VIII CONGRESSO NAZIONALE ECOCARDIOCHIRURGIA 2016
Milano 21-23 marzo 2016

LOWER IS BETTER: IL SOLO OBBIETTIVO NEL TRATTAMENTO DELLE DISLIPIDEMIE?

Cesare R. SIRTORI, M.D.,Ph.D.
Direttore Centro Dislipidemie, AO Niguarda Ca' Granda, Milano

Presidente On. SINUT

RISPOSTE DALLO STUDIO IMPROVE-IT

Simvastatina 40 mg vs simvastatina/ezetimibe (40/10 mg)

Pazienti stabilizzati post IMA ≥ 10 gg (n= 18.144)

LDL-C 50-100 mg/dl se in trattamento o 50-125 mg

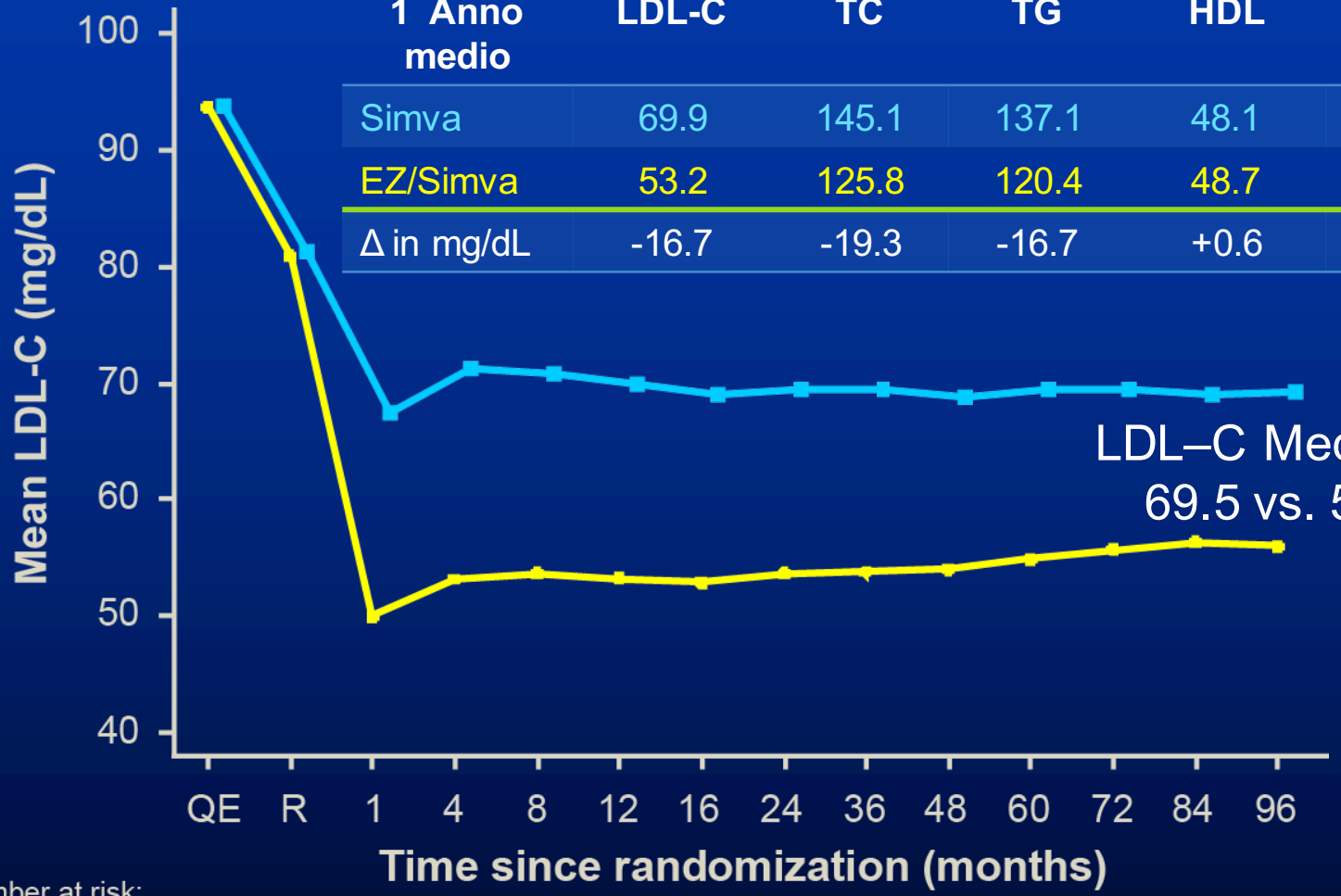
Cannon et al. N Engl J Med 372, 2386, 2015

STUDIO IMPROVE-IT – *DATI BASALI*

	Simvastatin (N=9077) %	EZ/Simva (N=9067) %
Age (years)	64	64
Female	24	25
Diabetes	27	27
MI prior to index ACS	21	21
STEMI / NSTEMI / UA	29 / 47 / 24	29 / 47 / 24
Days post ACS to rand (IQR)	5 (3, 8)	5 (3, 8)
Cath / PCI for ACS event	88 / 70	88 / 70
Prior lipid Rx	35	36
LDL-C at ACS event (mg/dL, IQR)	95 (79, 110)	95 (79,110)

STUDIO IMPROVE-IT – *DATI LIPIDEMICI*

1 Anno medio	LDL-C	TC	TG	HDL	hsCRP
Simva	69.9	145.1	137.1	48.1	3.8
EZ/Simva	53.2	125.8	120.4	48.7	3.3
Δ in mg/dL	-16.7	-19.3	-16.7	+0.6	-0.5



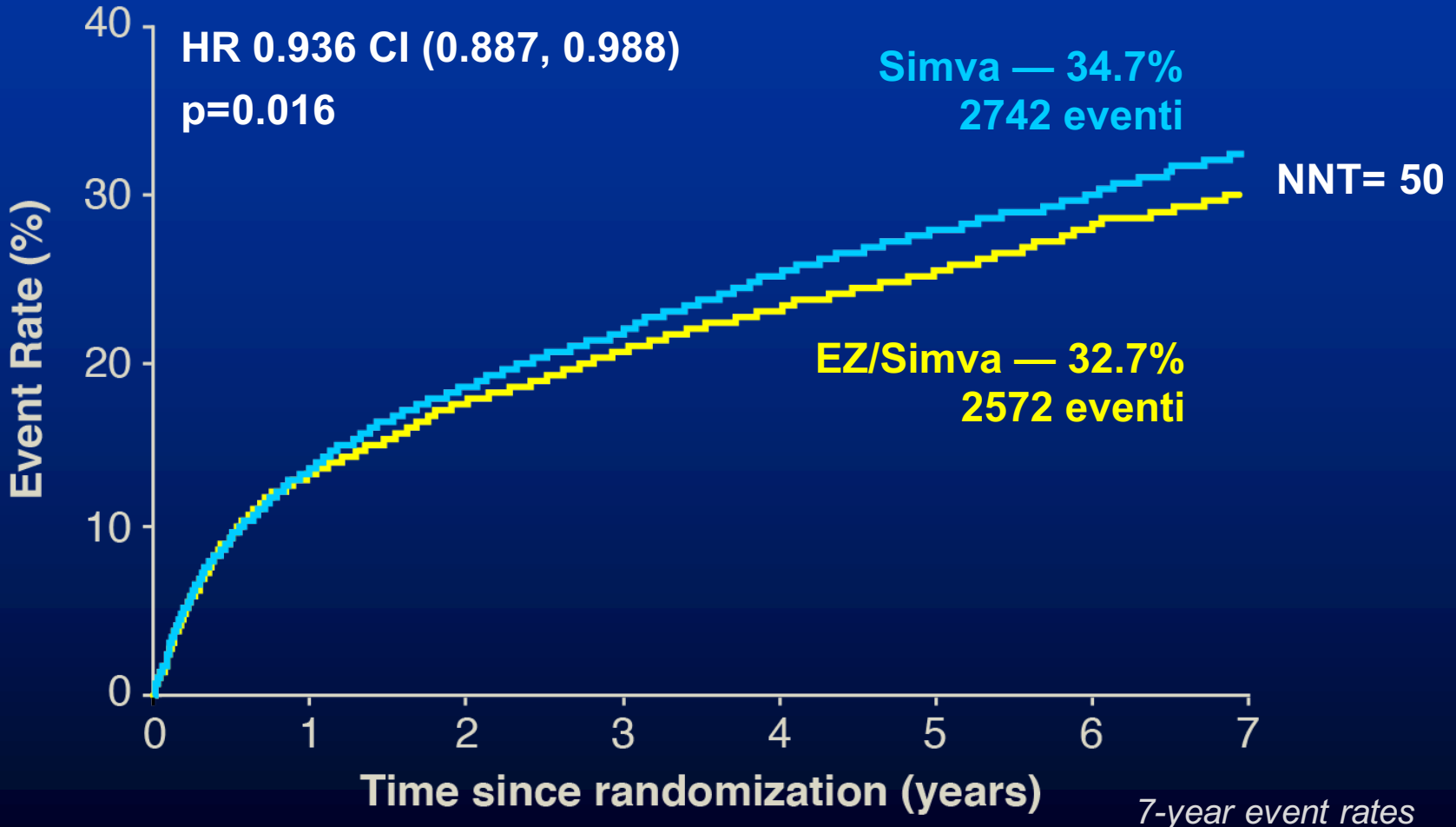
LDL–C Medio nel tempo
69.5 vs. 53.7 mg/dL

Number at risk:

EZ/Simva	8990	8889	8230	7701	7264	6864	6583	6256	5734	5354	4508	3484	2608	1078
Simva	9009	8921	8306	7843	7289	6939	6607	6192	5684	5267	4395	3387	2569	1068

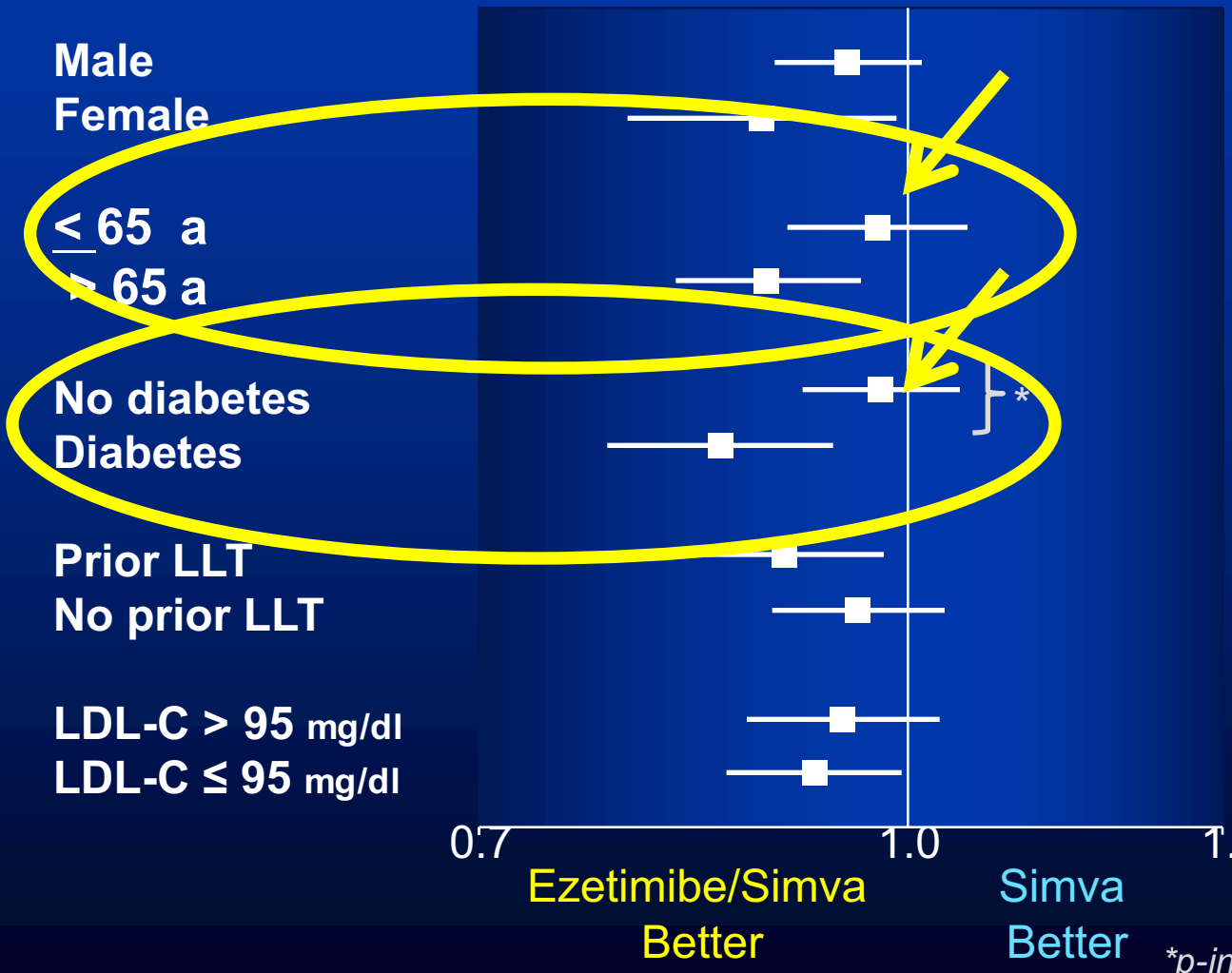
STUDIO IMPROVE-IT – *End-Point Primario*

Morte CV, IMA, angina instabile, rivascolarizzazione (> 30 gg), ictus



7-year event rates

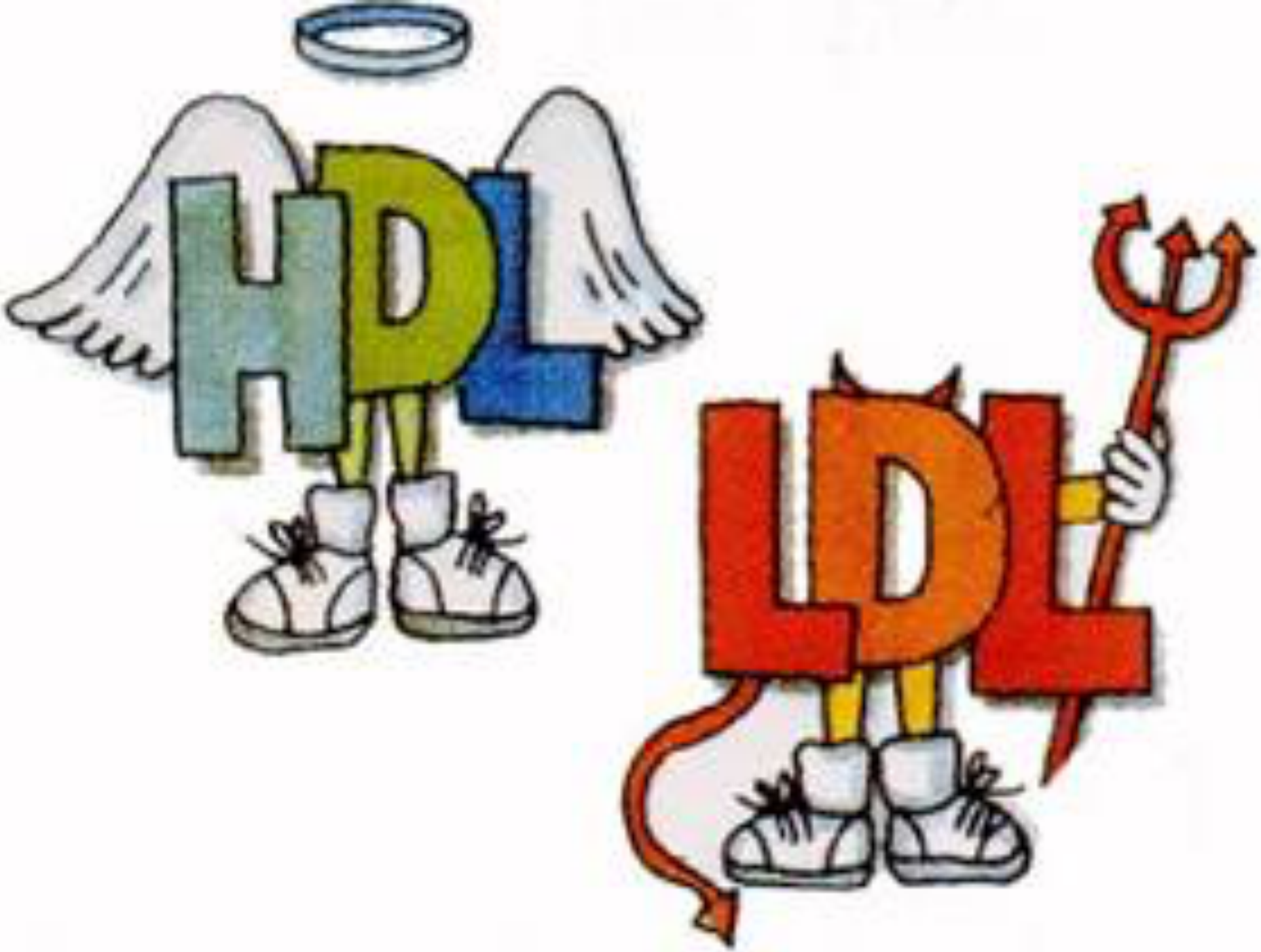
IMPROVE-IT SOLO PER GLI OVER 65 A? E IL DIABETE?



