.....КЪМ ОПТИМИЗИРАНЕ НА ПОВЕДЕНИЕТО ПРИ АТЕРОГЕННА ДИСЛИПИДЕМИЯ.....

Доц. Л. ВЛАДИМИРОВА-КИТОВА, дм
Кардиологична Клиника,
МУ - Пловдив

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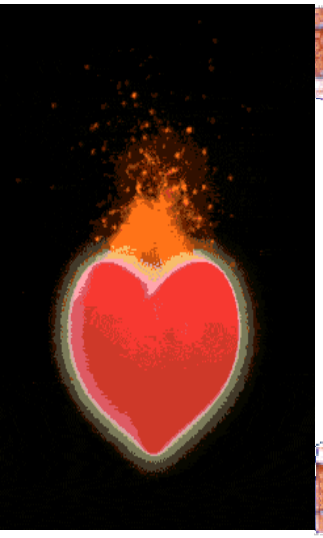
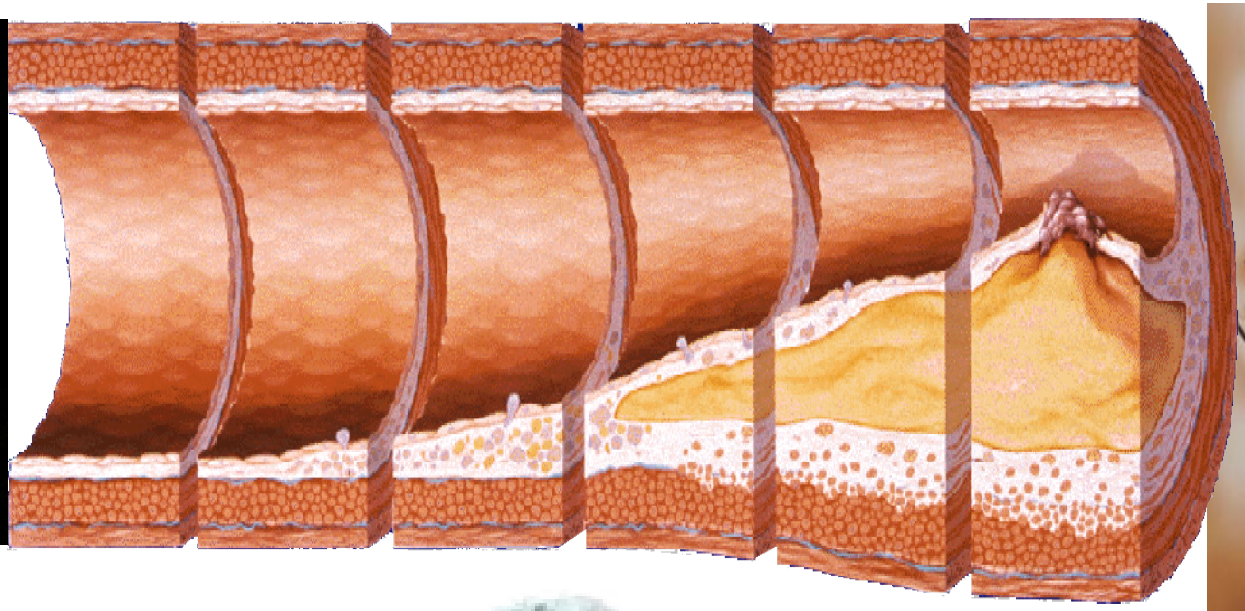


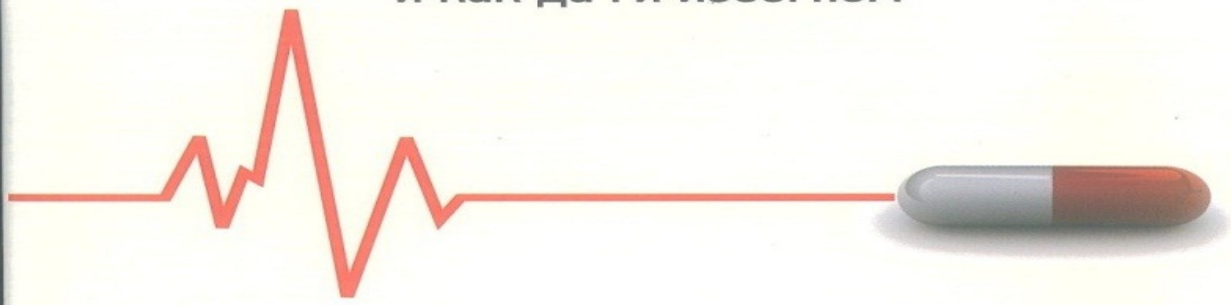



FUTURE
PAST
PRESENT

Д-р Малкълм Кендрик

ГОЛЯМАТА ИЗМАМА С ХОЛЕСТЕРОЛА

Истината за това, което предизвиква сърдечно-съдовите заболявания – и как да ги избегнем



