Società Medico Chirurgica di Ferrara dal 1846

SEDUTA MULTIDISCIPLINARE

Sabato 9 febbraio 2013

Aula Magna Nuovo Arcispedale S.Anna
Cona, Ferrara

Fibrato o statina nella dislipidemia diabetica

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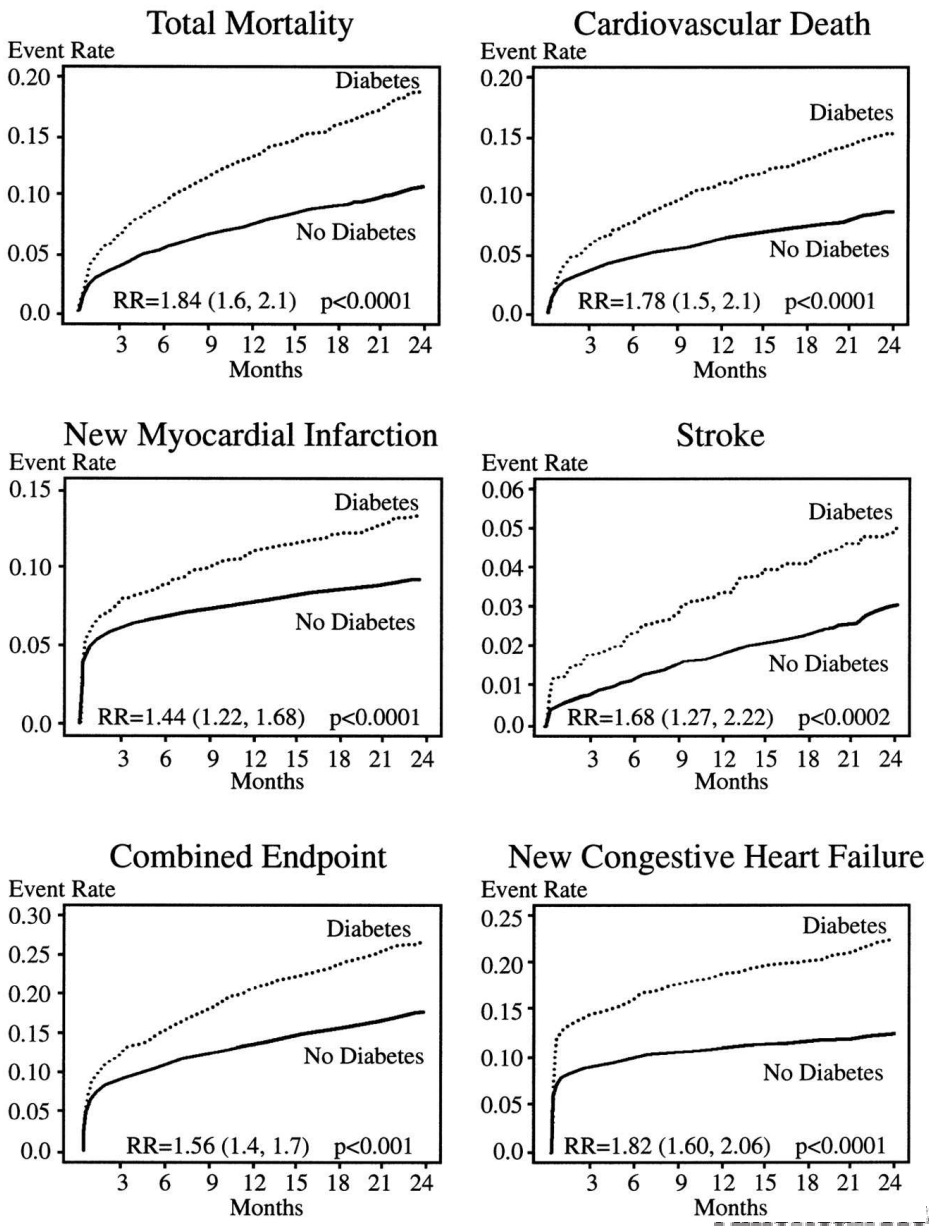
Università di Ferrara
Dipartimento Scienze Mediche
Sezione di Medicina Interna, Gerontologia e Nutrizione Clinica

Cumulative event curves for different outcomes in patients with and without diabetes.

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

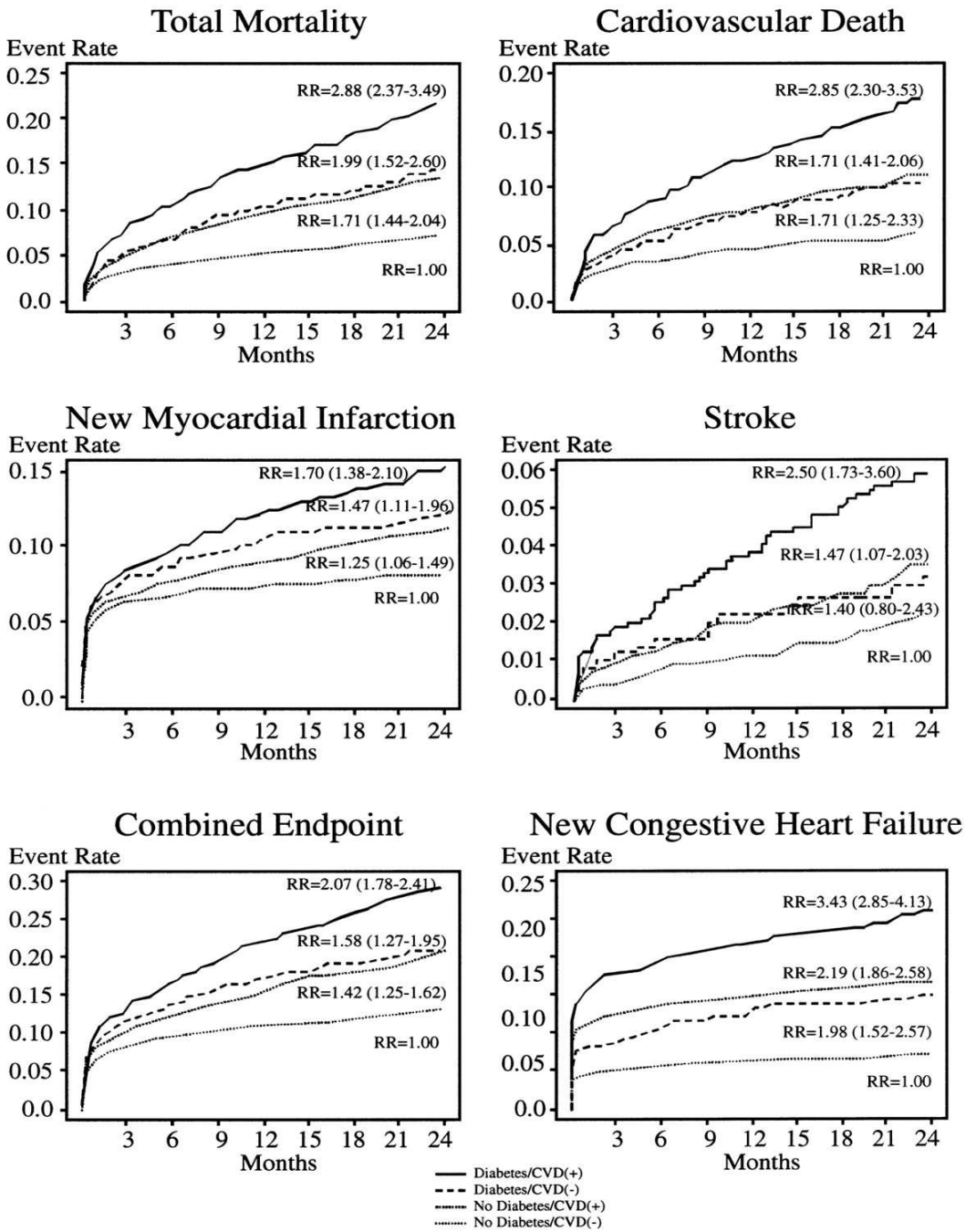
Impact of Diabetes on Long-Term Prognosis in Patients With Unstable Angina and Non–Q-Wave Myocardial Infarction : Results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) Registry

Klas Malmberg, Salim Yusuf, Hertzel C. Gerstein, Joanne Brown, Feng Zhao, David Hunt, Leopoldo Piegas, James Calvin, Matyas Keltai, Andrzej Budaj and for the OASIS Registry Investigators



Malmberg K et al. Circulation 2000;102:1014-1019

Cumulative event curves for patients with and without diabetes in relation to previously known CVD. Age- and sex-adjusted RRs (by Cox model) between nondiabetic patients without prior cardiovascular disease [(No Diabetes/CVD(−)] and other strata are given.



Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Impact of Diabetes on Long-Term Prognosis in Patients With Unstable Angina and Non–Q-Wave Myocardial Infarction : Results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) Registry

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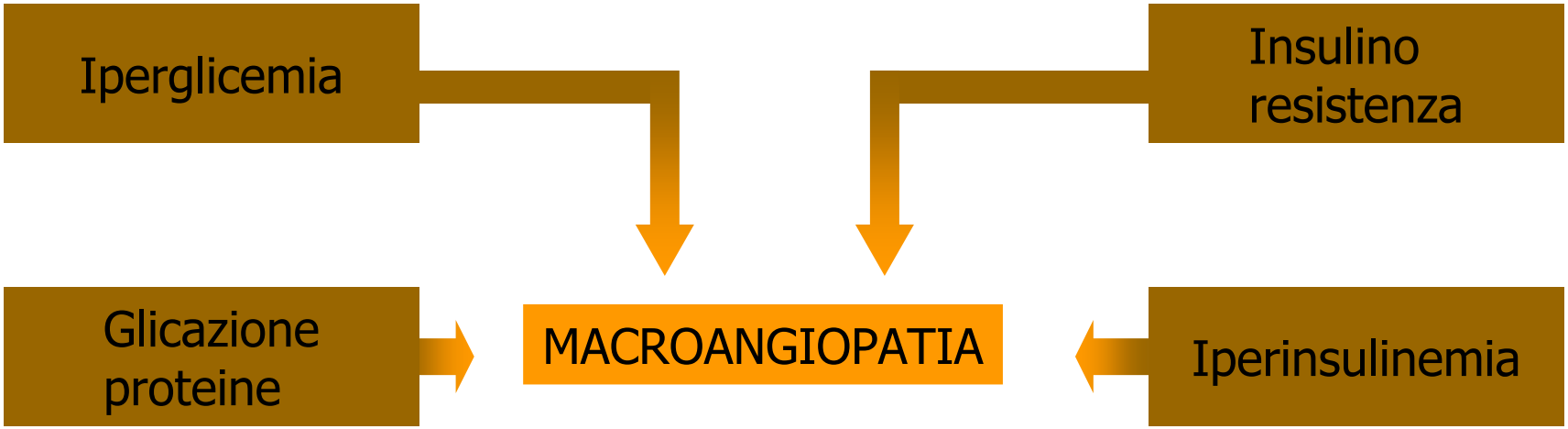
American Heart Association
Learn and Live

Malmberg K et al. Circulation 2000;102:1014-1019

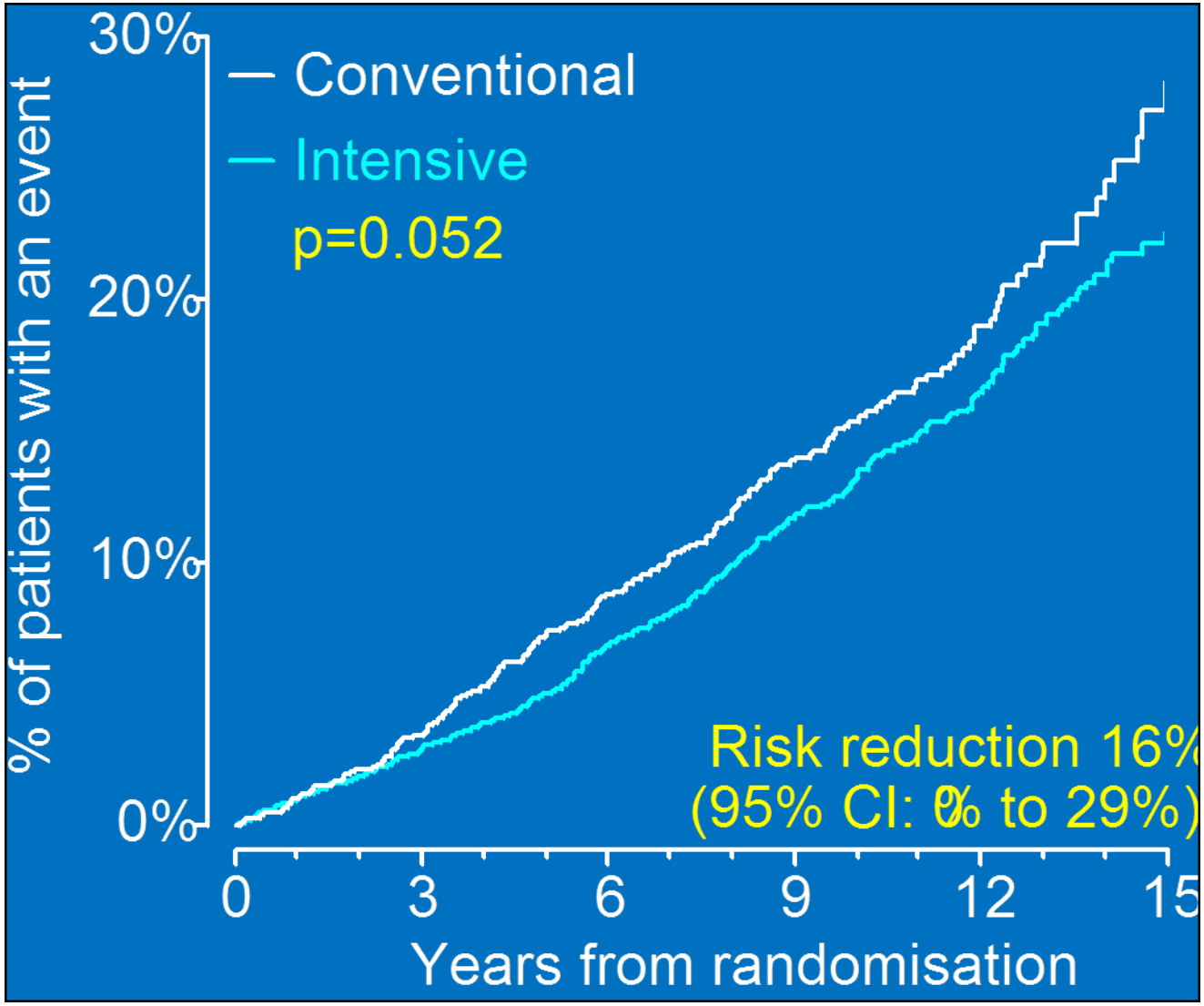
Patogenesi della Macroangiopatia Diabetica



Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33)

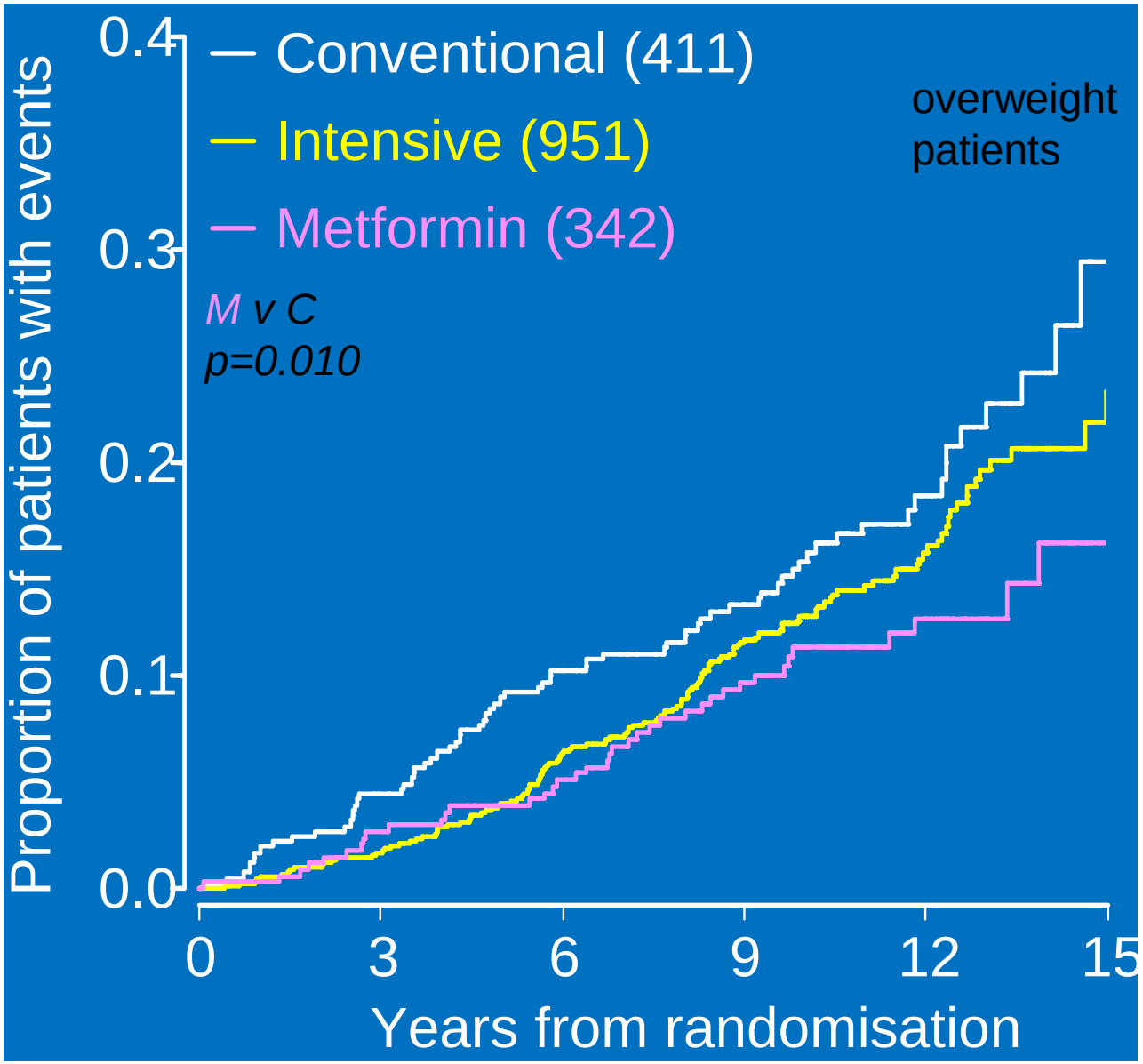
Myocardial Infarction (cumulative)

fatal or non fatal myocardial infarction, sudden death
573 of 3867 patients (15%)



Myocardial Infarction

Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34)



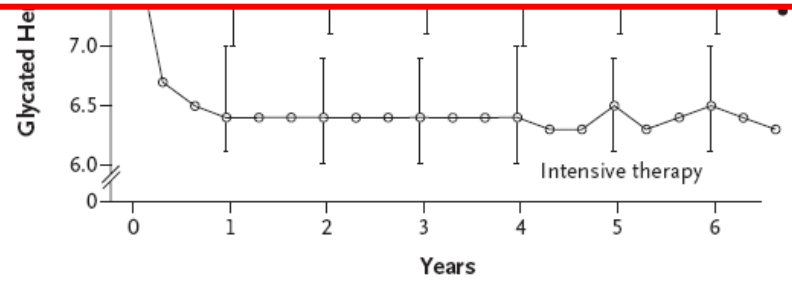
Kaplan–Meier Curves for the Primary Outcome and Death from Any Cause

The NEW ENGLAND JOURNAL of MEDICINE

Ef

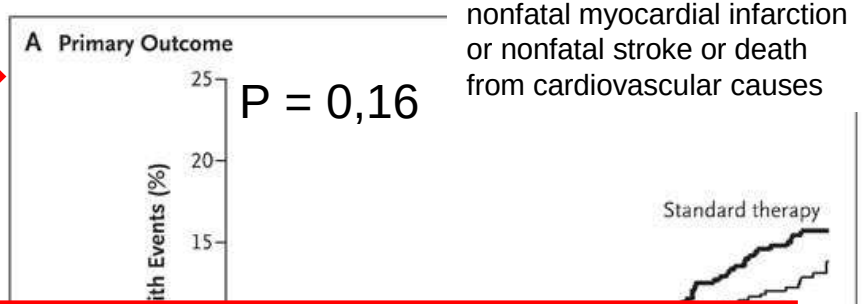
Conclusions

As compared with standard therapy, the use of intensive therapy to target normal glycated hemoglobin levels for 3.5 years increased mortality and did not significantly reduce major cardiovascular events. These findings identify a previously unrecognized harm of intensive glucose lowering in high-risk patients with type 2 diabetes.

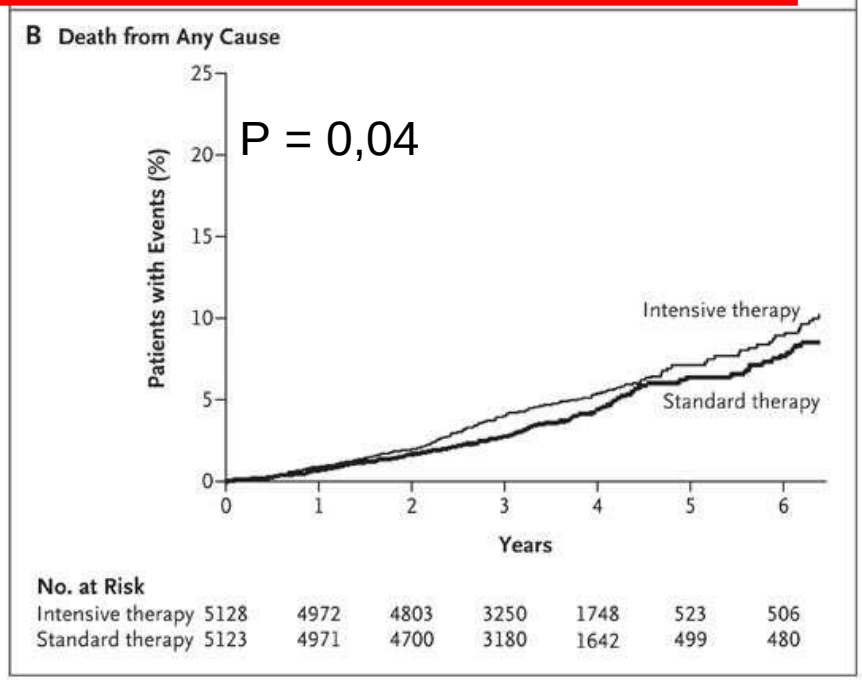


No. at Risk							
Standard therapy	5109	4774	4588	3186	1744	455	436
Intensive therapy	5119	4768	4585	3165	1706	476	471

Action to Control Cardiovascular Risk in Diabetes
ACCORD



nonfatal myocardial infarction or nonfatal stroke or death from cardiovascular causes



No. at Risk							
Intensive therapy	5128	4972	4803	3250	1748	523	506
Standard therapy	5123	4971	4700	3180	1642	499	480

The ADVANCE Trial: Major Macrovascular Events

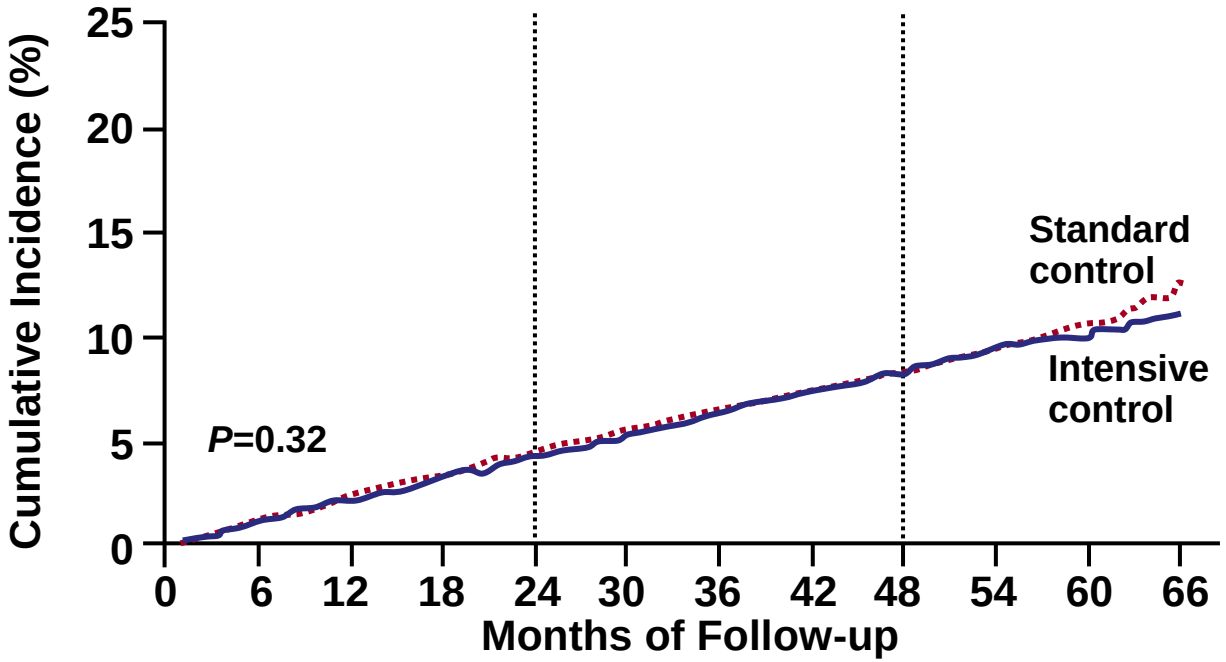
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes

The ADVANCE Collaborative Group*

Hazard ratio for intensive control vs standard control was 0.94 (95% CI: 0.84 to 1.06)



No. at Risk

Intensive	5570	5494	5428	5338	5256	5176	5097	5005	4927	4396	2071	486
Standard	5569	5486	5413	5330	5237	5163	5084	4995	4922	4385	2108	509

The ADVANCE Collaborative Group. *N Engl J Med.* 2008;358(24):2560-2572.

