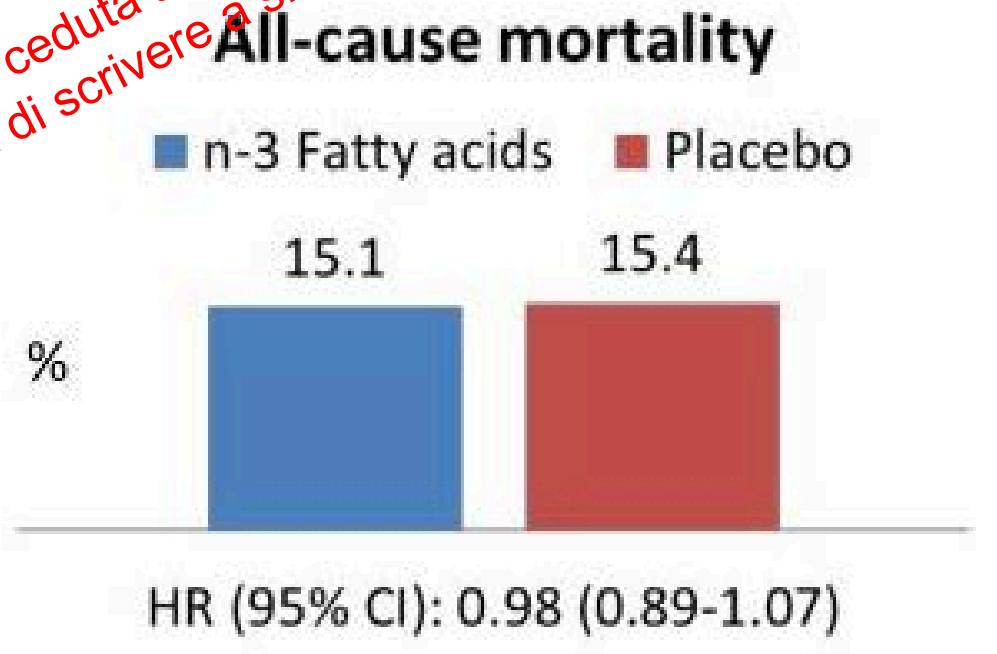
Risk Factor	n–3 Fatty Acids (N=6281)	Placebo (N=6255)	P Value
Blood pressure (mm Hg)			
Systolic	−4.37±22.5	−4.51±22.5	0.75
Diastolic	−4.93±12.8	−4.96±13.1	0.91
Heart rate (beats/min)	−0.13±12.3	0.25±12.2	0.13
Cholesterol (mg/dl)			
Total	−15.7±1.0	−14.6±1.0	0.17
Low-density lipoprotein	−11.8±0.8	−12.4±0.8	0.44
High-density lipoprotein	−0.1±0.3	−0.2±0.3	0.78
Triglycerides (mg/dl)	−23.5±3.0	−9.0±3.0	<0.001

* Plus–minus values are means ±SD for blood pressure and heart rate and means ±SE for cholesterol and triglycerides.

The ORIGIN Trial Investigators. N Engl J Med 2012;367:309-318.

Influence of the n-3 fatty acid regimen on mortality





The ORIGIN Trial Investigators. N Engl J Med 2012;367:309-318.

ORIGIN Omega-3
Conclusione

- Non hanno ridotto l'end-point primario (mortalità CV)
- Non hanno influenzato significativamente gli eventi cardiovascolari maggiori ne la mortalità da tutte le cause
- Hanno determinato una riduzione significativa dei trigliceridi, senza influenzare nessun altro parametro (LDL, HDL, HbA1c, glucosio, PA)

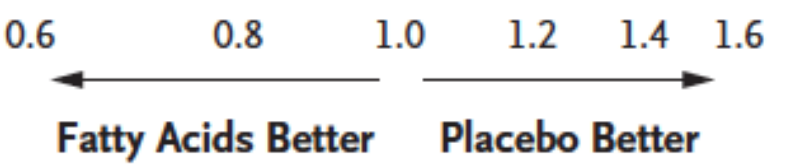
Effects of n–3 Fatty Acid Supplements in Diabetes Mellitus

The ASCEND Study Collaborative Group*

N ENGL J MED 379;16 NEJM.ORG OCTOBER 18, 2018

Among patients with diabetes without evidence of CVD disease, there was no significant difference in the risk of serious vascular events between those who were assigned to receive 1g of n−3 fatty acid supplementation and those who were assigned to receive placebo

Test for trend across years χ^2=0.22 (P=0.64)

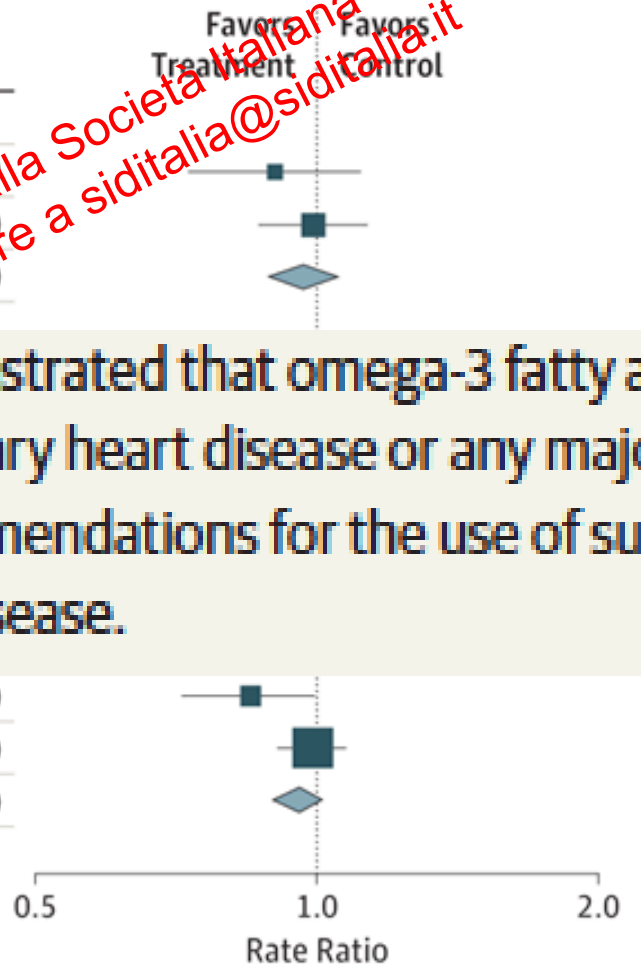


JAMA Cardiology | Original Investigation

Associations of Omega-3 Fatty Acid Supplement Use With Cardiovascular Disease Risks

Meta-analysis of 10 Trials Involving 77 917 Individuals

Source	No. of Events (%) Treatment	Control	Rate Ratios (CI)
Nonfatal myocardial infarction			
Open	285 (1.9)	316 (2.1)	0.90 (0.73-1.11)
Blind	836 (3.5)	839 (3.5)	0.99 (0.87-1.13)
All	1121 (2.9)	1155 (3.0)	0.97 (0.89-1.05)
			P = .40
Open	512 (3.4)	598 (4.0)	0.85 (0.72-0.99)
Blind	2573 (10.7)	2590 (10.8)	0.99 (0.91-1.07)
All	3085 (7.9)	3188 (8.2)	0.96 (0.90-1.01)
			P = .12



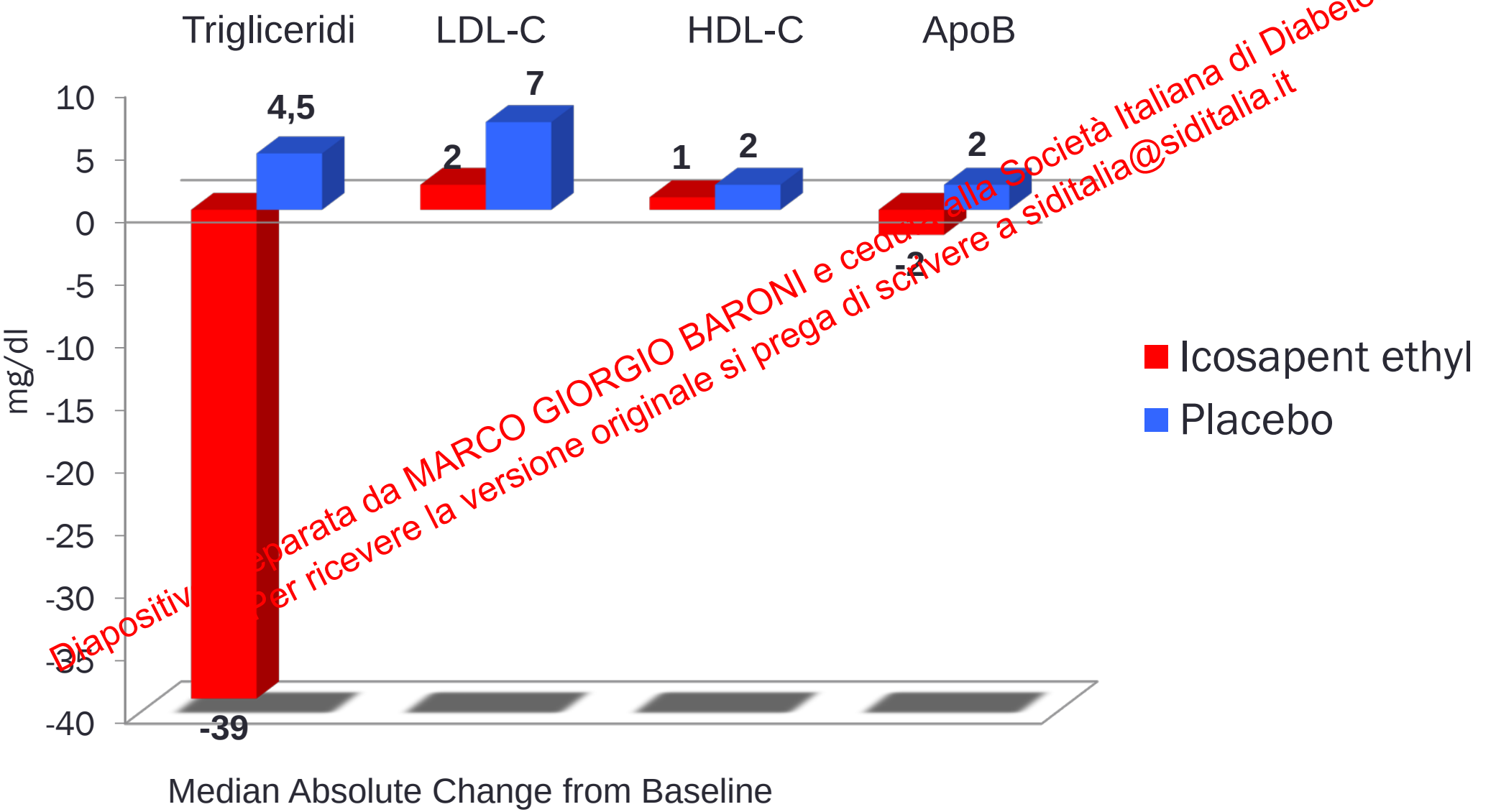
CONCLUSIONS AND RELEVANCE This meta-analysis demonstrated that omega-3 fatty acids had no significant association with fatal or nonfatal coronary heart disease or any major vascular events. It provides no support for current recommendations for the use of such supplements in people with a history of coronary heart disease.