ИЗТОК ЗАПАД

БИБЛИОТЕКА здраве

Atherosclerosis across 4000 years of human history: the Horus study of four ancient populations

Randall C Thompson, Adel H Allam, Guido P Lombardi, L Samuel Wann, M Linda Sutherland, James D Sutherland, Muhammad Al-Tohamy Soliman, Bruno Frohlich, David T Mininberg, Janet M Monge, Clide M Vallodolid, Samantha L Cox, Gomaa Abd el-Maksoud, Ibrahim Badr, Michael I Miyamoto, Abd el-Halim Nur el-din, Jagat Narula, Caleb E Finch, Gregory S Thomas

Summary

Background Atherosclerosis is thought to be a disease of modern human beings and related to contemporary lifestyles. However, its prevalence before the modern era is unknown. We aimed to evaluate preindustrial populations for atherosclerosis.

Methods We obtained whole body CT scans of 137 mummies from four different geographical regions or populations spanning more than 4000 years. Individuals from ancient Egypt, ancient Peru, the Ancestral Puebloans of southwest America, and the Unangan of the Aleutian Islands were imaged. Atherosclerosis was regarded as definite if a calcified plaque was seen in the wall of an artery and probable if calcifications were seen along the expected course of an artery.

Findings Probable or definite atherosclerosis was noted in 47 (34%) of 137 mummies and in all four geographical populations: 29 (38%) of 76 ancient Egyptians, 13 (25%) of 51 ancient Peruvians, two (40%) of five Ancestral Puebloans, and three (60%) of five Unangan hunter gatherers (p=NS). Atherosclerosis was present in the aorta in 28 (20%) mummies, iliac or femoral arteries in 25 (18%), popliteal or tibial arteries in 25 (18%), carotid arteries in 17 (12%), and coronary arteries in six (4%). Of the five vascular beds examined, atherosclerosis was present in one to two beds in 34 (25%) mummies, in three to four beds in 11 (8%), and in all five vascular beds in two (1%). Age at time of death was positively correlated with atherosclerosis (mean age at death was 43 [SD 10] years for mummies with atherosclerosis *vs* 32 [15] years for those without; p<0·0001) and with the number of arterial beds involved (mean age was 32 [SD 15] years for mummies with no atherosclerosis, 42 [10] years for those with atherosclerosis in one or two beds, and 44 [8] years for those with atherosclerosis in three to five beds; p<0·0001).

Interpretation Atherosclerosis was common in four preindustrial populations including preagricultural hunter-gatherers. Although commonly assumed to be a modern disease, the presence of atherosclerosis in premodern human beings raises the possibility of a more basic predisposition to the disease.