	Simva†	EZ/Simva†
Male	34.9	33.3
Female	34.0	31.0
≤ 65 a	30.8	29.9
> 65 a	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 mg/dl	38.4	36.0

†*7-year event rates*

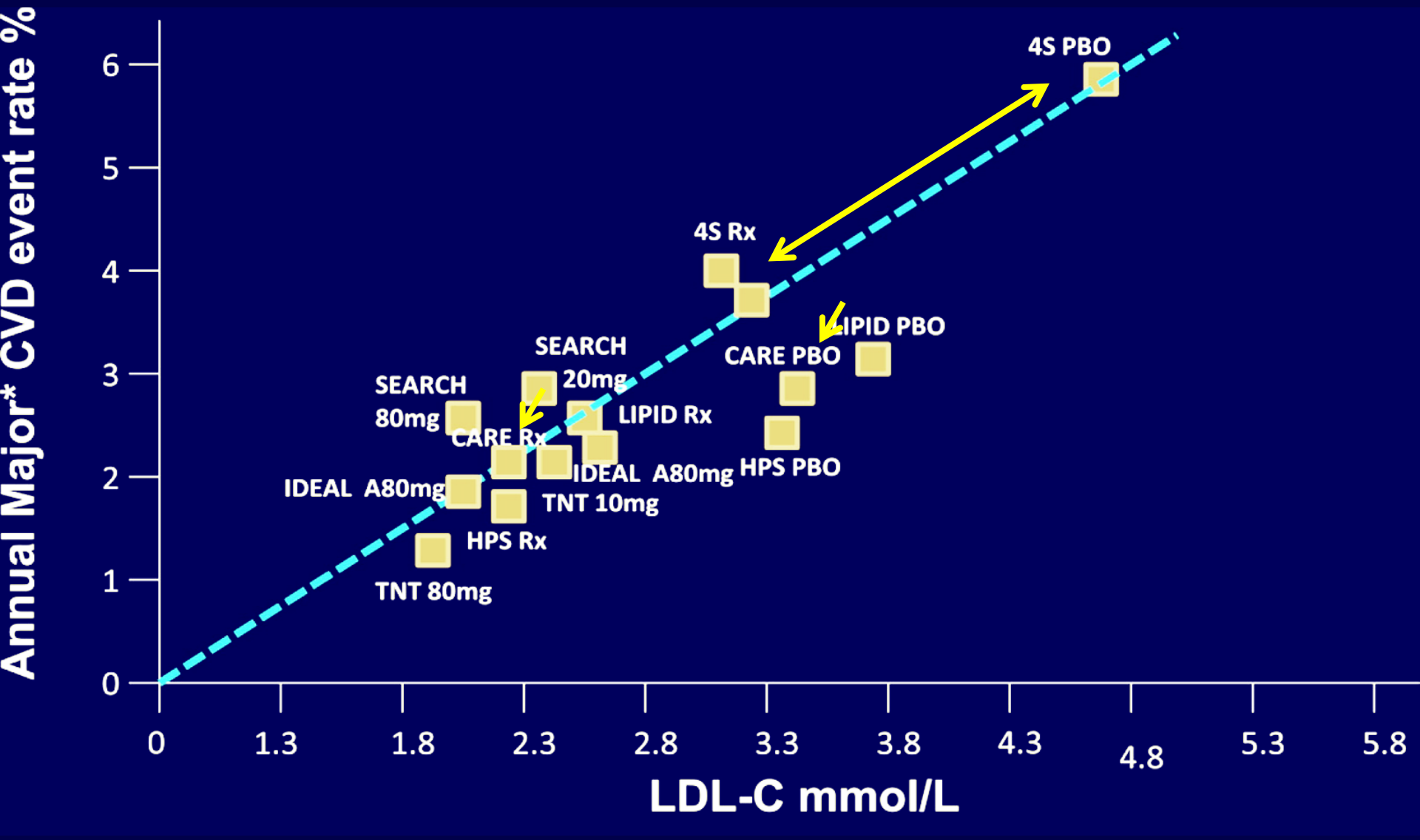
**p-interaction = 0.023, otherwise > 0.05*


HDL
LDL

LOWER IS BETTER *Outline:*

- Cosa significa? E' vero?
- Perchè? Gli effetti pleiotropi delle statine
- Il rischio "residuo"

CORRELAZIONE FRA LA RIDUZIONE ASSOLUTA DI LDL-C E RIDUZONE ANNUALE DI EVENTI CV



Stein et al, Best Pract. & Res Clin Endocrinol & Metab 28, 309, 2014

4 S - I TRATTAMENTI ASSOCIATI

LDL-C mg/dl	Morti, eventi CHD placebo per anno	ASA %	β-bloccante %	AP, Bypass %
188	5.7	37	57	8

Rosenson and Tangney, JAMA 281, 418, 1999

STUDI DI PREVENZIONE SECONDARIA
TRATTAMENTI ASSOCIATI

		LDL-C medio mg/dl	Morti, eventi CHD placebo per anno ↙	ASA % ↙	β-bloccante % ↙	PTCA Bypass % ↙
4S	Simva	188	5.7	37	57	8
LIPID	Prava	150	2.6	83	47	41
CARE	Prava	139	2.6	83	40	54

LOWER IS BETTER- ITALIA

Colesterolo, adulti 57 a, valori medi:

maschi Tot 205.3; LDL-C 123.3 mg/dl
femmine Tot 208.1; LDL-C 126.5 mg/dl
(Studio CHECK, Poli et al, NMCD 22, 327,2012)

Obbiettivi?
LDL <100 mg/dl (AHA 2005)
LDL-C < 70 mg/dl in prevenzione secondaria grave (AHA 2011)
Nessuno obiettivo specifico, Linee Guida ACC/AHA2013

LINEE GUIDA ACC/AHA 2013

Beneficiano del trattamento con statina:

1) **ogni prevenzione secondaria**
2) **LDL-C > 190 mg/dl**
3) **diabete, 40-75 a., LDL-C 70-189 mg/dl**

Senza patologie vascolari:

rischio stimato di 7.5%, 40-75 a.

LINEE GUIDA ACC/AHA 2013

Non obiettivo target LDL-C

In assenza di dati sulla titolazione della terapia farmacologica ad obiettivi specifici non vengono formulate raccomandazioni per o contro targets di LDL-C

"I clinici che trattano pazienti ad alto rischio con una risposta minore di quella prevista …… possono considerare l'aggiunta di una terapia non statinica"

Stone et al. J Am Coll Cardiol 63: 2889, 2014

LOWER IS BETTER- PUNTI DEBOLI

Targets dedotti da studi con dosi diverse di farmaci o associazioni

Non si tiene conto dell'età: calo del 10% di LDL-C, il rischio scende di:

- **39% a 50 a**
- **20% a 70 a**

Rischio e durata del trattamento:

- **11% nel primo anno**
- **36% dopo 6 anni**

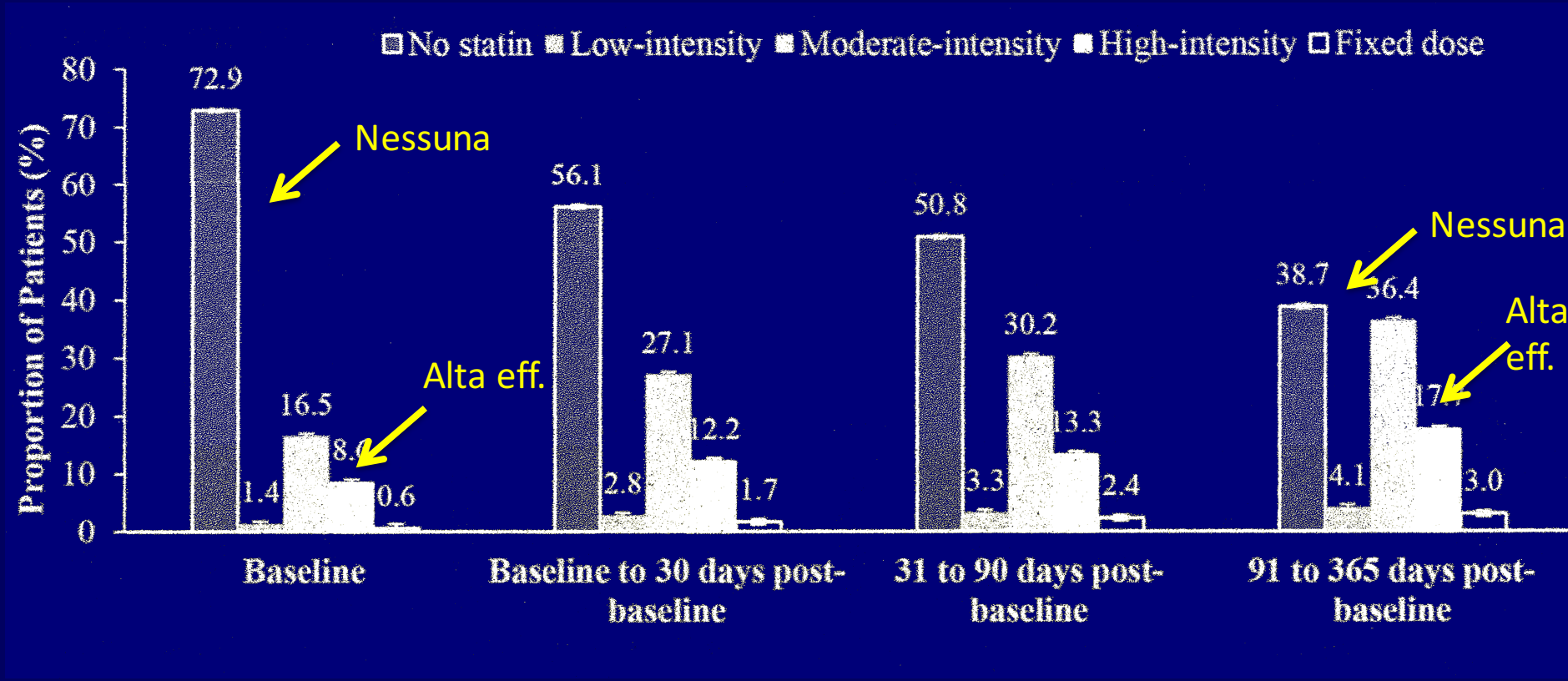
- **Errore nel calcolo di LDL –C (formula di Friedewald) con valori molto bassi di LDL**
- **Rischio di diabete**

LOWER IS BETTER – PUNTI FORTI

- LDL-colesterolemia a 50 mg/dl presenta vantaggi statistici rispetto a valori superiori

- Non sono emersi elementi negativi nei confronti di un calo drammatico della colesterolemia

IMPIEGO DI STATINE IN PAZIENTI DISLIPIDEMICI USA CON IMA O POST-EVENTO (Life-Link Database, n=175.103, 62.6 a)



Unni et al, J Clin Lipidol 10, 63, 2016

LOWER IS BETTER *Outline:*

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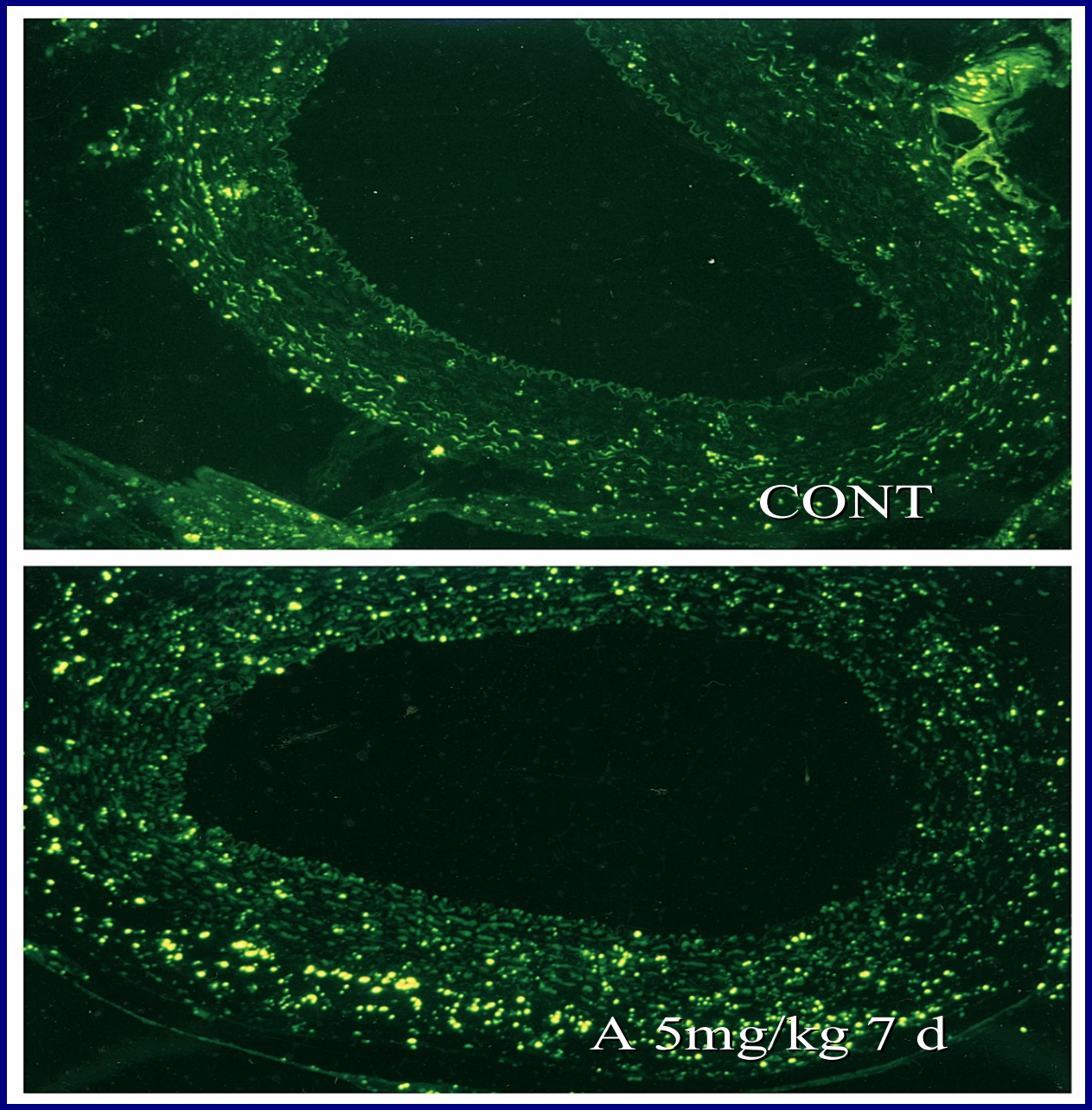
STATINE: GLI EFFETTI PLEIOTROPI