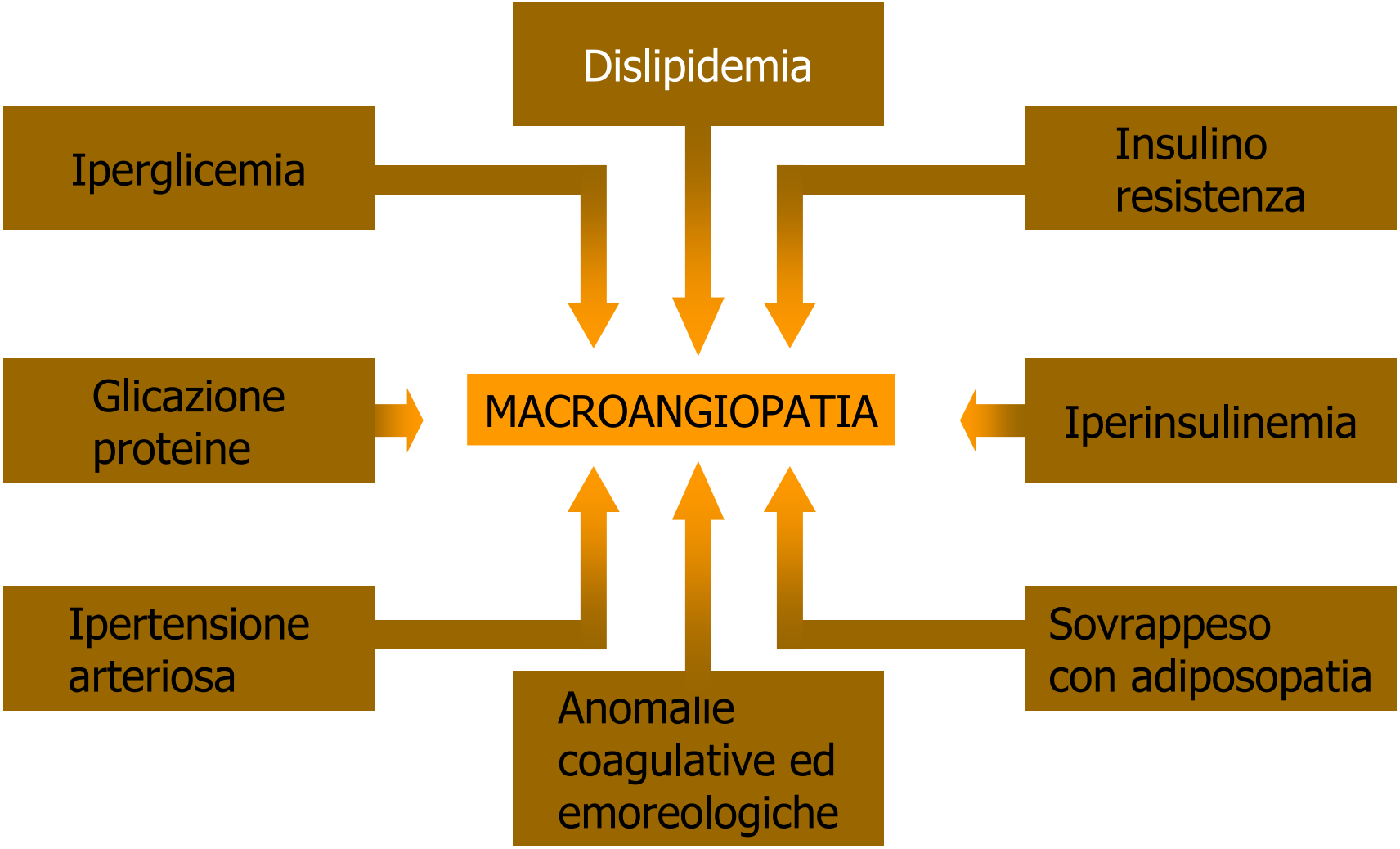
Despite clear epidemiology, controversy continues regarding the role of glucose lowering to prevent coronary events

- In type 1 and type 2 diabetes, randomized controlled trials of intensive versus standard glycemic control have not shown a significant reduction in CVD outcomes during the randomized portion of the trials. Long-term follow-up of the DCCT and UK Prospective Diabetes Study (UKPDS) cohorts suggests that treatment to A1C targets below or around 7% in the years soon after the diagnosis of diabetes is associated with long-term reduction in risk of macrovascular disease. Until more evidence becomes available, the general goal of <7% appears reasonable for many adults for macrovascular risk reduction. (B)

ADA position on glycemia and macrovascular disease in 2010 Standards of Care guideline

ADA Standards of Care. Diabetes Care 2010;33:S11-62

Patogenesi della Macroangiopatia Diabetica



VI. Prevention and management of complications

A. Cardiovascular disease

1. HTN control
2. Dyslipidemia management
3. Anti-platelet
4. Smoking cessation

Assetto lipidico alla diagnosi di DMT2

UKPDS

	Uomini		Donne	
	DMT2	Controlli	DMT2	Controlli
N° soggetti	2139	52	1574	143
TC (mg/dl)	213	205	224	217
LDL-C (mg/dl)	139	132	151*	135
HDL-C (mg/dl)	39 **	43	43*	55
TG (mg/dl)	159 *	103	159*	95

* P<0.001, ** P<0.02 DMT2 vs controlli

UKPDS Group. *Diabetes Care* 1997;20:1683-1687.

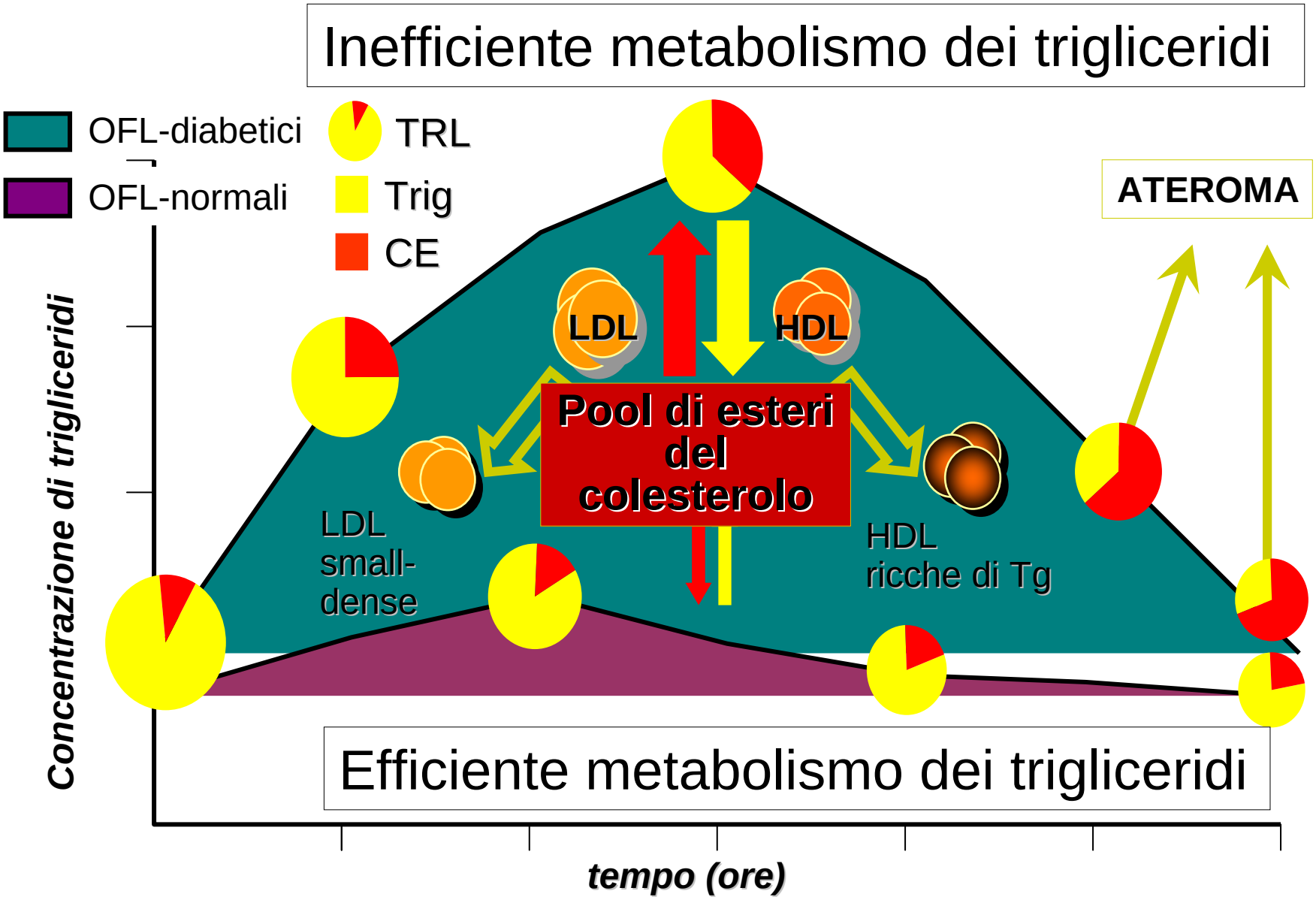
Prevalence of Dyslipidemia is high in Type 2 Diabetes

Control of Lipids	Patients With Diabetes, %	Patients Without Diabetes, %	P Value
LDL-C > 100 mg/dL	74.7	75.7	NS
HDL-C < 40 mg/dL (men) < 50 mg/dL (women)	63.7	40.0	< .001
Triglycerides > 150 mg/dL	61.6	25.5	< .001

N = 498 adults (projected to 13.4 million) aged > or = 18 years with diabetes representative of the US population and surveyed within the cross-sectional National Health and Nutrition Examination Survey 1999-2000.

Jacobs MJ, et al. Diabetes Res Clin Pract. 2005;70:263-269.

Lipemia post-prandiale dopo pasto grasso (OFL)



Stepwise Selection of Risk Factors* in 2693 White Patients with Type 2 Diabetes with Dependent Variable as Time to First Event: UKPDS

Coronary Artery Disease (n=280)

Position in Model	Variable	p Value
First	LDL Cholesterol	<0.0001
Second	HDL Cholesterol	0.0001
Third	Hemoglobin A_{1c}	0.0022
Fourth	Systolic Blood Pressure	0.0065
Fifth	Smoking	0.056

*Adjusted for age and sex.

Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom prospective diabetes study (UKPDS: 23)

R C Turner, H Millns, H A W Neil, I M Stratton, S E Manley, D R Matthews, R R Holman for the United Kingdom Prospective Diabetes Study Group

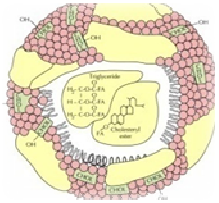
Turner RC et al. BMJ 1998;316:823-828.

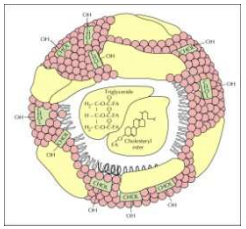
LDL particle count vs. cholesterol content

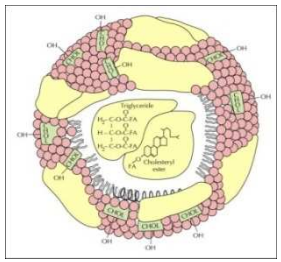
To carry the same amount of cholesterol, a larger number of particles are needed if they are smaller

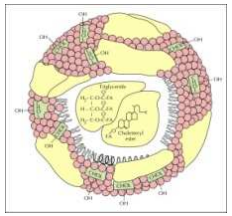
Large, buoyant: 30-35 nm

LDLc=115 mg/dl





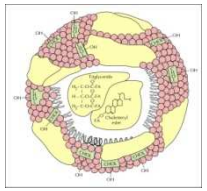


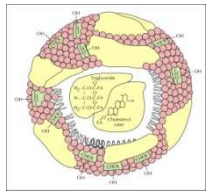


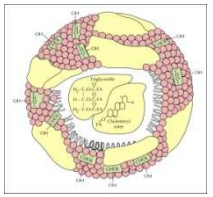
apoB is a measure of number of atherogenic lipoproteins (essentially VLDL, IDL, LDL). Non-HDL is measure of cholesterol carried in these same particles

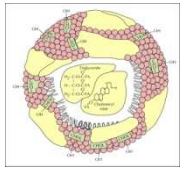
Small, dense: 25-30 nm

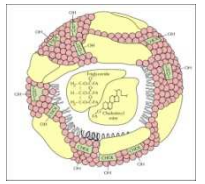
LDLc=115 mg/dl

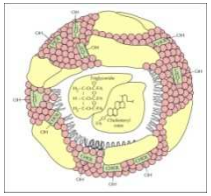












LDLc measures cholesterol carried in LDL and IDL

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

*Cholesterol Treatment Trialists' (CTT) Collaborators**

Lancet 2008; 371: 117-25

Qual'è l'outcome principale delle statine grazie al quale sono entrate in tutte le Linee Guida per la gestione del paziente con rischio cardiovascolare?