Published Online
March 10, 2013
http://dx.doi.org/10.1016/S0140-6736(13)60598-X

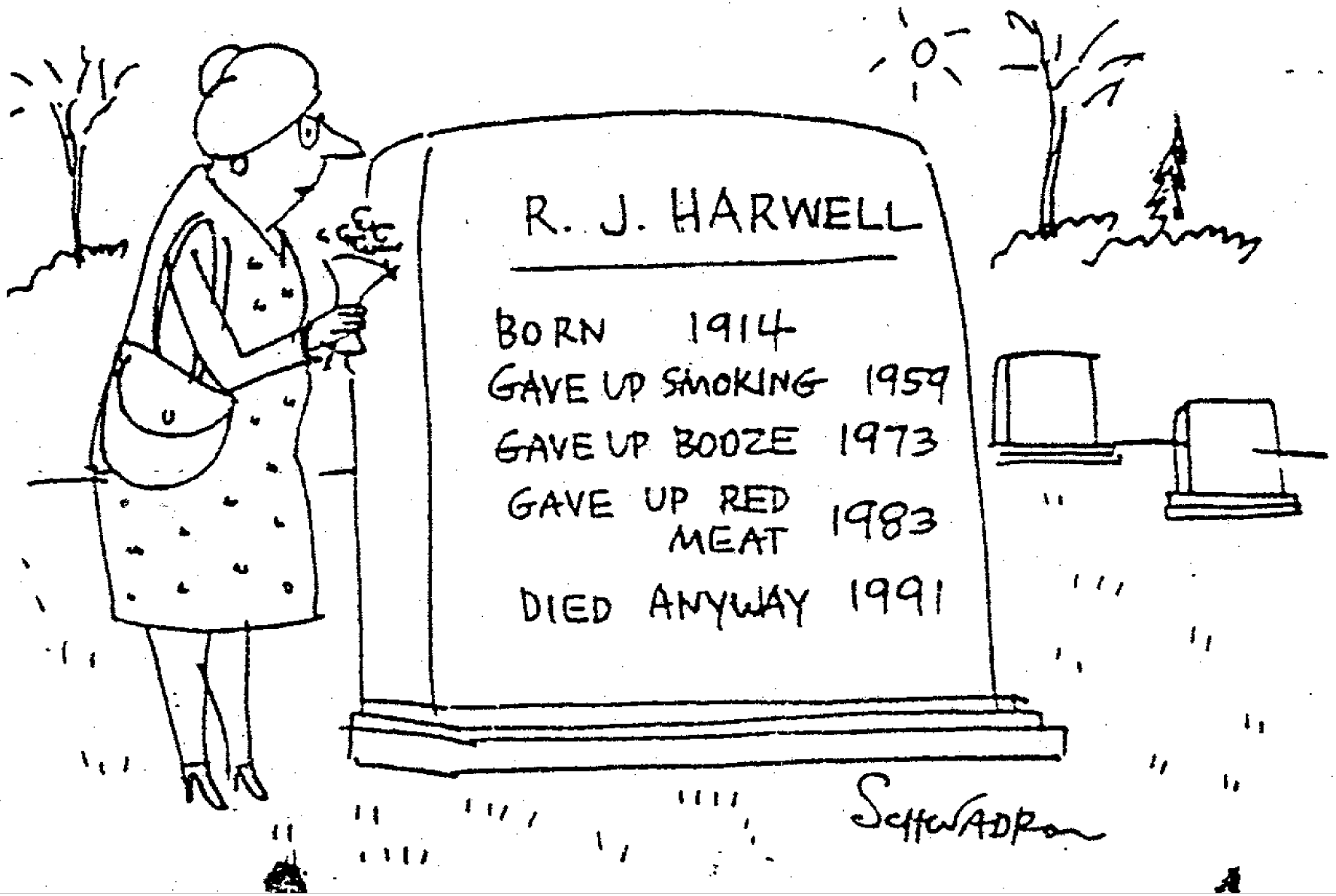
See Online/Comment
http://dx.doi.org/10.1016/S0140-6736(13)60639-X

Saint Luke's Mid America Hea Institute, and University of Missouri–Kansas City School c Medicine, Kansas City, MO, USA (Prof R C Thompson MD); **Al Azhar Medical School, Cair Egypt** (Prof A H Allam MD); **Laboratorio de Paleopatologi Catedra Pedro Weiss, and Universidad Peruana Cayetan Heredia, Lima, Peru** (G P Lombardi MD); **Columbia St Mary's Healthcare, Milwaukee, WI, USA** (L S Wann MD); **Newport Diagnostic Center, Newport Beach, CA, USA** (M L Sutherland MD); **South Coast Radiologic Medical Group, Laguna Hills, CA, USA** (J D Sutherland MD); **National Research Center, Giza, Egypt** (M Al-Tohamy Soliman PhD);

Наличието на атеросклероза при хора от предмодерната епоха показва, че заболяването е НЕОТМЕНЕН компонент на остаряването на човека и не характеризира конкретна диета или начин на живот.