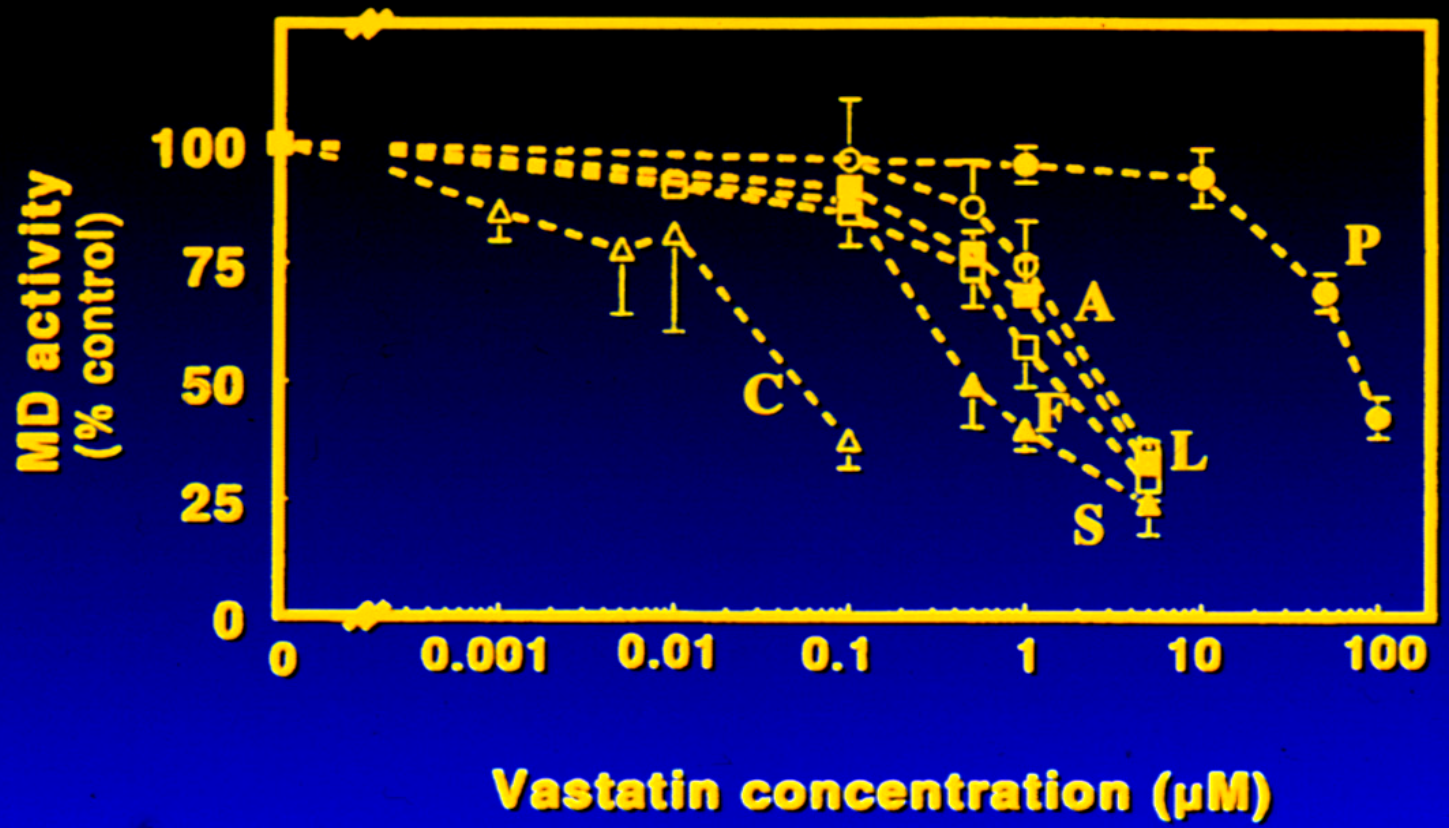
- Vasodilatazione (NO)
- Attività antitrombotica
  - *piastrine*
  - *Tissue Factor*
- Fibrinolisi
  - *antagonismo PAI-1*
- Ridotta proliferazione cellulare
- Attività antiinfiammatoria
- Ridotta viscosità

INCREASED APOPTOSIS IN COLLARED NC RABBIT BY ATORVASTATIN



Baetta et al, Pharmacol Res, 36, 115, 1997

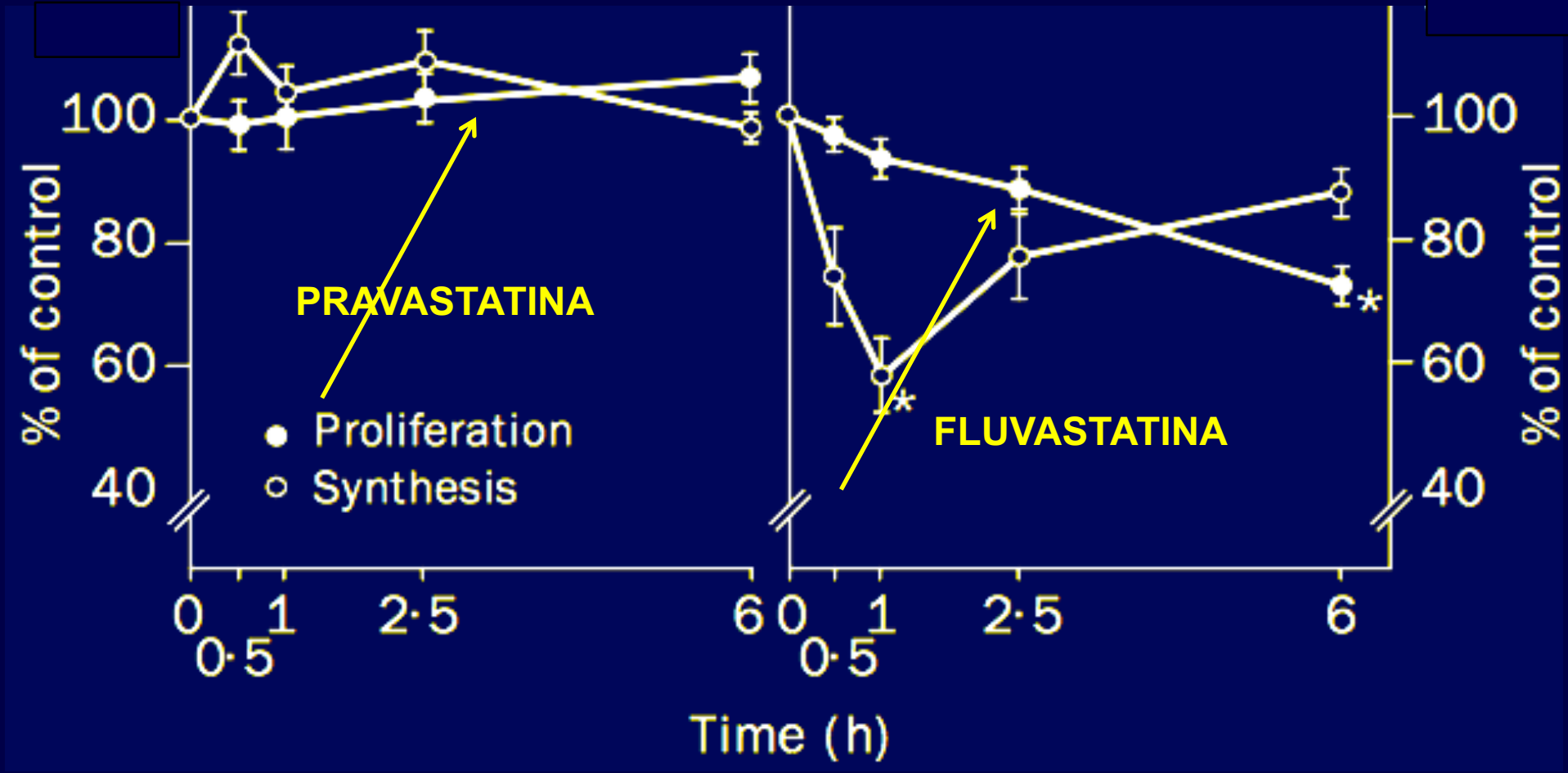
Antiproliferative effect of different statins on human arterial smooth muscle cells during 3-day incubation