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

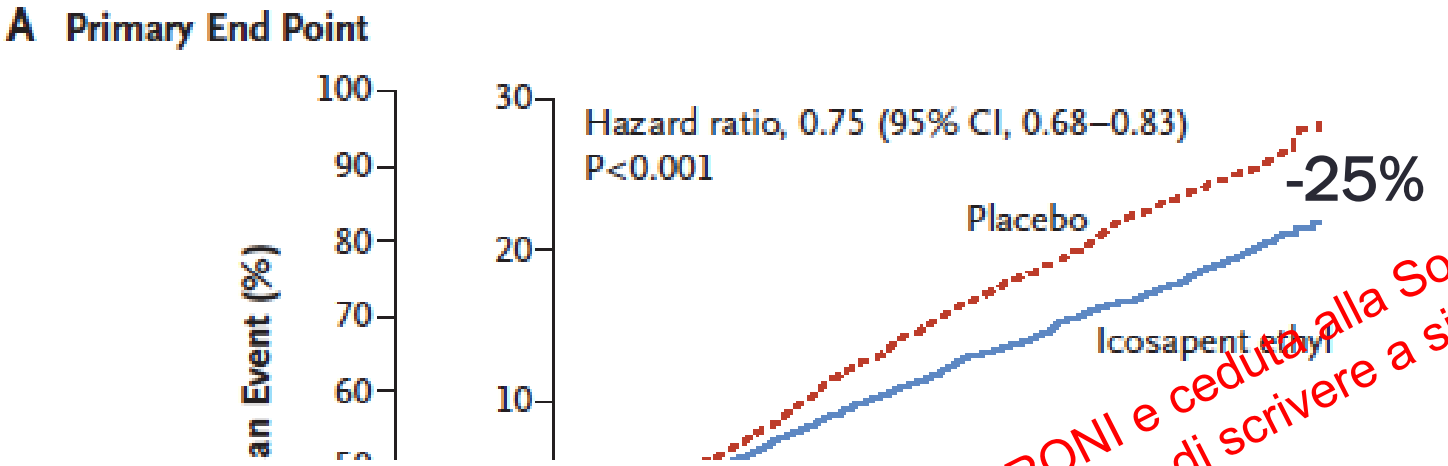
Deepak L. Bhatt, M.D., M.P.H., P. Gabriel Steg, M.D., Michael Miller, M.D., Eliot A. Brinton, M.D., Terry A. Jacobson, M.D., Steven B. Ketchum, Ph.D., Ralph T. Doyle, Jr., B.A., Rebecca A. Juliano, Ph.D., Lixia Jiao, Ph.D., Craig Granowitz, M.D., Ph.D., Jean-Claude Tardif, M.D., and Christie M. Ballantyne, M.D., for the REDUCE-IT Investigators*

- Icosapent ethyl is a highly purified and stable EPA ethyl ester that has been shown to lower triglyceride levels
- Icosapent ethyl may have antiinflammatory, antioxidative, plaque-stabilizing, and membrane-stabilizing properties
- Eligible patients had a fasting triglyceride level of 150 to 499 mg/dl and a low-density lipoprotein (LDL) cholesterol level of 41 to 100 mg/dl, and had been receiving a stable dose of a statin for at least 4 weeks
- The patients were enrolled mostly on the basis of secondary prevention (71%), and almost 60% had diabetes.

Icosapent Ethyl Effects on Lipids at 1 year



Cumulative Incidence of Cardiovascular Events



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

It is not known whether the lack of benefit from n−3 fatty acids in previous trials may be attributable to the low dose or to the low ratio of EPA to docosahexaenoic acid (DHA).

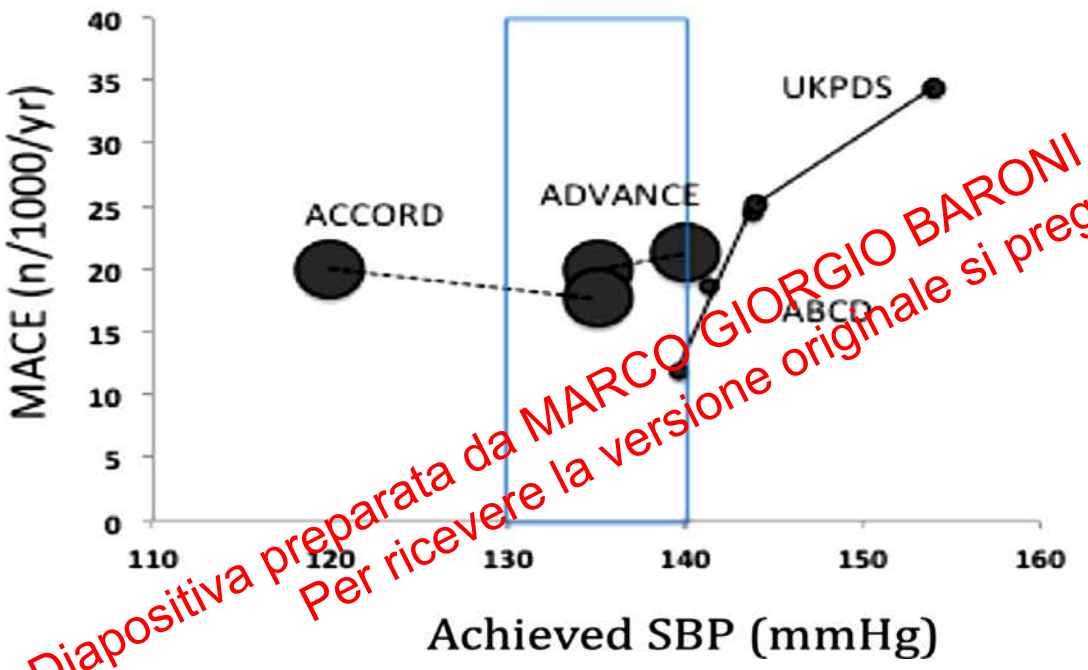
Both the formulation (a highly purified and stable EPA ethyl ester) and dose (total daily dose of 4 g) used in REDUCE-IT were different from those in previous outcome trials of n−3 fatty acids.

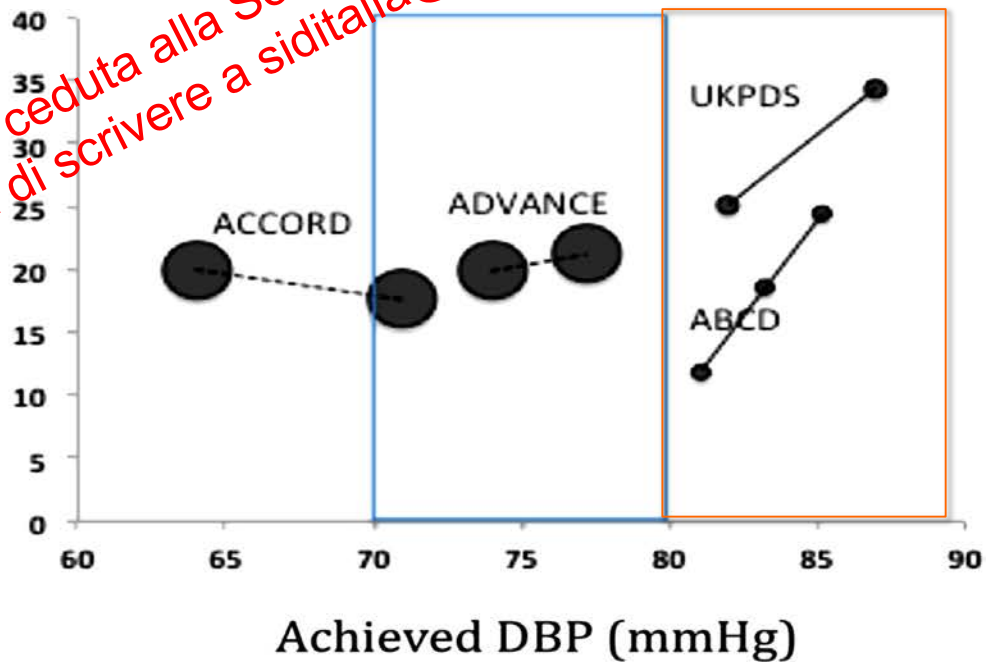
AGENDA

- Colesterolo LDL/fibrati
- Pressione
- Fumo
- Peso e Nutrizione

Pressione arteriosa ideale

Standard di cura AMD-SID 2018:
Tutti i pazienti <140/90 mmHg (I/A)