La riduzione della mortalità

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**

	Diabetes mellitus			No diabetes
	Type 1	Type 2*	Any type	
4S[15]	24 (0·5%)	178 (4·0%)	202 (4·5%)	4242 (95·5%)
WOSCOPS[16]	8 (0·1%)	68 (1·0%)	76 (1·2%)	6519 (98·8%)
CARE[17]	193 (4·6%)	393 (9·4%)	586 (14·1%)	3573 (85·9%)
Post-CABG[18]	27 (2·0%)	89 (6·6%)	116 (8·6%)	1235 (91·4%)
AFCAPS/TexCAPS[19]	0	155 (2·3%)	155 (2·3%)	6450 (97·7%)
LIPID[20]	106 (1·2%)	676 (7·5%)	782 (8·7%)	8232 (91·3%)
GISSI-P[21]	120 (2·8%)	462 (10·8%)	582 (13·6%)	3689 (86·4%)
LIPS[22]	39 (2·3%)	163 (9·7%)	202 (12·0%)	1475 (88·0%)
HPS[23]	615 (3·0%)	5348 (26·0%)	5963 (29·0%)	14573 (71·0%)
PROSPER[24]	51 (0·9%)	572 (9·9%)	623 (10·7%)	5181 (89·3%)
ALLHAT – LLT[25]	0	3638 (35·1%)	3638 (35·1%)	6717 (64·9%)
ASCOT – LLA[26]	0	2527 (24·5%)	2527 (24·5%)	7778 (75·5%)
ALERT[27]	280 (13·3%)	116 (5·5%)	396 (18·8%)	1706 (81·2%)
CARDS[28]	3 (0·1%)	2835 (99·9%)	2838 (100%)	0
Total	1466 (1·6%)	17 220 (19·1%)	18 686 (20·7%)	71370 (79·3%)

Data are number (%). *Includes 13 participants with diabetes of unknown type.

Table 1: **Number of participants with diabetes by trial**

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

*Cholesterol Treatment Trialists' (CTT) Collaborators**

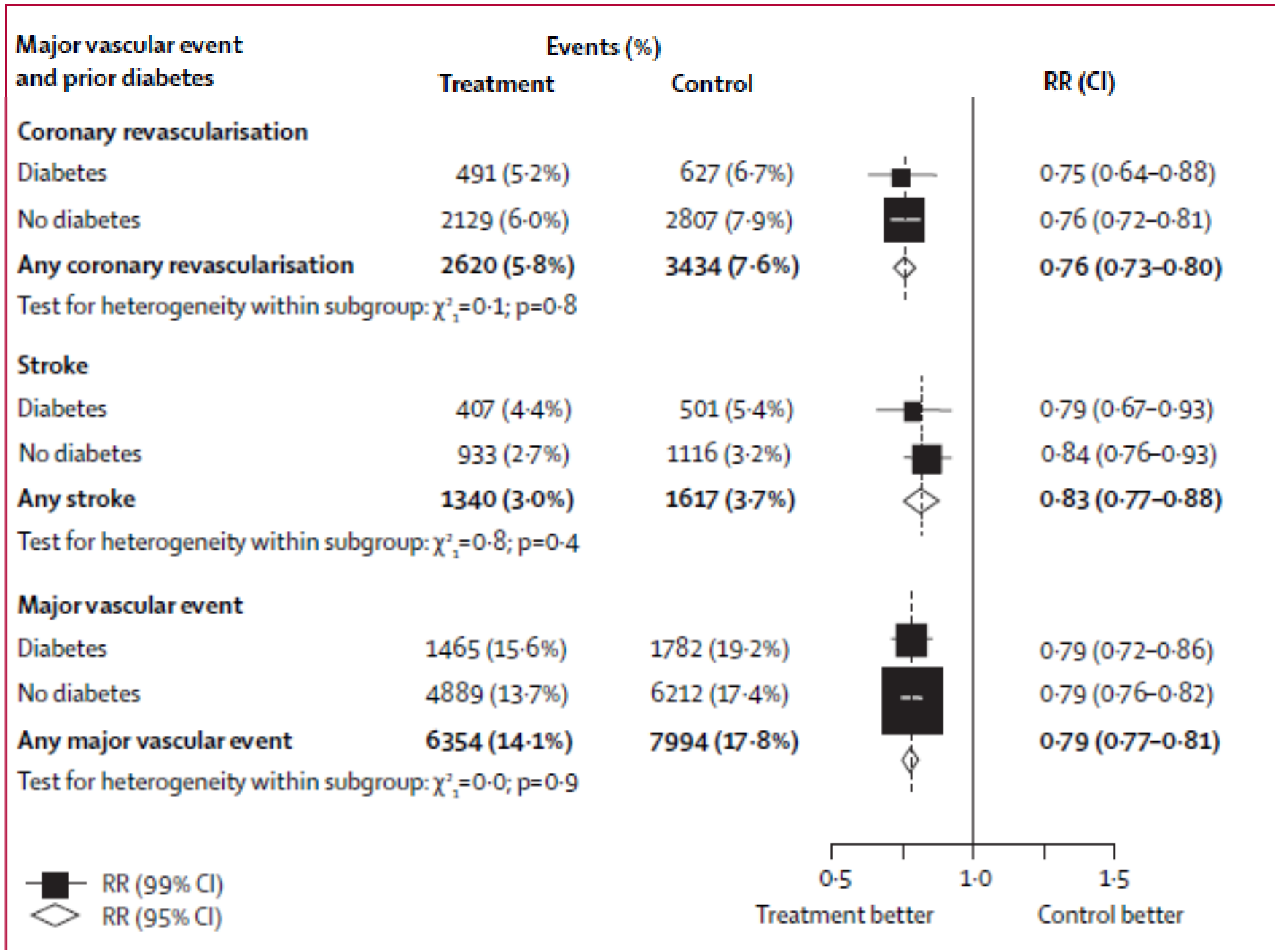
Lancet 2008; 371: 117-25

Eventi coronarici maggiori:

- **Riduzione del 22%**

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			

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



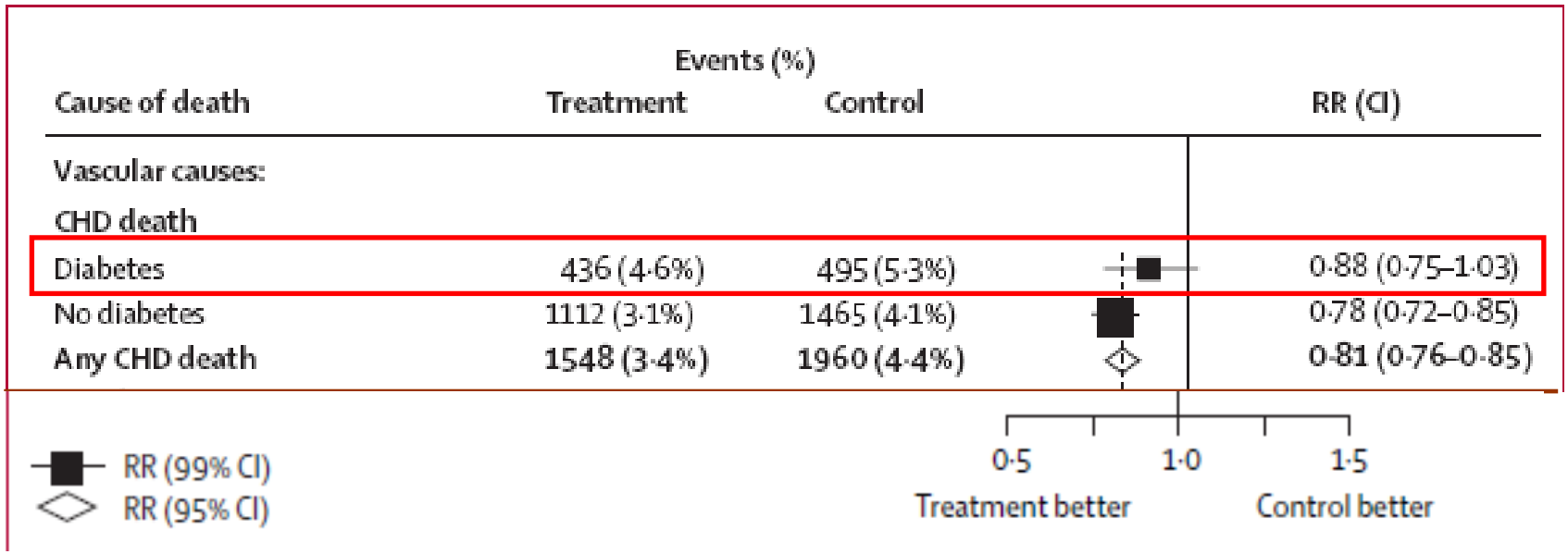
Efficacy of cholesterol-lowering therapy in 18 686 people with diabetes in 14 randomised trials of statins: a meta-analysis

*Cholesterol Treatment Trialists' (CTT) Collaborators**

Lancet 2008; 371: 117-25

Mortalità coronarica:

- **Riduzione del 12% non significativa**



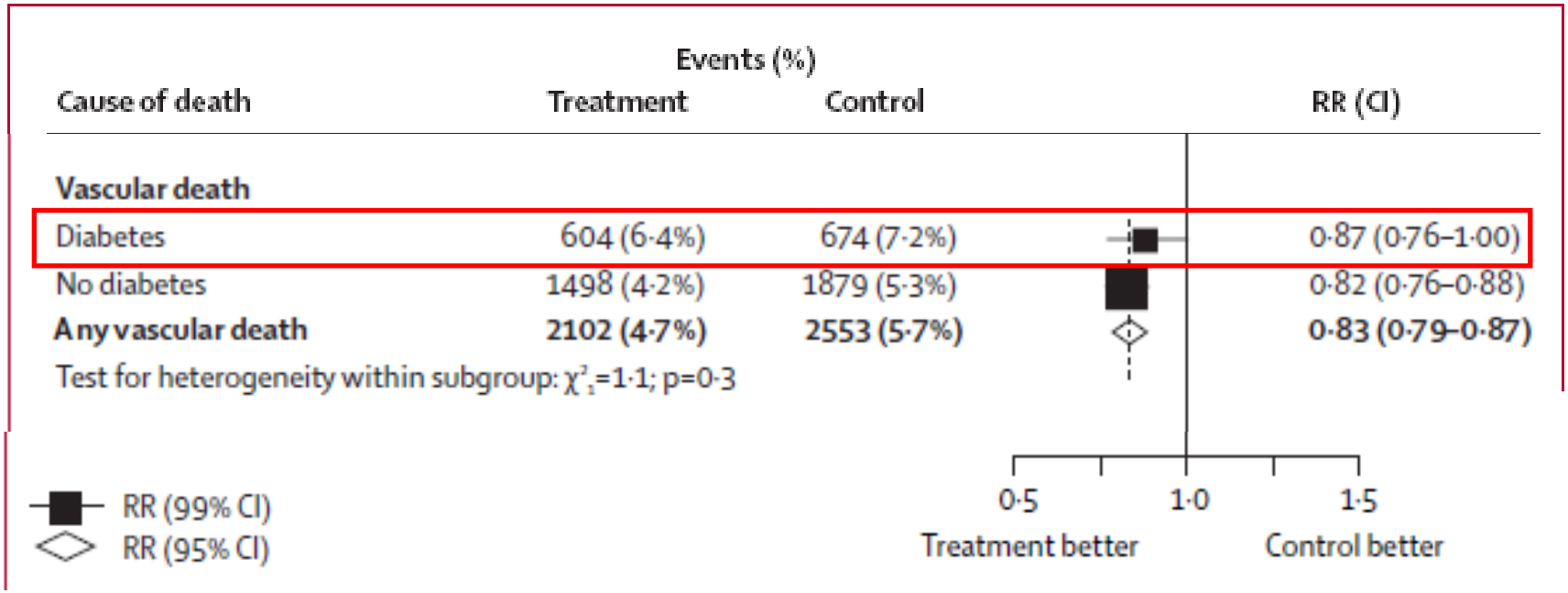
Efficacy of cholesterol-lowering therapy in 18 686 people with diabetes in 14 randomised trials of statins: a meta-analysis

*Cholesterol Treatment Trialists' (CTT) Collaborators**

Lancet 2008; 371: 117-25

Mortalità vascolare:

- **Riduzione del 13% non significativa**



Cumulative hazard of

primary endpoint

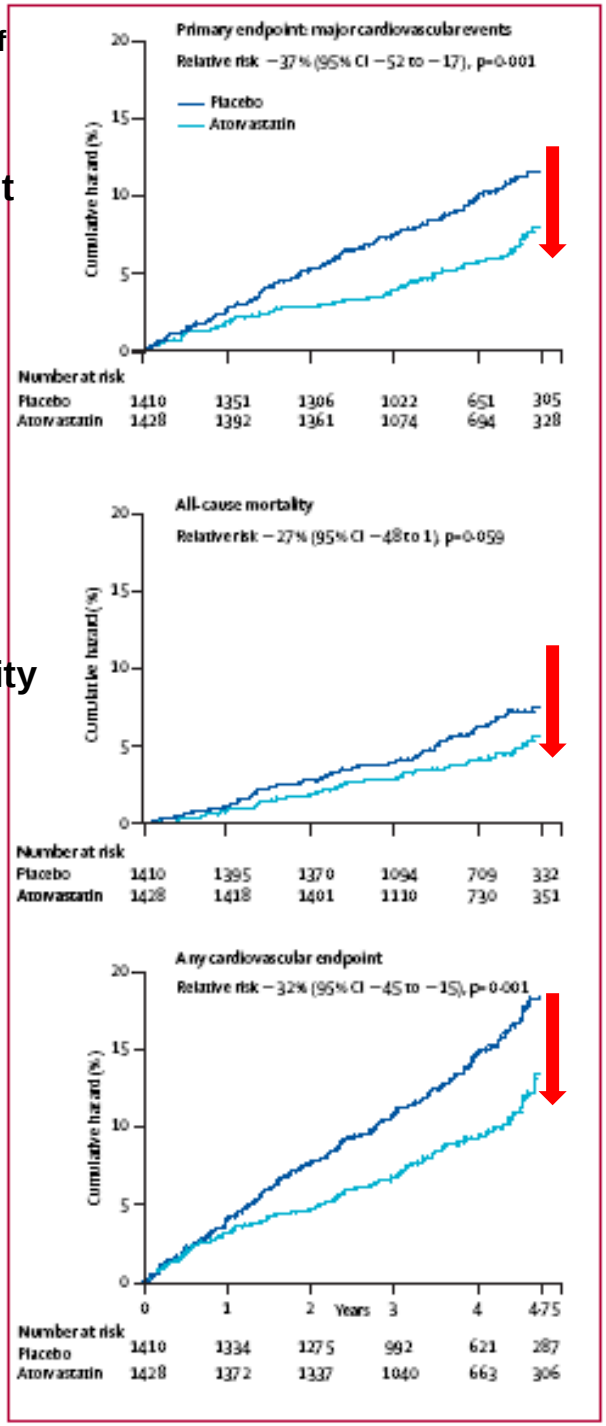
- 37 %; P=0,001

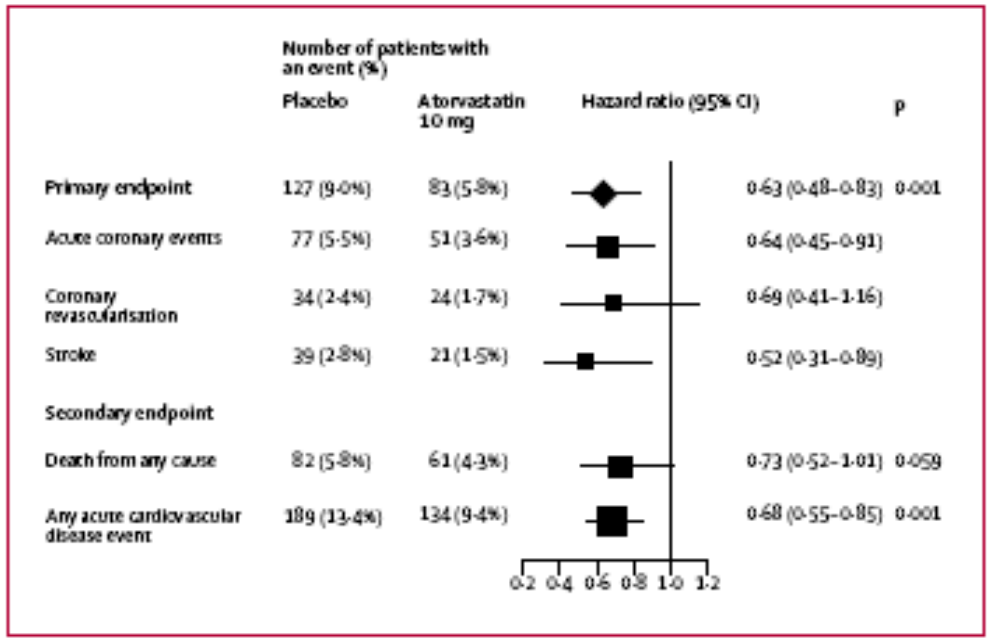
all-cause mortality

-27%; P=0,059

any cardiovascular endpoint

-32%; P=0,001





Effect of treatment on primary and secondary endpoints

Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial

*Helen M Colhoun, D John Betteridge, Paul N Durrington, Graham A Hitman, H Andrew W Neil, Shona J Livingst Michael I Mackness, Valentine Charlton-Menys, John H Fuller, on behalf of the CARDS investigators**

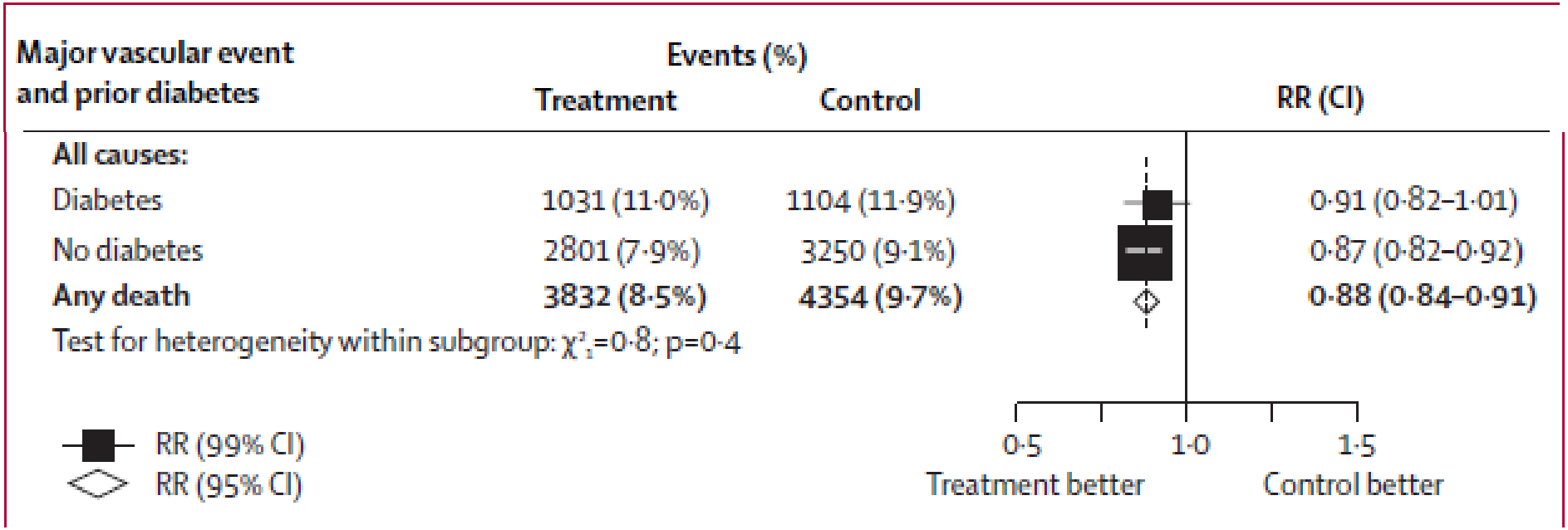
Lancet 2004; 364: 685–96

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

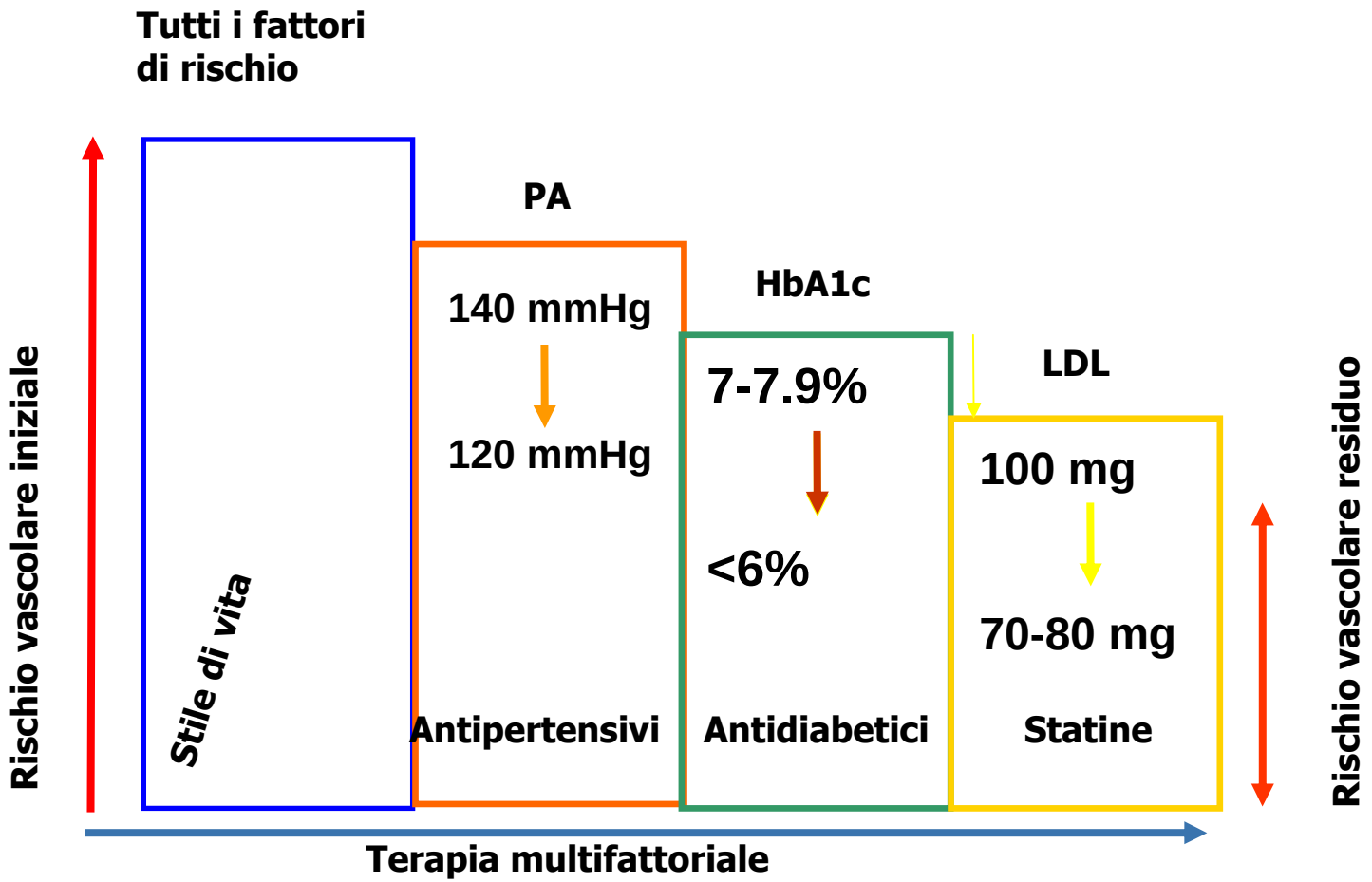
*Cholesterol Treatment Trialists' (CTT) Collaborators**

Lancet 2008; 371: 117-25

- Il 9% di **riduzione della mortalità** per tutte le cause ottenuta nei diabetici è **circa il 30% minore** rispetto a quella ottenuta nei non diabetici (13%).



Gli standard terapeutici attuali lasciano i pazienti con un importante rischio vascolare residuo



Atherosclerosis 206 (2009) 611–616

Contents lists available at ScienceDirect

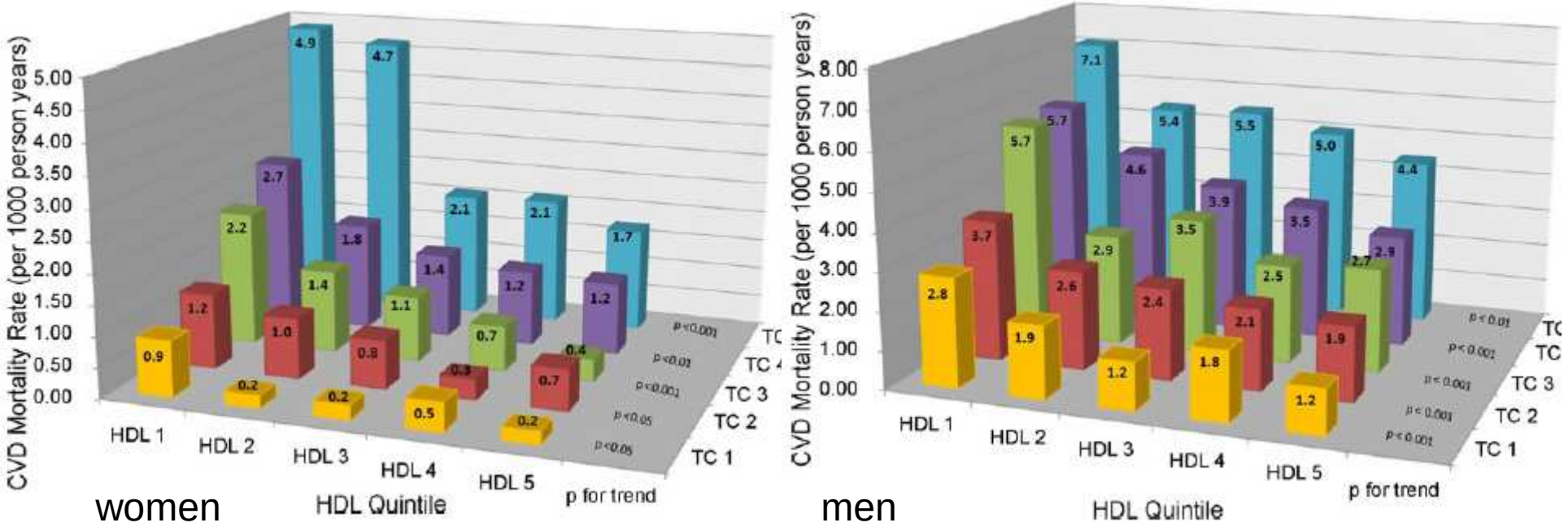
Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