A= atorva; C=ceriva; F=fluva; P=prava; S=simva

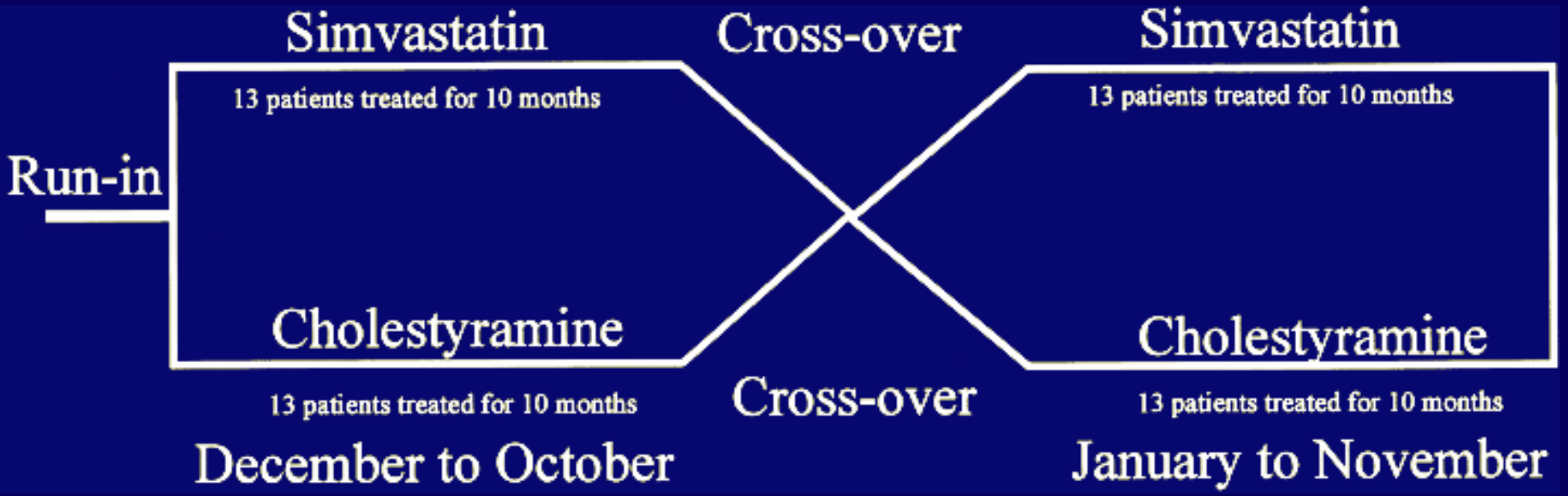
Nègre-Aminou et al, BBA 1345, 259, 1997

SIERI POST-TRATTAMENTO CON PRAVA E FLUVASTATINA DIFFERISCONO NELL'AZIONE SU SINTESI DI COLESTEROLO E PROLIFERAZIONE



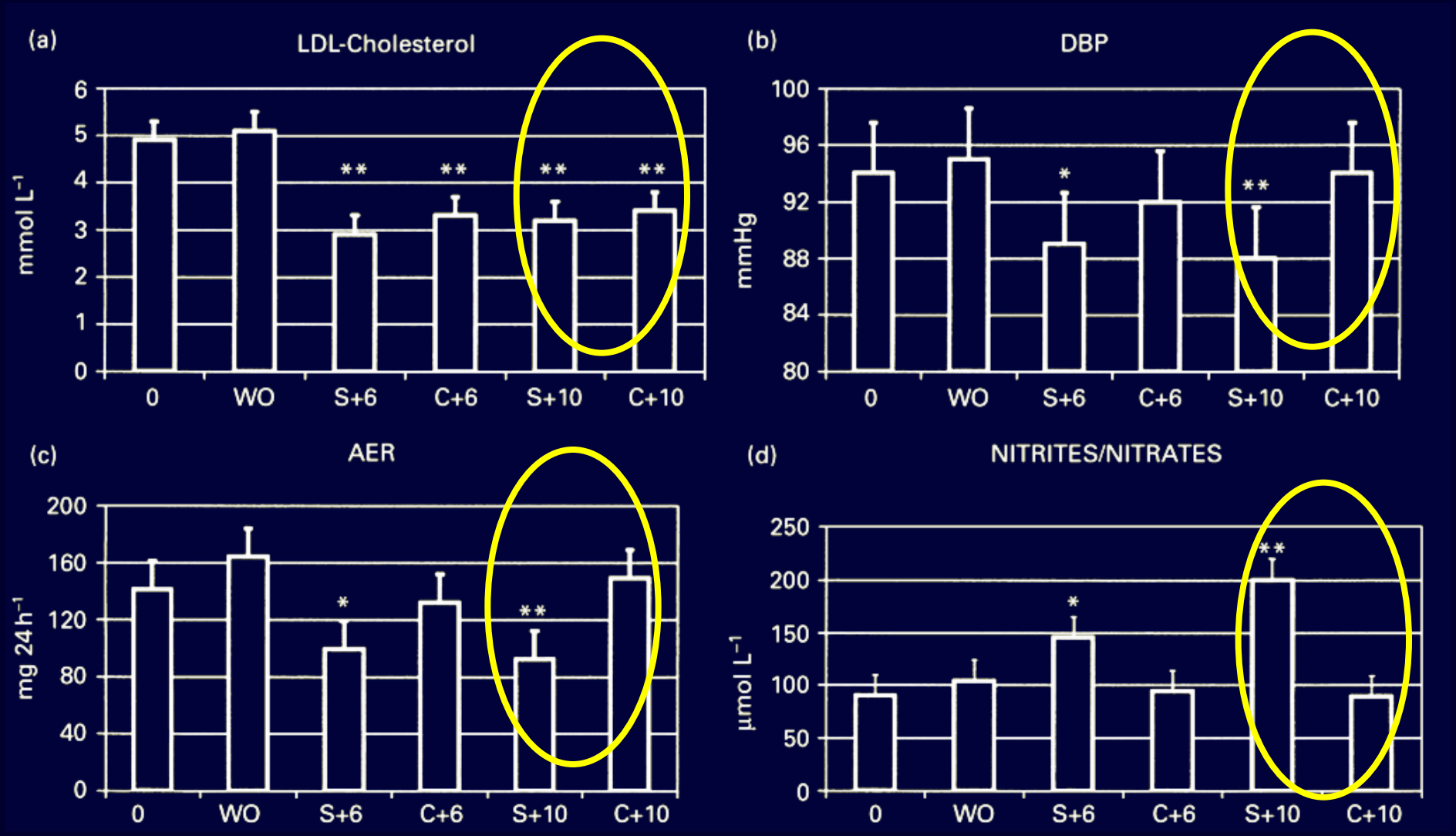
Corsini et al, Lancet 348, 1584, 1996

EFFETTI PLEIOTROPI DI SIMVASTATINA VS RESINA IN DIABETICI IPERTESI MICROALBUMINURICI



Tonolo et al, Eur J Clin Invest 30, 980, 2000

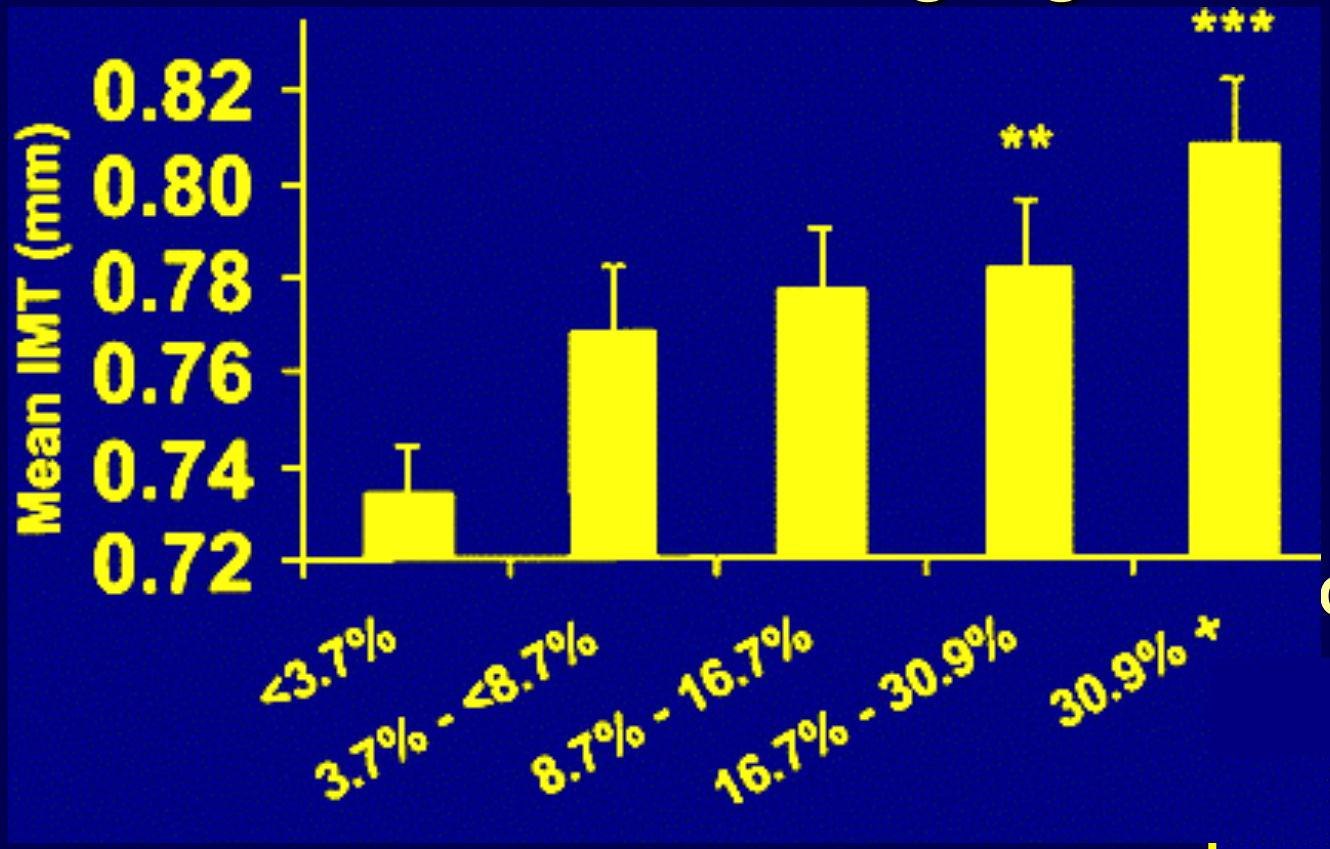
A PARITA DI CALO DI LDL-C SIMVASTATINA MIGLIORA I PARAMETRI RENALI IN DIABETICI MICROALBUMINURICI



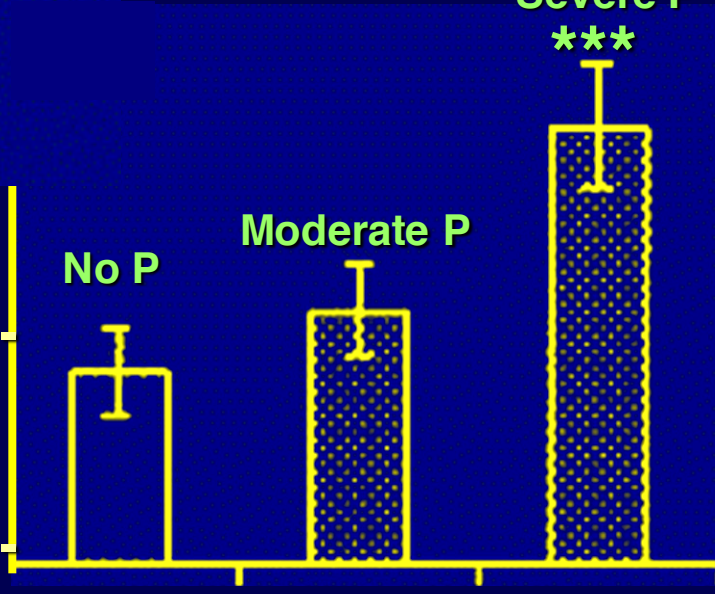
Tonolo et al, Eur J Clin Invest 30, 980, 2000


OM, m, 39 y, type IIb, T Chol 280 mg/dl, LDL 200 mg/dl, TG 290 mg/dl, HDL 44 mg/dl

Quintili di tasca gengivale



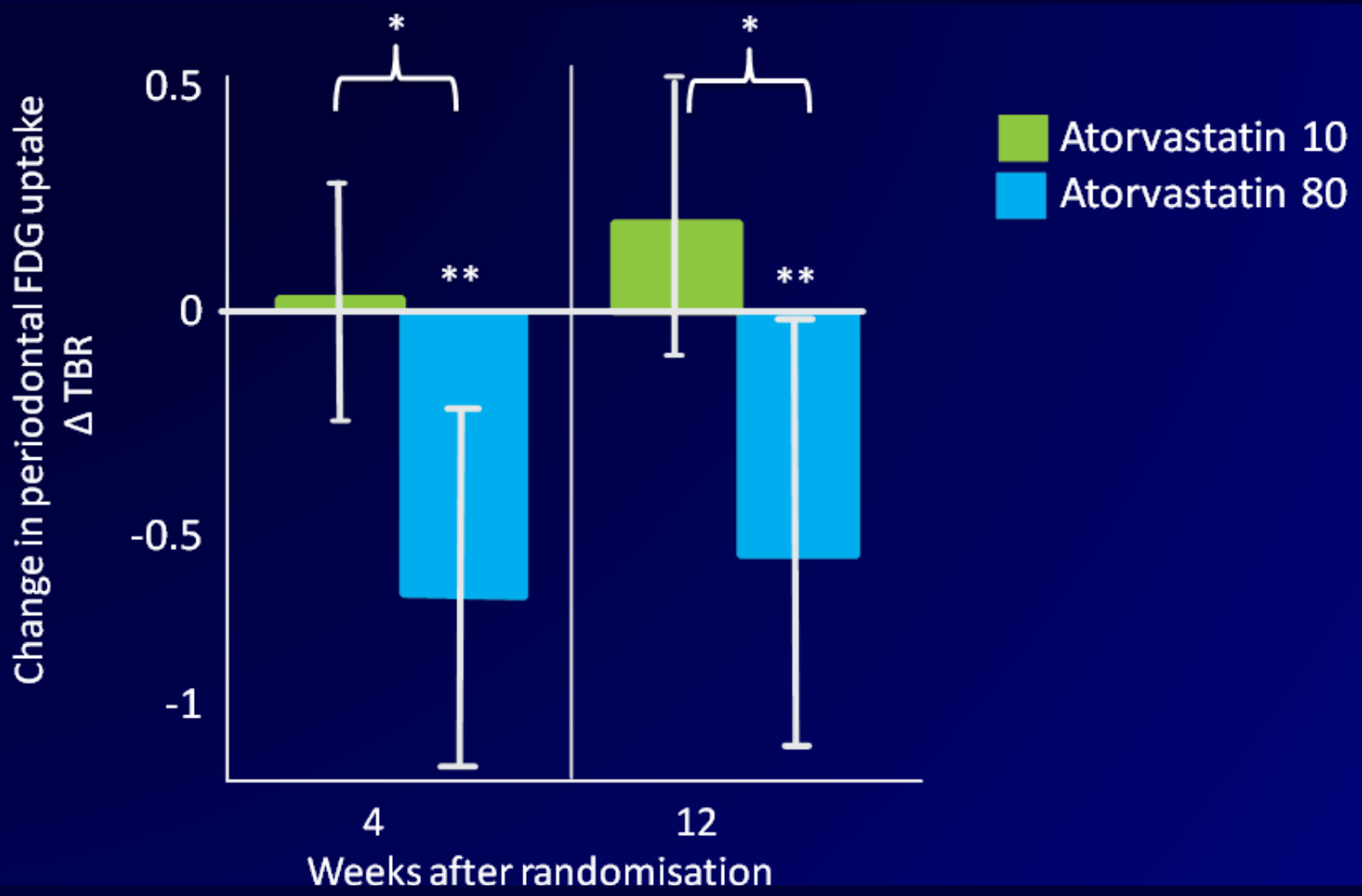
Gravità della patologia



LA PARODONTOPATIA È CORRELATA ALL'INTIMA MEDIA THICKNESS

Beck et al, ATVB 21, 1816, 2001

MIGLIORAMENTO DELLA TASCA GENGIVALE DOPO ALTA DOSE DI STATINA



Subramanian et al, J Am Coll Cardiol. 62, 2382, 2013

Use of statins for periodontal disease and bone regeneration

WO 2014030132 A2

Messina, Rosenberg, *Colombia*

For 10 ml:

Calcium atorvastatin 200 mg

Menthol 5 mg sodium fluoride 5 mg

Lutrol gel 250 mg

Base gel (enough quantity for) 10 ml

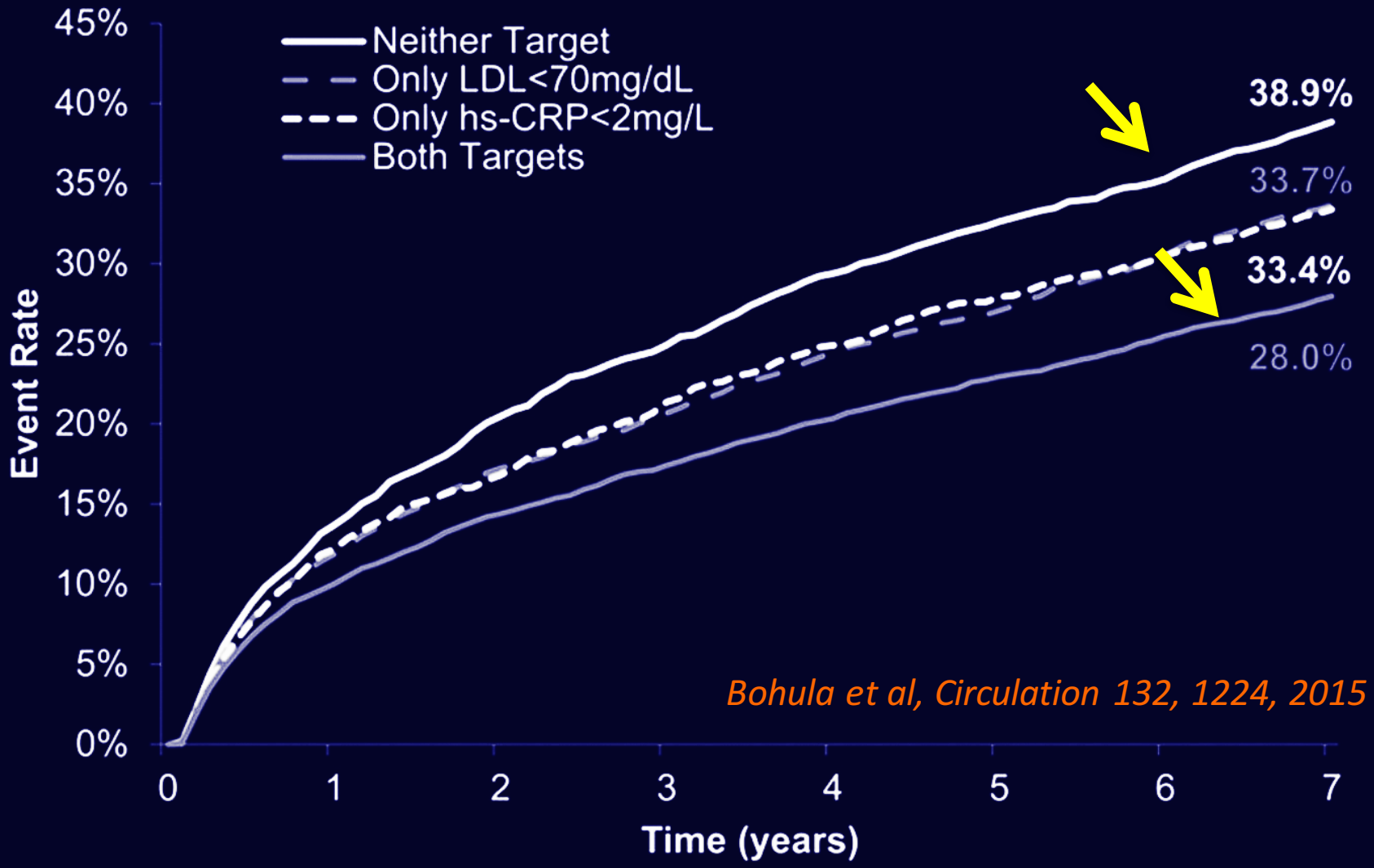
STATINE: SOLO COLESTEROLO?

A parità di effetto ipocolesterolemico, sembrano esercitare un maggiore effetto anti arteriosclerotico

- **attività "antiinfiammatoria"**
- **riduzione di CRP**
  - **di chemochine**
- **aumentata espressione di TLR4**

Possibile attività attraverso la riduzione del testosterone

STUDIO IMPROVE-IT : RISULTATO OTIMALE CON DISCESA SIA DI LDL-C CHE DI CRP



Bohula et al, Circulation 132, 1224, 2015

Neither Target	2074	1730	1540	1414	1256	898	704	370
Only LDL<70	5045	4311	3938	3667	3328	2468	1858	1072
Only hs-CRP<2	2065	1753	1619	1500	1386	1041	826	478
Both Targets	5995	5295	4930	4664	4318	3257	2612	1537

STATINE: SOLO COLESTEROLO?