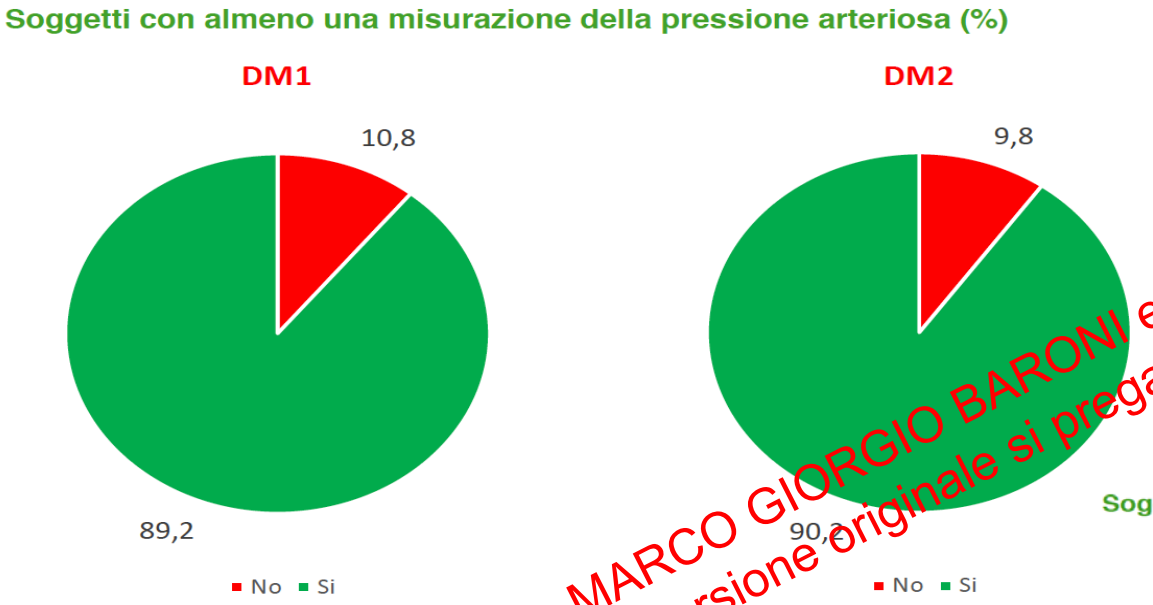




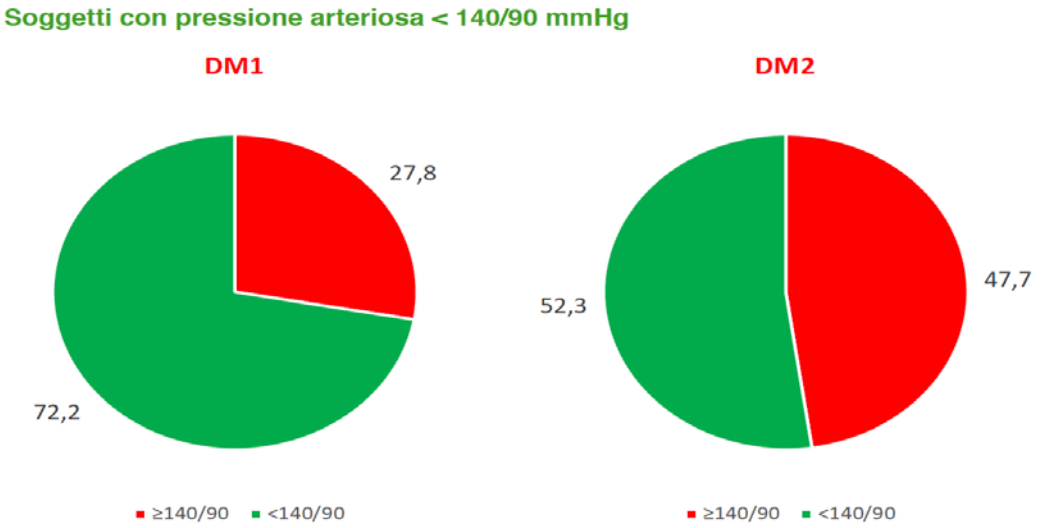
Frontoni S, NMCD 2014

BP and diabetes real world

La PA viene misurata



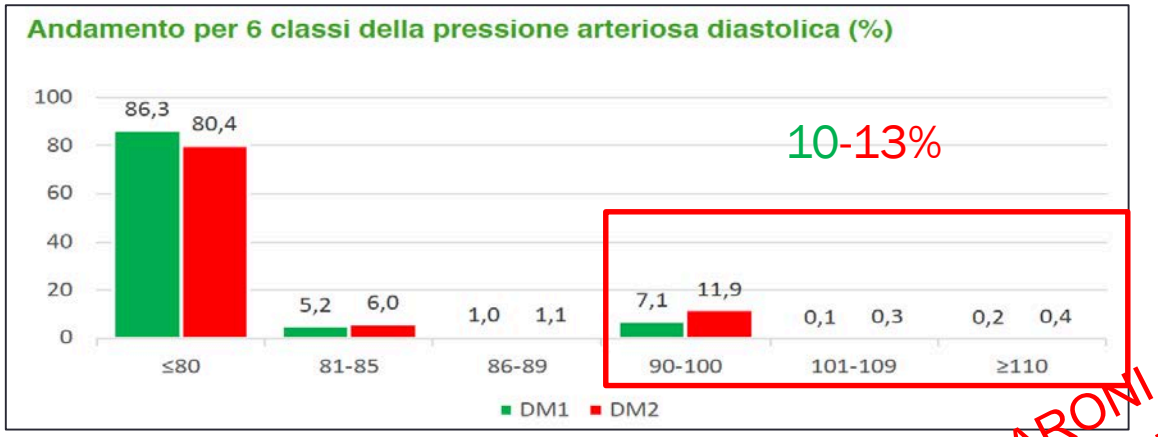
… ma il target viene raggiunto ?



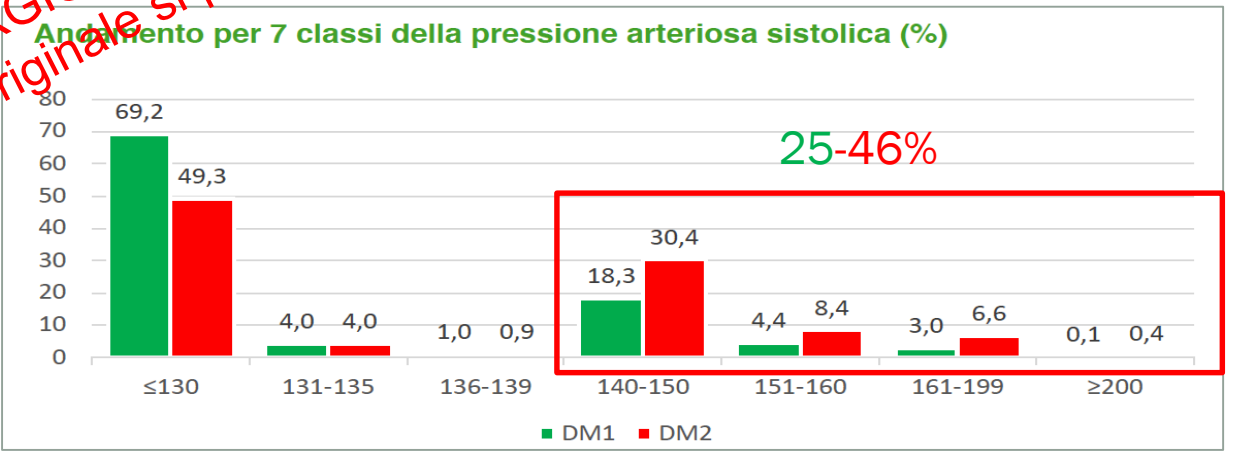
Sul totale dei monitorati nell'anno 2016, il 72.2% dei soggetti con DM1 e il 52.3% con DM2 mostra valori pressori a target sia per la pressione arteriosa sistolica che diastolica.

ANNALI AMD-SID 2018

BP and diabetes real world



Il target di PAD è OK

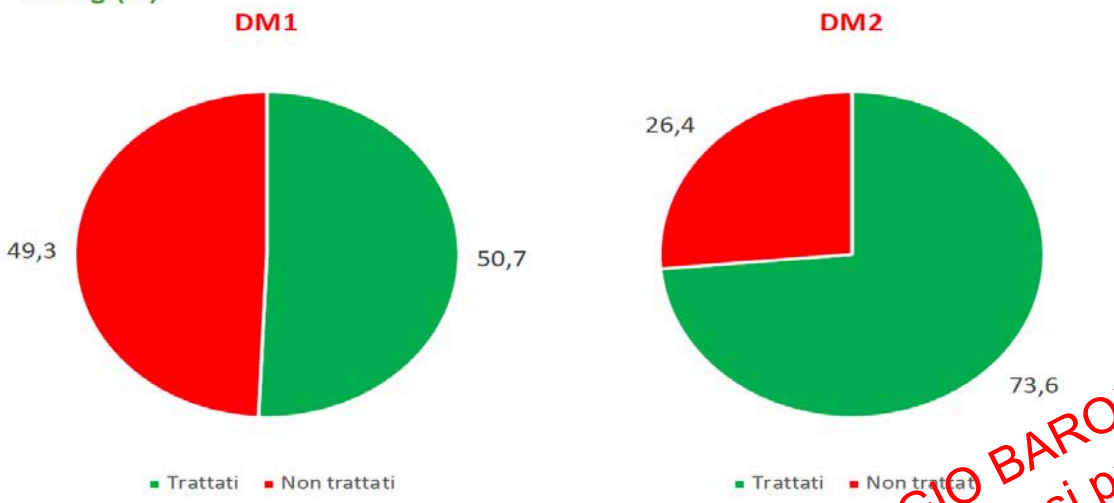


Il target di PAS !!!!