HDL cholesterol protects against cardiovascular disease in both genders, at all ages and at all levels of risk

M.T. Cooney[a], A. Dudina[a], D. De Bacquer[b], L. Wilhelmsen[c], S. Sans[d], A. Menotti[e], G. De Backer[b], P. Jousilahti[f], U. Keil[g], T. Thomsen[h], P. Whincup[i], I.M. Graham[a,*,1]

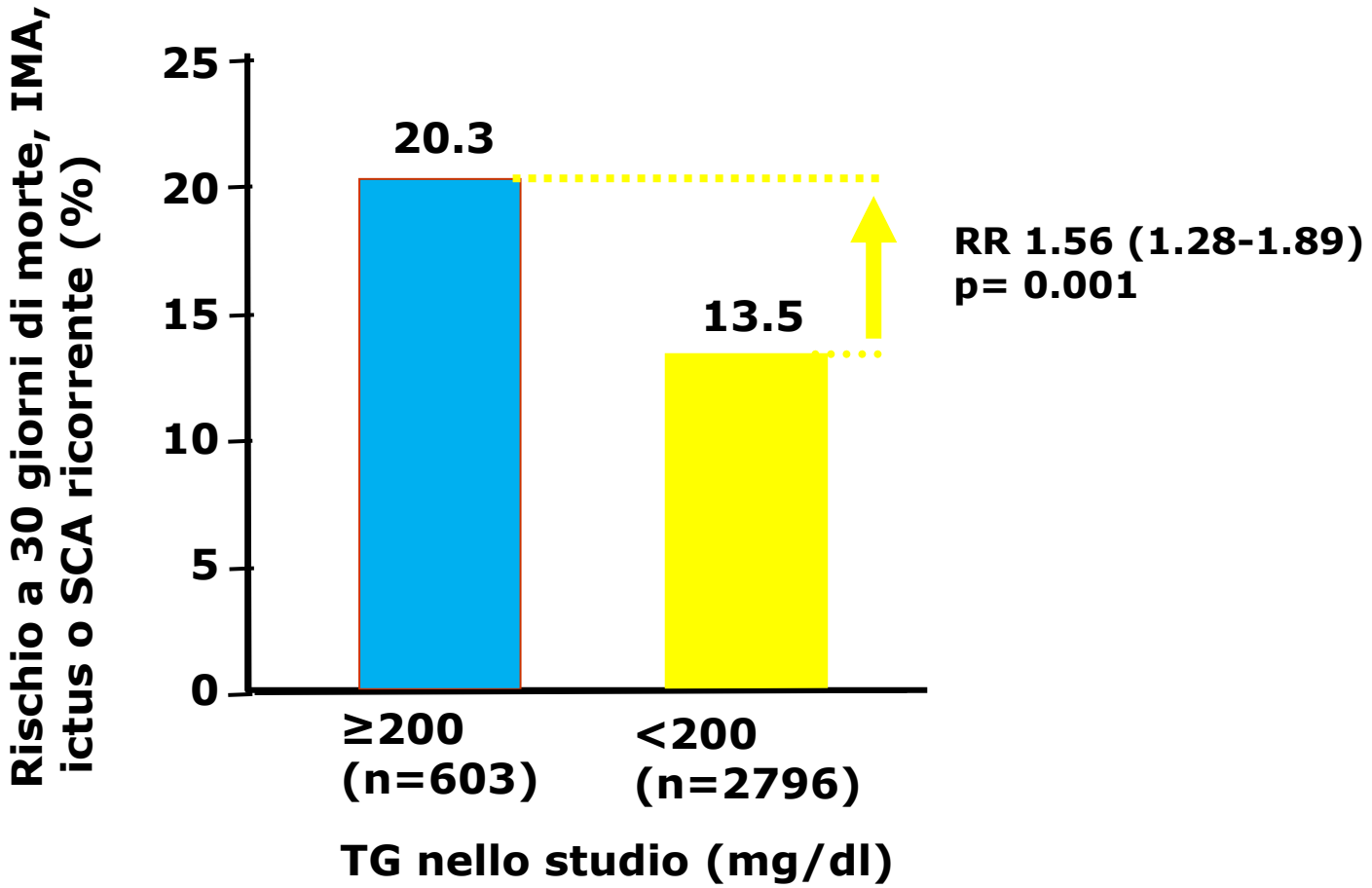
CVD mortality rates (per 1000 person years in HCL-c tertiles



women

men

Trigliceridi e eventi CVD ricorrenti in pazienti con Sindrome Coronarica Acuta PROVE-IT – TIMI-22



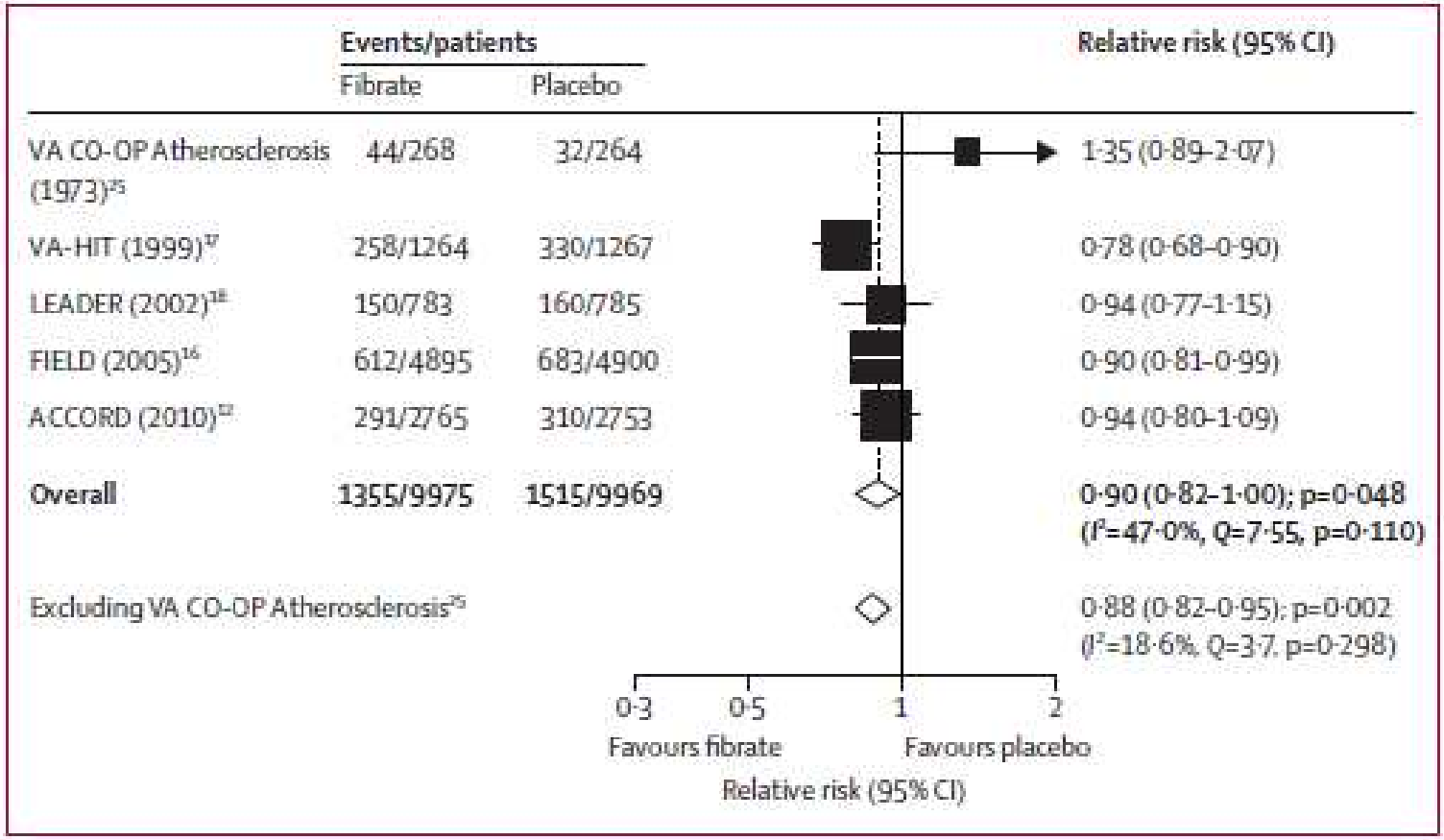
In pazienti che hanno raggiunto <u>C-LDL <70 mg/dl</u> in terapia con statine

Miller et al. 2008

Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis

Min Jun, Celine Foote, Jicheng Lv, Bruce Neal, Anushka Patel, Stephen J Nicholls, Diederick E Grobbee, Alan Cass, John Chalmers, Vlado Perkovic

Lancet 2010; 375: 1875–84



Fibrates in the prevention of cardiovascular disease in patients with type 2 diabetes mellitus – A pooled meta-analysis of randomized placebo-controlled clinical trials ☆

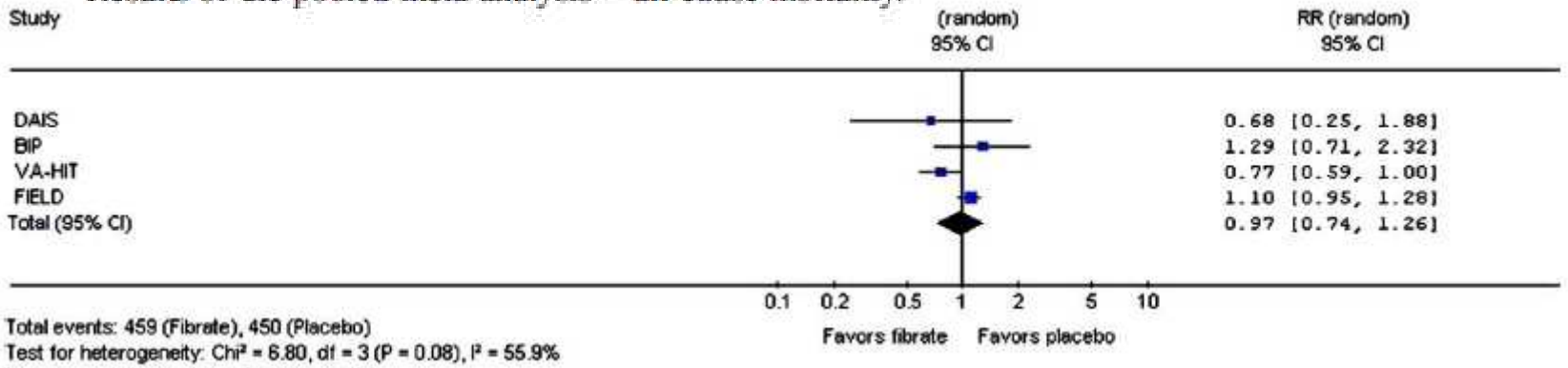
International Journal of Cardiology

www.elsevier.com/locate/ijcard

International Journal of Cardiology 141 (2010) 157–166

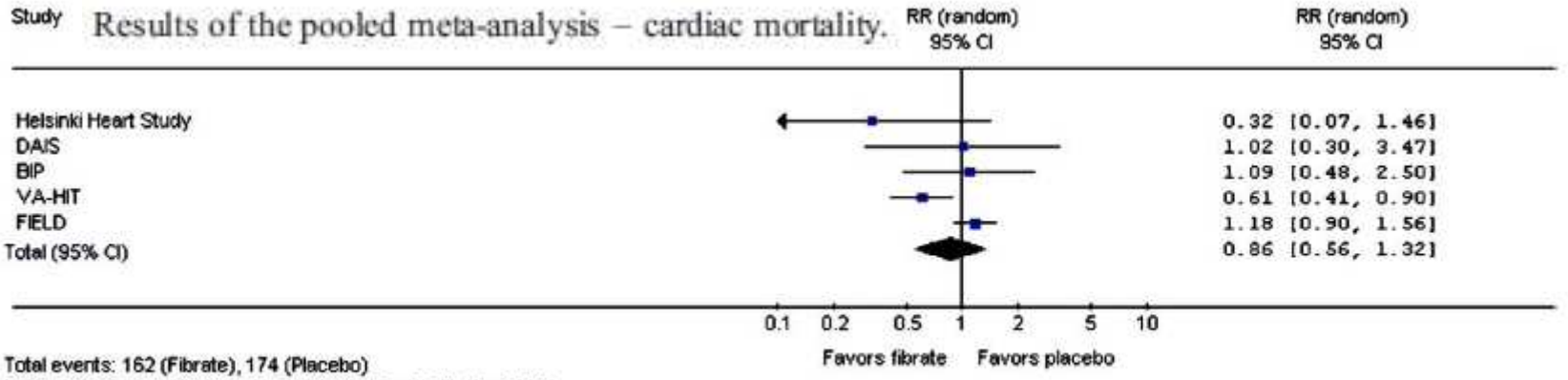
Sandeep A. Saha [a,b,*] Rohit R. Arora [c]

Results of the pooled meta-analysis – all-cause mortality.