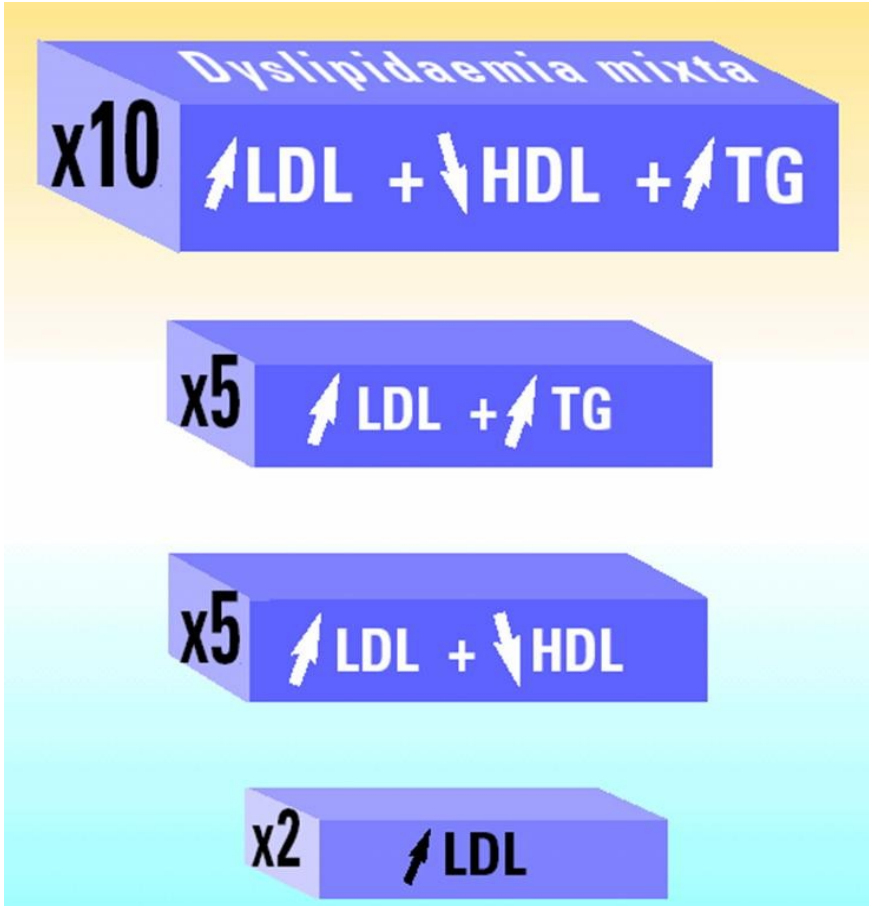
2014 → 2063

THE WALL STREET JOURNAL



Оценка на релативния риск

Triglycerid-rich LP
Apo C III
HDL - C
Small Dense LDL
Fibrinogen
Lp (a)
Uric acid
Homocysteine



Gerd Assmann A.M. J.M.Vol. 70, Sept. 15,1992

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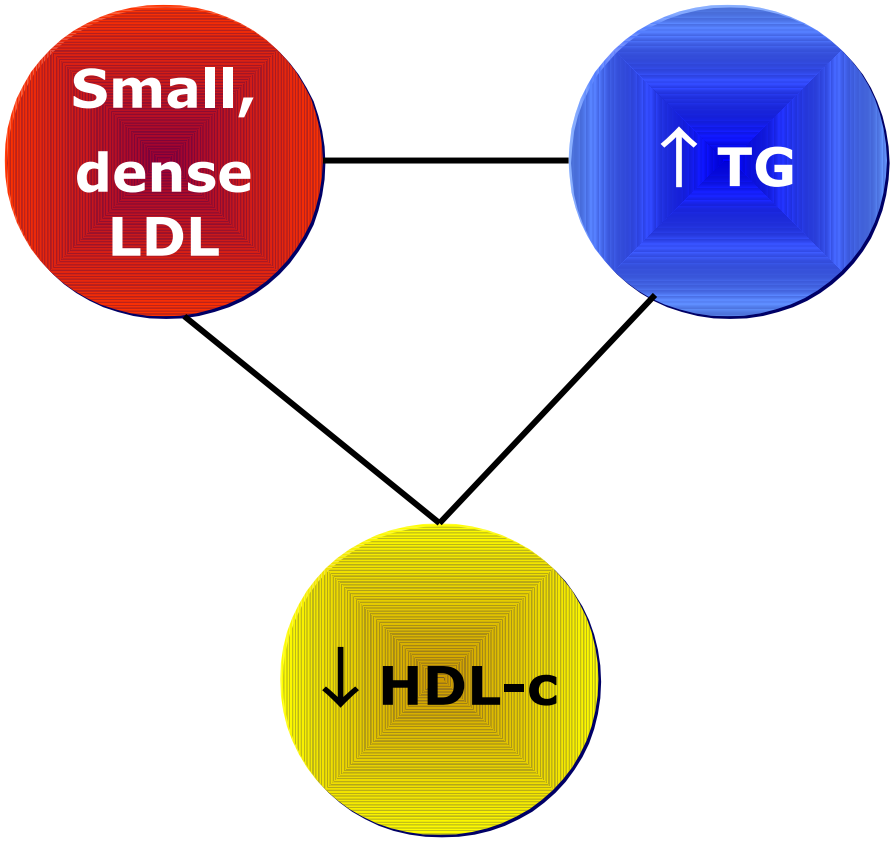
Диабет и Метаболитен синдром: типичен атерогенен липопротеинов профил