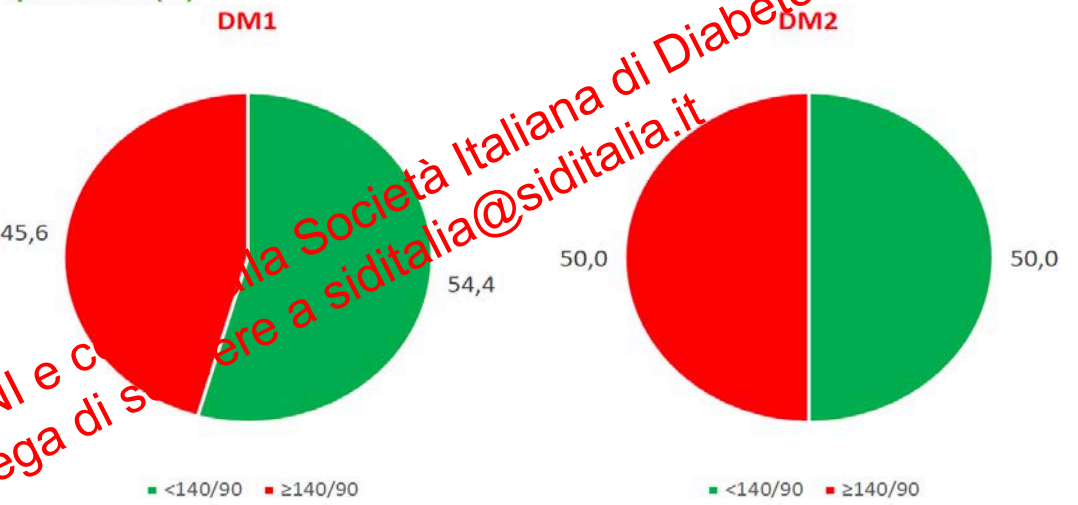
ANNALI AMD-SID 2018

BP and diabetes real world

Soggetti non trattati con antiipertensivi nonostante valori pressori ≥ 140/90 mmHg (%)



Soggetti con valori pressori ≥ 140/90 mmHg nonostante il trattamento con anti-ipertensivi (%)



… ACEi/AT2i a tutti

Soggetti non trattati con ACE-inibitori/Sartani nonostante la presenza di micro/macroalbuminuria (%)

ANNALI AMD-SID 2018

Aderenza

Tabella 4.3.4. Numero di pazienti trattati con farmaci antiipertensivi aderenti al trattamento [numeratore], sul totale dei pazienti trattati con antiipertensivi [denominatore].

	2015 N = 5.803.222		2014 N = 5.642.654		2013 N = 5.492.285	
	%	Var. %	%	Var. %	%	Var. %
TOTALE	**58,1**	**1,8**	**57,0**	**2,8**	**55,4**	/
Area geografica						
Nord	58,1	2,4	56,8	1,		
Centro	54,4	7,5	50,6	-9		
Sud	59,4	-0,5	59,7	9,		
Genere						
Maschio	59,9	1,8	58,8	2,		
Femmina	56,6	1,9	55,5	3,		
Classi di età						
≤45	34,8	0,7	34,6	4,		
46-65	53,1	1,0	52,5	2,		
66-75	62,9	1,9	61,8	2,		
>75	63,1	2,1	61,8	2,		
Pregresso trattamento§						
Nuovi trattati	24,3	-5,1	25,7	8,		
Già in trattamento	62,7	2,0	61,4	2,		
Comorbidità						
Senza pregresso evento CV o diabete	55,7	1,8	54,7	2,		
Con pregresso evento CV o diabete	69,5	1,6	68,4	2,		
TOTALE senza occasionali°	61,5	1,9	60,3	2,		

58%

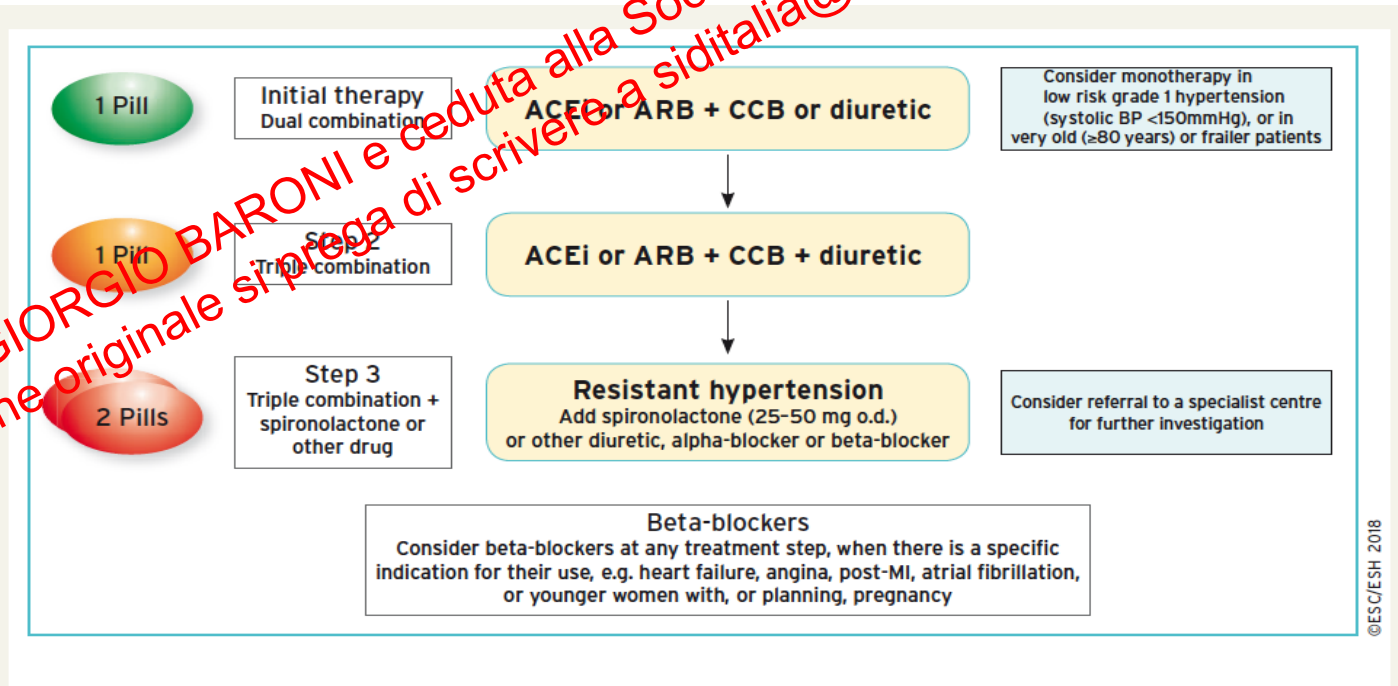


Figure 4 Core drug treatment strategy for uncomplicated hypertension. The core algorithm is also appropriate for most patients with HMOD, cerebrovascular disease, diabetes, or PAD. ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; HMOD = hypertension-mediated organ damage; MI = myocardial infarction; o.d. = omni die (every day); PAD = peripheral artery disease.

OSMED 2015

ESC/ESH Guidelines 2018

AGENDA

- Colesterolo LDL/fibrati
- Pressione
- Fumo
- Peso e Nutrizione

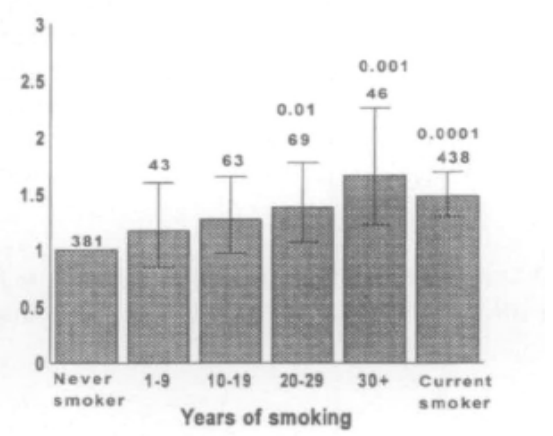
Fumo

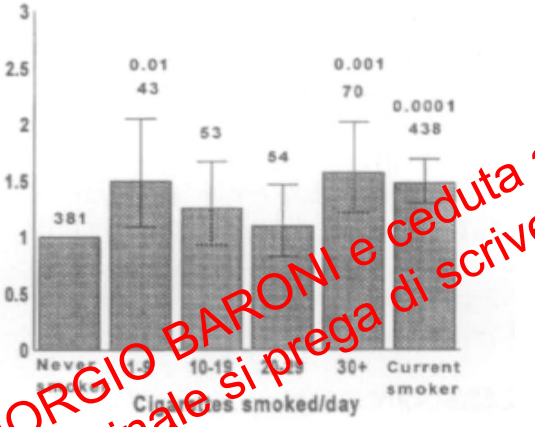
Which Features of Smoking Determine Mortality Risk in Former Cigarette Smokers With Diabetes?

DOSE-RISPOSTA

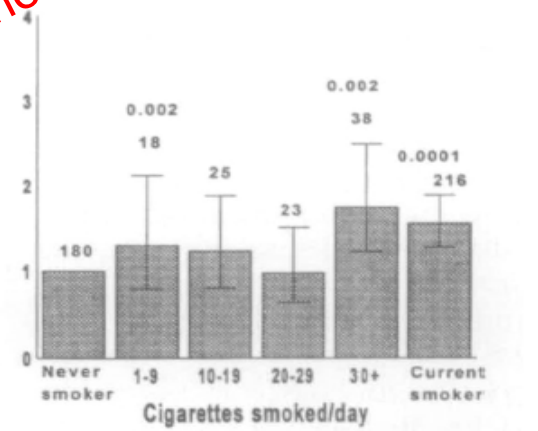
Chi smette quando torna al rischio normale?

