INCONTRO CON L'ESPERTO:

"LIPIDI"

Riccardo Candido

Formatore: **Roberta Assaloni**

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

Novartis

Roche Diagnostics

Johnson & Johnson Medical

Eli Lilly Italy

Astra Zeneca-Bristol Myers Squibb

Merck Sharp & Dohme

Chiesi Farmaceutici

Sigma-Tau

Novartis

ForFarma

Novo Nordisk

Rottapharm

Fattori di Rischio per IMA

Studio INTERHEART (n = 29.972, 52 nazioni)

- Fumo
- Ipertensione
- Diabete
- Dislipidemia
- Obesità addominale
- Stress
- Inattività fisica
- Scarso consumo di frutta e verdura
- Consumo regolare di alcool

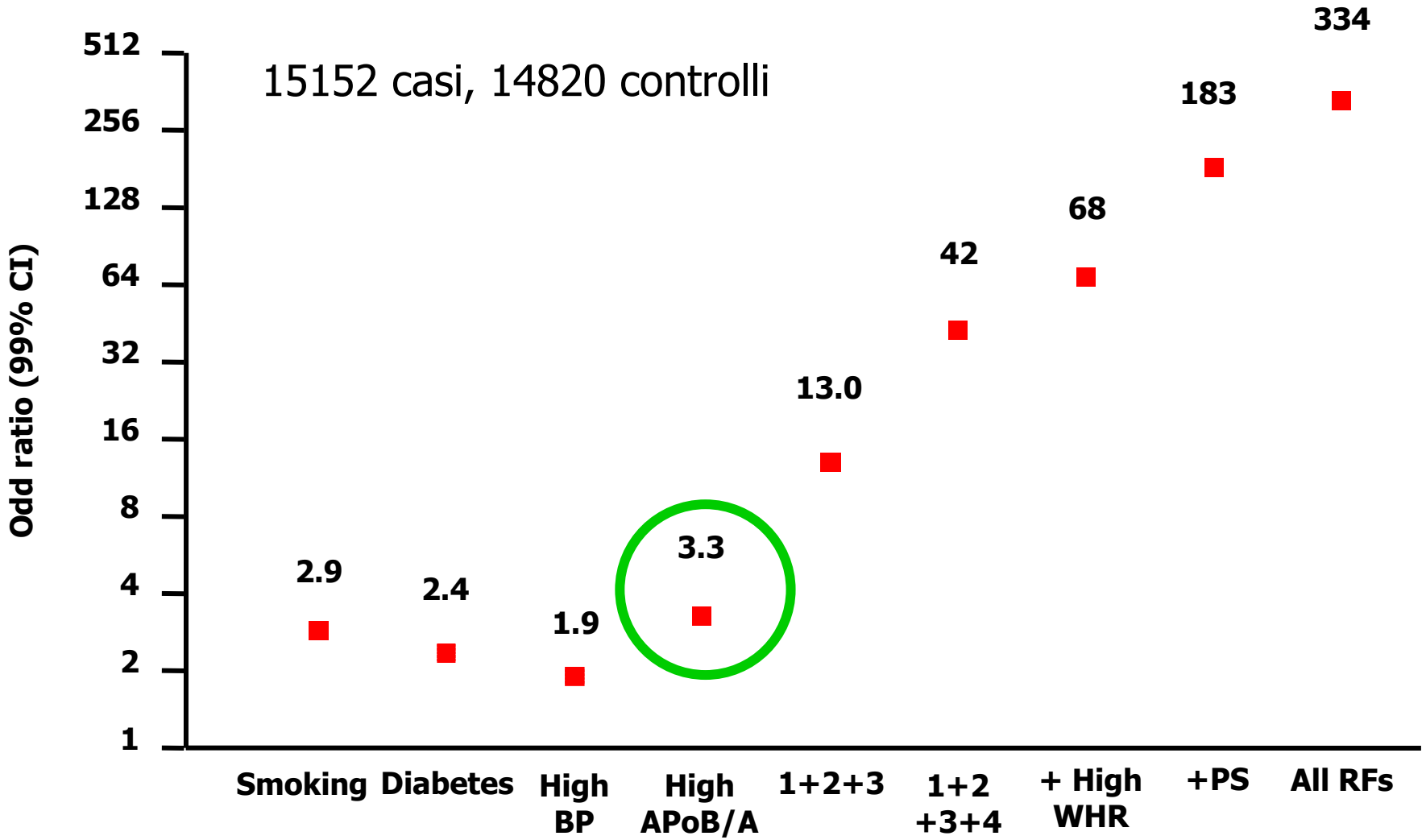
Nove fattori di rischio spiegano > 90% del rischio di IMA nella popolazione generale

Yusuf S Lancet 2004

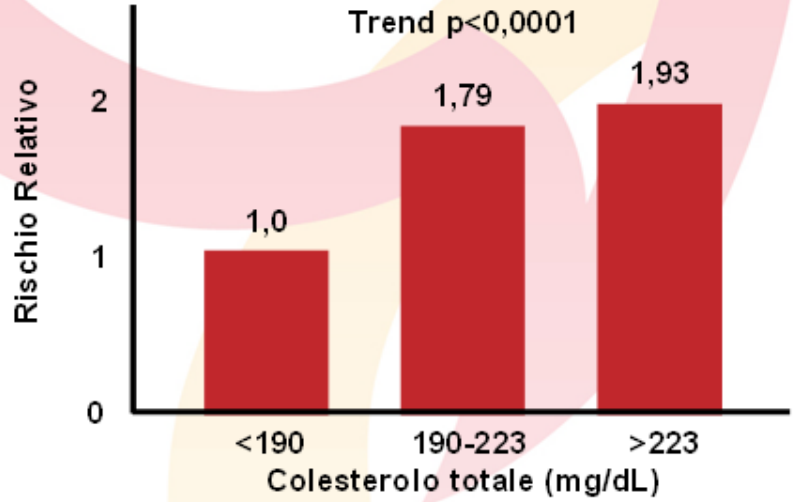
Fattori di Rischio per IMA

Studio INTERHEART (n = 29.972, 52 nazioni)

(Yusuf S et al; Lancet 364: 937-952 , 2004)

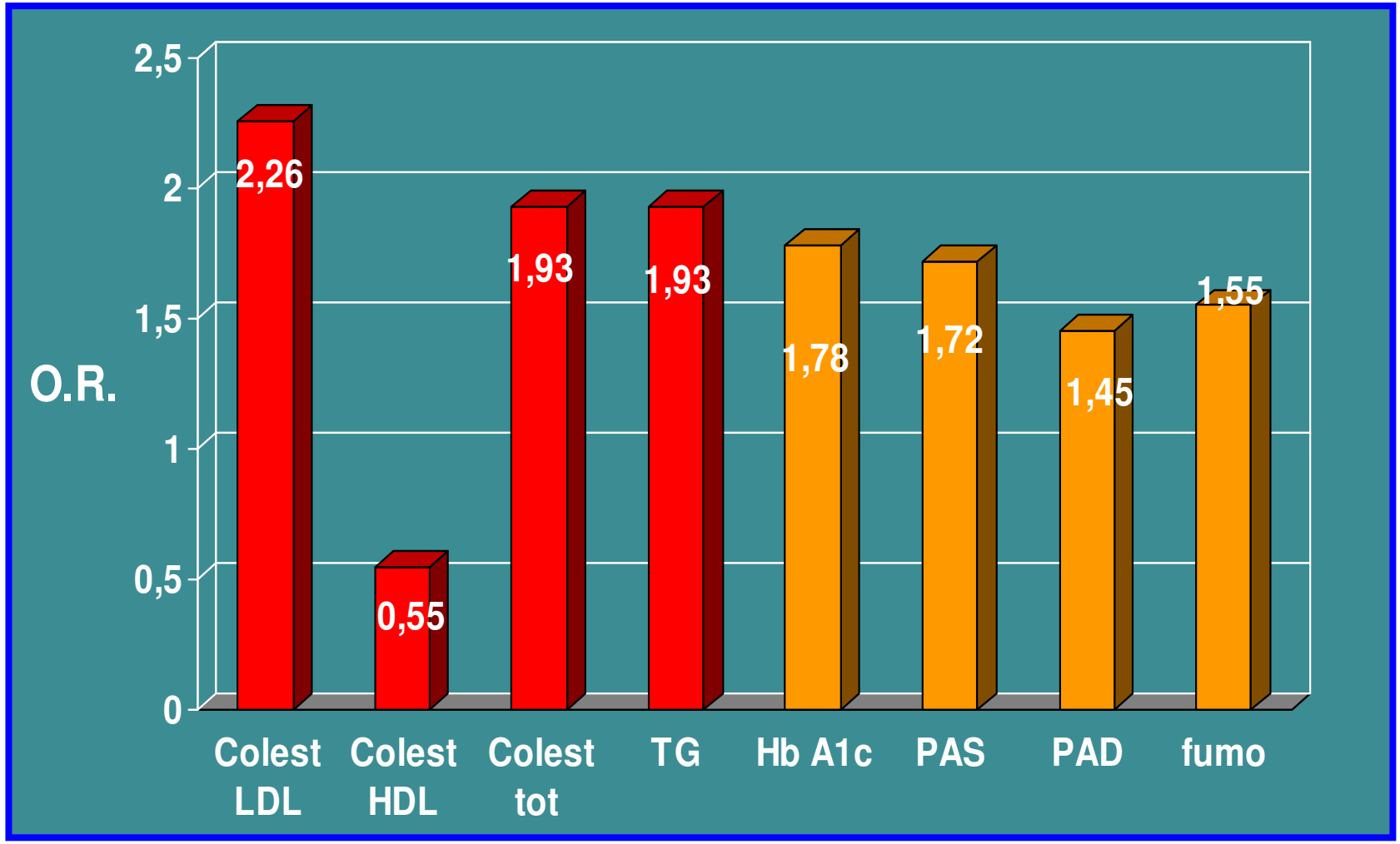


Fattori di Rischio Coronarico nel Diabete



Turner RC,UKPDS 23. BMJ 1998; 316:823–828

Significato predittivo per coronaropatia dei diversi fattori di rischio CV nei diabetici

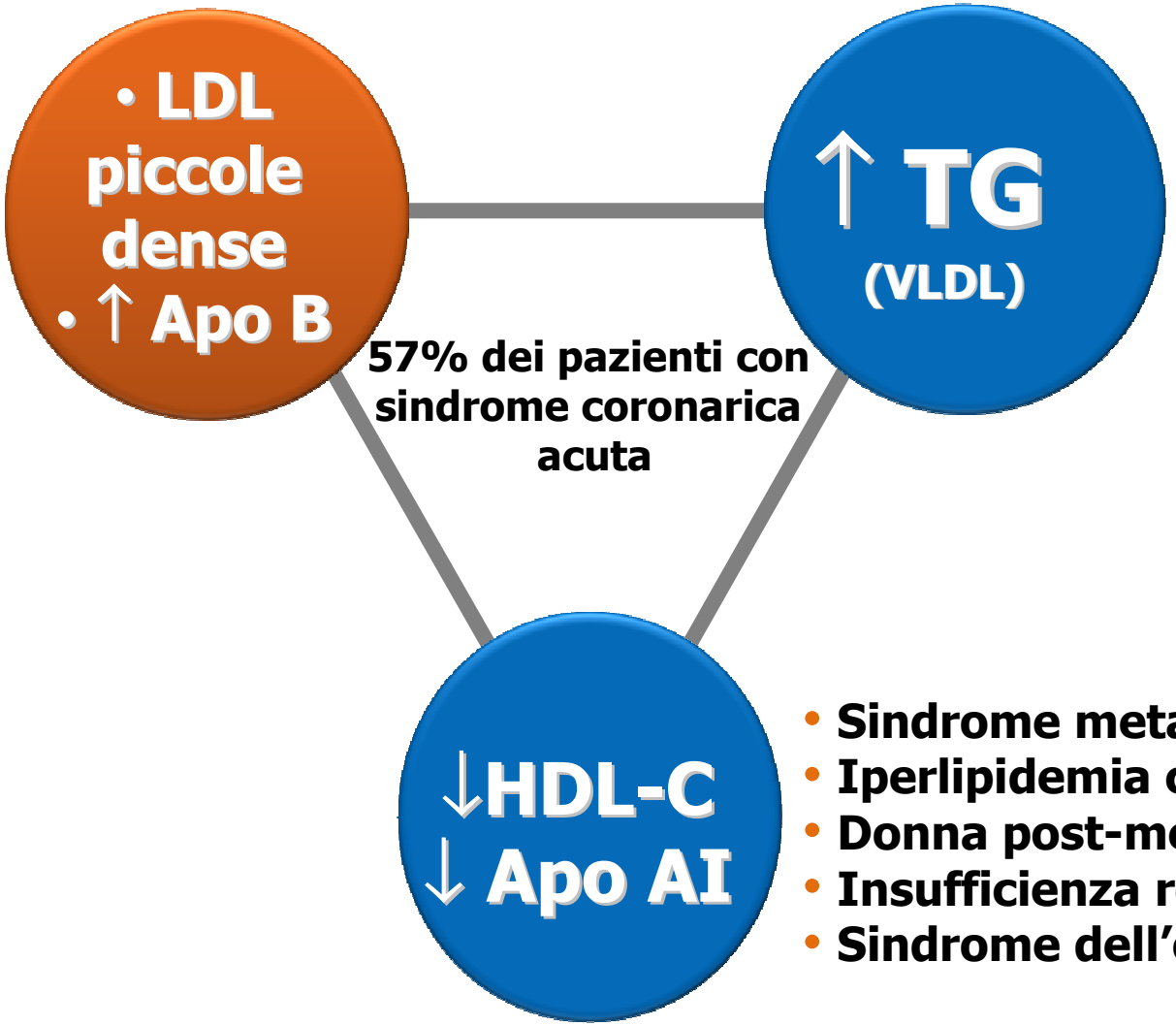


Turner RC,UKPDS 23. BMJ 1998; 316:823–828

Alterazioni lipidiche nel diabete

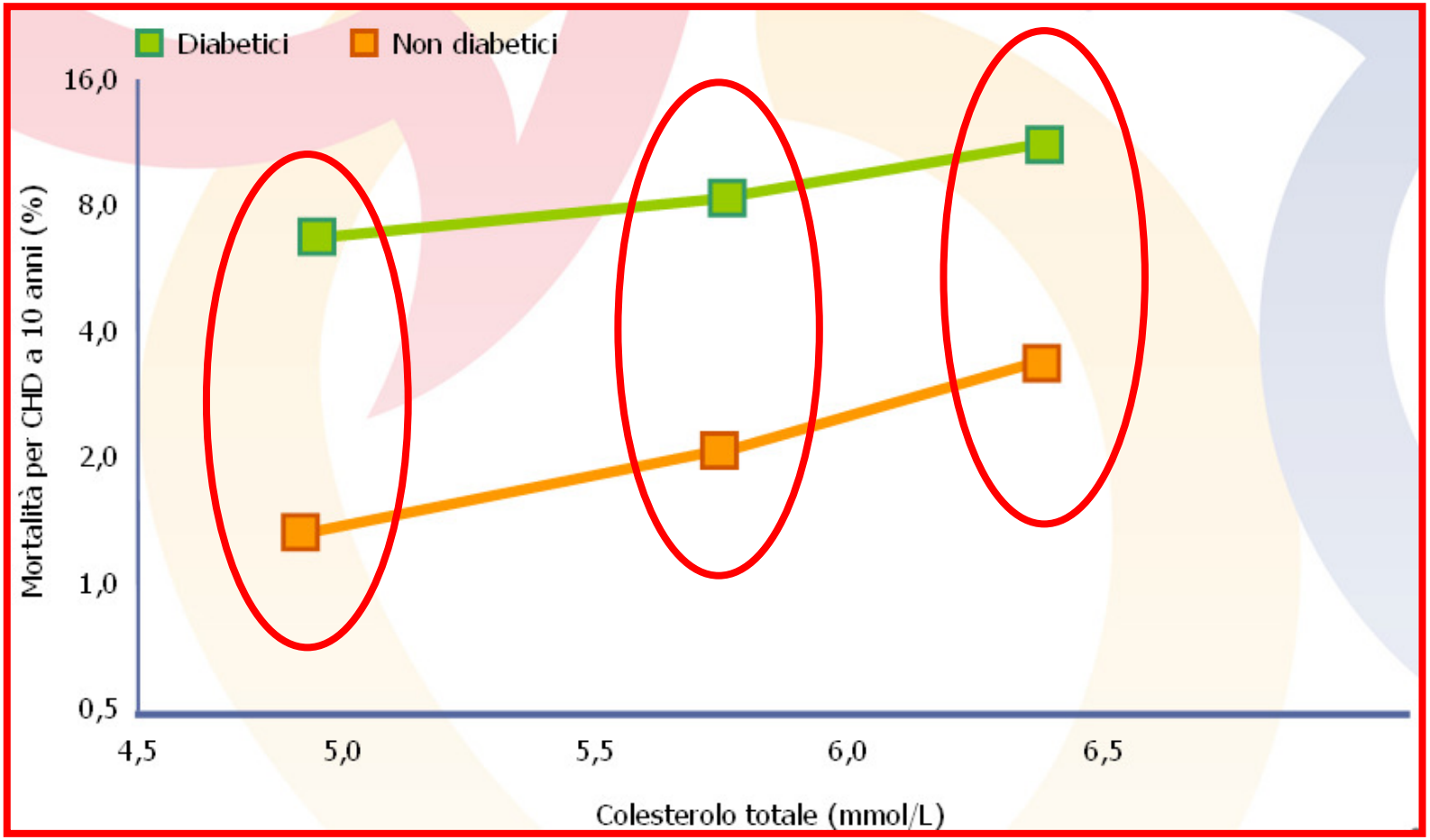
		CT	TG	VLDL	LDL	HDL
TIPO 1	Buon controllo	=	=	=	=	= / ↑
	Scarso controllo	= / ↑	↑ / ↑↑	↑ / ↑↑	= / ↑	↓