- Високи ТГ
- Нисък HDL-c
- Повишени малки, плътни LDL-c частици*

*LDL-c може да е повишен или нормален

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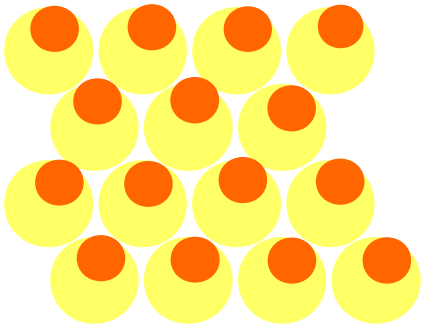
American Diabetes Association. Diabetes Care 2003;26 (Suppl. 1):S83-86

Малки плътни LDL-холестерол частици са по-атерогенни

Без диабет

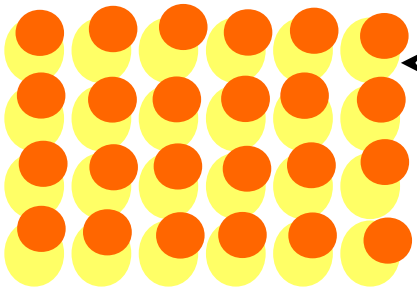
LDL частици



"Нормално" LDL-C ниво

С диабет

LDL частици



малки, плътни LDL с повече apoB

"Нормално" LDL-C ниво, независимо:

- ↑ Брой на LDL частици
- ↑ Концентрация на apoB

apoB

LDL-C

Нисък → **Висок**

Сърдечно-съдов риск

Adapted from Austin MA, Edwards KL *Curr Opin Lipidol* 1996;7:167-171; Austin MA et al *JAMA* 1988;260:1917-1921; Sniderman AD et al *Diabetes Care* 2002;25:579-582.