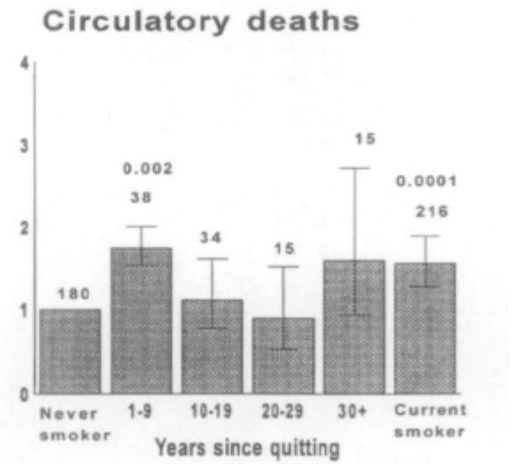
All cause death





Circulatory death





Anni

N° di sigarette

Chaturvedi N, Diab Care 1997

The harms of smoking and benefits of smoking cessation in women compared with men with type 2 diabetes: an observational analysis of the ADVANCE

Quitting smoking less than 10 years ago versus never smoking						
Outcome	Men (HR, 95% CI, p)			Women (HR, 95% CI, p)		
Major cardiovascular	1.16	0.91 – 1.48	0.24	1.03	0.64 – 1.66	0.90
All cardiovascular	1.21	1.02 – 1.43	0.028	1.50	1.14 – 1.97	0.0035
All cause mortality	1.55	1.20 – 1.99	0.0007	1.34	0.82 – 2.19	0.25
Major coronary	1.03	0.74 – 1.43	0.88	2.26	1.32 – 3.86	0.0028
Major cerebrovascular	1.10	0.75 – 1.63	0.62	0.33	0.10 – 1.04	0.058
Nephropathy	1.22	0.84 – 1.78	0.29	1.19	0.60 – 2.33	0.62
All cancer	1.86	1.35 – 2.57	0.0002	1.91	1.19 – 3.06	0.0072

Quitting smoking over 10 years ago versus never smoking						
Outcome	Men (HR, 95% CI, p)			Women (HR, 95% CI, p)		
Major cardiovascular	1.10	0.91 – 1.32	0.34	0.76	0.50 – 1.15	0.19
All cardiovascular	1.15	1.01 – 1.30	0.037	0.95	0.75 – 1.22	0.70
All cause mortality	1.24	1.03 – 1.51	0.026	1.03	0.69 – 1.52	0.90
Major coronary	1.24	0.98 – 1.56	0.068	1.04	0.61 – 1.77	0.89
Major cerebrovascular	0.92	0.68 – 1.25	0.60	0.69	0.36 - 1.30	0.25
Nephropathy	1.18	0.89 – 1.55	0.25	1.29	0.74 – 2.25	0.38
All cancer	1.67	1.31 – 2.13	<0.0001	1.22	0.80 – 1.85	0.36

Blomster JI, et al. BMJ Open 2016

Fumo e diabete

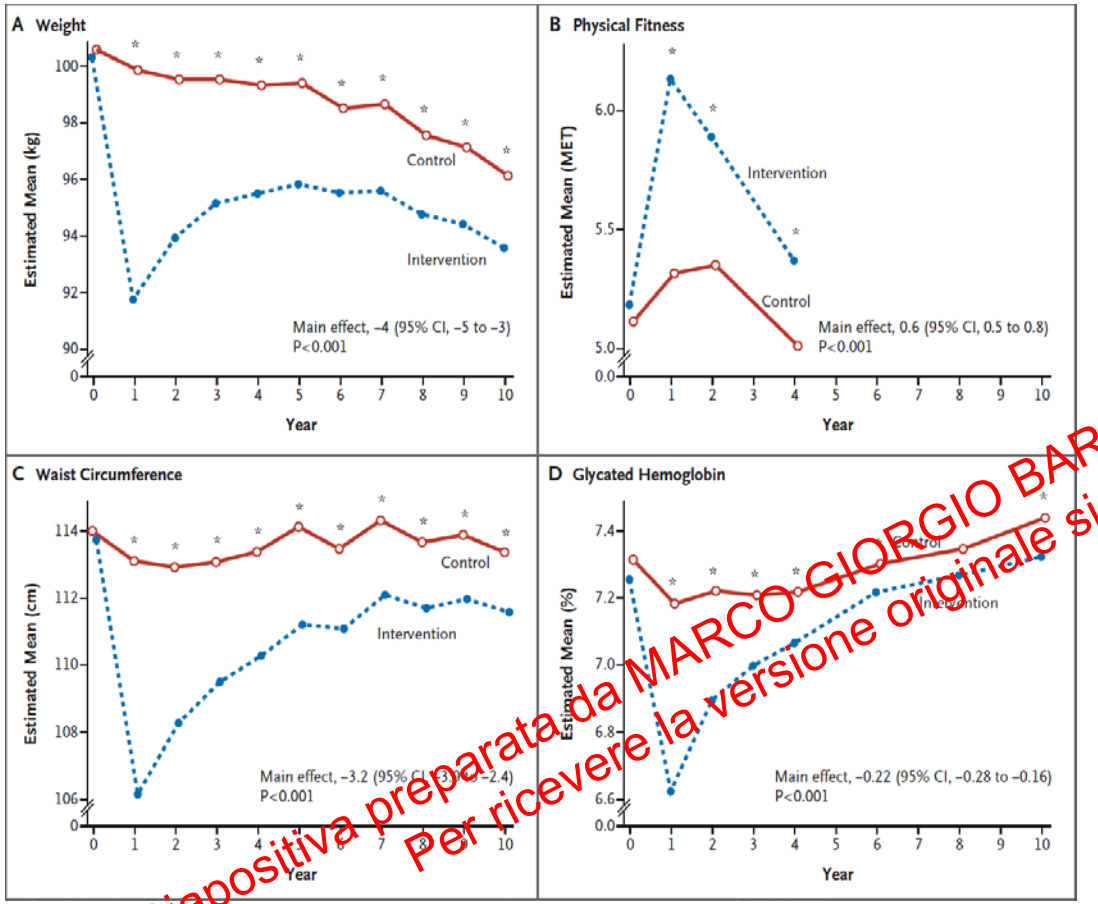
- Il rischio di mortalità si riduce significativamente dopo >10 anni dalla cessazione del fumo rispetto a chi ha smesso <10 anni, ma il rischio non si riduce a quello di chi non ha mai fumato
- La riduzione del rischio dipende dal numero di sigarette fumate e dagli anni di fumo.
  - Il rischio di mortalità scende poco in coloro che hanno fumato più di 20 sigarette al giorno, anche se hanno smesso da più di 10 anni.
- Va enfatizzato l'importanza dell'interruzione del fumo il più precocemente possibile

AGENDA

- Colesterolo LDL/fibrati
- Pressione
- Fumo
- Peso e Nutrizione

Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes

The Look AHEAD Research Group*



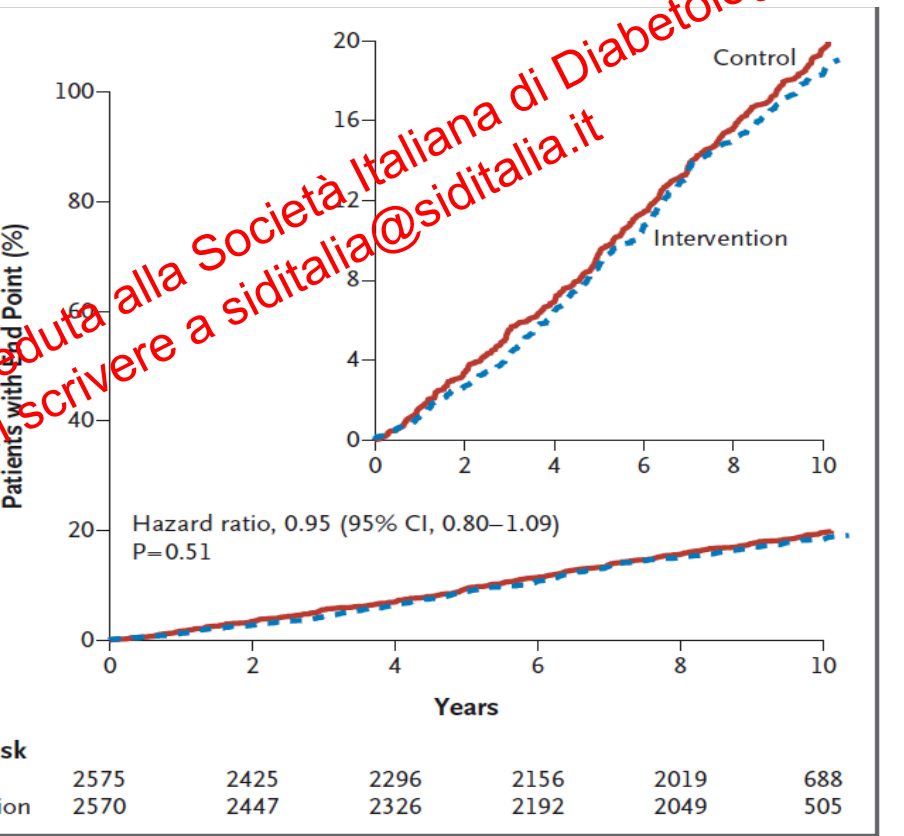
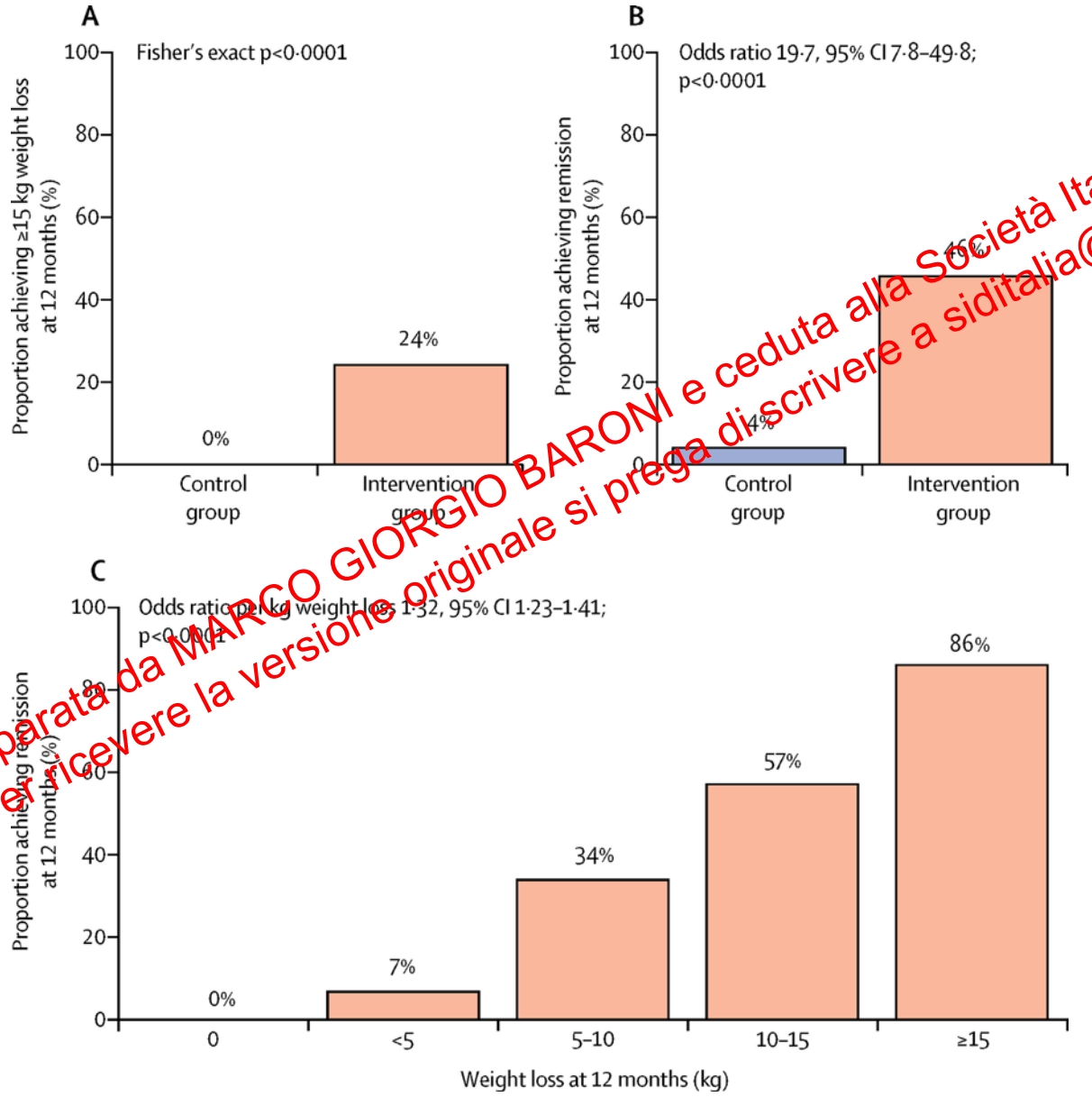