Profilo Lipidico Aterogeno nel DM2



- Sindrome metabolica
- Iperlipidemia combinata
- Donna post-menopausa
- Insufficienza renale
- Sindrome dell'ovaio policistico

Colesterolemia e rischio CV nei diabetici e nei non diabetici



Armitage J et al, Heart; 2000; 84:357-360

Effetti del diabete sulla lipemia post-prandiale

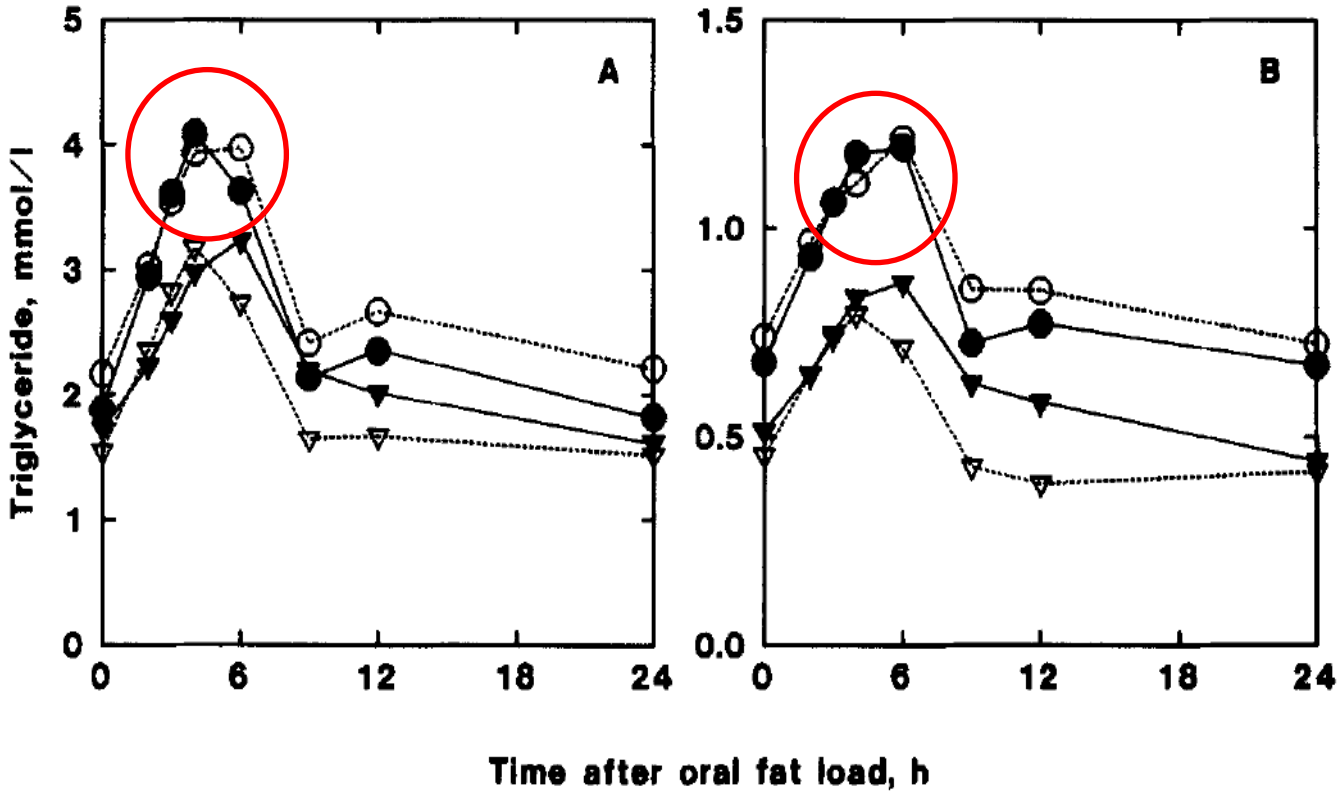
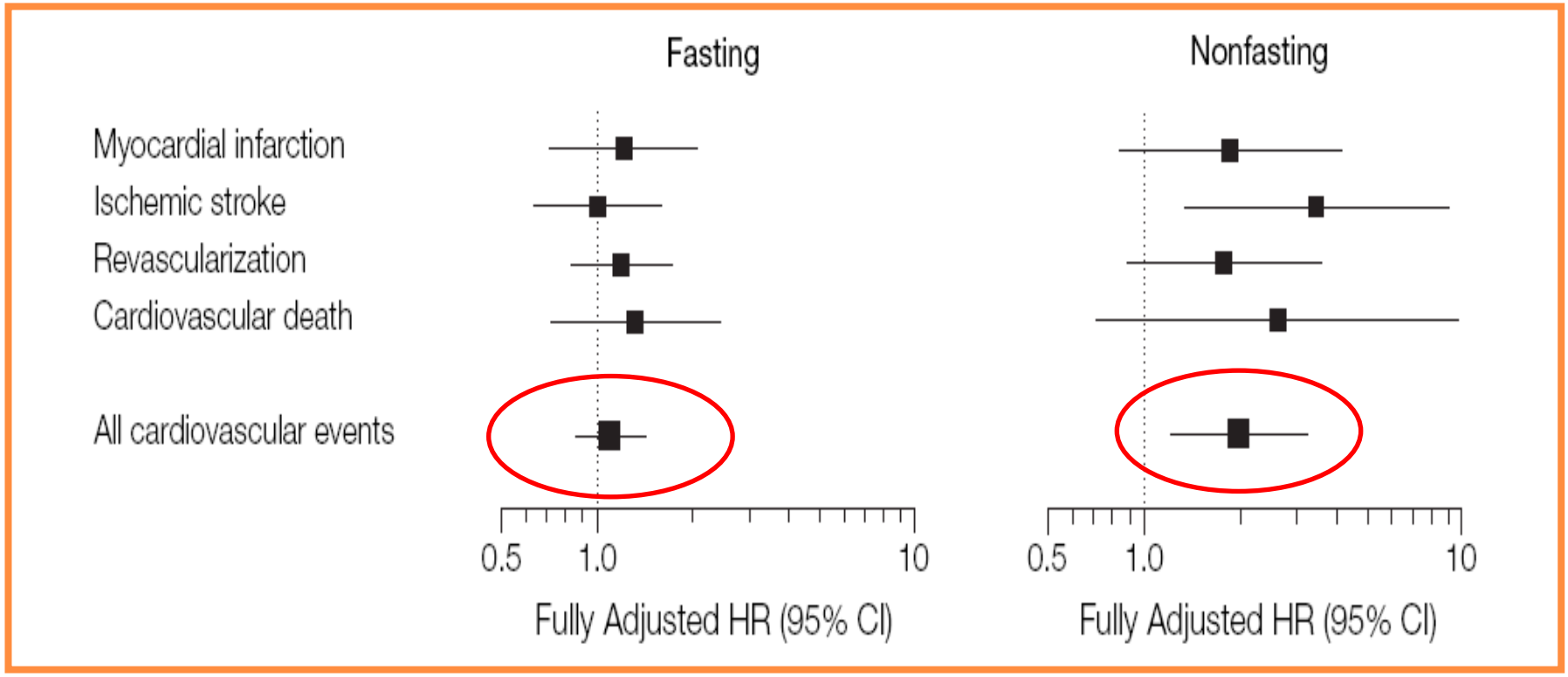


Fig. 1. Line graphs showing the postprandial triglyceride responses in plasma (panel A) and in the $VLDL_1$ (S_f 60-400) fraction (panel B). Group 1, DM+CAD+ (●); Group 2, DM−CAD+ (▼); Group 3, DM+CAD− (○); Group 4, DM−CAD− (▽).

Syvanne M et al, J Lipid Res; 1994; 35:15-26

Fasting Compared With Nonfasting Triglycerides and Risk of Cardiovascular Events in Women



Bansal S et al, JAMA; 2007; 298:309-316

Non-HDL Cholesterol and Apolipoprotein B Predict Cardiovascular Disease Events Among Men With Type 2 Diabetes

Rui Jiang, MD, DRPH[1,2]
Matthias B. Schulze, PHD[1]
Tricia Li, MD[1]
Nader Rifai, PHD[4]
Meir J. Stampfer, MD, DRPH[1,2,3]
Eric B. Rimm, SCD[1,2,3]
Frank B. Hu, MD, PHD[1,2,3]

OBJECTIVE — To evaluate the role of non-HDL cholesterol and apolipoprotein (apo)B markers of all potentially atherogeni in comparison with LDL cholestero

RESEARCH DESIGN AND M in the Health Professionals' Follow- cancer at the time of blood draw in 1 incident CVD cases.

RESULTS — We used Cox propo CVD. After adjustment for age, BM (the highest versus the lowest qu 2.31 (1.23–4.35) for apoB, ar models indicate that non-H CVD risk beyond LDL ch 0.685, 0.691, 0.695, a for non-HDL cholesterol total chol cholesterol ratio), pectively.

CONCLUSIONS — Non-HDL cholesterol and apoB are more potent predictors of CVD incidence among diabetic men than LDL cholesterol. Statistically, the ratio of total to HDL cholesterol is the best predictor of CVD in this cohort of diabetic men.

Diabetes Care 27:1991–1997, 2004

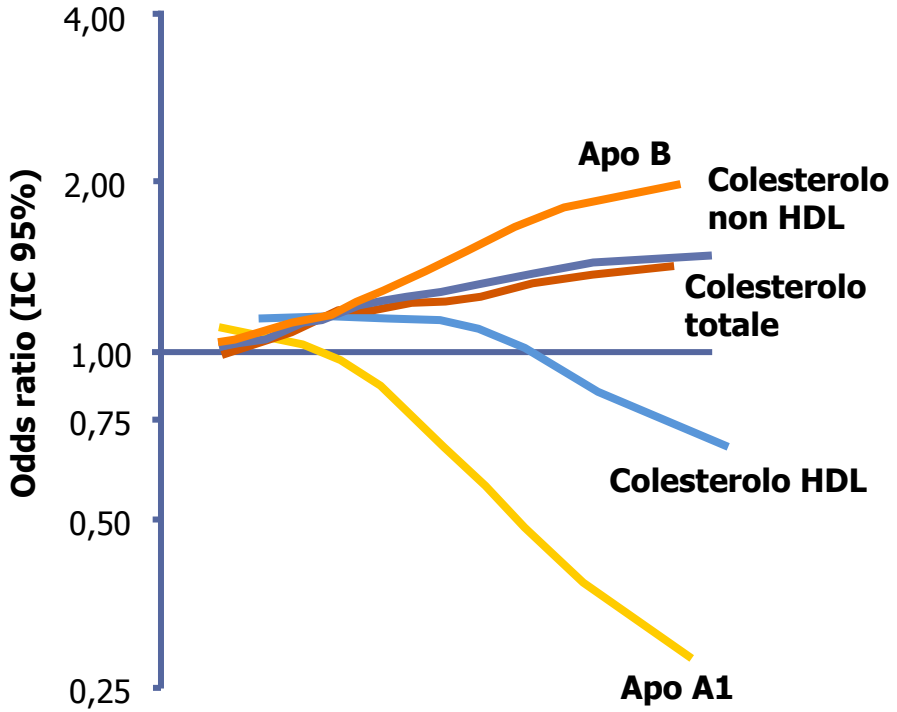
Non-HDL cholesterol and apoB are more potent predictors of CVD incidence among diabetic men than LDL cholesterol.

to LDL cholesterol alone as a predictor of CVD among diabetic patients, largely because cholesterol-enriched VLDL and IDL have been shown to be atherogenic in addition to LDL, and the total cholesterol in LDL, IDL, and VLDL may confer a greater CVD risk than LDL cholesterol alone (1–3). The recent National Cholesterol Edu- nel III d the ble of d rec- get of ividu- imary rotein , IDL, corre- ls (5). sterol, l con- flects the total particle number in these lipoproteins (2). Whether total apoB could be a better measure than LDL cholesterol in predicting CVD risk in diabetic patients, who often have elevated apoB levels, is unclear.

Although growing evidence suggests

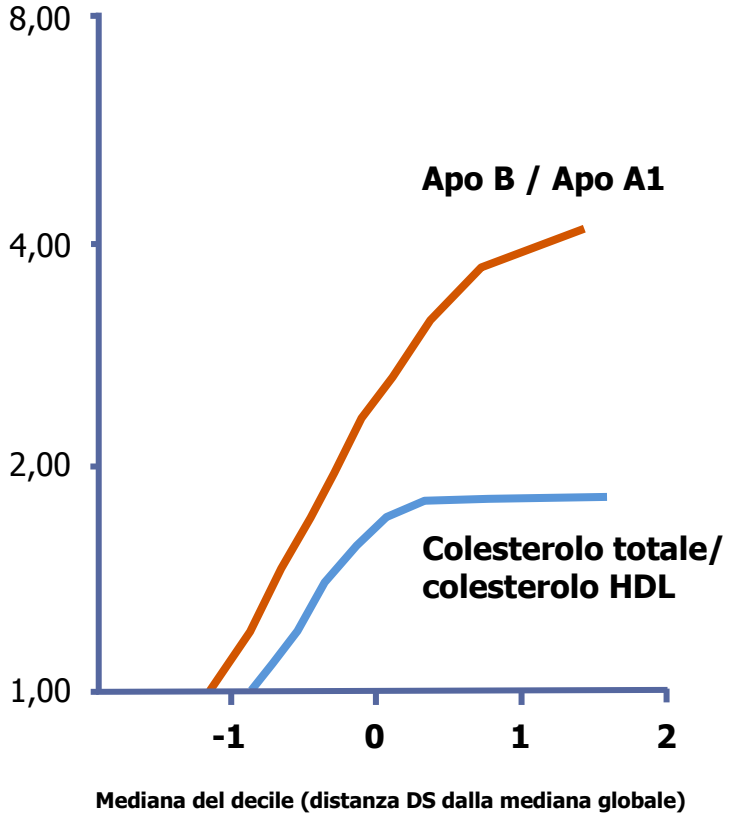
Apo B/Apo A1 e rischio cardiovascolare

Lo Studio INTERHEART



Mediana dei decili globale (casi+controlli)

Decile	1	2	3	4	5	6	7	8	9	10
ApoA1	0,80	0,95	1,03	1,10	1,16	1,23	1,30	1,37	1,49	1,69
ApoB	0,54	0,66	0,74	0,80	0,88	0,93	0,99	1,07	1,17	1,36
Colesterolo non-HDL	2,33	2,89	3,25	3,56	3,84	4,13	4,43	4,77	5,23	6,13
Colesterolo HDL	0,59	0,73	0,82	0,90	0,98	1,06	1,15	1,28	1,45	1,78
Colesterolo totale	3,32	3,95	4,34	4,65	4,94	5,23	5,53	5,89	6,34	7,22



Mediana dei decili globale (casi+controlli)

Decile	1	2	3	4	5	6	7	8	9	10
ApoB / ApoA1	0,43	0,53	0,60	0,66	0,72	0,78	0,85	0,93	1,04	1,28
Colesterolo totale / HDL	2,74	3,37	3,82	4,23	4,64	5,08	5,58	6,21	7,15	9,20

McQueen MJ et al. Lancet 2008;372:224-233

Particolari categorie di pazienti: i pazienti diabetici

• Le LDL sono impoverite in colesterolo e arricchite in trigliceridi.