Total events: 459 (Fibrate), 450 (Placebo)
Test for heterogeneity: Chi² = 6.80, df = 3 (P = 0.08), I² = 55.9%
Test for overall effect: Z = 0.25 (P = 0.80)

Results of the pooled meta-analysis – cardiac mortality.



Total events: 162 (Fibrate), 174 (Placebo)
Test for heterogeneity: Chi² = 9.45, df = 4 (P = 0.05), I² = 57.7%
Test for overall effect: Z = 0.70 (P = 0.48)

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)

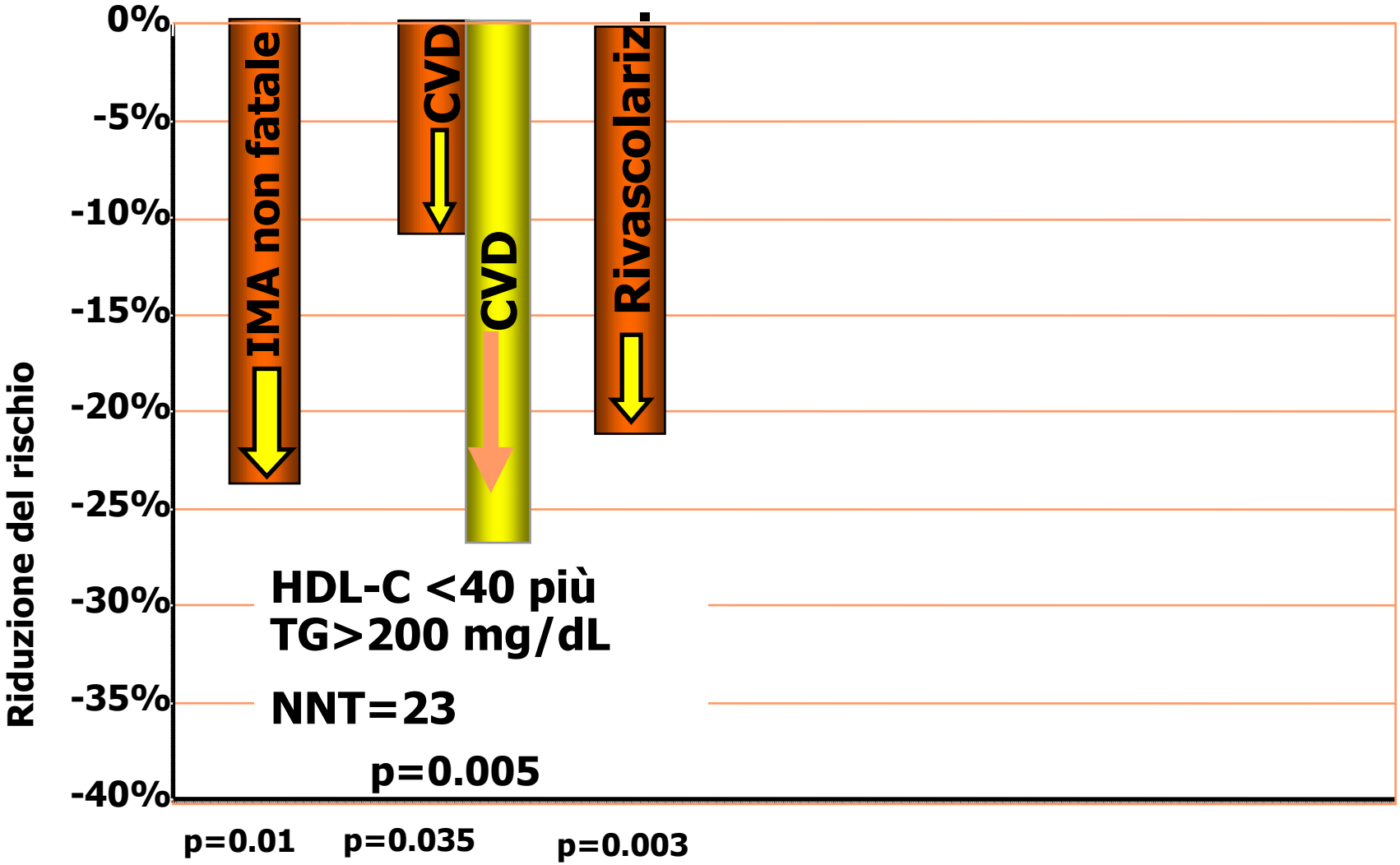
la riduzione del rischio cardiovascolare è stata

del 27% (p< 0.005)

NNT numero necessario da trattare **= 23**
…per ogni 23 pazienti trattati si evita un evento CVD

Diabetes Care 2009;32:493–498

Fenofibrato: Riduzione del rischio macrovascolare



Diabetes Care 2009;32:493–498

ACCORD Programme

Since the FIELD results turned out to be complicated to interpret, Action to Control Cardiovascular Risk in Diabetes (ACCORD) study was expected to clarify the position of fibrates in treating the residual risk in diabetic dyslipidemia

- **Obiettivo dello studio:**

  Valutare se gli eventi Macrovascolari e le complicanze Microvascolari possono essere ridotte in pazienti con Diabete di tipo 2 grazie al trattamento intensivo di 3 importanti fattori di rischio:

Iperglicemia | **Dislipidemia** | **Ipertensione**

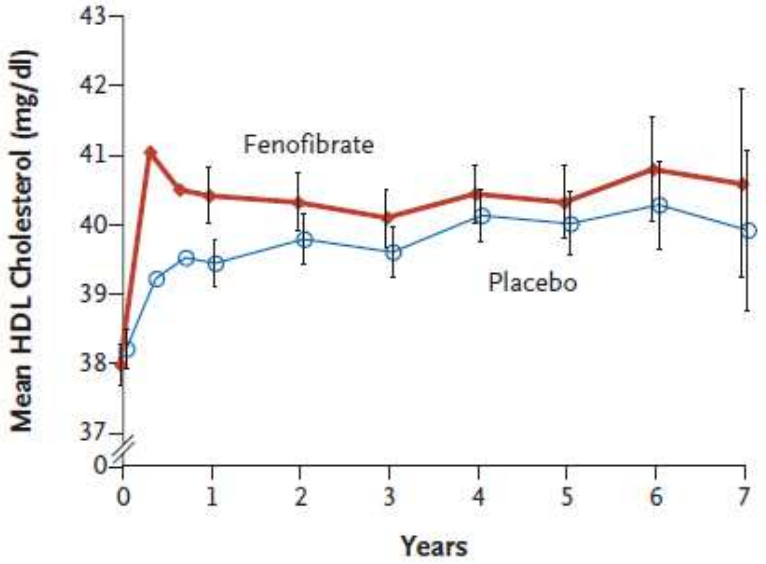
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 29, 2010 VOL. 362 NO. 17

Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus

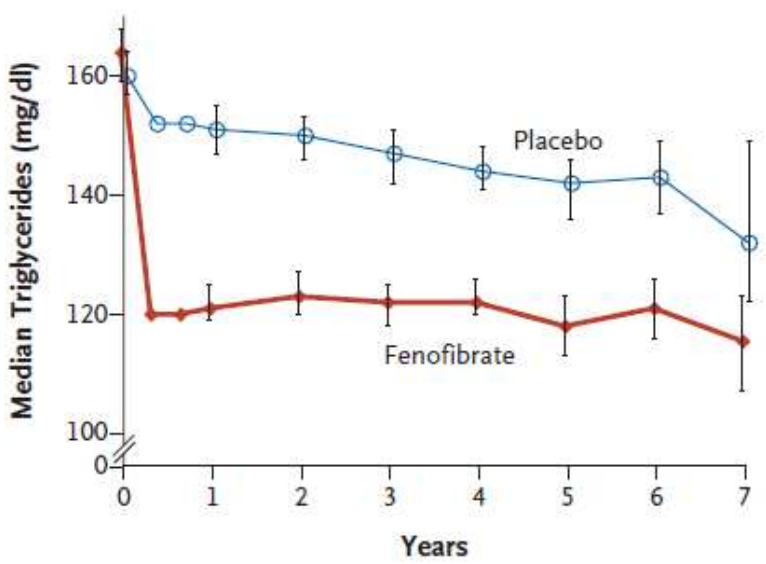
The ACCORD Study Group*

C HDL Cholesterol



No. of Patients								
Fenofibrate	2747	2593	2505	2417	2361	1477	796	248
Placebo	2736	2591	2484	2375	2364	1480	801	243

D Triglycerides



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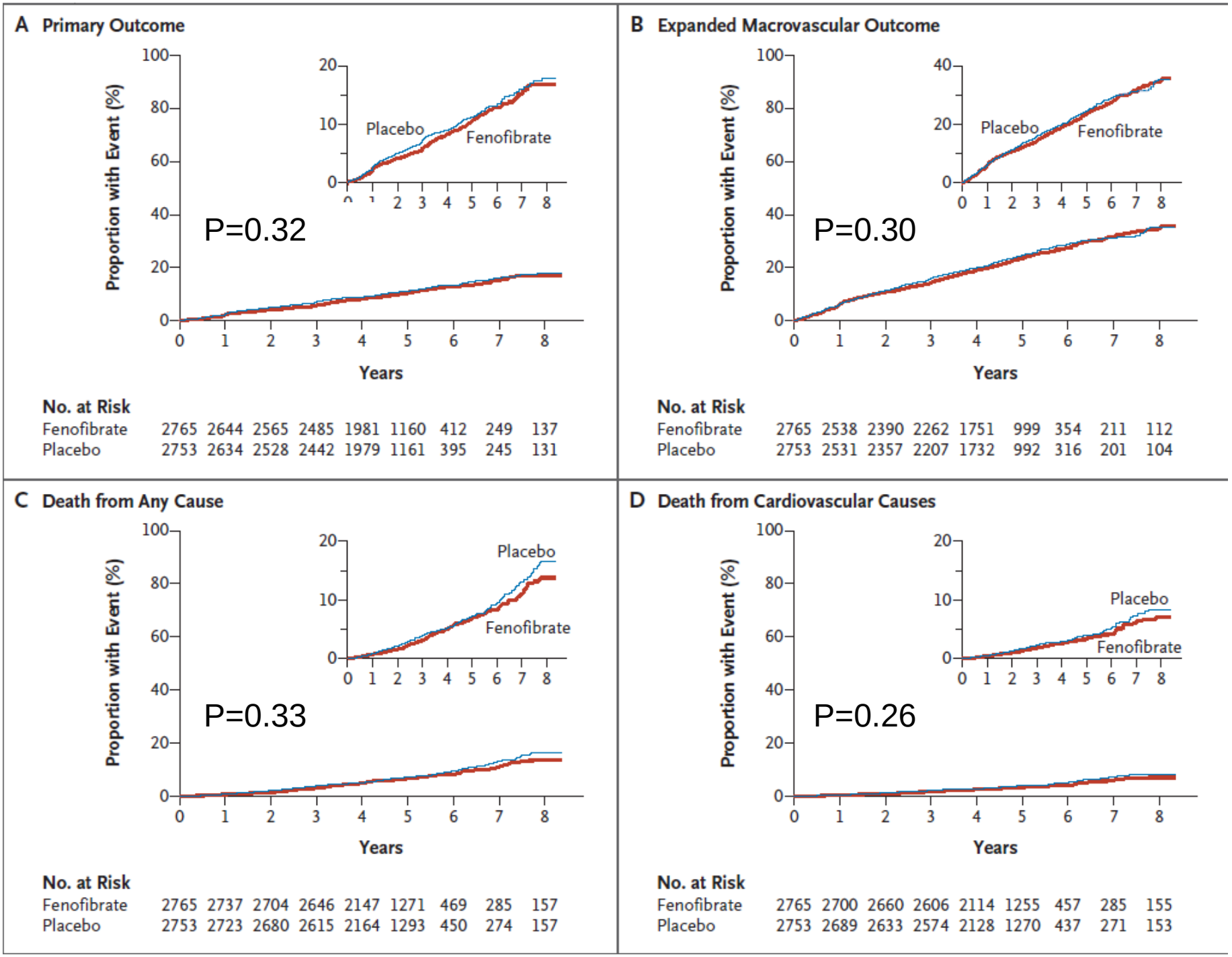
A Primary Outcome
Proportion with Event (%)
Placebo
Fenofibrate
P=0.32
Years
No. at Risk
Fenofibrate 2765 2644 2565 2485 1981 1160 412 249 137
Placebo 2753 2634 2528 2442 1979 1161 395 245 131
B Expanded Macrovascular Outcome
Proportion with Event (%)
Placebo
Fenofibrate
P=0.30
Years
No. at Risk
Fenofibrate 2765 2538 2390 2262 1751 999 354 211 112
Placebo 2753 2531 2357 2207 1732 992 316 201 104
C Death from Any Cause
Proportion with Event (%)
Placebo
Fenofibrate
P=0.33
Years
No. at Risk
Fenofibrate 2765 2737 2704 2646 2147 1271 469 285 157
Placebo 2753 2723 2680 2615 2164 1293 450 274 157
D Death from Cardiovascular Causes
Proportion with Event (%)
Placebo
Fenofibrate
P=0.26
Years
No. at Risk
Fenofibrate 2765 2700 2660 2606 2114 1255 457 285 155
Placebo 2753 2689 2633 2574 2128 1270 437 271 153