Figure 2. Cumulative Hazard Curves for the Primary Composite End Point.
Shown are Kaplan–Meier estimates of the cumulative proportion of patients with a primary event. The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for angina. The numbers below the graph are the numbers of patients at risk in each study group at years 2, 4, 6, and 8 and at 10.4 years, when the last observed event occurred. The inset shows the same data on an expanded y axis.

5,145 OW T2D
Stopped for futility after 9.6 yrs

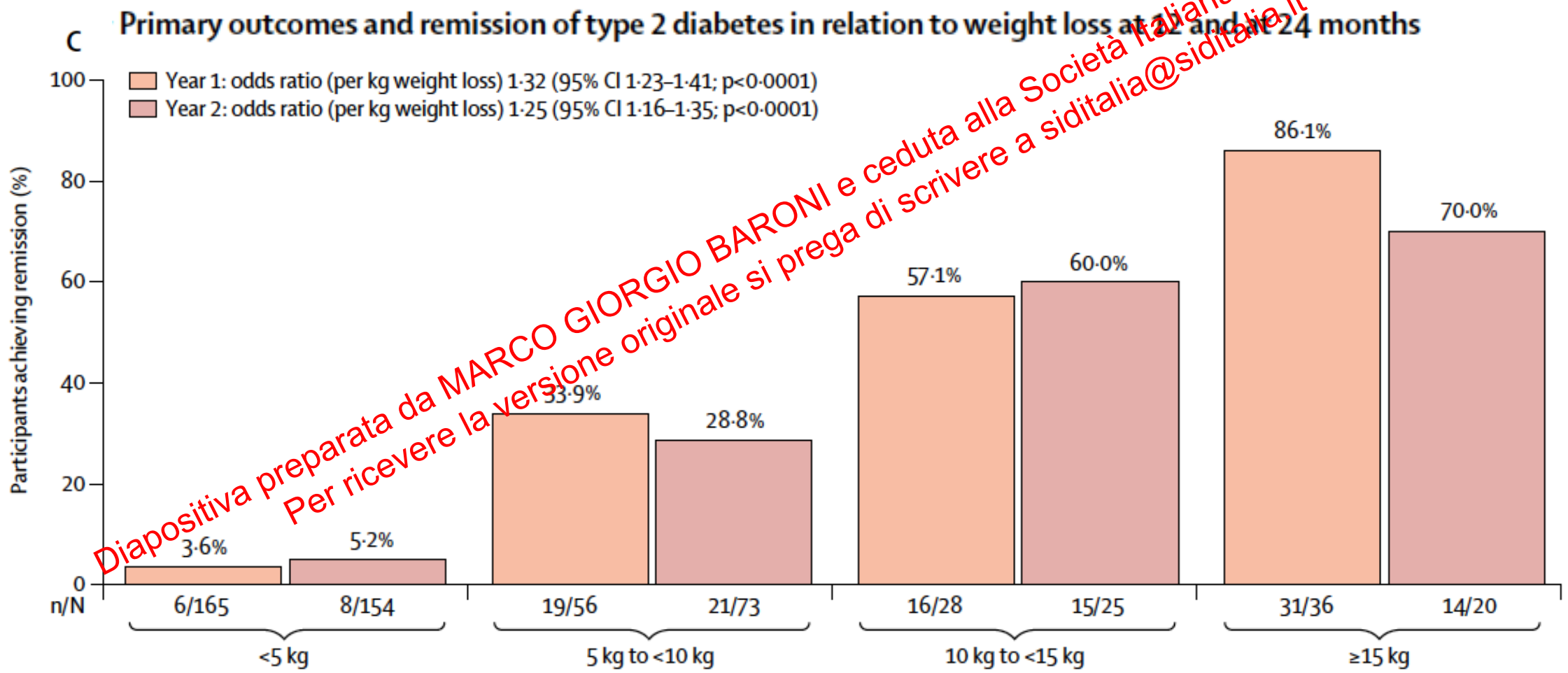
N Engl J Med 2013;369:145-54.

Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial



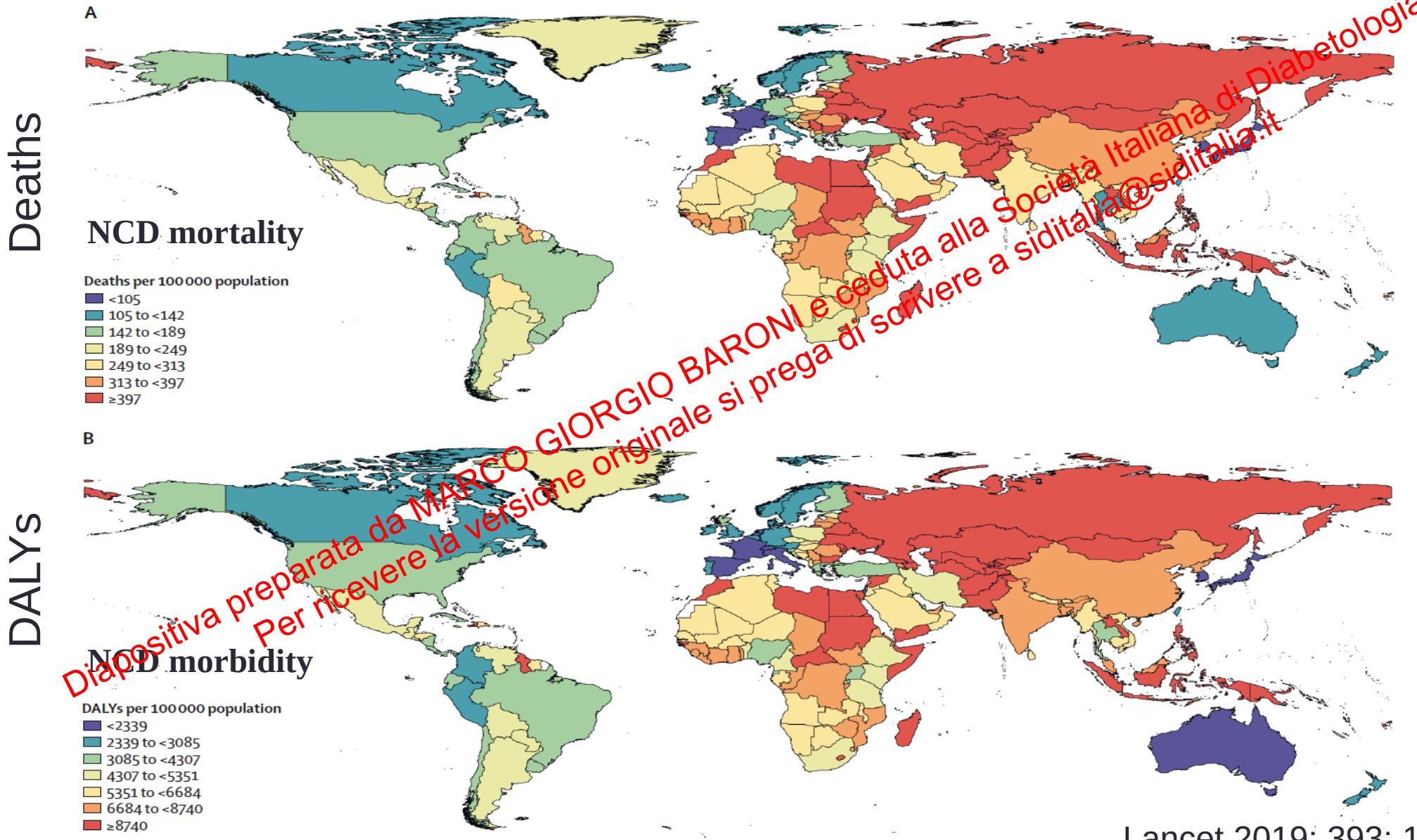
Lancet 2018; 391: 541–51

Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial



Lancet Diabetes Endocrinol
2019; 7: 344–55

Health effects of dietary risks in 195 countries, 1990–2017

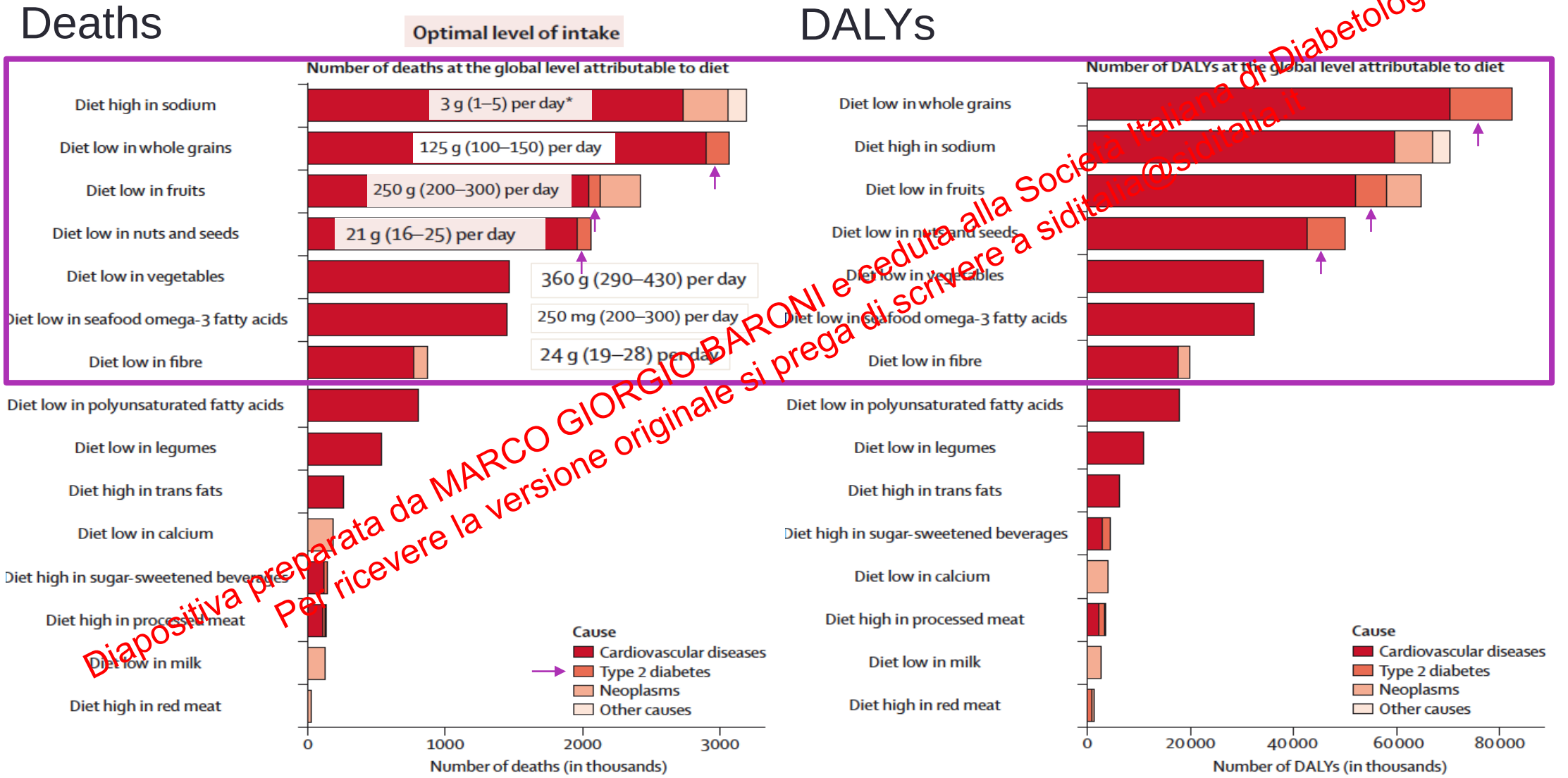


Lancet 2019; 393: 1958–72

Quali elementi della dieta sono i maggiori determinanti dell'aumento di diabete?

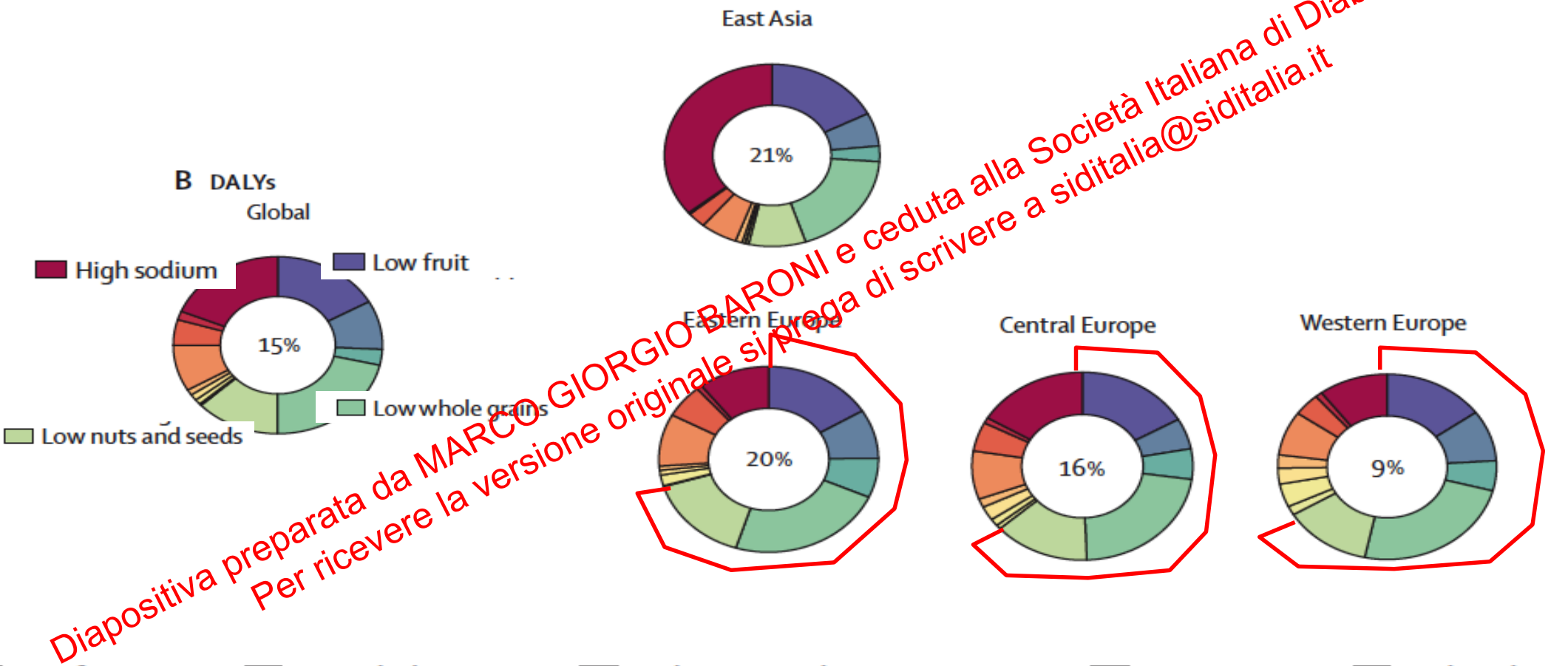
A. Dieta ricca in sodio
B. Dieta povera di noci e frutta secca
C. Dieta povera di legumi
D. Dieta ricca in carni rosse