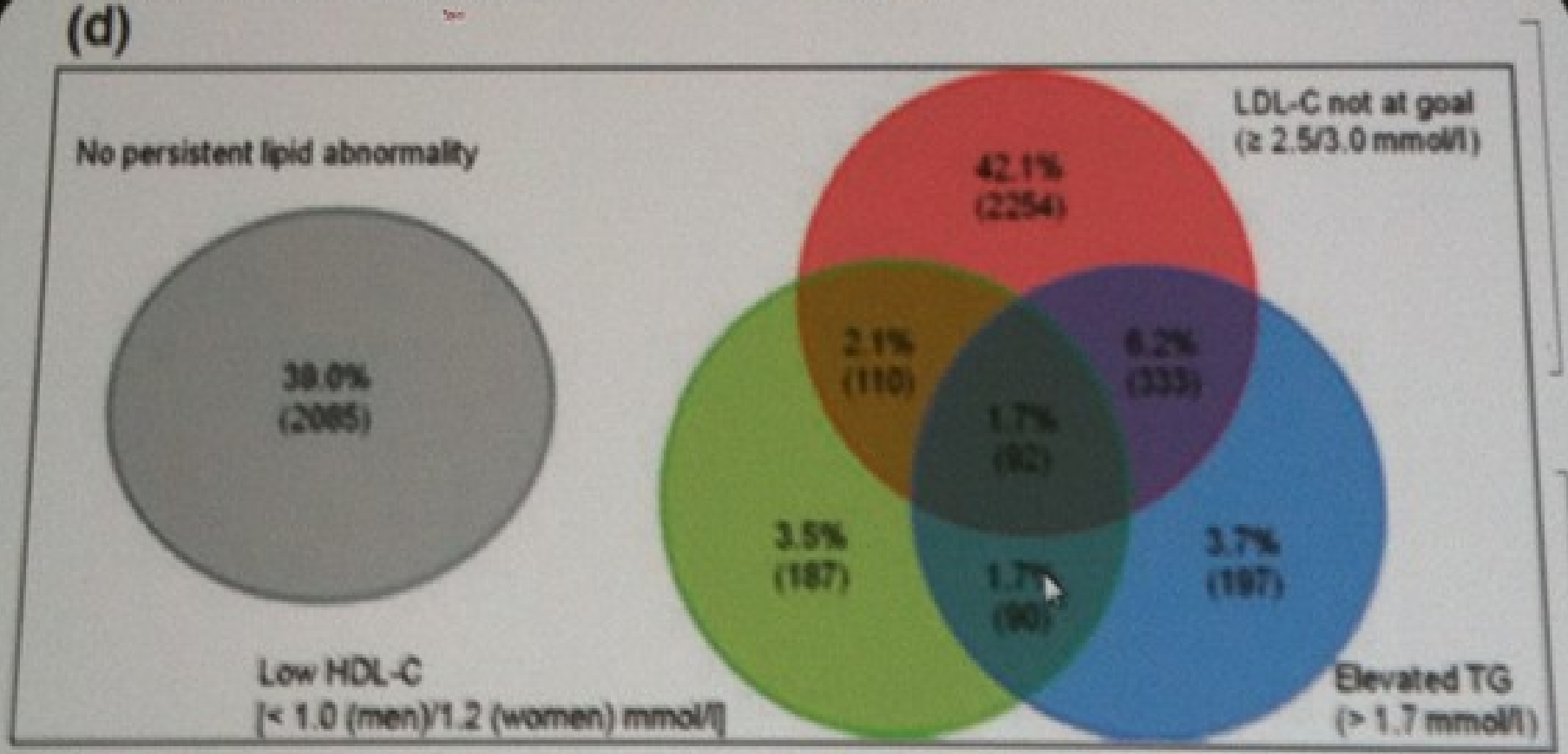
Circulation 1990;82:495-506

INCREASE RISK OF CHD

TABLE 3. Adjusted Plasma Lipid, Apolipoprotein, and Lipoprotein Mass Levels by Atherogenic Lipoprotein Phenotype

	ALP phenotype A		ALP phenotype B	
	n	Mean ± SD	n	Mean ± SD
Total cholesterol*	208	177 ± 37	93	197 ± 40
Triglycerides†	208	69 ± 26	93	141 ± 79
VLDL cholesterol‡†	208	14 ± 5	93	28 ± 16
LDL cholesterol§	208	116 ± 35	92	126 ± 36
HDL cholesterol*	208	46 ± 15	92	37 ± 14
Apo A-II	206	131 ± 29	92	122 ± 31
Apo B*	206	76 ± 34	93	98 ± 36
VLDL mass††	151	18 ± 31	60	111 ± 68
LDL mass				
Large*	151	119 ± 38	60	87 ± 34
Small*	151	164 ± 55	60	221 ± 64
IDL mass*	151	20 ± 14	60	38 ± 17
HDL_2 mass*	151	55 ± 44	60	13 ± 26
HDL_3 mass	151	189 ± 47	60	180 ± 59

Persistent lipid abnormalities in statin-treated patients with diabetes mellitus in Europe and Canada: results of the Dyslipidaemia International Study



Persistent lipid abnormalities in statin-treated patients with diabetes mellitus in Europe and Canada: results of the Dyslipidaemia International Study

	ALL	High Risk	CVD	Diabetes (no CVD)	Score < 5 %	Score > 5 %
	n= 21,797	n=17.583	n=10.587	n=4.524	n=2,472	n=4.214
LDL-C not at goal (%)	48.5	46.8	41.9	45.3	70.7	55.8
Low HDL-C (%)	26.4	28.3	30.6	29.9	15.2	18.7
Elevated TG (%)	38.8	39.6	38.5	44.5	35.5	35.3