• Il dosaggio del colesterolo LDL non fornisce una adeguata informazione sul suo reale valore e quindi anche sul TT che deve essere raggiunto.

• Dovrebbe quindi essere considerato anche il dosaggio dell'ApoB sia per stabilire il momento di inizio della terapia, sia per quanto riguarda il TT da raggiungere.

• L'ApoB infatti è indicativo del numero di particelle circolanti dato che ogni particella di LDL contiene una molecola di ApoB.

• Il dosaggio dell'ApoB sarebbe utile anche nei soggetti con sindrome metabolica e nei pazienti con insufficienza renale cronica.

• Il colesterolo non HDL, inoltre, la cui determinazione può essere utile se non è possibile il dosaggio dell'Apo B, si calcola facilmente dal colesterolo totale (TC) meno HDL-C.

European Heart Journal (2011) **32**, 1769–1818
doi:10.1093/eurheartj/ehr158

ESC/EAS Guidelines for the management of dyslipidaemias

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS)

Developed with the special contribution of: European Association for Cardiovascular Prevention & Rehabilitation†

Authors/Task Force Members: Željko Reiner* (ESC Chairperson) (Croatia) Alberico L. Catapano* (EAS Chairperson)* (Italy), Guy De Backer (Belgium), Ian Graham (Ireland), Marja-Riitta Taskinen (Finland), Olov Wiklund (Sweden), Stefan Agewall (Norway), Eduardo Alegria (Spain), M. John Chapman (France), Paul Durrington (UK), Serap Erdine (Turkey), Julian Halcox (UK), Richard Hobbs (UK), John Kjekshus (Norway), Pasquale Perrone Filardi (Italy), Gabriele Riccardi (Italy), Robert F. Storey (UK), David Wood (UK).

NOTA 13 Allegato 1

Preambolo

La presente revisione della nota 13 nasce dalla necessità di adeguare la definizione del livello di rischio alle linee guida ESC/EAS, apparse in letteratura subito dopo la pubblicazione della nota stessa. L'adeguamento a tali linee guida ha comportato la reintroduzione delle relative carte di rischio. Si confida sulla disponibilità della classe medica ad utilizzare questo strumento, peraltro di facile applicazione, al fine di tenere conto delle evidenze scientifiche più recenti.

European Heart Journal (2011) **32**, 1769–1818
doi:10.1093/eurheartj/ehr158

ESC/EAS GUIDELINES

ESC/EAS Guidelines for the management of dyslipidaemias

• The SCORE system estimates the **10 year risk of a first fatal atherosclerotic event**, whether heart attack, stroke, or other occlusive arterial disease, including sudden cardiac death.

• The reasons for retaining a system that estimates fatal as opposed to total fatal + non-fatal events are that **non-fatal events are dependent on definition, developments in diagnostic tests, and methods of ascertainment, all of which can vary, resulting in very variable multipliers to convert fatal to total events**.

• The SCORE data indicate that the total **CVD event risk is about three times higher than the risk of fatal CVD for men**, so that a SCORE risk of 5% translates into a CVD risk of 15% of total (fatal plus non-fatal) hard CVD endpoints; the multiplier is slightly higher in women and lower in older persons.

1. Very high risk

- **Documented CVD by invasive or non-invasive testing** (such as coronary angiography, nuclear imaging, stress echocardiography, carotid plaque on ultrasound), previous myocardial infarction (MI), ACS, coronary revascularization [percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG)] and other arterial revascularization procedures, ischaemic stroke, PAD.
- Patients with **type 2 diabetes**, patients with **type 1 diabetes with target organ damage (such as microalbuminuria)**.
- Patients with **moderate to severe CKD** [glomerular filtration rate (GFR) ,60 mL/min/1.73 m2).
- A calculated 10 year risk SCORE ≥10%.

2. High risk

- Markedly elevated single risk factors such as familial dyslipidaemias and severe hypertension.
- A calculated SCORE ≥5% and ,10% for 10 year risk of fatal CVD.

Reiner Z et al. Eur Heart J 2011; 32:1769-1818

3. Moderate risk

• Subjects are considered to be at moderate risk when their SCORE is ≥1% and ,5% at 10 years. Many middle-aged subjects belong to this risk category. This risk is further modulated by a family history of premature CAD, abdominal obesity, physical
activity pattern, HDL-C, TG, hs-CRP, Lp(a), fibrinogen, homocysteine, apo B, and social class.

4. Low risk

• The low risk category applies to individuals with SCORE < 1%.

Reiner Z et al. Eur Heart J 2011; 32:1769-1818

ESC/EAS Guidelines 2011
Recommendations for treatment targets for LDL-C

Recommendations	Class[a]	Level[b]
In patients at VERY HIGH CV risk (established CVD, type 2 diabetes, type 1 diabetes with target organ damage, moderate to severe CKD or a SCORE level ≥10%) the LDL-C goal is <1.8 mmol/L (less than ~70 mg/dL) and/or ≥50% LDL-C reduction when target level cannot be reached.	I	A
In patients at HIGH CV risk (markedly elevated single risk factors, a SCORE level ≥5 to <10%) an LDL-C goal <2.5 mmol/L (less than ~100 mg/dL) should be considered.	IIa	A
In subjects at MODERATE risk (SCORE level >1 to ≤5%) an LDL-C goal <3.0 mmol/L (less than ~115 mg/dL) should be considered.	IIa	C

Reiner Z et al. Eur Heart J 2011; 32:1769-1818

ESC/EAS Guidelines 2011

Recommendations for treatment of dyslipidemia in diabetes

Recommendations	Class[a]	Level[b]	Ref[c]
In all patients with type 1 diabetes and in the presence of microalbuminuria and renal disease, LDL-C lowering (at least 30%) with statins as the first choice (eventually drug combination) is recommended irrespective of the basal LDL-C concentration.	I	C	
In patients with type 2 diabetes and CVD or CKD, and in those without CVD who are over the age of 40 years with one or more other CVD risk factors or markers of target organ damage, the recommended goal for LDL-C is <1.8 mmol/L (less than ~70 mg/dL) and the secondary goal for non-HDL-C is <2.6 mmol/L (100 mg/dL) and for apo B is <80 mg/dL.	I	B	15, 16
In all people with type 2 diabetes LDL-C <2.5 mmol/L (less than ~100 mg/dL) is the primary target. Non-HDL-C <3.3 mmol/L (130 mg/dL) and apo B <100 mg/dL are the secondary targets.	I	B	15, 16

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
apo = apolipoprotein; CKD = chronic kidney disease; CVD = cardiovascular disease; LDL-C = low-density lipoprotein-cholesterol.

Reiner Z et al. Eur Heart J 2011; 32:1769-1818

CONSENSUS STATEMENT

Lipoprotein Management in Patients With Cardiometabolic Risk

Consensus statement from the American Diabetes Association and the American College of Cardiology Foundation

JOHN D. BRUNZELL, MD, FACP[1]
MICHAEL DAVIDSON, MD, FACC[2]
CURT D. FURBERG, MD, PHD[3]
RONALD B. GOLDBERG, MD[4]
BARBARA V. HOWARD, PHD[5]
JAMES H. STEIN, MD, FACC, FACP[6]
JOSEPH L. WITZTUM, MD[7]

DIABETES CARE, VOLUME 31, NUMBER 4, APRIL 2008

LDL-C	Non-HDL cholesterol	Apo B
< 70 mg/dl	< 100 mg/dl	< 80 mg/dl
<100 mg/dl	< 130 mg/dl	< 90 mg/dl

RACCOMANDAZIONI

Screening e monitoraggio

- Il controllo del profilo lipidico completo (colesterolo totale, colesterolo HDL e trigliceridi) deve essere effettuato almeno annualmente e a intervalli di tempo più ravvicinati in caso di mancato raggiungimento dell'obiettivo terapeutico. (**Livello della prova III, Forza della raccomandazione B**)

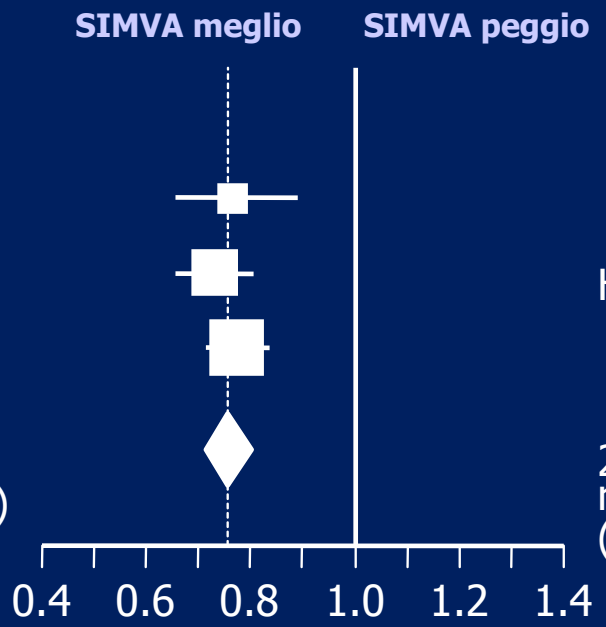
- Il rapporto apoB/apoA1 può costituire un ulteriore indice di rischio cardiovascolare nel diabetico (rischio elevato: uomini > 0,9, donne > 0,8). (**Livello della prova III, Forza della raccomandazione B**)

HPS: Major Vascular Events in Patients With Low Baseline Cholesterol

EVENTI VASCOLARI PER LIVELLI DI LDL

Simvastatina: endpoint secondari

CARATTERISTICHE AL BASALE	SIMVA (10269)	PLACEBO (10267)	Rischio Relativo IC 95%
LDL (mg/dl)			
< 100 (2.6 mmol/l)	285	360	
100-130	670	881	
> 130 (3.4 mmol/l)	1087	1365	
TUTTI I PAZIENTI	2042 (19.9%)	2606 (25.4%)	



Het χ^2_2 = 0.8

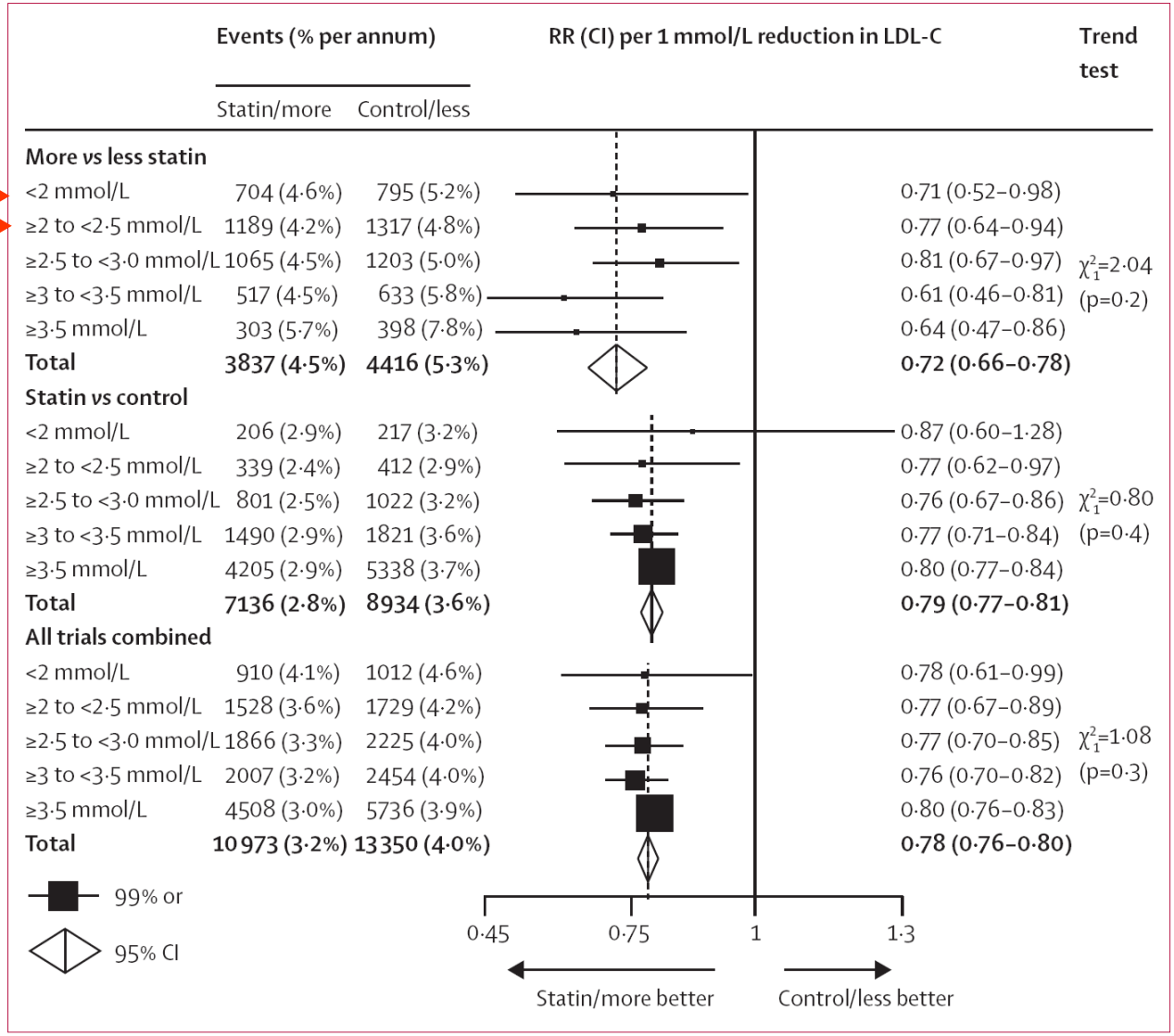
24%SE 2.6 riduzione (2P<0.00001)

Heart Protection Study Collaborative Group. *Lancet*. 2002;360:7-22

Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials

Lancet 2010;376(9753):1670-81

*Cholesterol Treatment Trialists' (CTT) Collaboration**



Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials

Lancet 2010;376(9753):1670-81

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Webfigure 10: Effects on MAJOR VASCULAR EVENTS per mmol/L reduction in LDL cholesterol, by baseline prognostic factors in 21 statin vs control trials