A parità di effetto ipocolesterolemico, sembrano esercitare un maggiore effetto anti arteriosclerotico

- **attività "antiinfiammatoria"**
- **riduzione di CRP**
  - **di chemochine**
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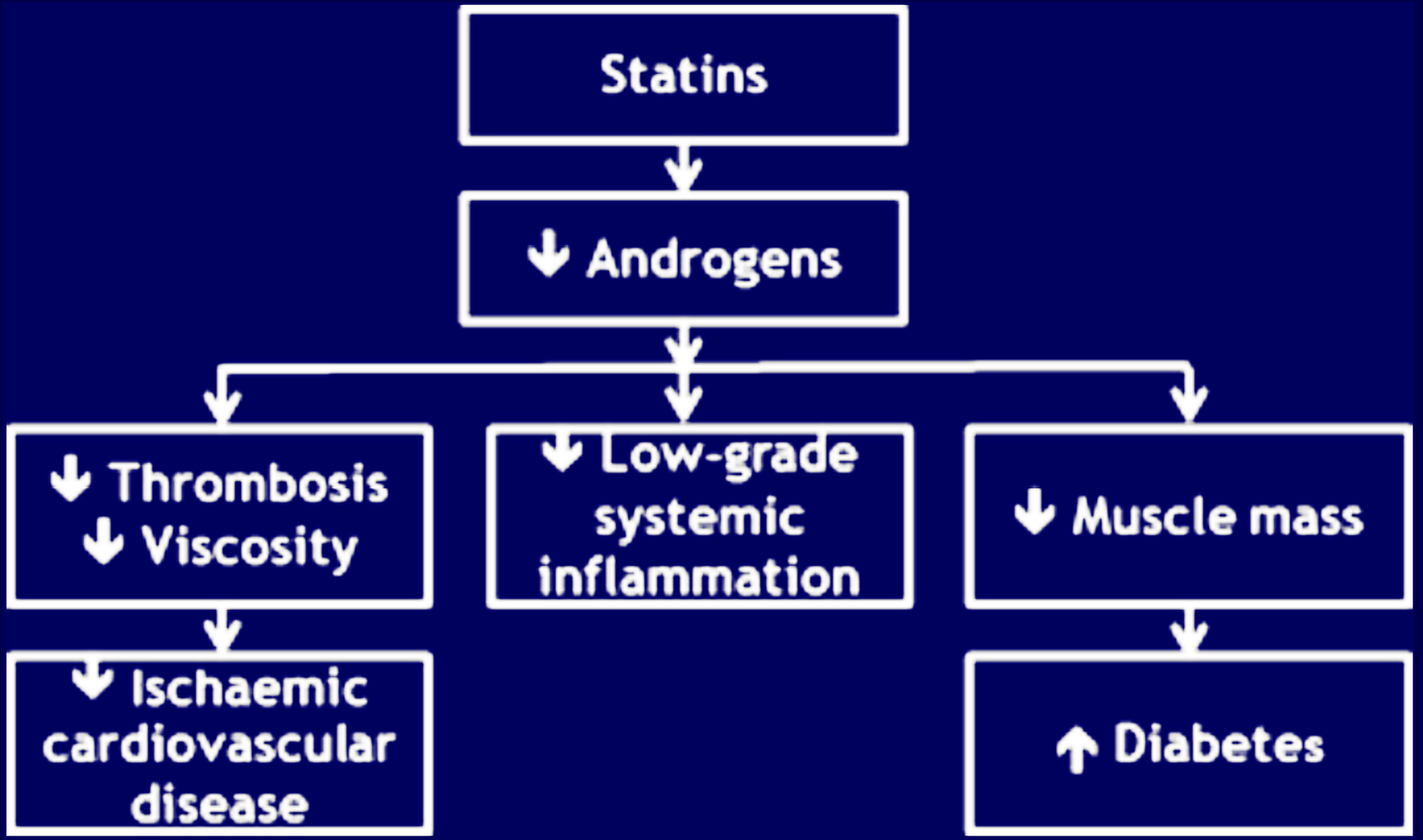
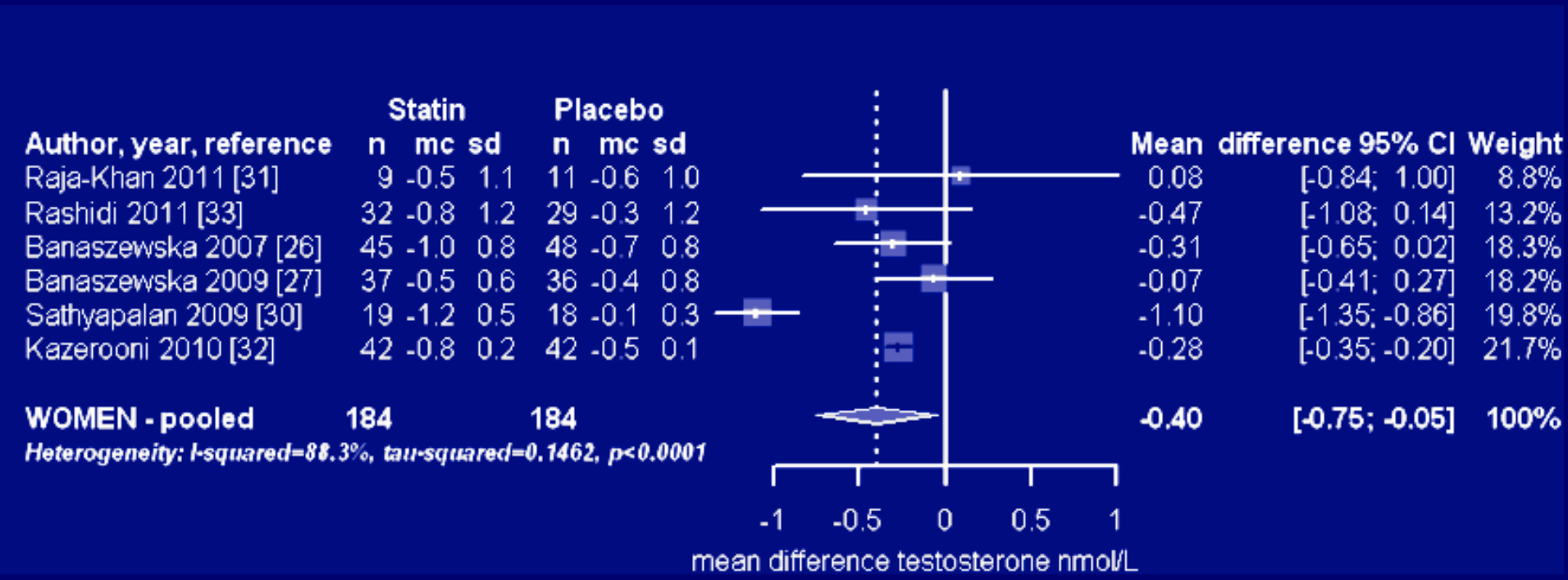
Possibile attività attraverso la riduzione del testosterone

STATINE-TESTOSTERONE: *THE CONNECTION*



CM Schooling Eur J Clin Invest 44, 1135, 2014

STATINE RIDUCONO IL TESTOSTERONE NELLE DONNE



Schooling et al, BMC Medicine 11-57, 2013

LOWER IS BETTER *Outline:*

- Cosa significa? E' vero?
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IMPROVE-IT
I RISULTATI

Aggiunta di ezetimibe 10 mg a simvastatina 40 mg riduce significativamente gli eventi vascolari (%) ***NNT = 56***

	Simvastatina	Simvastatina/Ezetimibe
End point primario (morte, evento coronarico, AI, ictus)	34,7	32,7
End point pre-specificato (morte CV, IMA, ictus)	22,2	20,4
IMA non fatale	14,4	12,8
Ictus ischemico	4,1	3,4

IL RISCHIO RESIDUO: COME AFFRONTARLO?

- **Nello studio IMPROVE-IT il 35% dei trattati hanno avuto IMA in sei anni.**

Cause

-poca efficacia della statina/scarsa compliance

-altra patologia:
dislipidemia aterogena (s. metabolica)
alti trigliceridi
basse HDL

TG-HDL MORTALITA' TOTALE E CORONARICA

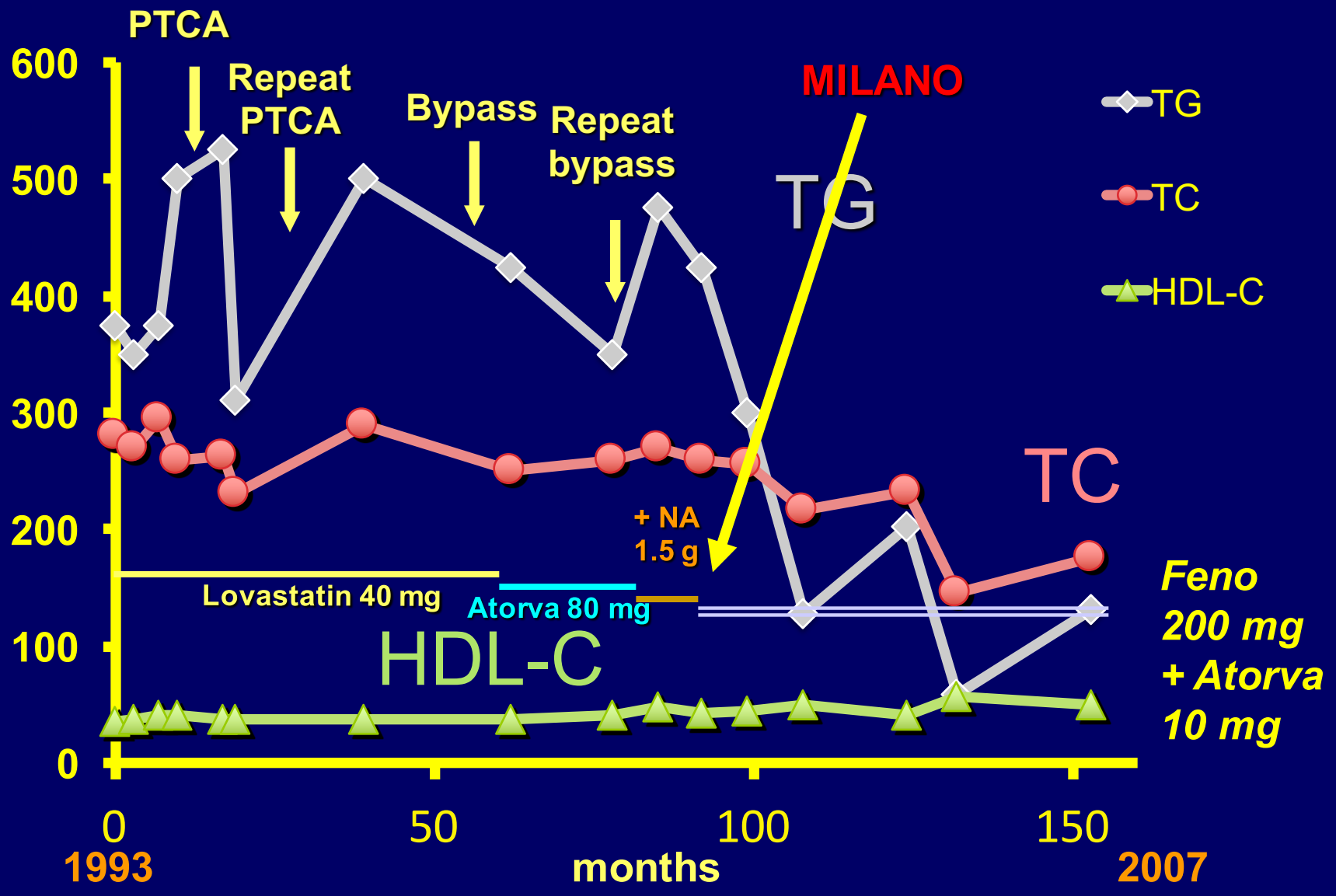
COPENHAGEN MALE STUDY, 8 y, 2,906 m, 53 -74y

TG (mM/L) thirds

	0.88 (0.44-1.09) (n=825)	1.33 (1.10-1.59) (n=832)	2.45 (1.60-22.4) (n=715)
HDL-C mM/L		IHD (%)	
1.00	3.2	8.1	11.7
1.32	3.8	9.2	9.3
1.76	3.9	4.4	11.1
Overall	3.8	7.3	10.9
All cause mortality	8.7	13.3	11.5