Health effects of dietary risks in 195 countries, 1990–2017



Lancet 2019; 393: 1958–72

Age-standardised proportions of DALYs attributable to individual dietary risks



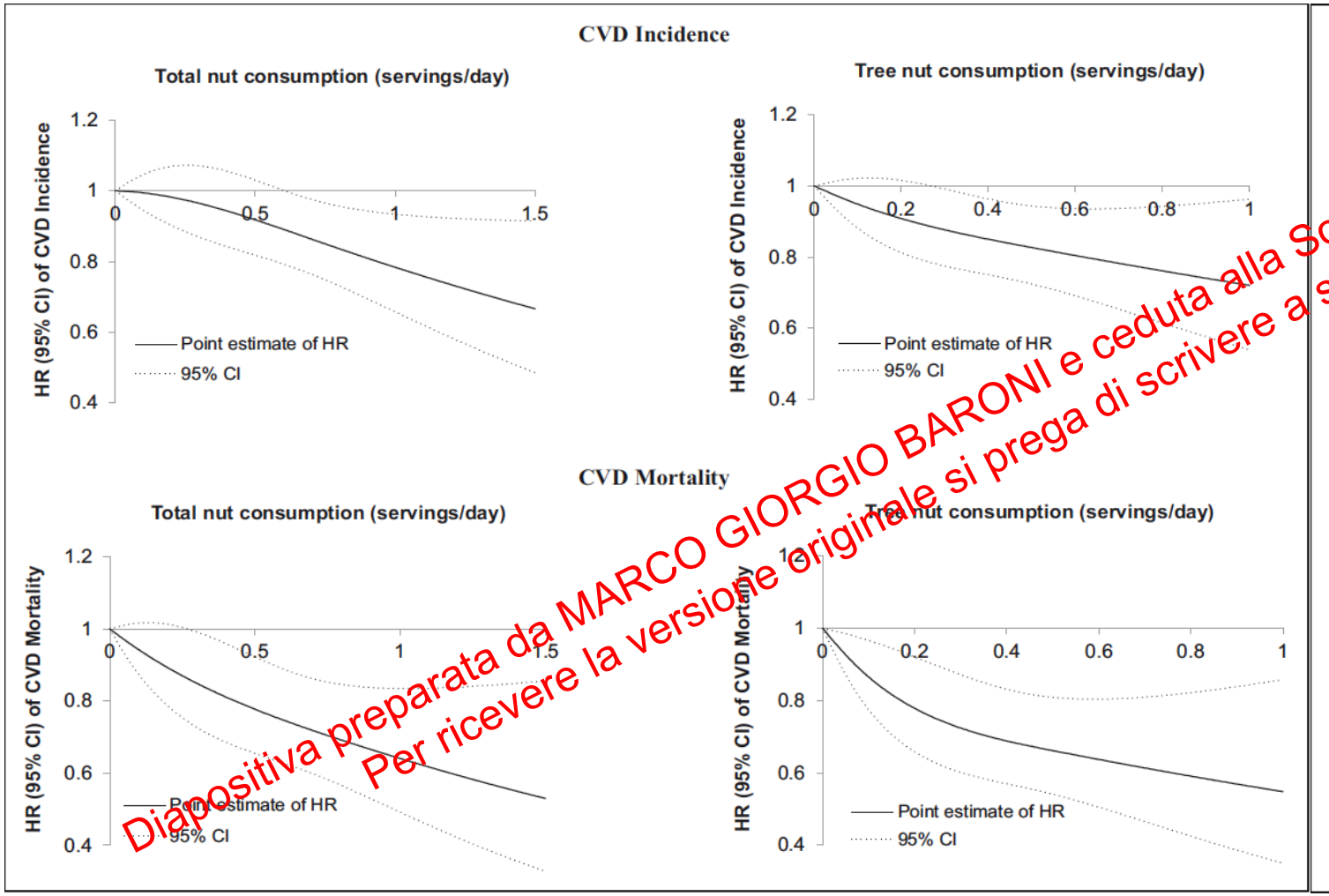
Lancet 2019; 393: 1958–72

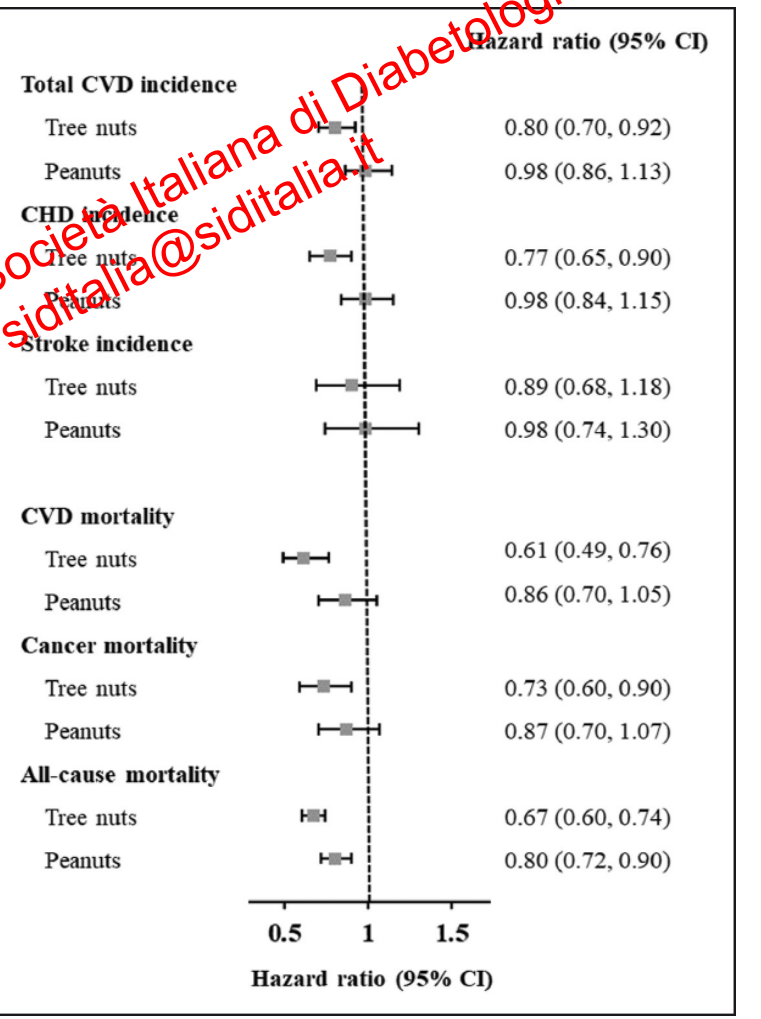
Nutrienti in Italia

	Cut-offs	Italy ($n=2831$)			
		Mean	Median	(P25; P75)	%adh
Foods to increase					
Fruit, g/day	≥200	199*	160	(76; 275)	40%
Vegetables, g/day	≥200	239*	206	(138; 300)	53%
Legumes. g/day	≥19	11.0	0.0	(0.0; 2.4)	19%
Nuts and seeds, g/day	≥15	0.5*	0.0	(0.0; 0.0)	1%
Dairy products, g/day	≥300	129	116	(8.0; 20)	8%
Fish, g/day	≥21	44.6*	6.5	(0.0; 77)	42%
Foods to decrease					
Red and processed meat, g/day	≤71	84	77	(39.2; 119)	51%
Cheese, g/day	≤21	53*	47.2	(16.2; 76)	28%
Sweet beverages[a], ml/day	≤71	47.5*	0.0	(0.0; 65)	76%
Alcohol (ethanol), g/day	≤10	8.2	0.1	(0.0; 13.7)	67%

Mertens E et al. European Journal of Nutrition (2019) 58:1475–1493

Nuts and T2D Nurses' Health (NHS&HPFS)





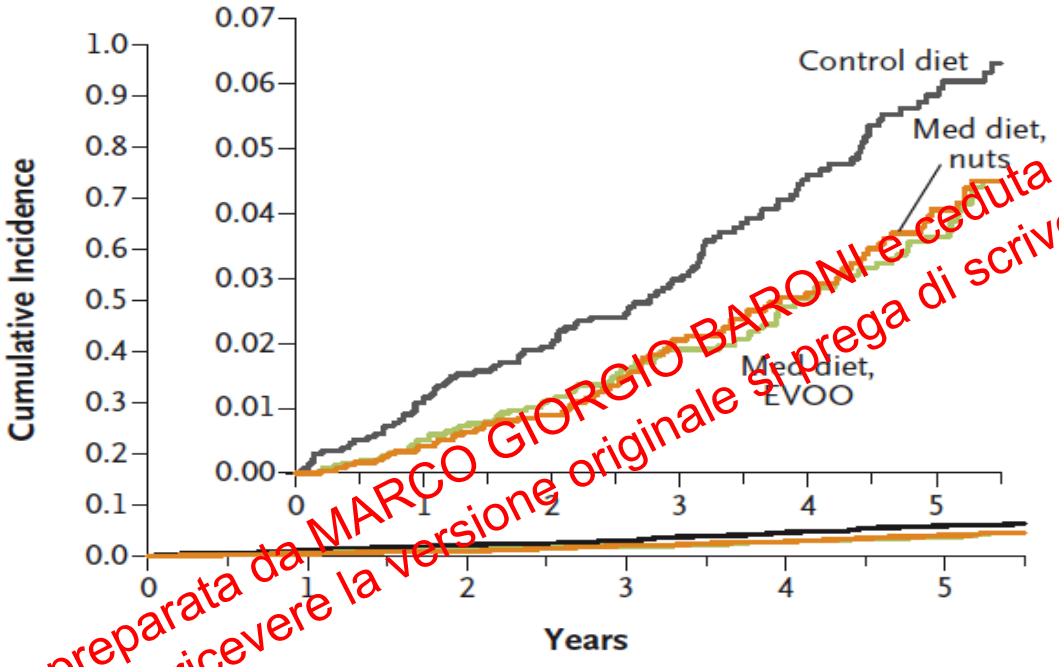
16.217 men and women with diabetes mellitus

Liu G et al. *Circ Res* 2019

Nuts and CVD – PREDIMED trial

A Primary End Point (acute myocardial infarction, stroke, or death from cardiovascular causes)

Med diet, EVOO: hazard ratio, 0.69 (95% CI, 0.53–0.91)
Med diet, nuts: hazard ratio, 0.72 (95% CI, 0.54–0.95)



No. at Risk						
Control diet	2450	2268	2020	1583	1268	946
Med diet, EVOO	2543	2486	2320	1987	1687	1310
Med diet, nuts	2454	2343	2093	1657	1389	1031

Food	Goal
Mediterranean diet	
Recommended	
Olive oil*	≥4 tbsp/day
Tree nuts and peanuts†	≥3 servings/wk

Type 2 diabetes — no. (%)	1282 (50.4)	1143 (46.6)	1189 (48.5)

Estruch R et al. *N Engl J Med* 2018

Mechanism Underlying The Beneficial Effects Of Nut Consumption For Individuals With Diabetes Mellitus

- Nut consumption may improve glycemic control, blood pressure, lipid metabolism, inflammation, and endothelial dysfunction.
- These beneficial effects can be at least partially explained by the unique nutritional composition of nuts, including:
  - unsaturated fatty acids,
  - fiber,
  - vitamins (such as vitamin E and folate),
  - minerals (such as calcium, potassium, and magnesium),
  - phytochemicals (such as flavonoids and phytosterols)

QUINDI.....

1) Abbassare “energicamente” il colesterolo LDL (statine +ezetimibe, +fenofibrato, +PCSK9)
2) Controllare la PA sistolica (con terapia di associazione)
3) MNT: 1 dose di frutta a guscio/die, 125 g di cereali integrali/die, 200-400g verdura/die
4) Controllo del peso (perché facilita il controllo della glicemia)
5) Smettere di fumare