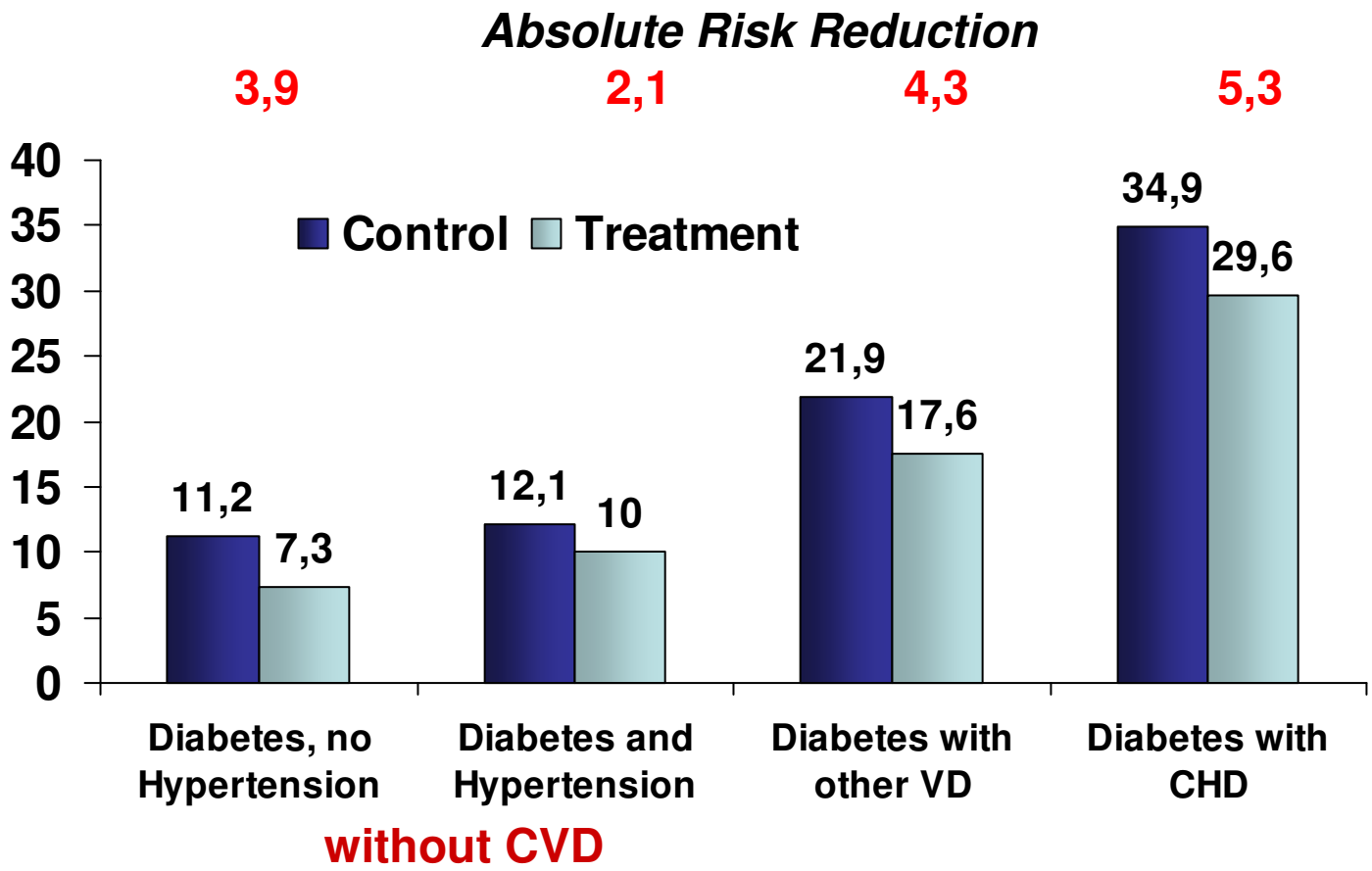
Subgroup	Events (% p.a.) Statin/more	Events (% p.a.) Control/less	RR (CI) per 1 mmol/L reduction in LDL−C	Heterogeneity/ trend test
Previous vascular disease:				
CHD	4558 (4.6)	5707 (5.9)	0.80 (0.77 – 0.83)	χ^2_2=3.15 (p=0.2)
Non−CHD vascular	674 (3.1)	802 (3.7)	0.81 (0.71 – 0.92)	
None	1904 (1.4)	2425 (1.8)	0.75 (0.69 – 0.82)	
Diabetes:				
Type 1 diabetes	137 (4.4)	184 (6.0)	0.77 (0.58 – 1.01)	χ^2_2=0.21 (p=0.9)
Type 2 diabetes	1791 (3.6)	2128 (4.5)	0.80 (0.74 – 0.86)	
No diabetes	5146 (2.8)	6547 (3.6)	0.79 (0.76 – 0.82)	
Sex:				
Male	5572 (3.1)	7103 (4.0)	0.78 (0.75 – 0.81)	χ^2_1=3.93 (p=0.05)
Female	1564 (2.1)	1831 (2.5)	0.84 (0.77 – 0.91)	
Age (years):				
≤ 65	3885 (2.4)	4940 (3.1)	0.79 (0.75 – 0.83)	χ^2_1=0.68 (p=0.4)
>65, ≤ 75	2676 (3.3)	3342 (4.2)	0.79 (0.74 – 0.84)	
> 75	575 (4.2)	652 (4.7)	0.85 (0.73 – 0.99)	
Treated hypertension:				
Yes	4306 (3.3)	5216 (4.0)	0.81 (0.77 – 0.85)	χ^2_1=2.53 (p=0.1)
No	2576 (2.2)	3425 (2.9)	0.77 (0.73 – 0.81)	

Efficacy of cholesterol-lowering therapy in 18 686 people with diabetes in 14 randomised trials of statins: a meta-analysis

Lancet 2008; 371: 117–25

*Cholesterol Treatment Trialists' (CTT) Collaborators**

Incidence of major vascular events in control and treatment (per 39 mg/dl reduction in LDL cholesterol)



Reduction in 10-year risk of major CVD end points (CHD death/non-fatal MI) in major statin trials, or substudies of major trials in primary prevention in diabetic subjects

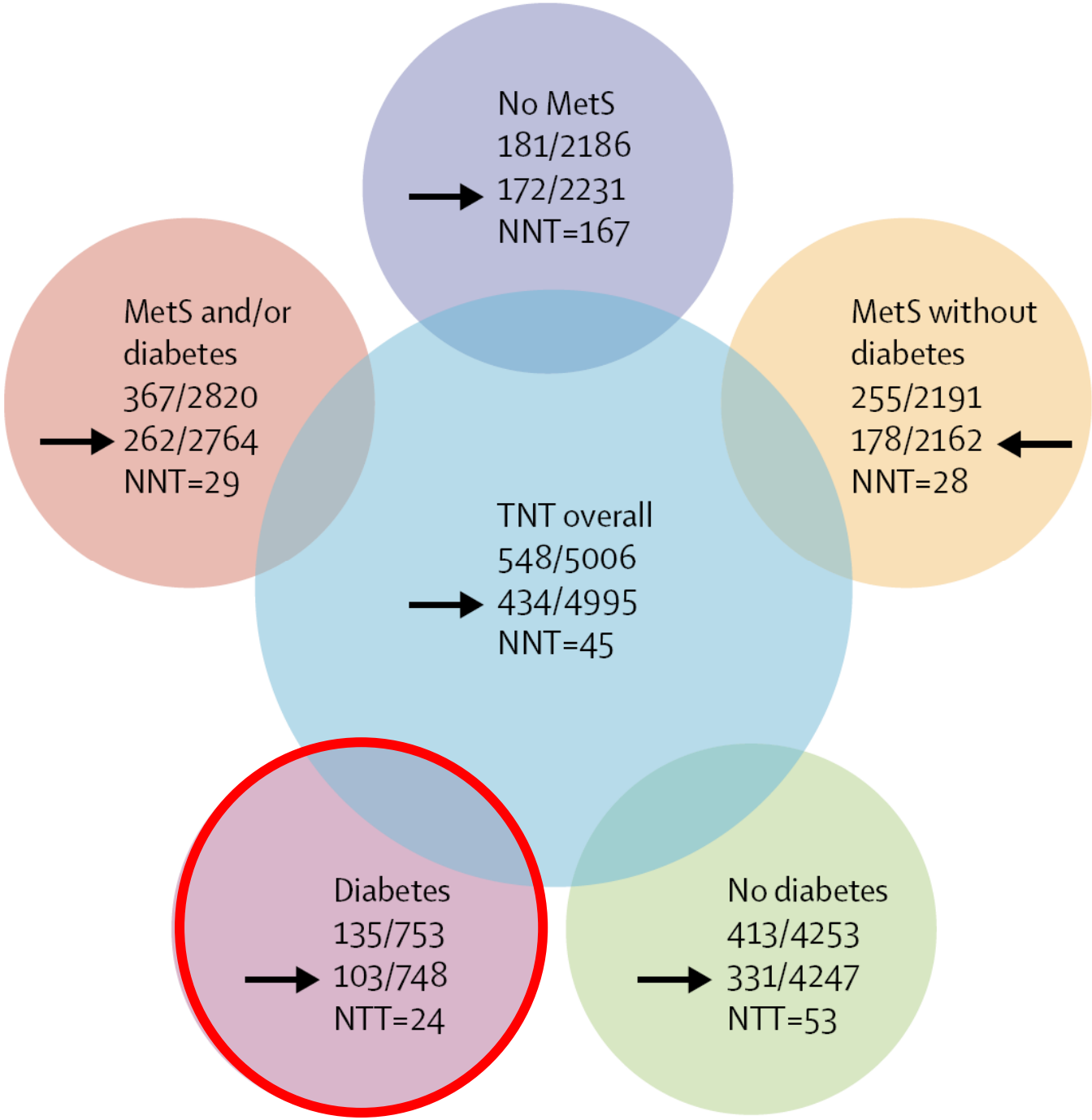
Study (ref.)	CVD	Statin dose and comparator	Risk reduction (%)	Relative risk reduction (%)	Absolute risk reduction (%)	LDL cholesterol reduction (mg/dl)	LDL cholesterol reduction (%)
HPS-DM (216)	1°	Simvastatin 40 mg vs. placebo	17.5 to 11.5	34	6.0	124 to 86	31
CARDS (221)	1°	Atorvastatin 10 mg vs. placebo	11.5 to 7.5	35	4	118 to 71	40
ASPEN 1° (220)	1°	Atorvastatin 10 mg vs. placebo	9.8 to 7.9	19	1.9	114 to 80	30
ASCOT-DM (219)	1°	Atorvastatin 10 mg vs. placebo	11.1 to 10.2	8	0.9	125 to 82	34

Standard of Medical Care in Diabetes, ADA. Diabetes Care. 2011;34(S1) S11-S61.

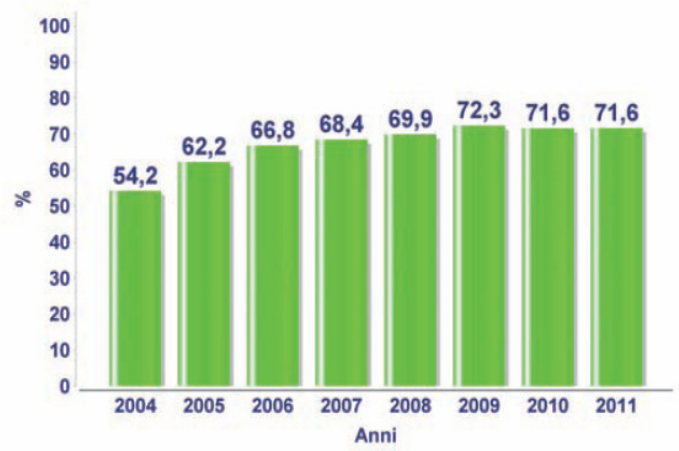
Reduction in 10-year risk of major CVD end points (CHD death/non-fatal MI) in major statin trials, or substudies of major trials in secondary prevention in diabetic subjects

Study (ref.)	CVD	Statin dose and comparator	Risk reduction (%)	Relative risk reduction (%)	Absolute risk reduction (%)	LDL cholesterol reduction (mg/dl)	LDL cholesterol reduction (%)
4S-DM (215)	2°	Simvastatin 20–40 mg vs. placebo	85.7 to 43.2	50	42.5	186 to 119	36
ASPEN 2° (220)	2°	Atorvastatin 10 mg vs. placebo	39.5 to 24.5	34	15	112 to 79	29
HPS-DM (216)	2°	Simvastatin 40 mg vs. placebo	43.8 to 36.3	17	7.5	123 to 84	31
CARE-DM (217)	2°	Pravastatin 40 mg vs. placebo	40.8 to 35.4	13	5.4	136 to 99	27
TNT-DM (218)	2°	Atorvastatin 80 mg vs. 10 mg	26.3 to 21.6	18	4.7	99 to 77	22

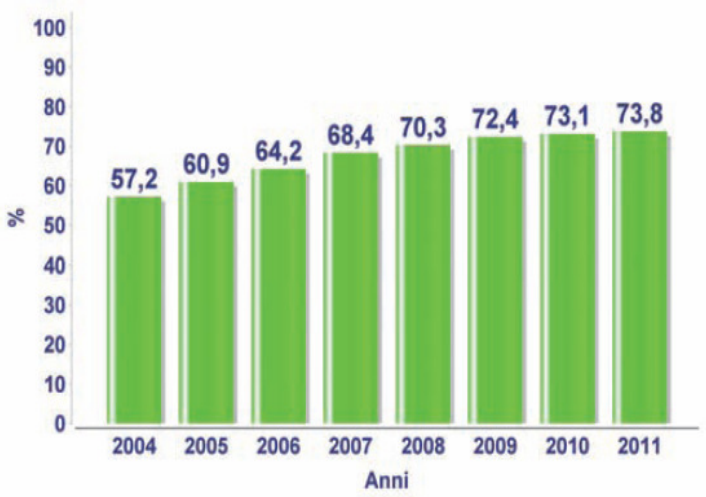
Standard of Medical Care in Diabetes, ADA. Diabetes Care. 2011;34(S1) S11-S61.

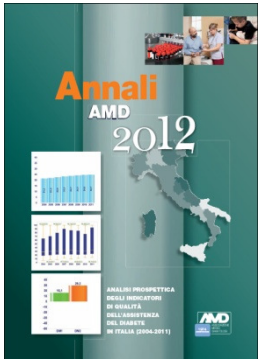

No MetS
181/2186
172/2231
NNT=167
MetS and/or
diabetes
367/2820
262/2764
NNT=29
MetS without
diabetes
255/2191
178/2162
NNT=28
TNT overall
548/5006
434/4995
NNT=45
Diabetes
135/753
103/748
NTT=24
No diabetes
413/4253
331/4247
NTT=53

Soggetti ai quali è stata eseguita almeno una misurazione del profilo lipidico — DM1

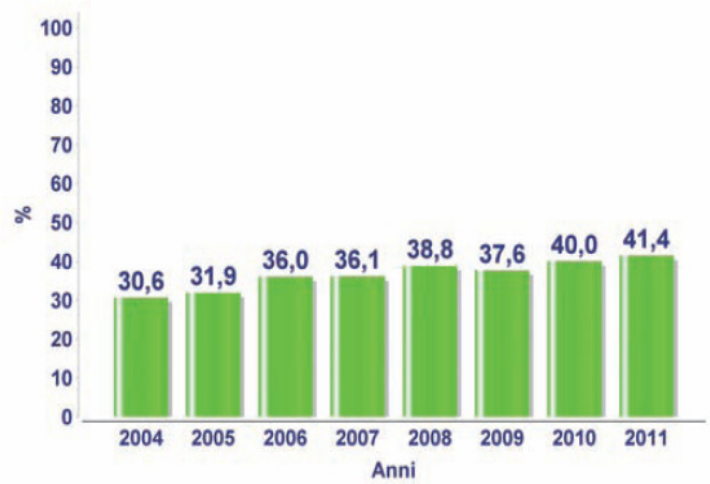


Soggetti ai quali è stata eseguita almeno una misurazione del profilo lipidico — DM2

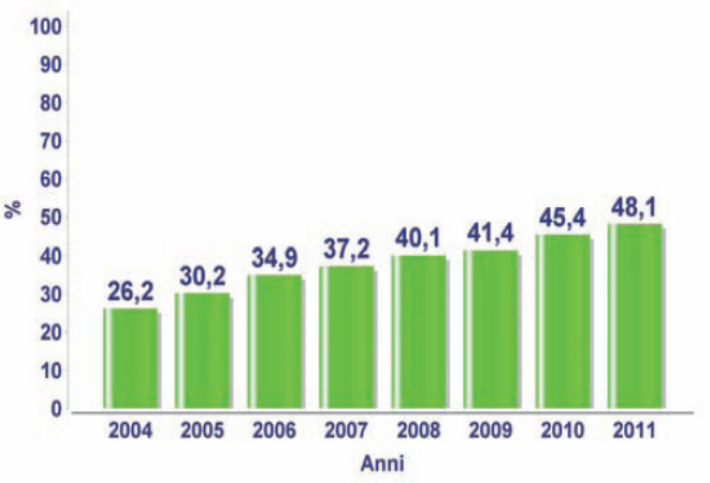




Soggetti con C-LDL <100 mg/dl DM1



Soggetti con C-LDL <100 mg/dl DM2



N Engl J Med. 2013 Apr 25;368(17):1613-24.