Jeppesen et al. Circulation 97, 1027, 1998

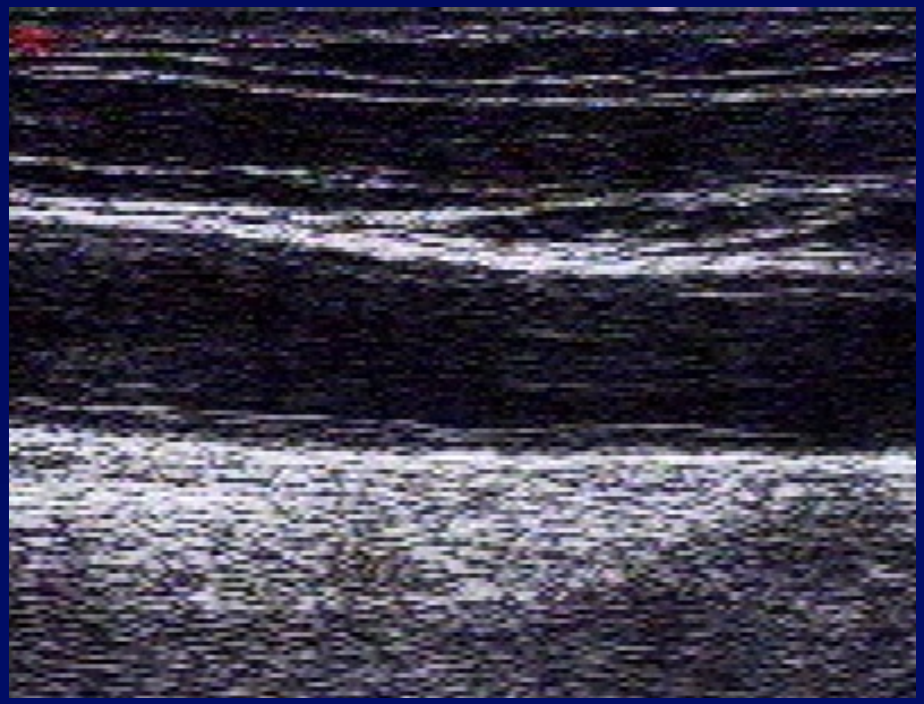
RESULTS OF THERAPY IN A SEVERELY HYPERTRIGLYCERIDEMIC US PT



JC, born 1957

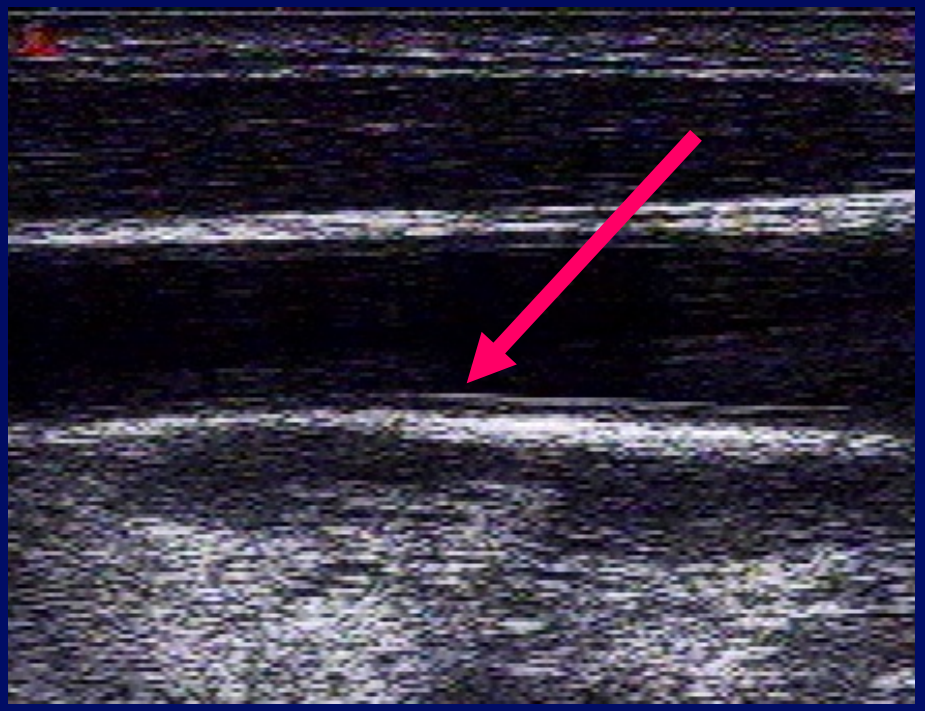
Pt. JC, pre and post-treatment

2000



IMT 1.22 mm

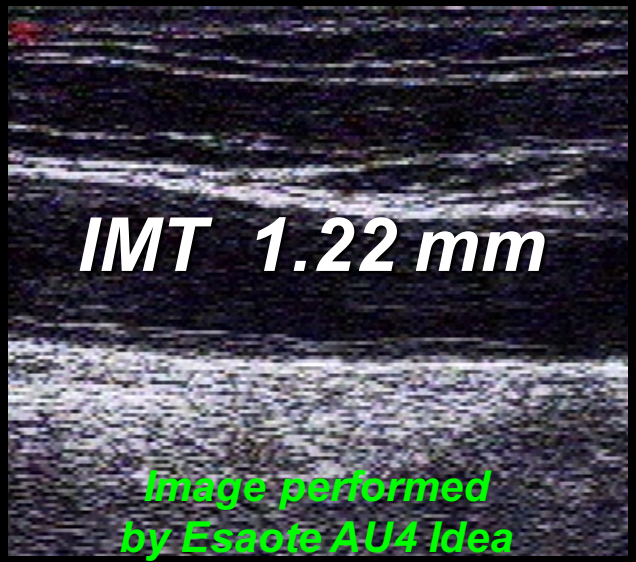
2004



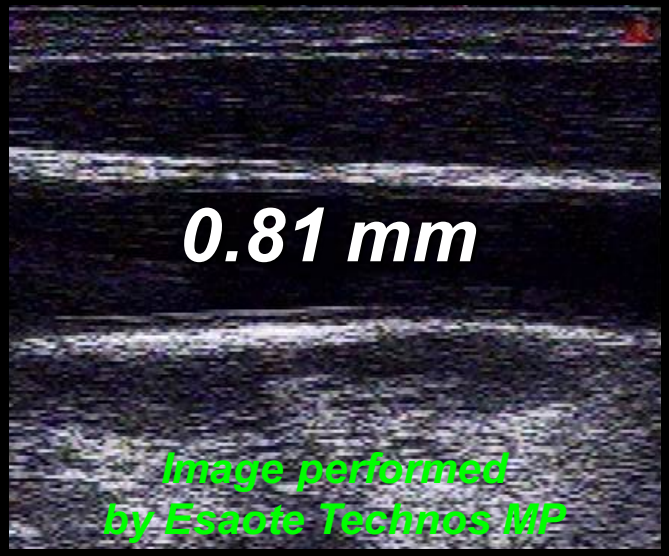
0.81 mm

Pt. JC, pre and post-treatment

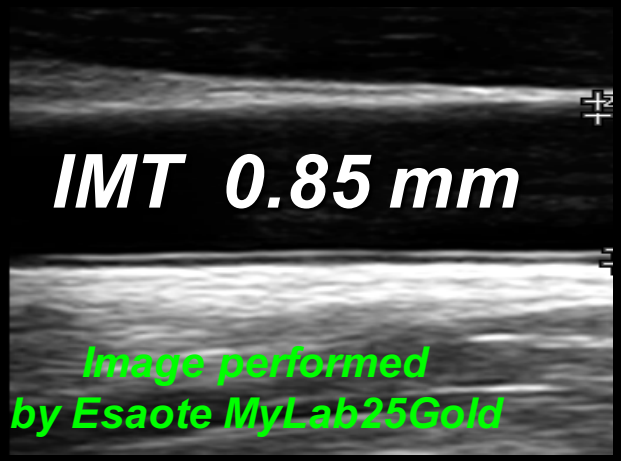
2000



2004

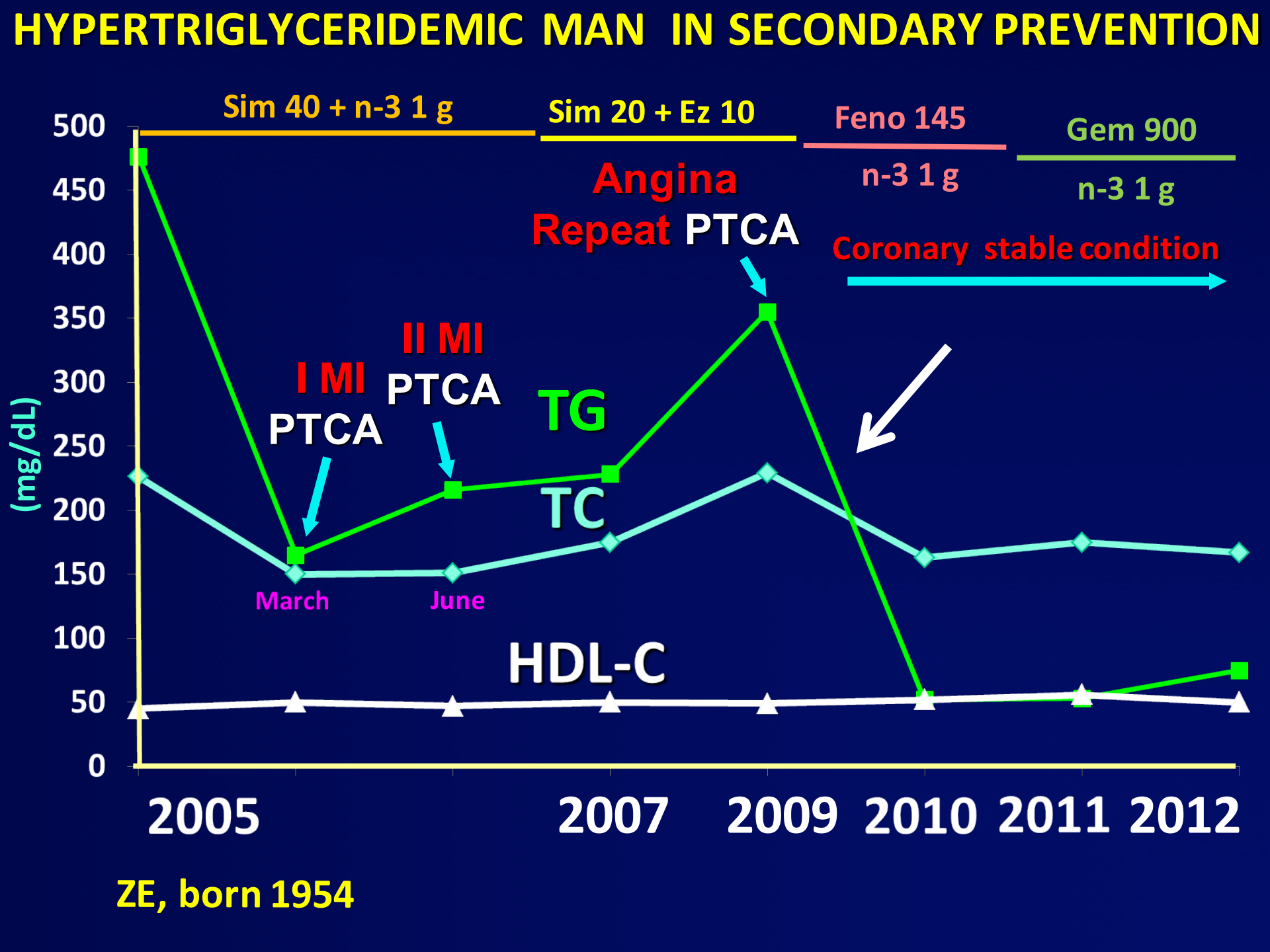


2012




CNN REPUBLICAN
PRESIDENTIAL DEBATE

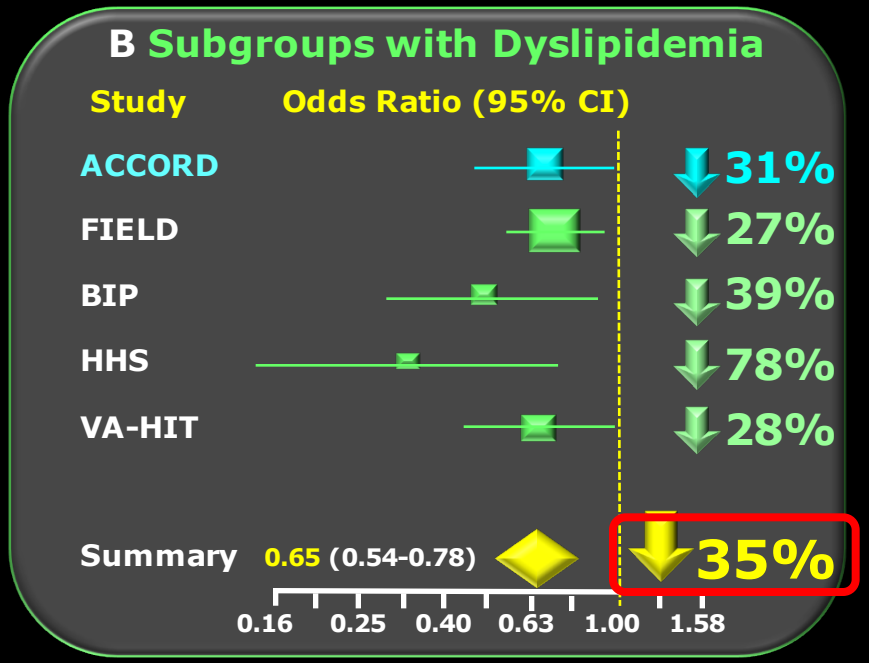
HYPERTRIGLYCERIDEMIC MAN IN SECONDARY PREVENTION

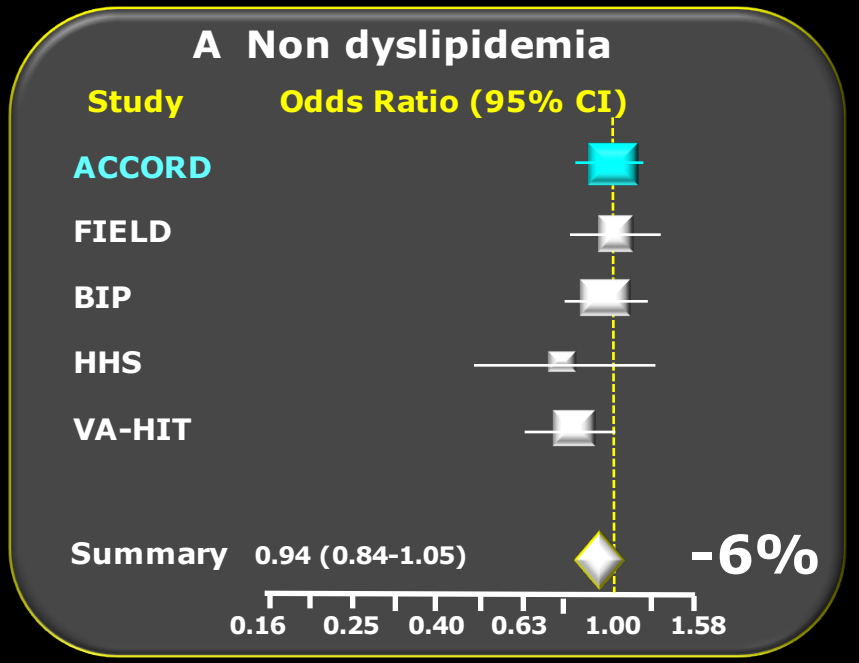


ZE, born 1954

Effect of fibrates in subgroups without (A) and with (B) dyslipidemia

A total of 2428 fibrate-treated subjects (302 events) and 2298 placebo-treated subjects (408 events) with dyslipidemia were included in the analysis



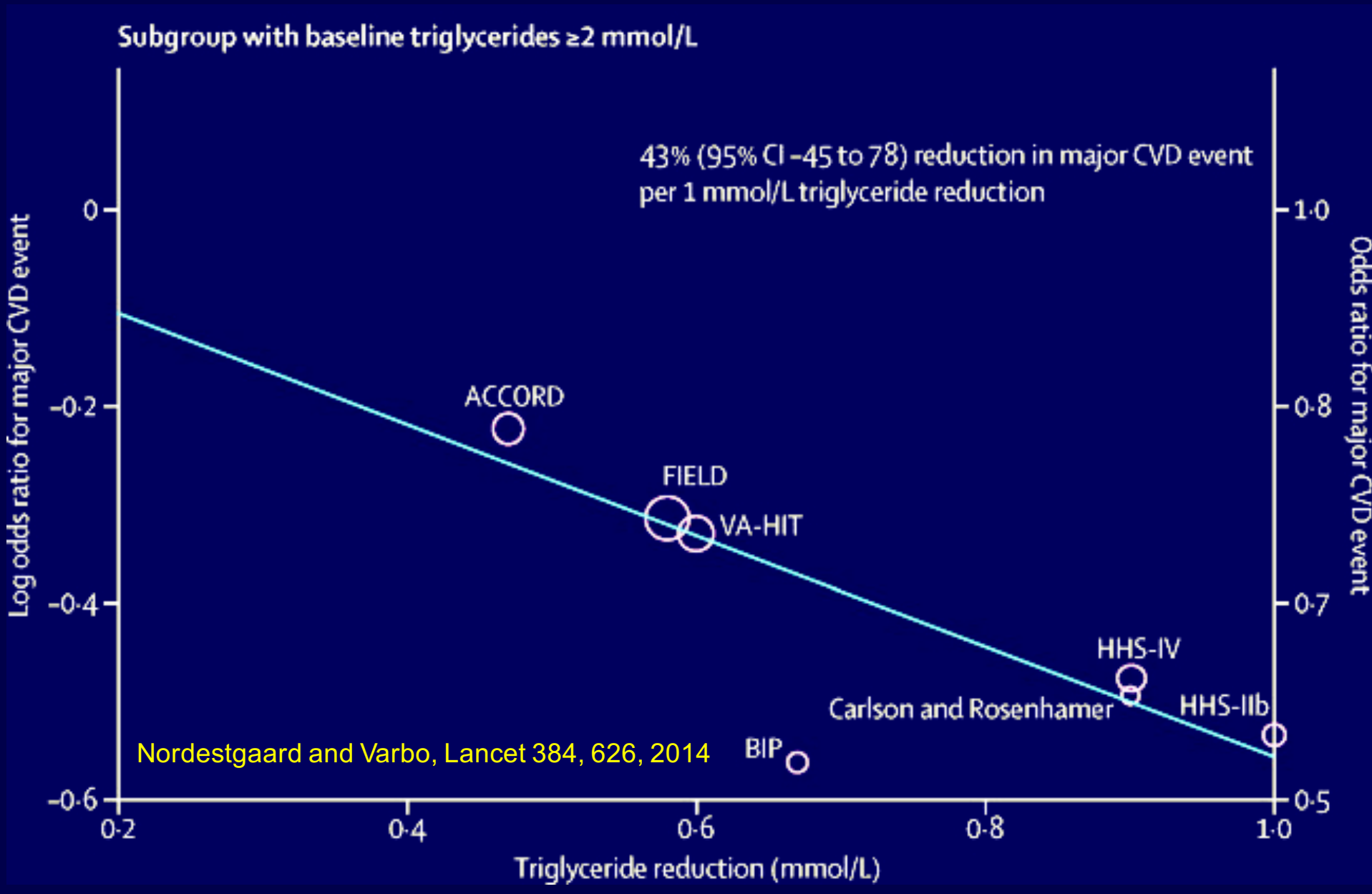


LIPID CRITERIA FOR DYSLIPIDEMIA

Trial	Triglycerides cut-off (mg/dL)	HDL cholesterol cut-off (mg/dL)
FIELD	≥204 (2.2 mmol/L)	<40 in men (1.0) ; <50 in women (1.3)
BIP	≥200	<35
Helsinki Heart Study	>204	<42
VA-HIT	>180	<40