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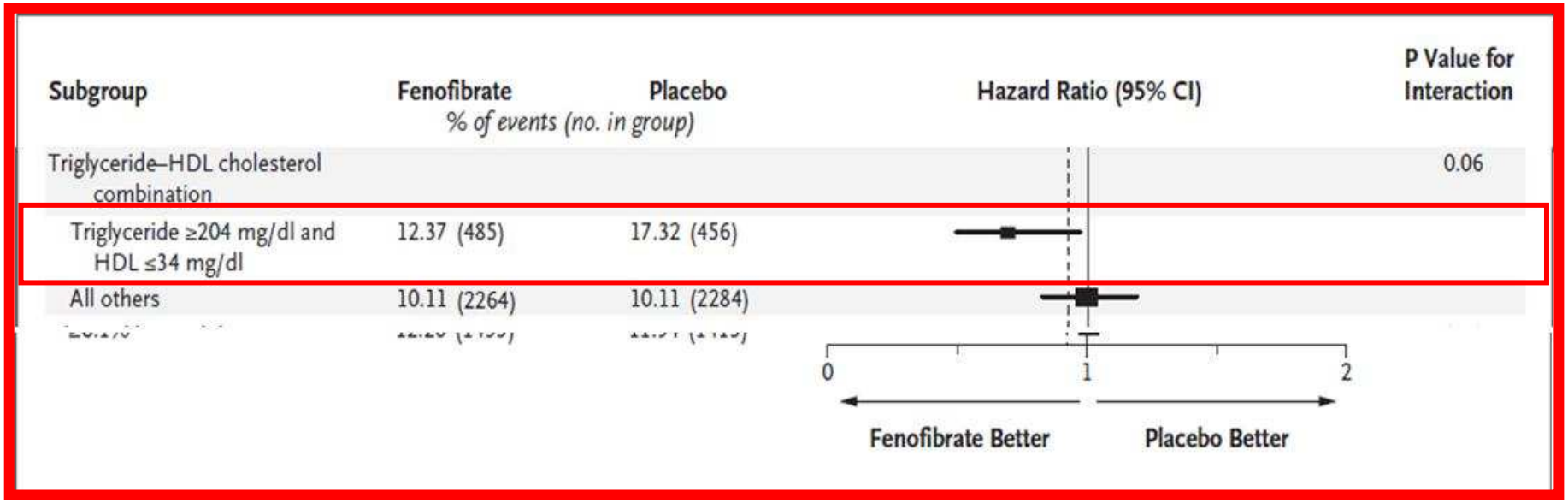
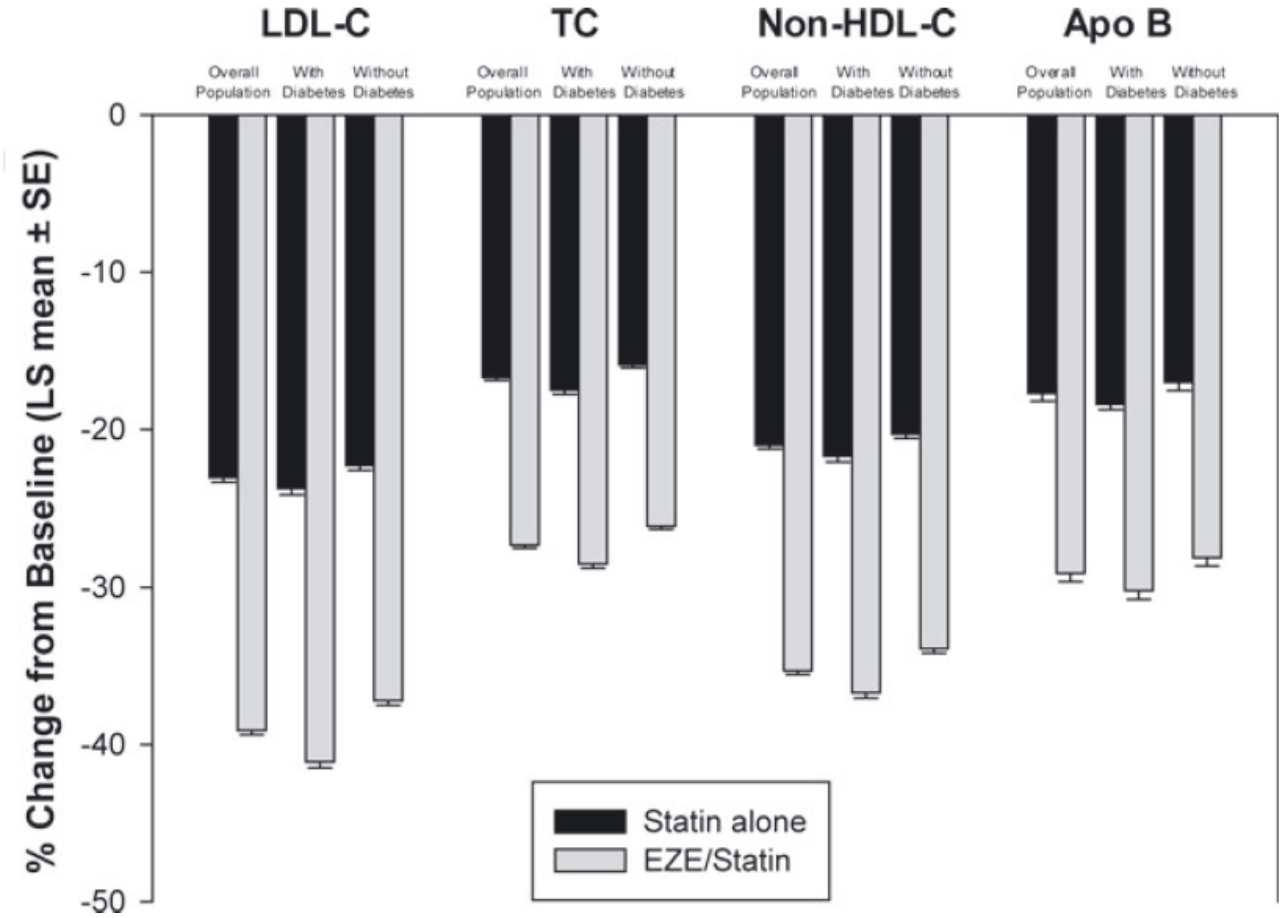


Lipid-altering efficacy and safety profile of combination therapy with ezetimibe/statin vs. statin monotherapy in patients with and without diabetes: an analysis of pooled data from 27 clinical trials

L. A. Leiter[1], D. J. Betteridge[2], M. Farnier[3], J. R. Guyton[4], J. Lin[5], A. Shah[5], A. O. Johnson-Levonas[5] & P. Brudi[5]

Diabetes, Obesity and Metabolism 13: 615–628, 2011.



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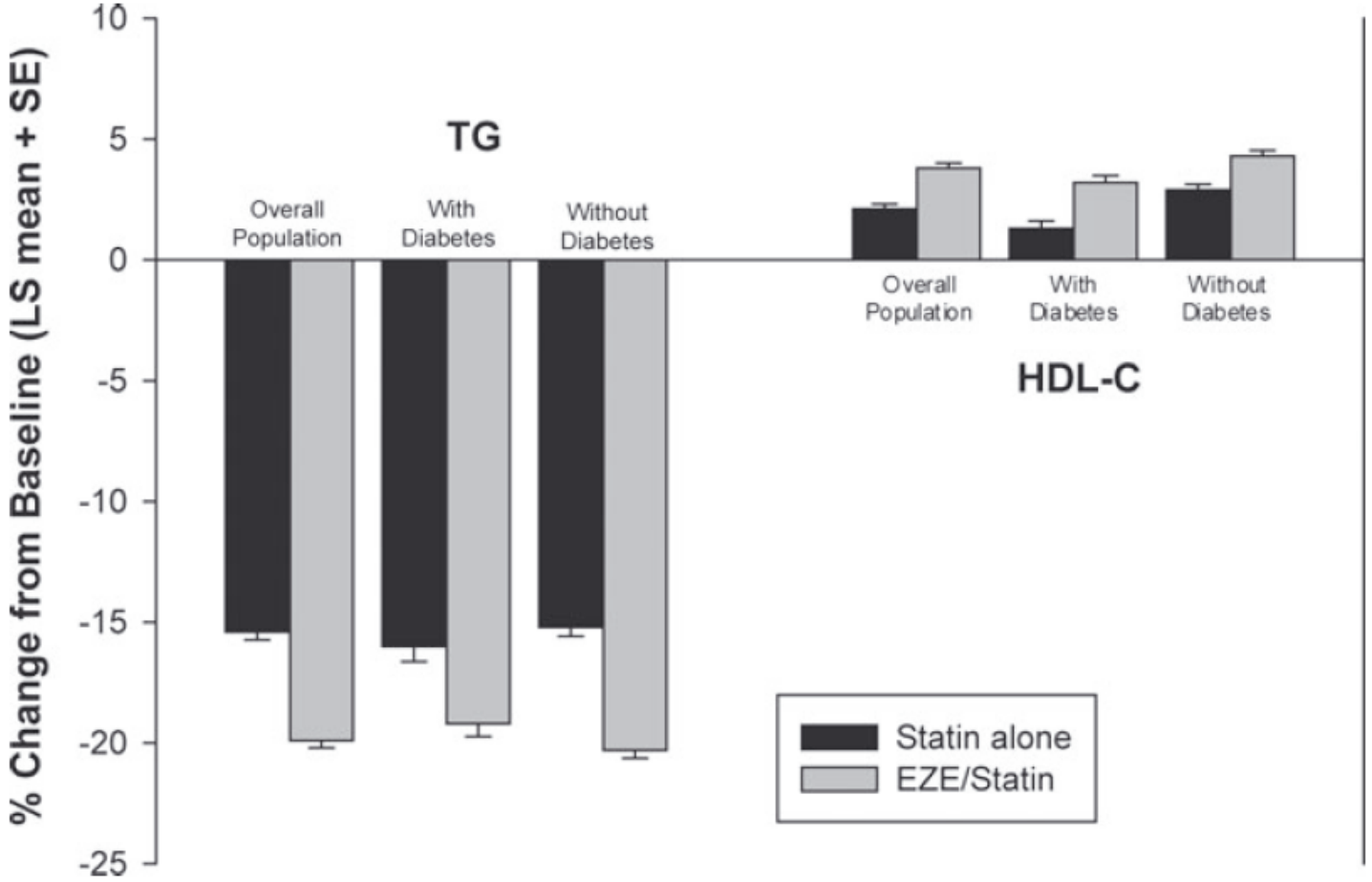

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Effect of Statins Alone Versus Statins Plus Ezetimibe on Carotid Atherosclerosis in Type 2 Diabetes

The SANDS (Stop Atherosclerosis in Native Diabetics Study) Trial

Jerome L. Fleg, MD,* Mihriye Mete, PHD,† Barbara V. Howard, PHD,† Jason G. Umans, MD, PHD,† Mary J. Roman, MD,‡ Robert E. Ratner, MD,† Angela Silverman, MSN, CANP,† James M. Galloway, MD,§ Jeffrey A. Henderson, MD, MPH,‖ Matthew R. Weir, MD,¶ Charlton Wilson, MD,# Mario Stylianou, PHD,* Wm. James Howard, MD**

Bethesda, Hyattsville, and Baltimore, Maryland; New York, New York; Tucson and Phoenix, Arizona; Rapid City, South Dakota; and Washington, DC

Conclusions Reducing LDL-C to aggressive targets resulted in similar regression of CIMT in patients who attained equivalent LDL-C reductions from a statin alone or statin plus ezetimibe. Common carotid artery IMT increased in those achieving standard targets. (Stop Atherosclerosis in Native Diabetics Study [SANDS]

Conclusioni

- I pazienti con Diabete hanno un alto rischio cardiovascolare anche durante terapia con statine
- Alla base del controllo del rischio residuo in aggiunta a una rigorosa gestione LDL dovrebbe esserci sia la riduzione della produzione epatica di VLDL sia il miglioramento del catabolismo delle lipoproteine ricche in TG

Conclusioni

- I dati disponibili evidenziano che la dieta, la perdita di peso e l'esercizio fisico forniscono i metodi migliori per ridurre la produzione di VLDL.
- Anche dopo la terapia più efficace con statine e nonostante gli interventi aggressivi sullo stile di vita, un numero considerevole di soggetti con T2D rimangono ad alto rischio residuo e, ovviamente, richiedono un’aggiuntiva terapia ipolipemizzante che dovrebbe essere basata sull'analisi individuale rischio/beneficio.
- Aumentare l'HDL è un bersaglio nei programmi di sviluppo di nuovi farmaci.