Achievement of goals in U.S. diabetes care, 1999-2010

Ali MK, Bullard KM, Saaddine JB, Cowie CC, Imperatore G, Gregg EW

Abstract

BACKGROUND: Tracking national progress in diabetes care may aid in the evaluation of past efforts and identify residual gaps in care.

METHODS: We analyzed data for adults with self-reported diabetes from the National Health and Nutrition Examination Survey and the Behavioral Risk Factor Surveillance System to examine risk-factor control, preventive practices, and risk scores for coronary heart disease over the 1999-2010 period.

RESULTS: From 1999 through 2010, the weighted proportion of survey participants who met recommended goals for diabetes care increased, by 7.9 percentage points (95% confidence interval [CI], 0.8 to 15.0) for glycemic control (glycated hemoglobin level <7.0%), 9.4 percentage points (95% CI, 3.0 to 15.8) for individualized glycemic targets, 11.7 percentage points (95% CI, 5.7 to 17.7) for blood pressure (target, <130/80 mm Hg), and 20.8 percentage points (95% CI, 11.6 to 30.0) for lipid levels (target level of low-density lipoprotein [LDL] cholesterol, <100 mg per deciliter [2.6 mmol per liter]). Tobacco use did not change significantly, but the 10-year probability of coronary heart disease decreased by 2.8 to 3.7 percentage points.

However, 33.4 to 48.7% of persons with diabetes still did not meet the targets for glycemic control, blood pressure, or LDL cholesterol level.

Only 14.3% met the targets for all three of these measures and for tobacco use. Adherence to the recommendations for annual eye and dental examinations was unchanged, but annual lipid-level measurement and foot examination increased by 5.5 percentage points (95% CI, 1.6 to 9.4) and 6.8 percentage points (95% CI, 4.8 to 8.8), respectively. Annual vaccination for influenza and receipt of pneumococcal vaccination for participants 65 years of age or older rose by 4.5 percentage points (95% CI, 0.8 to 8.2) and 6.9 percentage points (95% CI, 3.4 to 10.4), respectively, and daily glucose monitoring increased by 12.7 percentage points (95% CI, 10.3 to 15.1).

CONCLUSIONS: Although there were improvements in risk-factor control and adherence to preventive practices from 1999 to 2010, tobacco use remained high, and almost half of U.S. adults with diabetes did not meet the recommended goals for diabetes care.

Priorità di Intervento Terapeutico

1. **Ridurre LDL-C**
   - Statine
   - Ezetimibe
   - Resine o Fenofibrato
2. **Elevare HDL-C**
   - Stile di vita (Dieta/Attività fisica)
   - Fibrati o Acido nicotinico
   - Inibitori della CETP
3. **Ridurre Trigliceridi**
   - Dieta/Attività fisica
   - Ottimizzazione compenso glicemico
   - Fibrati (Gemfibrozil, Fenofibrato)
   - Statine a dosi elevate

NOTA 13 – NOVEMBRE

		Trattamento di 1° livello	Tratta…	…nto …llo
PAZIENTI A RISCHIO MODERATO	C-LDL<115 mg/dl	Simvastatina Pravastatina Atorvastatina (**)		
PAZIENTI AD ALTO RISCHIO	C-LDL<100 mg/dl	Simvastatina Pravastatina Atorvastatina (**) preferenzialmente atorvastatina se necessaria rid. LDL>50%	Rosuvastatina EZETIMIBE + statine	
PAZIENTI A RISCHIO MOLTO ALTO	C-LDL<70 mg/dl	Atorvastatina Pravastatina Simvastatina (**) preferenzialmente rosuvastatina se necessaria rid. LDL>50% o rischio di eff. coll. atorvastatina	EZETIMIBE + statine	

Mancanza di fluva e lovastaina

Inserimento atorva al I livello e definita come preferenziale

Chiarita la prescrivibilità di ezetimibe sia in associazione che che in monoterapia

** nei pazienti intolleranti alle statine è rimborsato il trattamento aggiuntivo con **ezetimibe** in monoterapia

La mancanza nella nota di alcune molecole ancora presenti nel mercato, come la fluvastatina e la lovastatina, potrebbe creare problemi di continuità terapeutica e indurre ad ingiustificate modifiche di terapie in pazienti che sono a target e con farmaci ben tollerati.

Modifica alla Nota 13 di cui alla Determina del 14 novembre 2012. n. 83 del 09/04/2013.

NOTA 13 Allegato 1

Precisazioni

• Il calcolo del rischio CV secondo le carte va **effettuato solo per i pazienti senza evidenza di malattia**.

• Sono considerati per definizione **a rischio alto** (e il loro target terapeutico è pertanto un **valore di colesterolo LDL < 100**), oltre a coloro che presentano un risk score ≥5% e <10% per CVD fatale a 10 anni, i pazienti con dislipidemie familiari, quelli con ipertensione severa, **i pazienti diabetici senza fattori di rischio CV e senza danno d'organo**, i pazienti con IRC moderata (FG 30-59 ml/min/1.73m^2).

• Sono invece considerati a **rischio molto alto** (e pertanto con **target terapeutico di colesterolo LDL < 70**), oltre ai soggetti con score ≥10%, i pazienti con malattia coronarica, stroke ischemico, arteriopatie periferiche, pregresso infarto, bypass aorto-coronarico, **i pazienti diabetici con uno o più fattori di rischio CV e/o markers di danno d'organo (come la microalbuminuria)** e i pazienti con IRC grave (FG 15-29 ml/min/1.73m^2)

Ipolipemizzanti:

Fibrati:
- bezafibrato
- fenofibrato
- gemfibrozil

Statine:
- simvastatina
- pravastatina
- fluvastatina
- lovastatina
- atorvastatina
- rosuvastatina

Altri:
- PUFA-N3
- ezetimibe

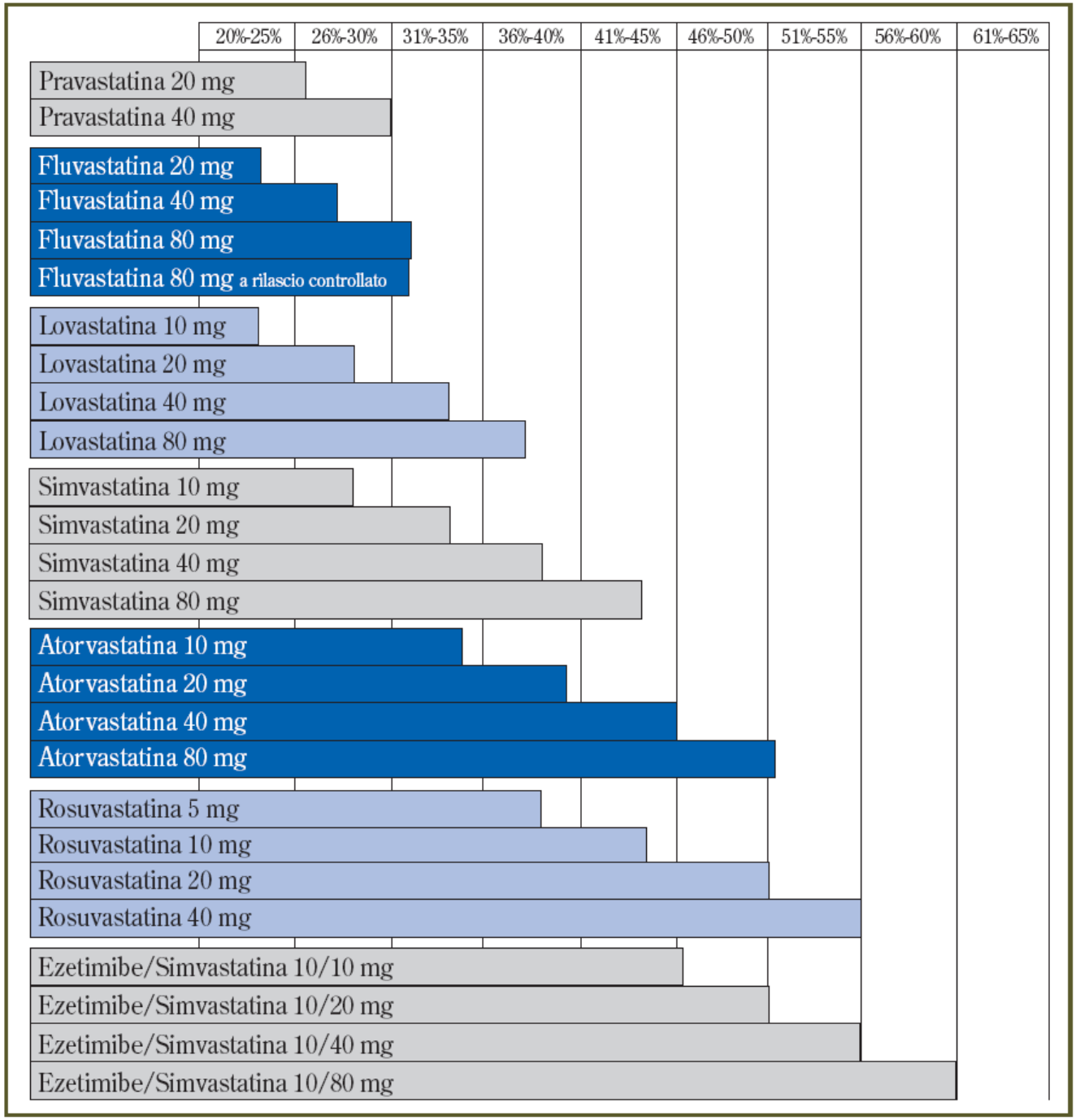
La prescrizione a carico del SSN è limitata ai pazienti affetti da:

Ipercolesterolemia non corretta dalla sola dieta, seguita per almeno tre mesi°, e ipercolesterolemia poligenica secondo i criteri specificati al relativo paragrafo

Classificazione dei pazienti	Target terapeutico (Colesterolo LDL in mg/dl	Farmaci prescrivibili a carico del SSN in funzione del raggiungimento del target terapeutico	
CATEGORIE DI RISCHIO*		**Trattamento di 1° livello**	**Trattamento di 2° livello**
Pazienti con rischio medio: - score 2-3%	Colesterolo LDL < 130	Modifica dello stile di vita per almeno 6 mesi	simvastatina pravastatina fluvastatina lovastatina atorvastatina(**)
Pazienti con rischio moderato: - score 4-5%	Colesterolo LDL < 115	simvastatina pravastatina fluvastatina lovastatina atorvastatina(**)	
Pazienti con rischio alto: -score >5% <10%	Colesterolo LDL < 100	simvastatina pravastatina fluvastatina lovastatina atorvastatina(**) Preferenzialmente atorvastatina se necessaria riduzione del colesterolo LDL > 50%	rosuvastatina ezetimibe più statine (in associazione estemporanea o precostituita) (**)
Pazienti con rischio molto alto: - score ≥10%	Colesterolo LDL < 70 (riduzione di almeno il 50% del colesterolo LDL)	atorvastatina§ pravastatina fluvastatina lovastatina simvastatina(**)§ rosuvastatina nei pazienti in cui ci sia stata evidenza di effetti collaterali severi nei primi 6 mesi di terapia con altre statine	ezetimibe più statine (in associazione estemporanea o precostituita) (**)

Pazienti con diabete

Confronto dell'efficacia ipo-colesterolemizzante delle diverse statine e della associazione fissa simvastatina + ezetimibe



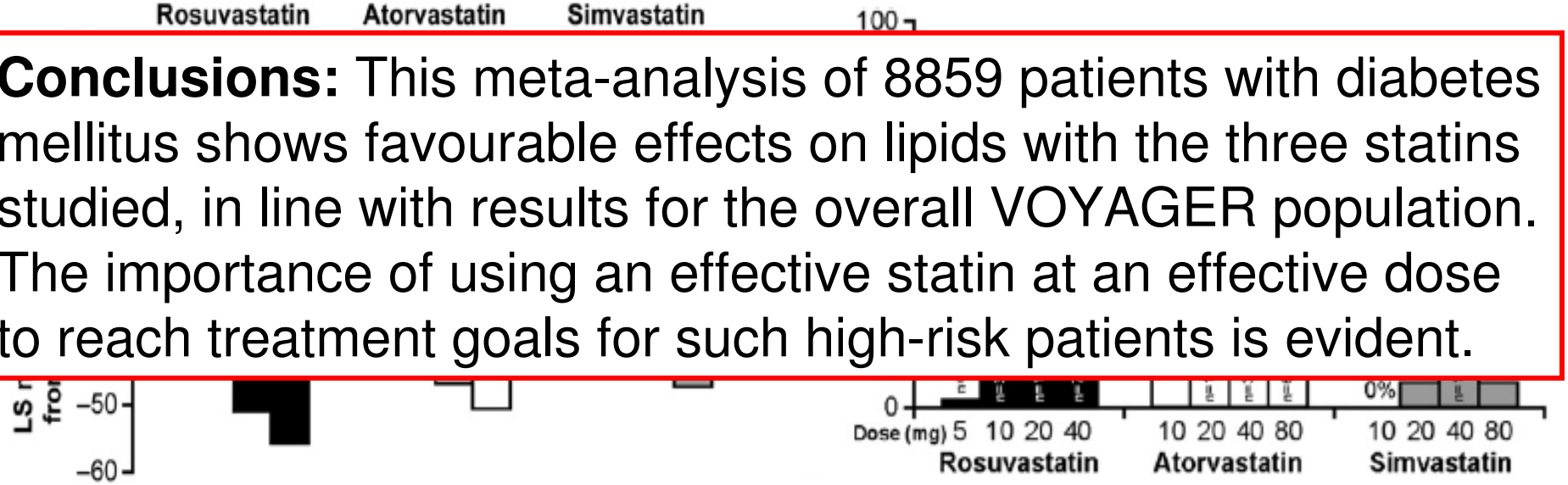
META-ANALYSIS

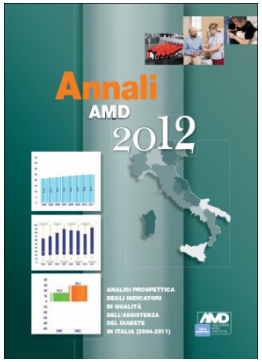
Nutrition, Metabolism & Cardiovascular Diseases (2012) 22, 697–703

Comparison of the effects of different statins and doses on lipid levels in patients with diabetes: Results from VOYAGER

B.W. Karlson [a,b,*], P.J. Barter [c], M.K. Palmer [d], P. Lundman [e], S.J. Nicholls [f]

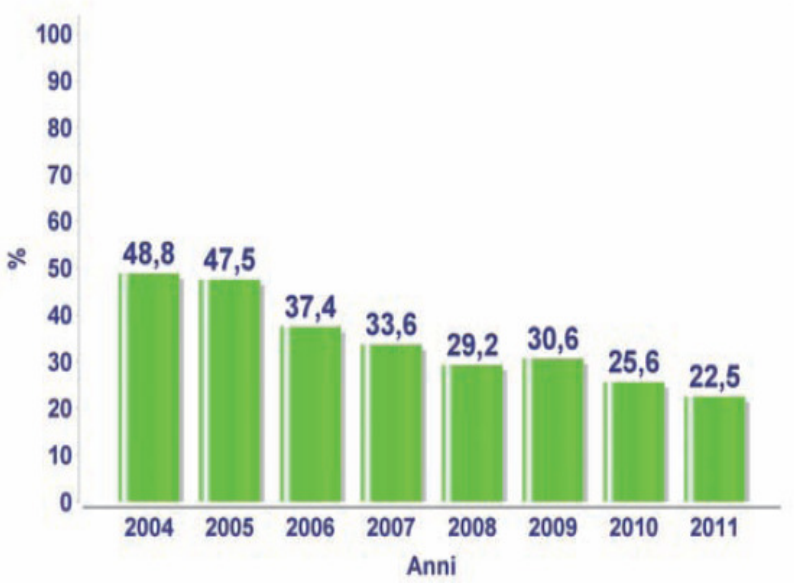
Conclusions: This meta-analysis of 8859 patients with diabetes mellitus shows favourable effects on lipids with the three statins studied, in line with results for the overall VOYAGER population. The importance of using an effective statin at an effective dose to reach treatment goals for such high-risk patients is evident.