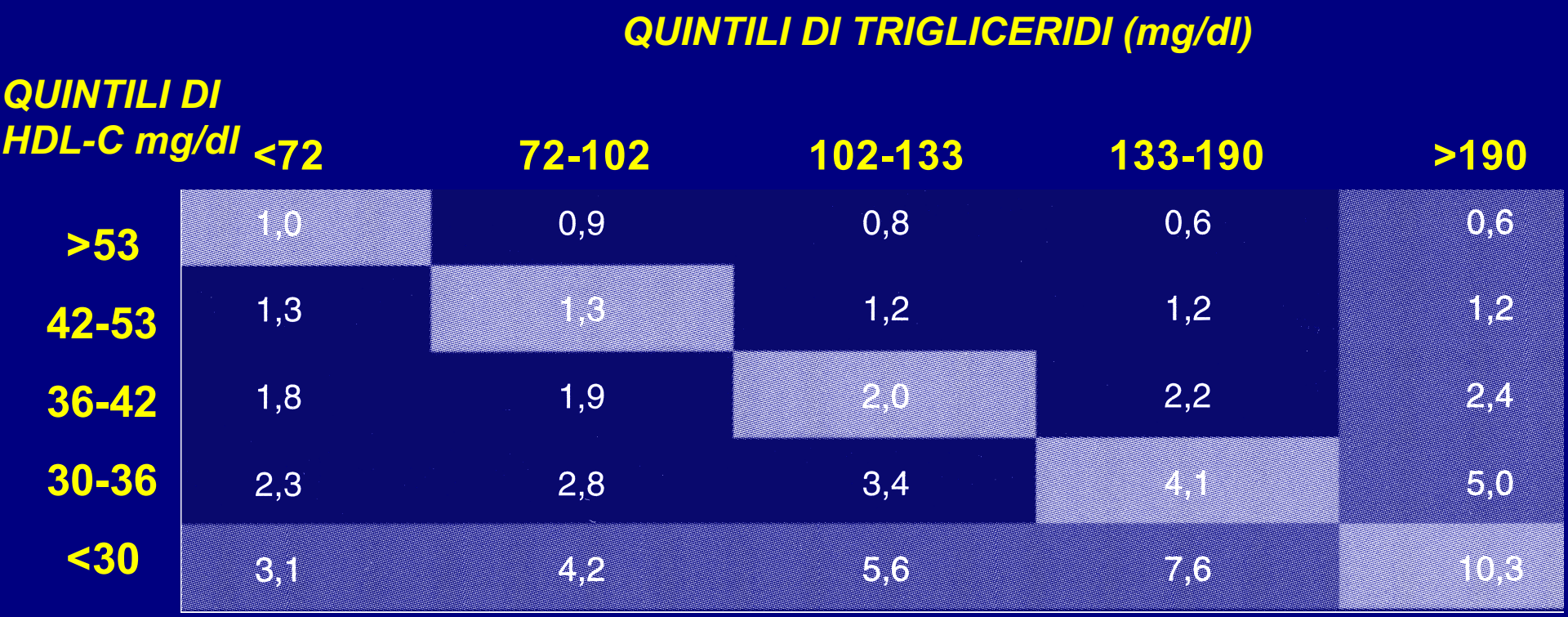
Lee et al., Atherosclerosis 217, 492, 2011

RELAZIONE DI CADUTA DI TRIGLICERIDI E RIDUZIONE DI EVENTI CV



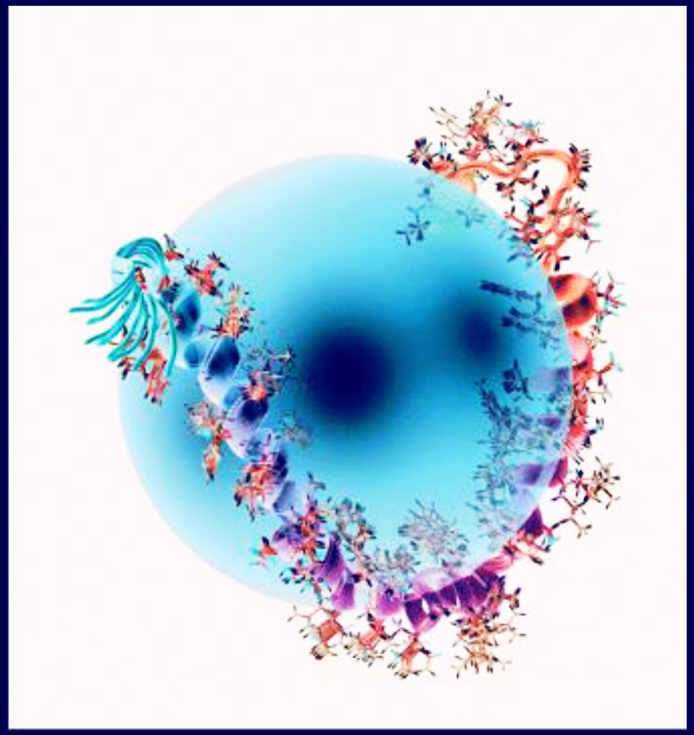
MOLTIPLICATORI DI RICHIO DA TRIGLICERIDI/HDL IN PAZIENTI A TARGET

345 PAZIENTI, 61% MASCHI, MEDIA 66 a



Carey et al., Am J. Cardiol 106, 757, 2010

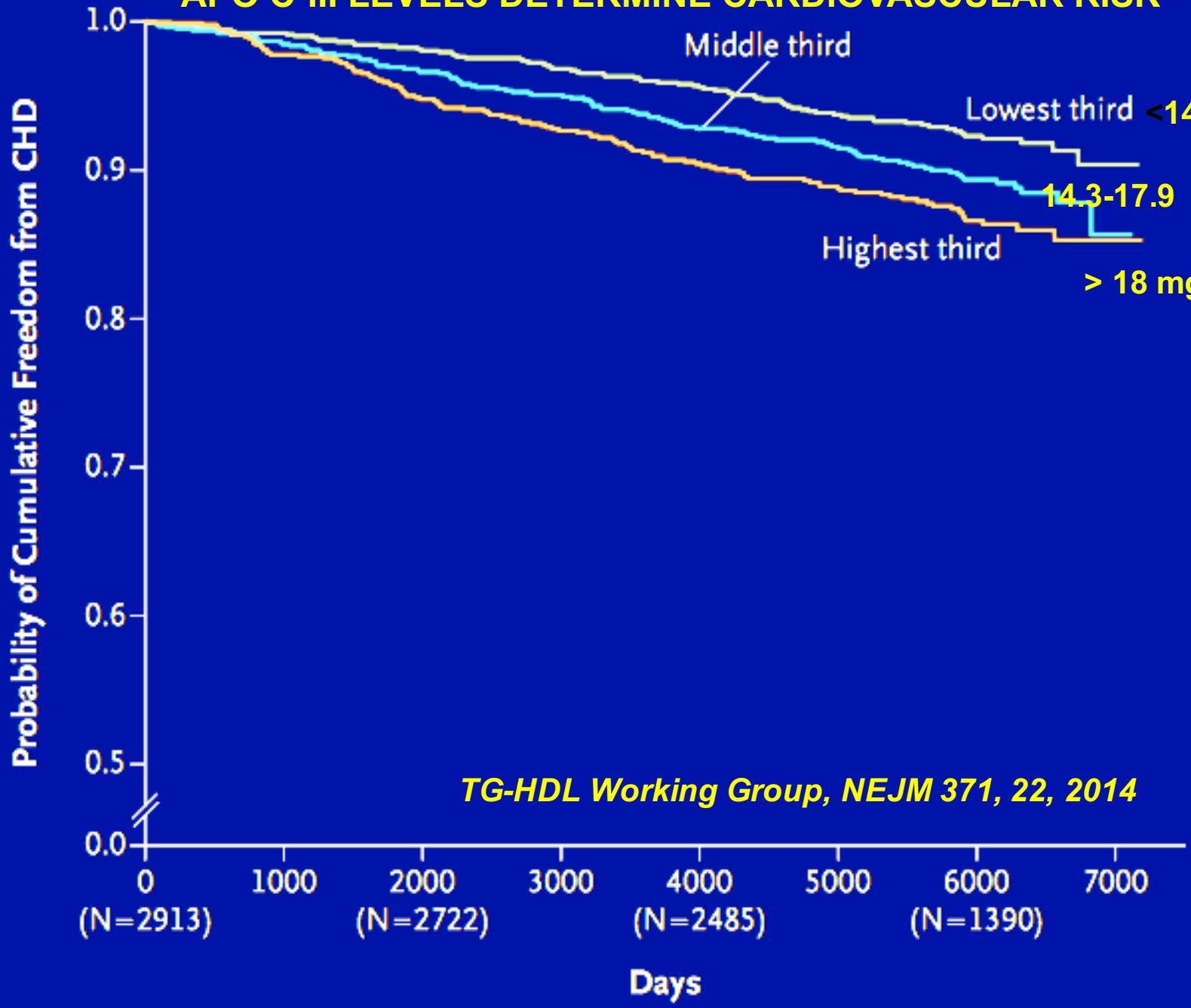
WHAT IS APO C-III



ApoC-III in a complex with an SDS micelle as derived by NMR

- **ApoC-III is a 79 aminoacid glycoprotein synthesized principally in the liver**
  - **Multiple apoC-III proteins on VLDL and HDL particles**
- **Plays a key role in determining serum triglyceride (TG) levels**
  - **Potent inhibitor of LPL**
  - **Inhibits hepatic uptake of TRLs**
- **Individuals with loss of function mutations in ApoC-III exhibit a favorable lipid profile, reduced CHD and increased longevity**
  - Old World Amish
  - Ashkenazi Jews
  - Exome Sequencing Project
  - Copenhagen City cohorts

APO C-III LEVELS DETERMINE CARDIOVASCULAR RISK



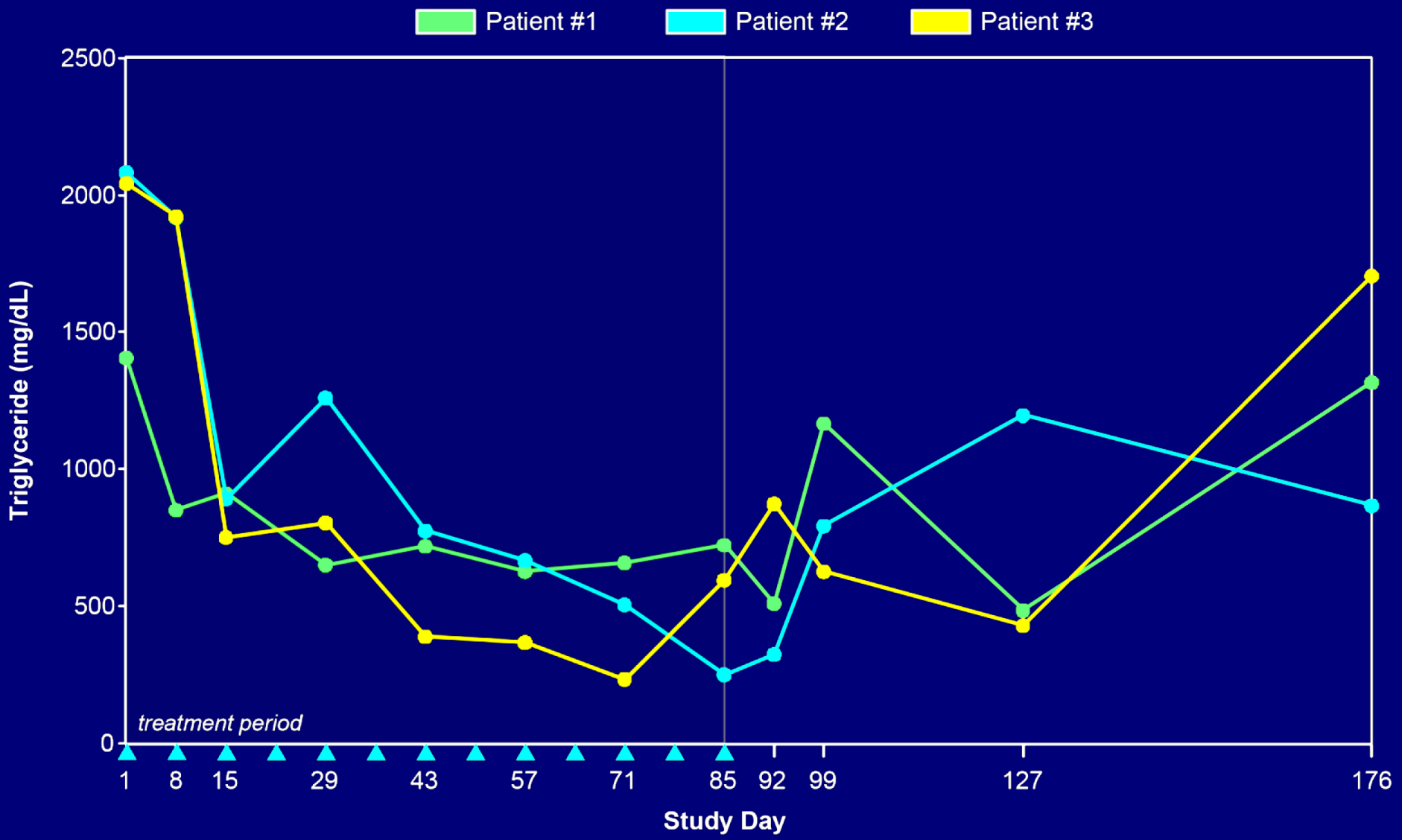
<14.2 mg/dl

14.3-17.9 mg/dl

> 18 mg/dl

TG-HDL Working Group, NEJM 371, 22, 2014

ISIS-APOCIII$_{Rx}$ ANTISENSE TREATMENT OF PATIENTS WITH FASTING CHYLOMICRONEMIA



Gaudet et al, NEJM 373, 428, 2015

LOWER IS BETTER *Outline:*

- **Cosa significa? E' vero?**
- **Perchè? Gli effetti pleiotropi delle statine**
- **Il rischio "residuo"**

e HDL, Lp(a), sindrome metabolica, insulino-resistenza, Proteina C reattiva..?