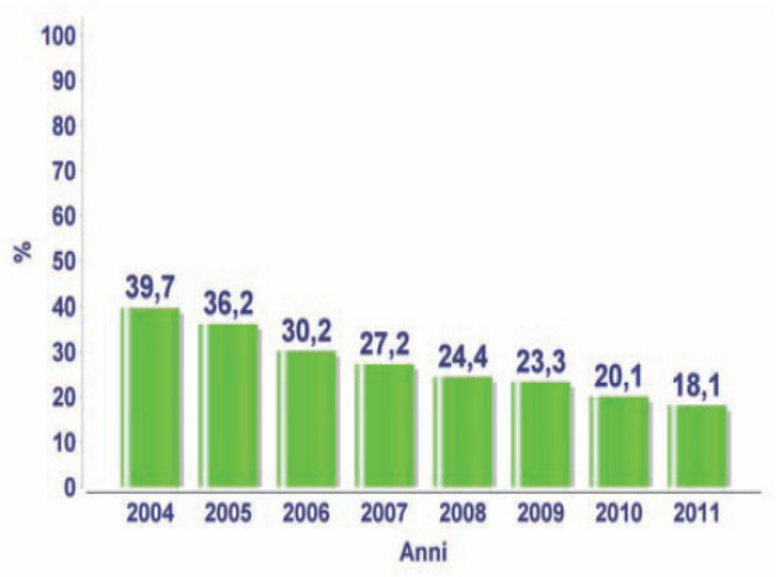
Soggetti con valori di C-LDL ≥130 mg/dl nonostante il trattamento con statine

DM1



Soggetti con valori di C-LDL ≥130 mg/dl nonostante il trattamento con statine

DM2



NOTA 13 – APRILE 2013

PARTICOLARI CATEGORIE DI PAZIENTI	
Pazienti in trattamento con statine con HDL basse (<40 mg/dl nei M e 50 mg/dl nelle F) e/o trigliceridi elevati (> 200 mg/dl)	Fibrati*

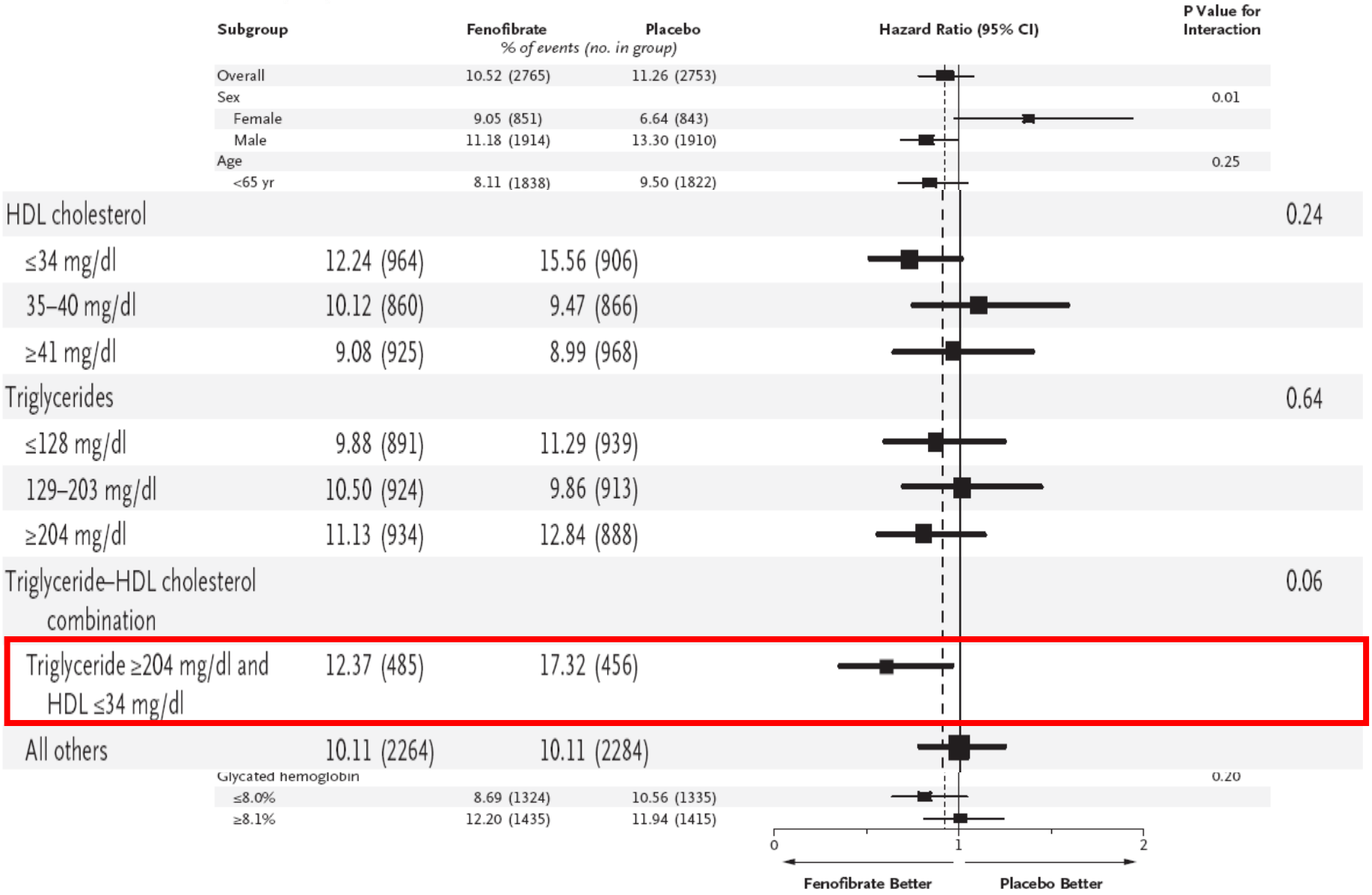
*Il farmaco di prima scelta è il fenofibrato per la maggiore sicurezza di uso nei pazienti in terapia con statine; la combinazione di statine e gemfibrozil è invece associata ad un aumentato rischio di miopatia.

ORIGINAL ARTICLE

N Engl J Med 2010; 362:1563-74

Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus

The ACCORD Study Group*

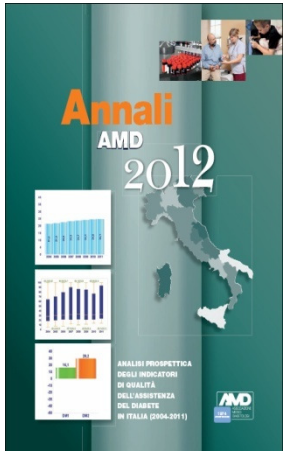


Trial (Drug)	Primary Endpoint: Entire Cohort (P-value)	Lipid Subgroup Criterion	Primary Endpoint: Subgroup (P-value)
HHS (Gemfibrozil)	-34% (0.02)	TG > 200 mg/dl LDL-C/HDL-C > 5.0	-71% (0.005)
BIP (Bezafibrate)	-7.3% (0.24)	TG ≥ 200 mg/dl	-39.5% (0.02)
FIELD (Fenofibrate)	-11% (0.16)	TG ≥ 204 mg/dl HDL-C < 42 mg/dl	-27% (0.005)
ACCORD (Fenofibrate)	-8% (0.32)	TG ≥ 204 mg/dl HDL-C ≤ 34 mg/dl	-31%

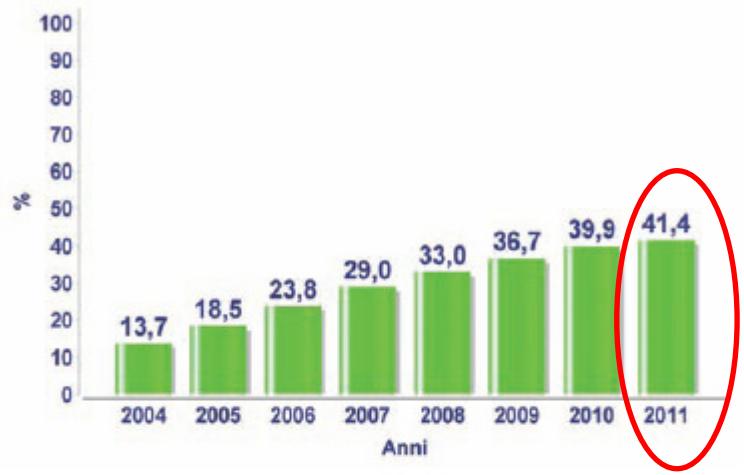
NOTA 13 – APRILE 2013

- Per i pazienti con **dislipidemia aterogena** (TG>200 mg/dl, HDL<34 mg/dl) e per quelli con ipertrigliceridemia i farmaci di seconda linea da somministrare in associazione sono i fibrati.

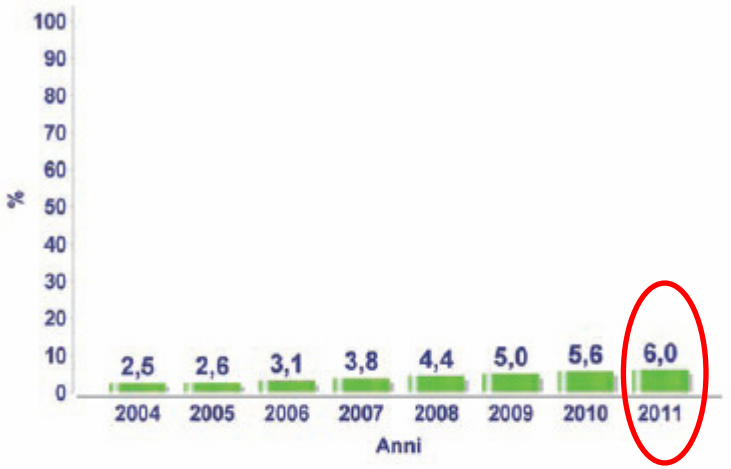
- Tra questi ultimi farmaci l'unico con evidenza di sicurezza di uso nei pazienti in terapia con statine è il **Fenofibrato**.



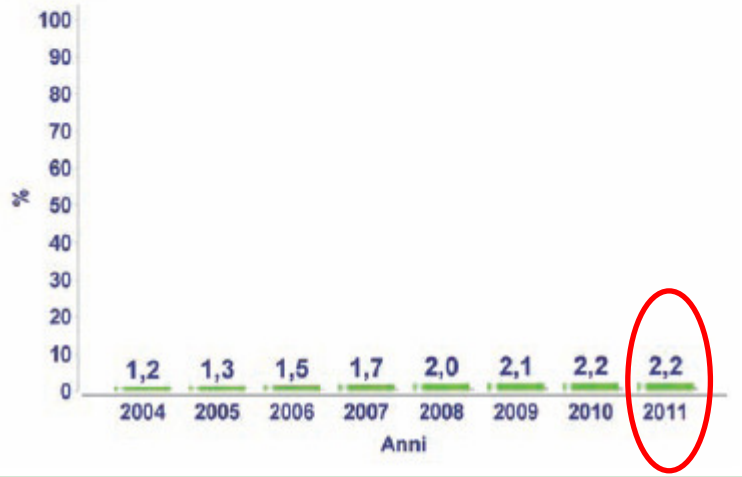
Soggetti trattati con statine



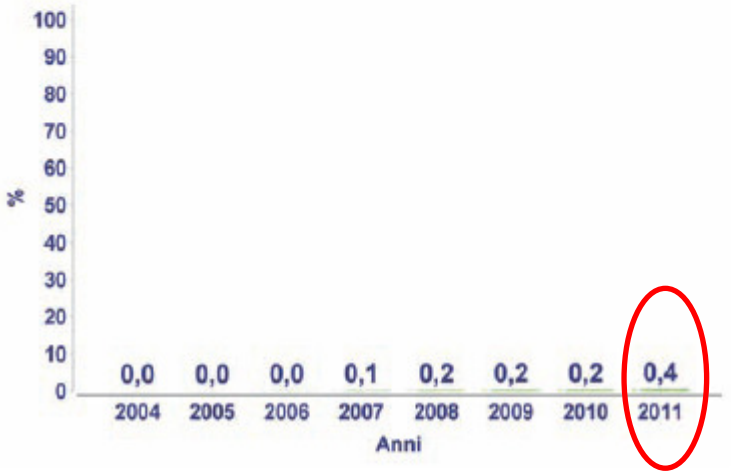
Soggetti trattati con omega-3



Soggetti trattati con fibrati



Soggetti trattati con ezetimibe

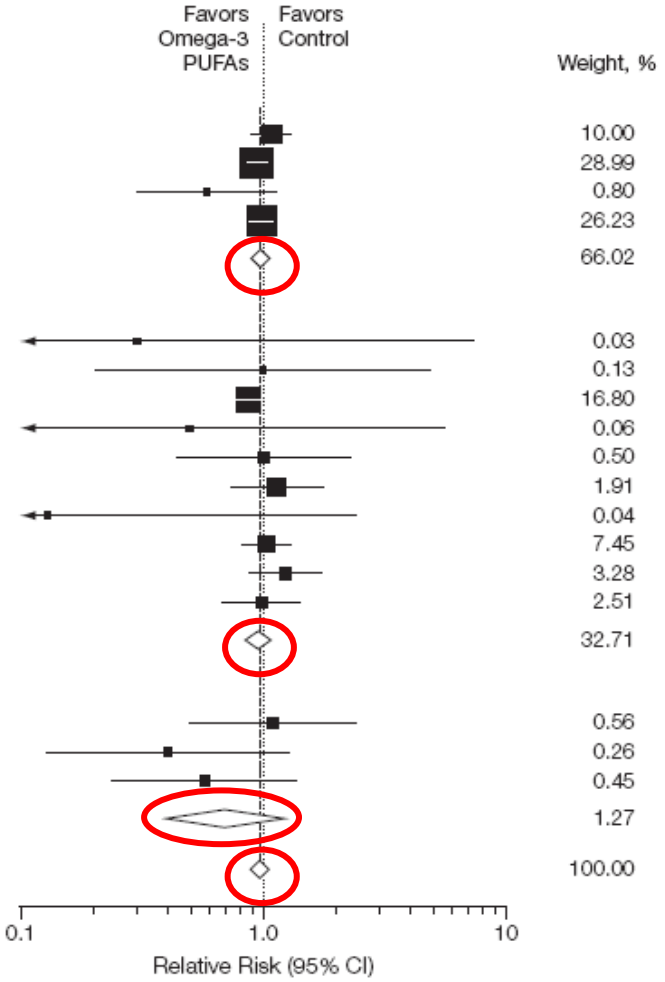


Association Between Omega-3 Fatty Acid Supplementation and Risk of Major Cardiovascular Disease Events

A Systematic Review and Meta-analysis

Figure 4. Meta-analysis of Omega-3 Supplements for All-Cause Mortality

	No. of Events		No. of Participants			
	Omega-3 PUFAs	Control	Omega-3 PUFAs	Control	RR (95% CI)	Weight, %
Mixed prevention						
Yokoyama et al,[3] 2007	286	265	9326	9319	1.08 (0.91-1.27)	10.00
Tavazzi et al,[2] 2008	955	1014	3494	3481	0.94 (0.87-1.01)	28.99
Einvik et al,[37] 2010	14	24	282	281	0.58 (0.31-1.10)	0.80
ORIGIN,[5] 2012	951	964	6281	6255	0.98 (0.90-1.07)	26.23
Subtotal: I^2=38.9%, P=.18	2206	2267	19383	19336	0.97 (0.90-1.05)	66.02
Secondary prevention						
Sacks et al,[27] 1995	0	1	31	28	0.30 (0.01-7.13)	0.03
Leng et al,[26] 1998	3	3	60	60	1.00 (0.21-4.76)	0.13
Marchioli et al,[1] 1999	472	545	5666	5658	0.86 (0.77-0.97)	16.80
von Schacky et al,[25] 1999	1	2	112	111	0.50 (0.05-5.39)	0.06
Nilsen et al,[24] 2001	11	11	150	150	1.00 (0.45-2.24)	0.50
Svensson et al,[32] 2006	34	30	103	103	1.13 (0.75-1.70)	1.91
Garbagnati et al,[38] 2009	0	3	20	18	0.13 (0.01-2.34)	0.04
Kromhout et al,[4] 2010	186	184	2404	2433	1.02 (0.84-1.24)	7.45
Rauch et al,[36] 2010	88	70	1919	1885	1.23 (0.91-1.68)	3.28
Galan et al,[29] 2010	58	59	1253	1248	0.98 (0.69-1.39)	2.51
Subtotal: I^2=1.5%, P=.43	853	908	11718	11694	0.95 (0.86-1.04)	32.71
ICD						
Leaf et al,[34] 2005	13	12	200	202	1.09 (0.51-2.34)	0.56
Raitt et al,[33] 2005	4	10	100	100	0.40 (0.13-1.23)	0.26
Brouwer et al,[35] 2006	8	14	273	273	0.57 (0.24-1.34)	0.45
Subtotal: I^2=19.9%, P=.29	25	36	573	575	0.69 (0.39-1.23)	1.27
Overall: I^2=11.7%, P=.32	3084	3211	31674	31605	0.96 (0.91-1.02)	100.00