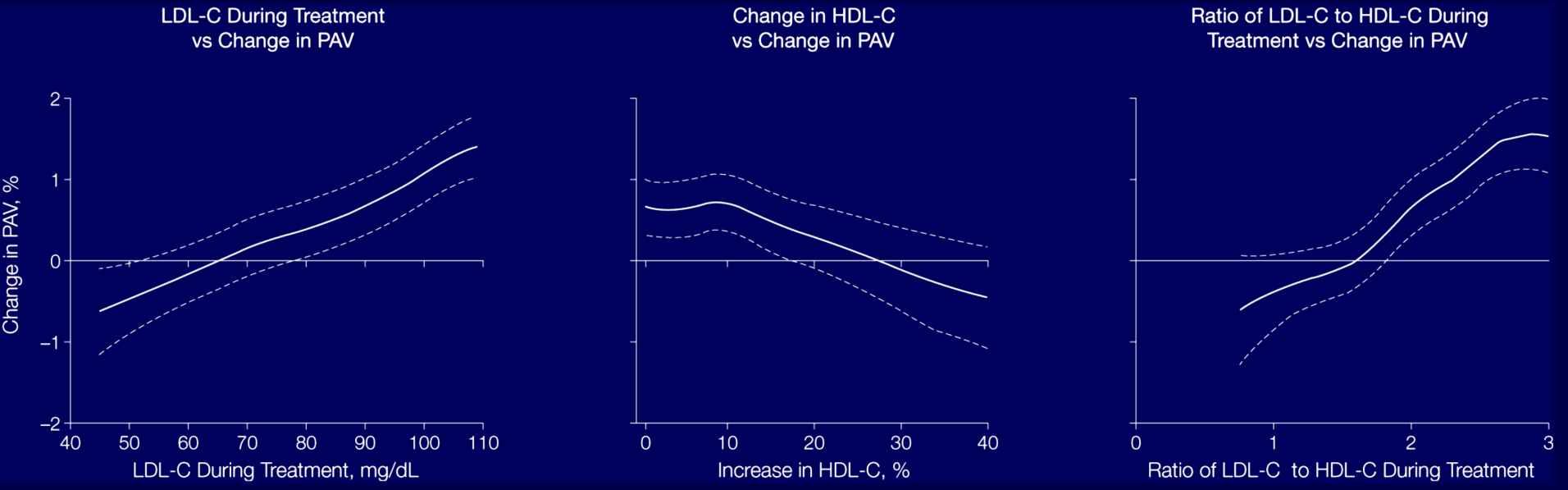
LDL-C: I VALORI TARGET

LDL-colesterolo:

< 100 mg/dl? ***(AHA 2001)***

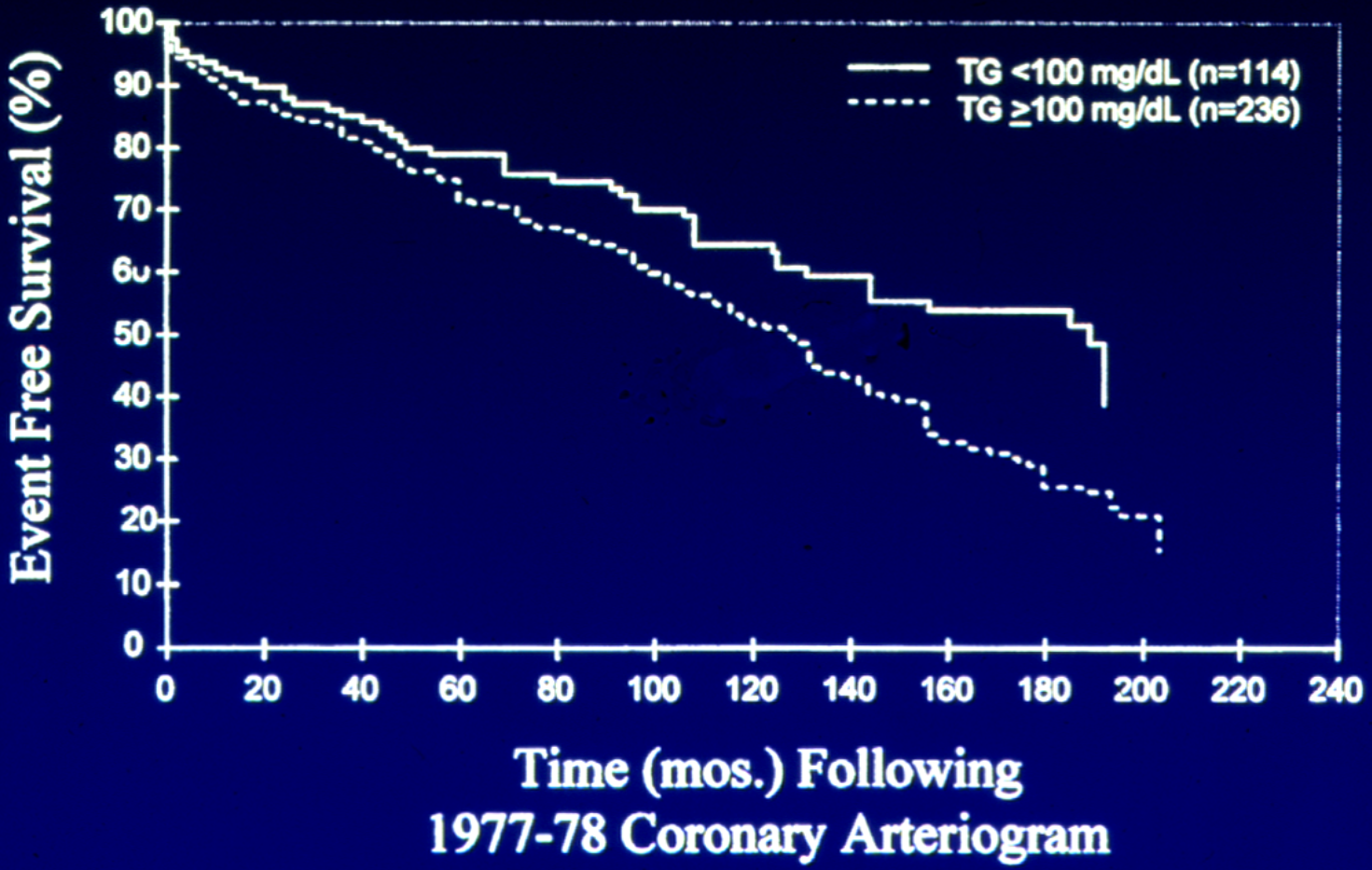
< 70 mg/dl? ***(AHA 2004)***

Valutare l'accettabilità della terapia, eventuali costi.
I dati sono convincenti?


LDL-C During Treatment
vs Change in PAV
Change in PAV, %
2
1
0
−1
−2
40
50
60
70
80
90
100
110
LDL-C During Treatment, mg/dL
Change in HDL-C
vs Change in PAV
0
10
20
30
40
Increase in HDL-C, %
Ratio of LDL-C to HDL-C During
Treatment vs Change in PAV
0
1
2
3
Ratio of LDL-C to HDL-C During Treatment

TRIGLYCERIDEMIA PREDICTS SURVIVAL AFTER CORONARY ANGIOGRAPHY

350 CAD pts followed for 20 years



Miller et al, JACC 31, 1252, 1998

Therapeutic Targets in Patients With FH

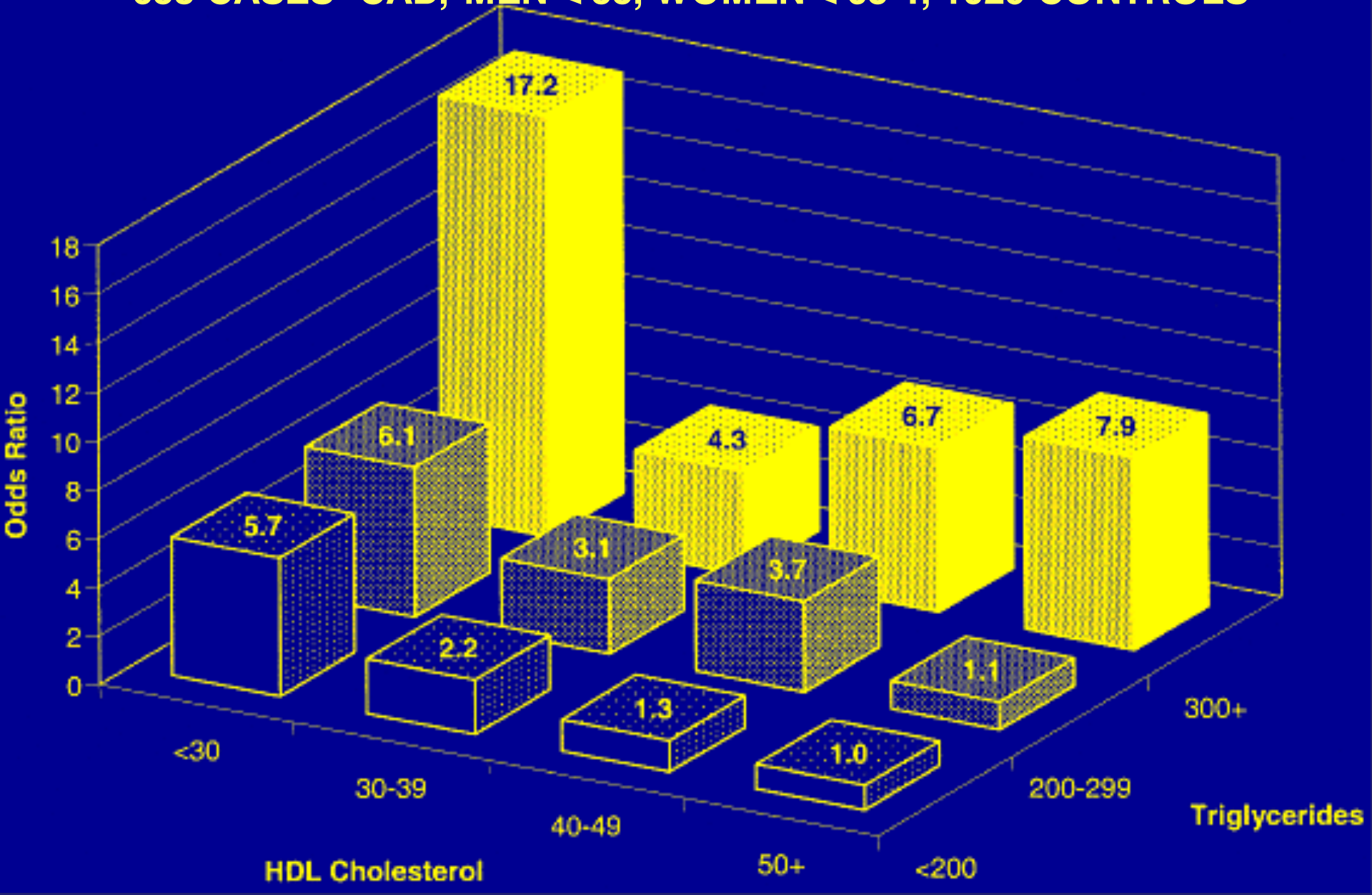
Average LDL-C decrease needed depending on baseline levels[a]

Baseline LDL-C Levels	190 mg/dL	220 mg/dL	250 mg/dL	280 mg/dL	310 mg/dL
To reach LDL-C < 160 mg/dL	–16%	–27%	–36%	–43%	–48%
To reach LDL-C < 100 mg/dL	–47%	–55%	–60%	–64%	–68%

In addition to high baseline LDL-C levels, not achieving targets may be due to many other causes in patients with FH, including statin intolerance[b]

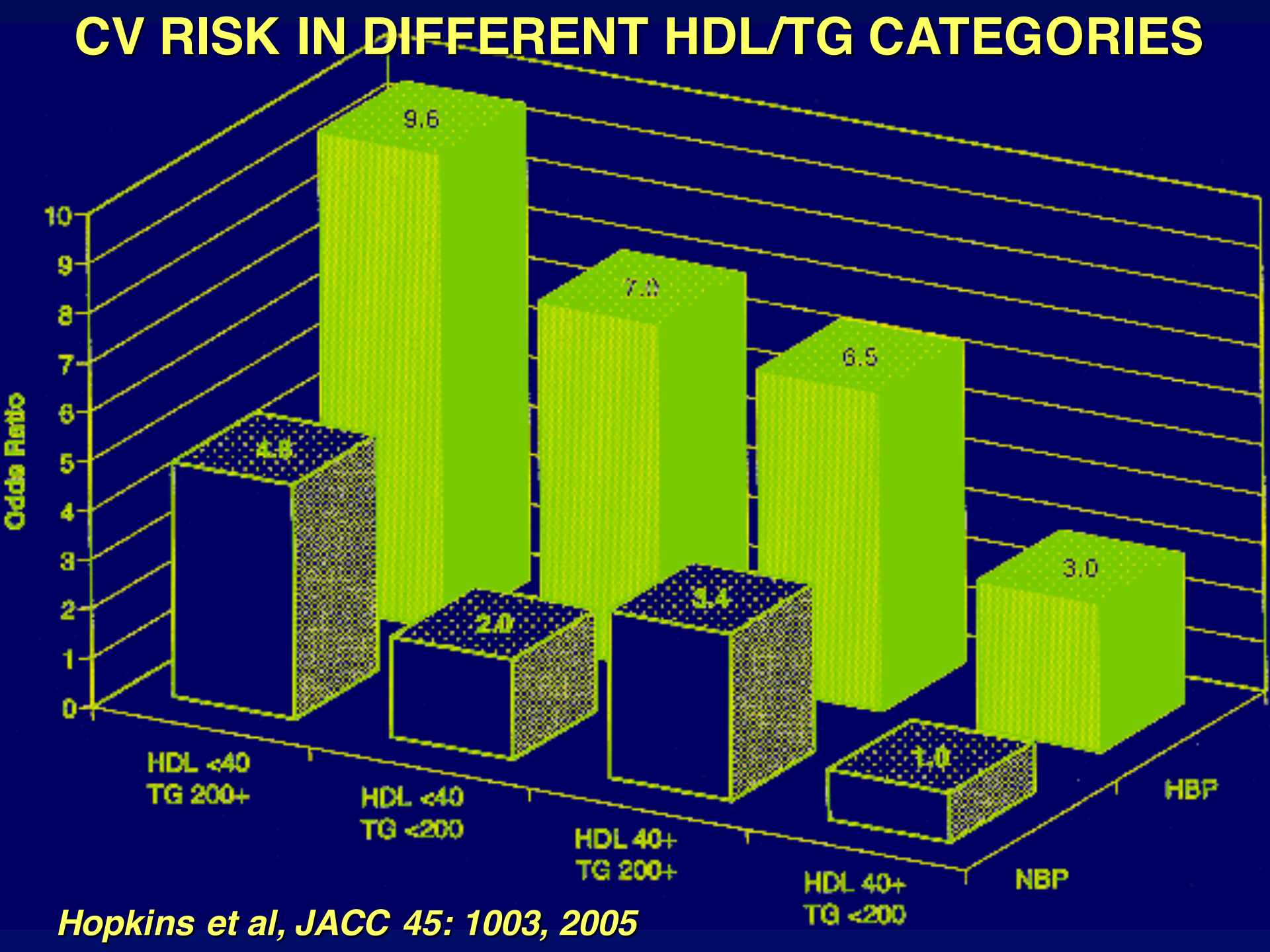
Sabatine. HeartOrg 2012

HYPERTRIGLYCERIDEMIA INDEPENDENTLY ASSOCIATED WITH CV RISK
653 CASES CAD, MEN < 55, WOMEN < 65 Y, 1029 CONTROLS



Hopkins et al, JACC 45: 1003, 2005

CV RISK IN DIFFERENT HDL/TG CATEGORIES



Hopkins et al, JACC 45: 1003, 2005