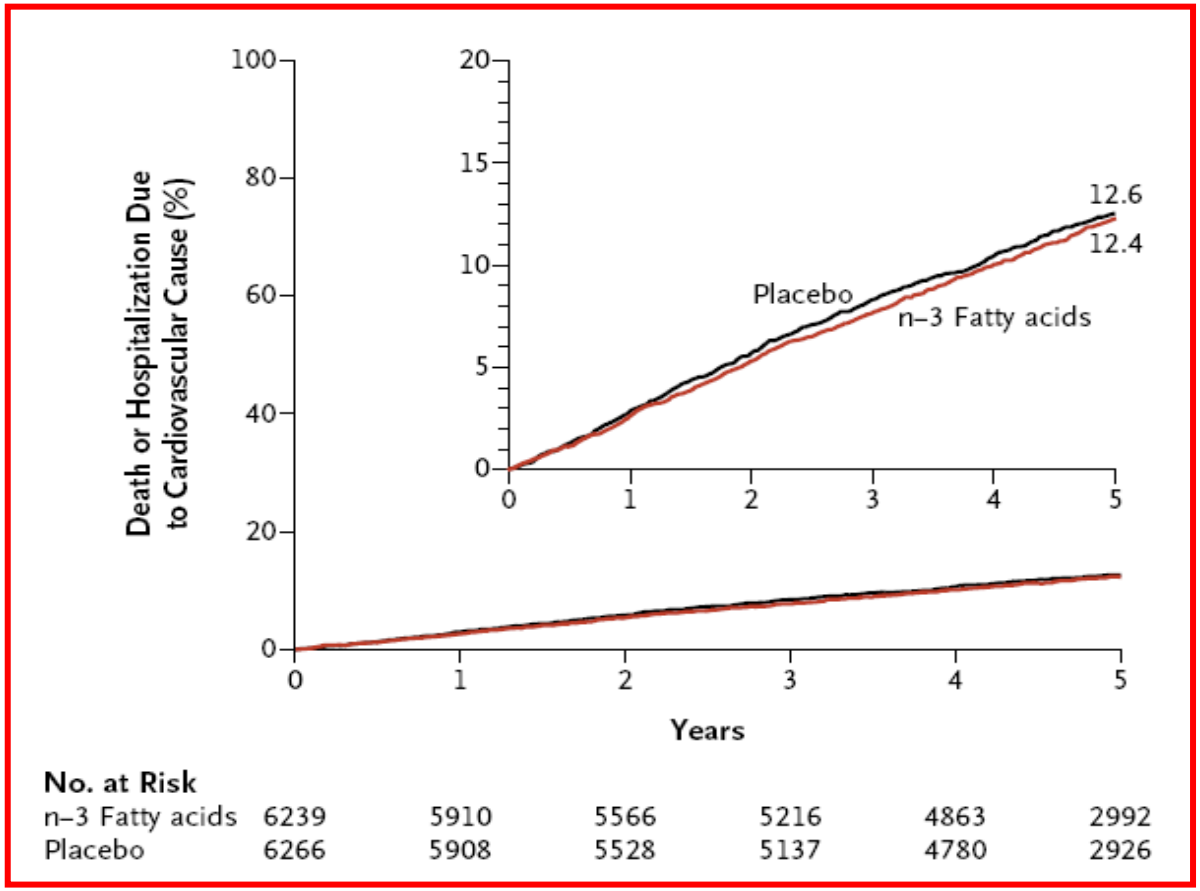
Rizos EC et al. *JAMA. 2012;308(10):1024-1033*

ORIGINAL ARTICLE

n–3 Fatty Acids in Patients with Multiple Cardiovascular Risk Factors

The Risk and Prevention Study Collaborative Group*

Kaplan–Meier Curves for Death or First Hospitalization Due to Cardiovascular Cause

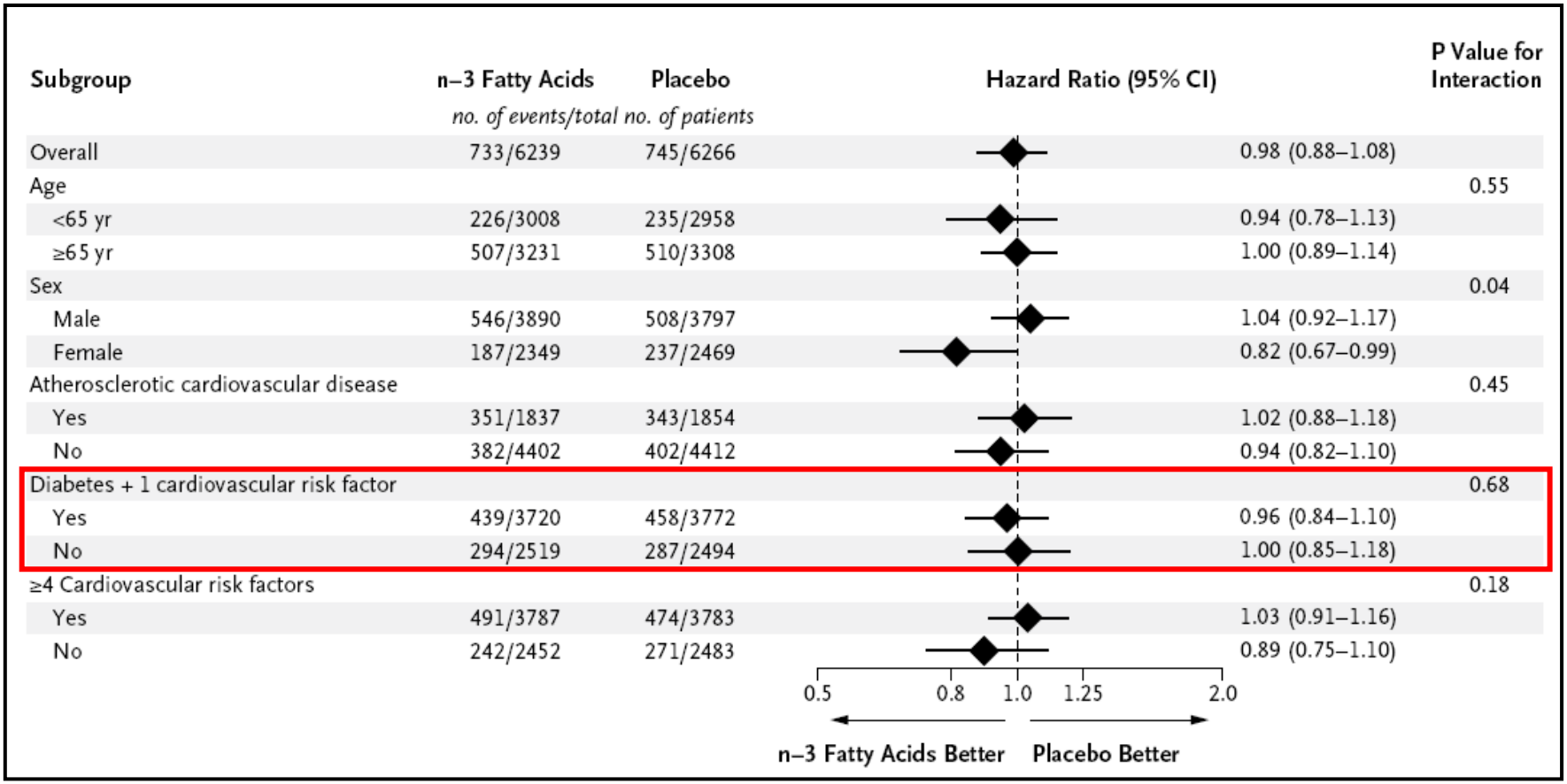


N Engl J Med 2013;368:1800-8

ORIGINAL ARTICLE

n–3 Fatty Acids in Patients with Multiple Cardiovascular Risk Factors

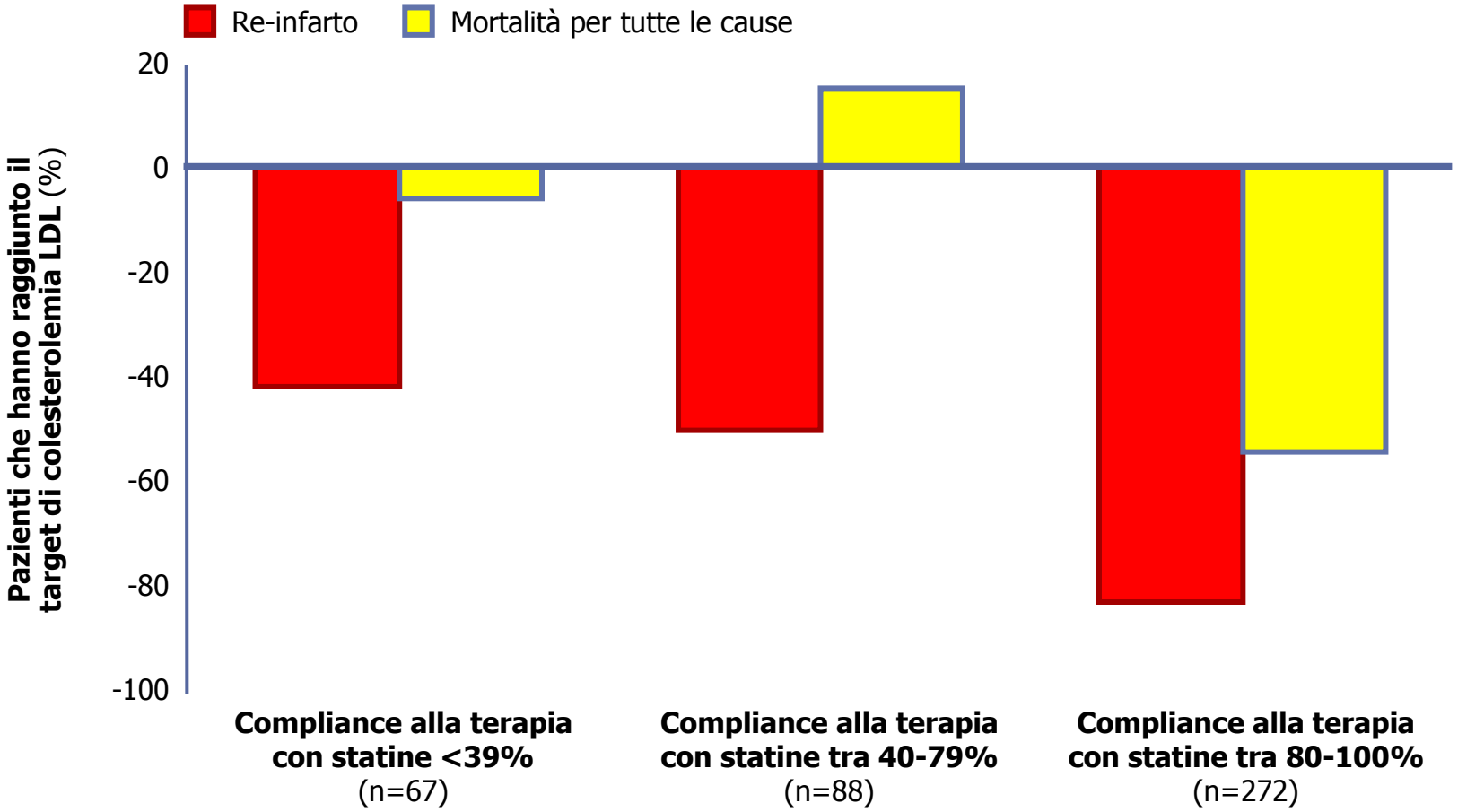
The Risk and Prevention Study Collaborative Group*

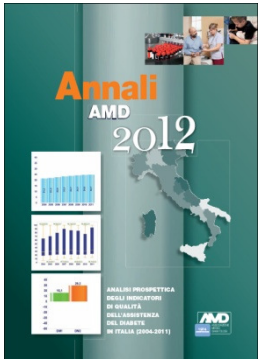


N Engl J Med 2013;368:1800-8

Compliance alla terapia con statine ed eventi cardiovascolari

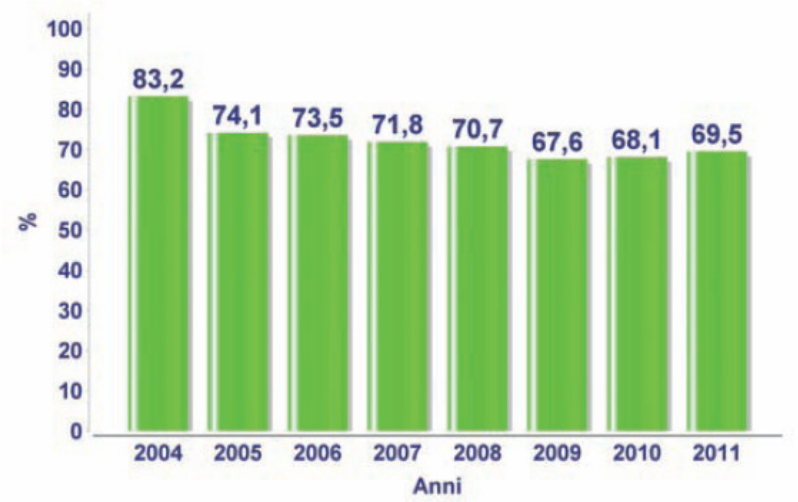
Wei L et al. Heart 2002; 88:229-233

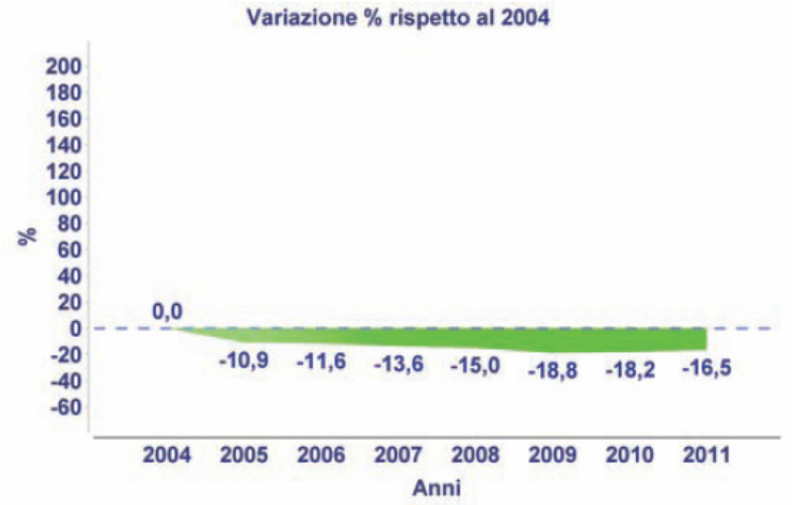




Soggetti non trattati con statine nonostante valori di C-LDL ≥130 mg/dl

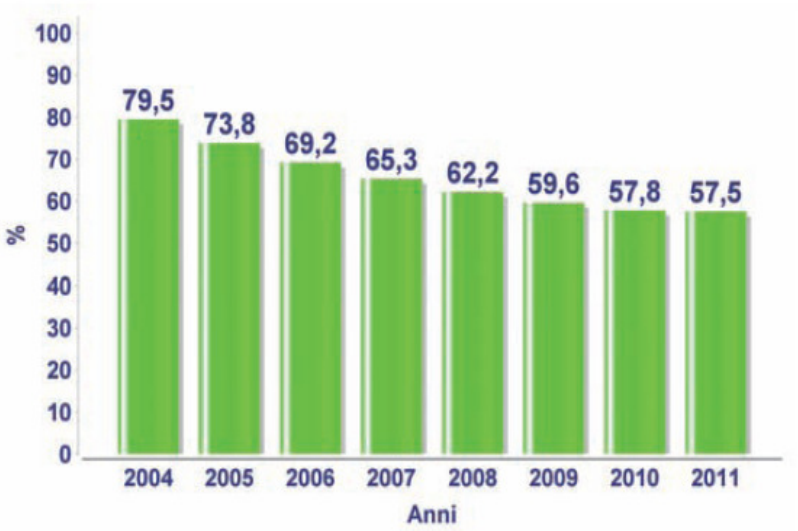
DM1

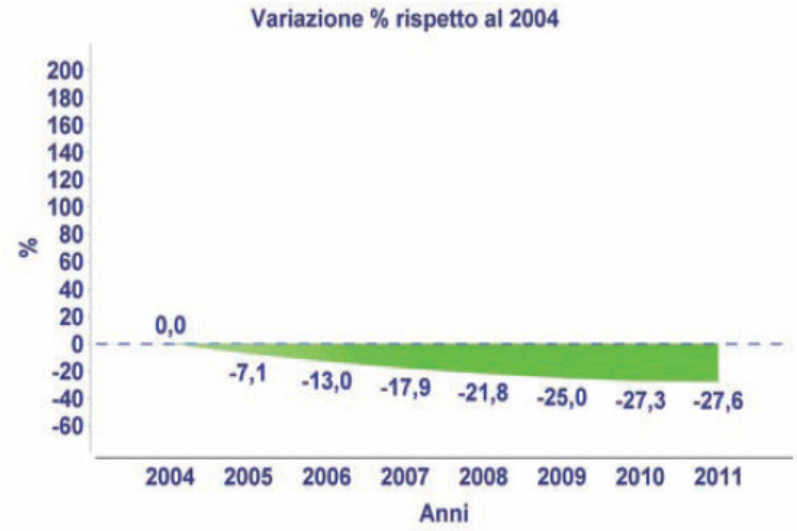




Soggetti non trattati con statine nonostante valori di C-LDL ≥130 mg/dl

DM2





NOTA 13 – APRILE 2013

• E’ inoltre **raccomandabile**, nell’ambito di ciascuna classe di farmaci, la scelta dell’**opzione terapeutica meno costosa**.

• E’ sempre necessario assicurare **l’ottimizzazione del dosaggio** della statina prima di prendere in considerazione la sua sostituzione o la sua associazione.

• L’ impiego di **farmaci di seconda** ed eventualmente terza scelta può essere ammesso solo quando il trattamento di prima linea a dosaggio adeguato si sia dimostrato insufficiente al raggiungimento della riduzione attesa del LDL-C e/o della riduzione di almeno il 50% del colesterolo LDL o abbia indotto effetti collaterali.

Am J Cardiol. 2010 Jan 1;105(1):69-76.

Meta-analysis of comparative efficacy of increasing dose of Atorvastatin versus Rosuvastatin versus Simvastatin on lowering levels of atherogenic lipids (from VOYAGER).

Nicholls SJ, Brandrup-Wognsen G, Palmer M, Barter PJ

Abstract

Statins are the most commonly prescribed agents for lowering levels of low-density lipoprotein (LDL) cholesterol. Althoug
observed with all statins,
individual patient data pool
the efficacy of rosuvastatin
dose on lowering LDL chol
and apolipoprotein B was ir
4% to 7% greater degree
observed between changes
apolipoprotein B (r = 0.76,
analysis, baseline lipid leve
predictors of achieving tre
independent predictor of a
cholesterol goals was also r
and patients without atherosclerotic disease (p = 0.0002). In contrast, normal triglyceride levels were more often observed in men (p <0.0001) and patients without diabetes mellitus (p = 0.03).

Conclusion: doubling statin dose was associated with greater lowering of LDL cholesterol by 4% to 6% and non-HDL cholesterol by 3% to 6%. Greater lipid goal achievement with increasing dose supports the use of high-dose statin therapy for more effective cardiovascular prevention.

- **Doubling statin dose was associated with greater lowering of LDL cholesterol by 4% to 6% and non-HDL cholesterol by 3% to 6%.**
- **Greater lipid goal achievement with increasing dose supports the use of high-dose statin therapy for more effective cardiovascular prevention.**

Se il target non viene raggiunto?

1. Aumentare il dosaggio → **<u>regola del "6%"</u>**
   (ha senso solo se siamo vicini al target)
2. Sostituire con statina più potente
3. Passare a doppia inibizione
   (simva. + ezetimibe)
4. Cambiare strategia
   (fibrato; niacina; inib. CETP)

NOTA 13 – APRILE 2013

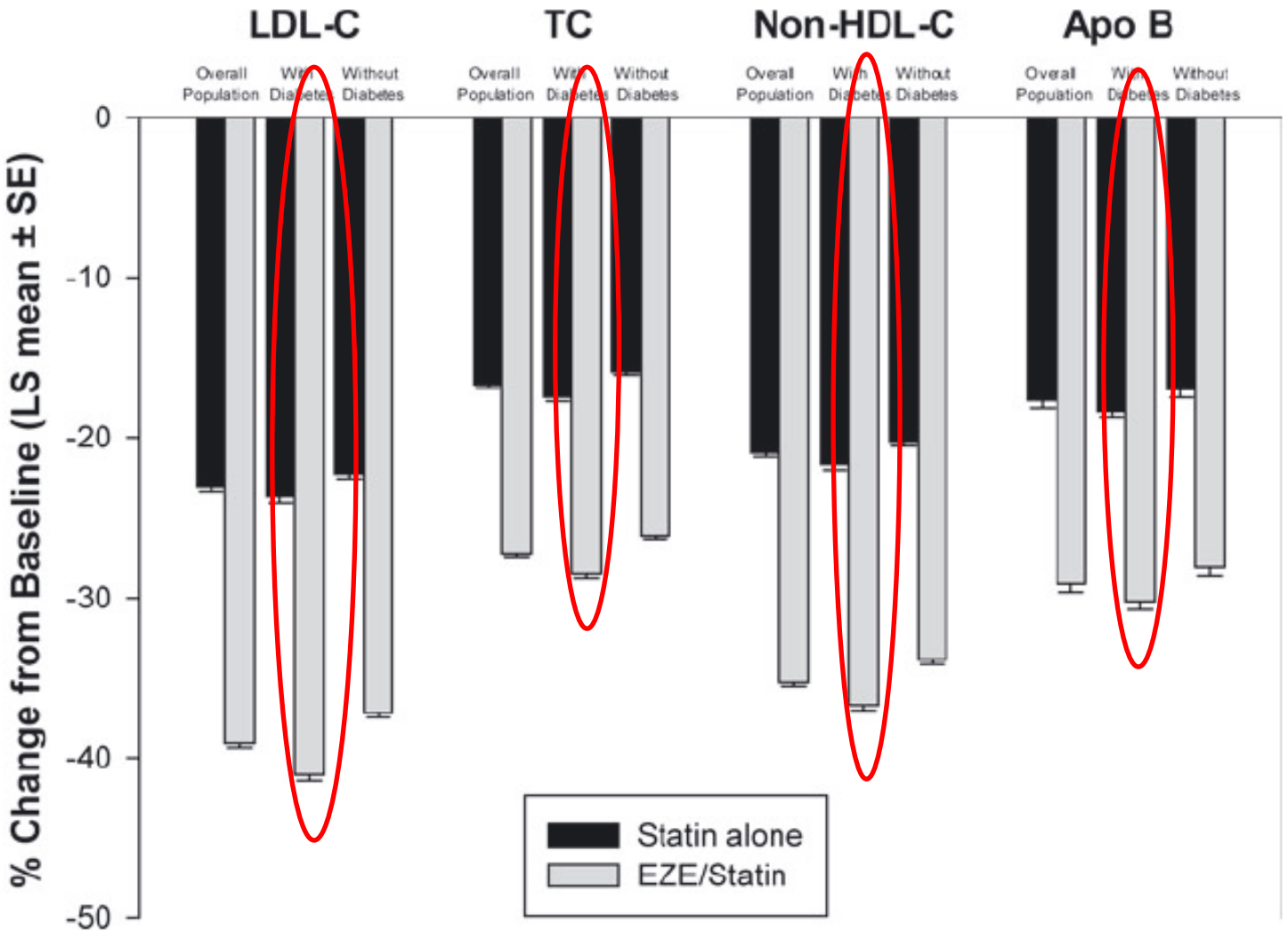
• La nota 13 ha riconsiderato, su aggiornate basi farmaco-terapeutiche, il ruolo dell'associazione tra ezetimibe e statine.

• L'ezetimibe inibisce l'assorbimento del colesterolo e in monoterapia, riduce i livelli di LDL-C dal 15% al 22% dei valori di base.

• L'ezetimibe in associazione ad una statina può determinare una ulteriore riduzione di LDL-C (indipendentemente dalla statina utilizzata e dalla sua posologia) del 15%-20%.

• Quindi, l'associazione tra ezetimibe e statine sia in forma precostituita che estemporanea è utile e rimborsata dal SSN solo nei pazienti nei quali le statine a dose considerata ottimale non consentono di raggiungere il target terapeutico.

• Nei pazienti che siano intolleranti alle statine è altresì ammessa, a carico del SSN, la monoterapia con ezetimibe.



Leiter LA et al. *Diabetes, Obesity and Metabolism 13: 615–628, 2011*

Efficacy and Safety of *Ezetimibe* Added on to *Atorvastatin* (40 mg) Compared With Uptitration of *Atorvastatin* (to 80 mg) in Hypercholesterolemic Patients at High Risk of Coronary Heart Disease

Lawrence A. Leiter, MD[a,*], Harold Bays, MD[b], Scott Conard, MD[c], Steven Bird, MS[d], Joseph Rubino, MBA[d], Mary E. Hanson, PhD[d], Joanne E. Tomassini, PhD[d], and Andrew M. Tershakovec, MD[d]

The percentage of change from baseline in low-density lipo
the addition of ezetimibe 10 mg to atorvastatin 40 mg was
atorvastatin 80 mg. In this multicenter, double-blind, para
cholesterolemic patients using atorvastatin 40 mg/day were
statin 40 mg plus ezetimibe 10 mg or uptitration to atorva
treatment, compared with atorvastatin 80 mg, atorvastatin
cantly reduced the primary end point of LDL cholesterol by
mg by −11% (p <0.001), as well as significantly reduced
cholesterol, apolipoprotein B, total cholesterol, and triglyc
atorvastatin 80 mg (all p <0.001). Percentages of change
protein, high-density lipoprotein cholesterol, and apolipopr
groups. Significantly more patients treated with atorvastatin
LDL cholesterol <70 mg/dl versus patients treated with at
p <0.001). Safety and tolerability profiles and incidence of liver and muscle adverse experiences were generally similar between groups. In conclusion, these results showed that adding ezetimibe to atorvastatin 40 mg was significantly more effective than uptitrating to atorvastatin 80 mg at lowering LDL cholesterol and other lipid parameters. Both treatments were generally well tolerated (clinical trial no. NCT00276484). (Am J Cardiol 2008;102:1495–1501)

Adding ezetimibe to atorvastatin 40 mg was significantly more effective than uptitrating to atorvastatin 80 mg at lowering LDL cholesterol and other lipid parameters

Published in final edited form as:
Curr Opin Cardiol. 2011 July ; 26(4): 342–347. doi:10.1097/HCO.0b013e3283470359.

Are statins diabetogenic?

Key points

- Sustained statin use appears to moderately increase the risk of developing diabetes.
- Patients older than 65 may be particularly susceptible to this unwanted effect of therapy.
- The mechanism may be related more to induction of β-cell dysfunction and apoptosis than to reduction of insulin sensitivity.
- The favorable ratio between cardiovascular benefits of therapy and risk of diabetes (9:1) supports the current approach of widespread statin use in high-risk populations.
- For low-risk patients, particularly if older than 65, risk of diabetes should be added to the list of considerations in deciding to start a statin.

BMJ. 2013 May 23;346:f2610. doi: 10.1136/bmj.f2610.

Risk of incident diabetes among patients treated with statins: population based study.

Carter AA, Gomes T, Camacho X, Juurlink DN, Shah BR, Mamdani MM

Abstract

OBJECTIVE: To examine the risk of new onset diabetes among patients treated with different HMG-CoA reductase inhibitors (statins).

DESIGN: Population based cohort study with time to event analyses to estimate the relation between use of particular statins and incident diabetes. Hazard ratios were calculated to determine the effect of dose and type of statin on the risk of incident diabetes.

PARTICIPANTS: All patients aged 66 or older without diabetes who started treatment with statins from 1 August 1997 to 31 March 2010. The analysis was restricted to new users who had not been prescribed a statin in at least the preceding year. Patients with established diabetes before the start of treatment were excluded.

RESULTS: Compared with pravastatin (the reference drug in all analyses), there was an increased risk of incident diabetes with atorvastatin (adjusted hazard ratio 1.22, 95% confidence interval 1.15 to 1.29), rosuvastatin (1.18, 1.10 to 1.26), and simvastatin (1.10, 1.04 to 1.17). There was no significantly increased risk among people who received fluvastatin (0.95, 0.81 to 1.11) or lovastatin (0.99, 0.86 to 1.14). The absolute risk for incident diabetes was about 31 and 34 events per 1000 person years for atorvastatin and rosuvastatin, respectively. There was a slightly lower absolute risk with simvastatin (26 outcomes per 1000 person years) compared with pravastatin (23 outcomes per 1000 person years). Our findings were consistent regardless of whether statins were used for primary or secondary prevention of cardiovascular disease. Although similar results were observed when statins were grouped by potency, the risk of incident diabetes associated with use of rosuvastatin became non-significant (adjusted hazard ratio 1.01, 0.94 to 1.09) when dose was taken into account.

CONCLUSIONS: Compared with pravastatin, **treatment with higher potency statins, especially atorvastatin and simvastatin, might be associated with an increased risk of new onset diabetes.**

Diabetes mellitus and cardiovascular events in older patients with myocardial infarction prescribed intensive-dose and moderate-dose statins.

• At 5 years, 13.6% of patients receiving intensive-dose statins and 13.0% of patients receiving moderate-dose statins had new-onset diabetes, which was not significantly different (P=0.19)

Conclusions: In older patients with myocardial infarction, we found **intensive-dose statin therapy to be effective in reducing repeat hospitalization for acute coronary syndrome**. The rate of new-onset diabetes mellitus at long term was not significantly different between intensive-dose and moderate-dose statins.

with intensive-dose statins.

• No significant difference in mortality rates (34.8% in both groups) was observed between the treatment groups during the study period (P=0.89).

Ko DT et al. Circ Cardiovasc Qual Outcomes.2013;6:315-22.

Conclusioni

• Le alterazioni del profilo lipidico risultano i maggiore predittori di eventi CV soprattutto nel paziente con diabete, il quale presenta un **rischio CV alto** o **molto alto.**

• L'**atorvastatina** risulta come **preferenziale** se la riduzione del colesterolo LDL da ottenere è intorno a 35-50%,

• In alternativa per percentuali di riduzioni superiori può essere considerata la **rosuvastatina** (ancora non genericata), la quale può essere prescritta anche nei pazienti in cui ci sia stata **evidenza di effetti collaterali severi nei primi 6 mesi con altre statine**

• L'**ezetimibe** va considerata sia in associazione precostituita, o estemporanea nei pazienti che non raggiungono il target terapuetico, o in monoterapie in pazienti intolleranti alle statine.

• I pazienti con **IRC moderata e grave** devono essere tutti considerati a **rischio alto e molto alto** ed il farmaco di **prima scelta diventa ezetimibe + simvastatina** (studio SHARP)