Eur J Prev Rehab 2011

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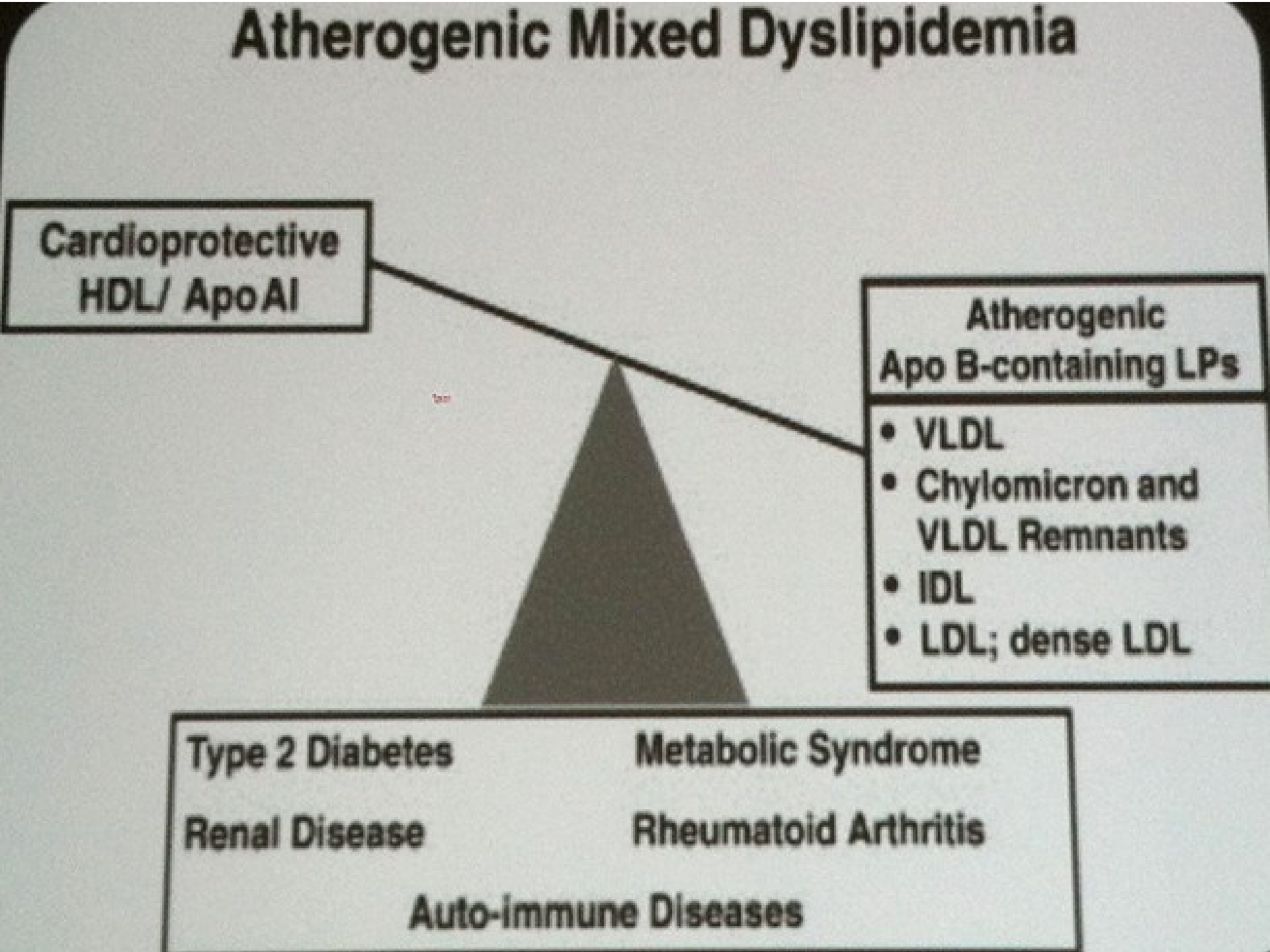
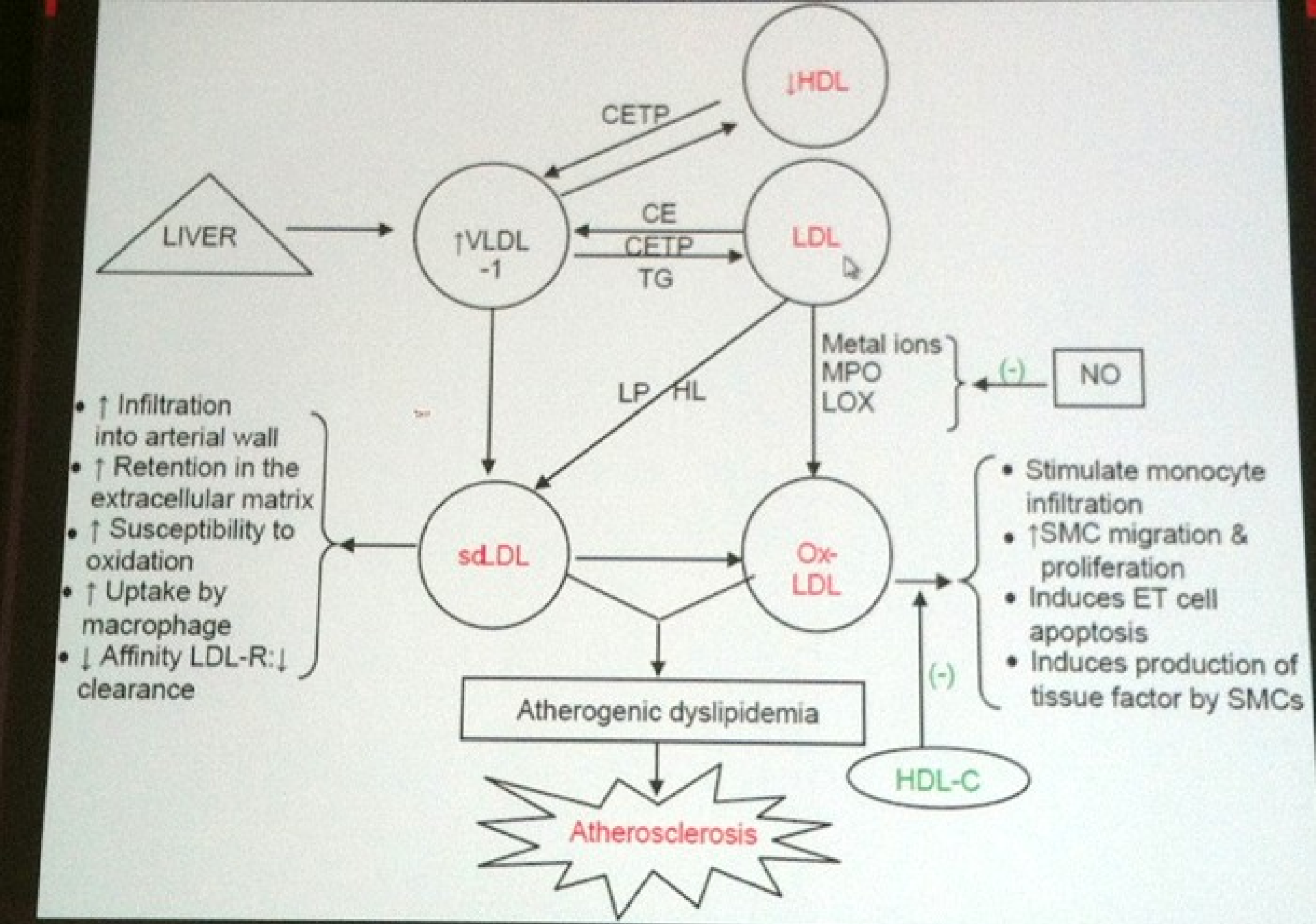
Atherogenic Mixed Dyslipidemia



МЕХАНИЗМИ НА АТЕРОГЕННАТА ДИСЛИПИДЕМИЯ

1. **ХИПЕРТРИГЛИЦЕРИДЕМИЯТА /VLDL/ Е В ОСНОВАТА НА АД – ПОВИШЕНА ПРОДУКЦИЯ И НАМАЛЕН КАТАБОЛИЗЪМ**

2. **НИСКИЯТ HDL И малките и плътни LDL частици са в основата на хипертриглицеридемията**


↓HDL
CETP
LIVER
↑VLDL -1
CE
CETP
TG
LDL
Metal ions
MPO
LOX
(-)
NO
LP HL
• ↑ Infiltration into arterial wall
• ↑ Retention in the extracellular matrix
• ↑ Susceptibility to oxidation
• ↑ Uptake by macrophage
• ↓ Affinity LDL-R:↓ clearance
sdLDL
Ox-LDL
• Stimulate monocyte infiltration
• ↑SMC migration & proliferation
• Induces ET cell apoptosis
• Induces production of tissue factor by SMCs
Atherogenic dyslipidemia
(-)
HDL-C
Atherosclerosis

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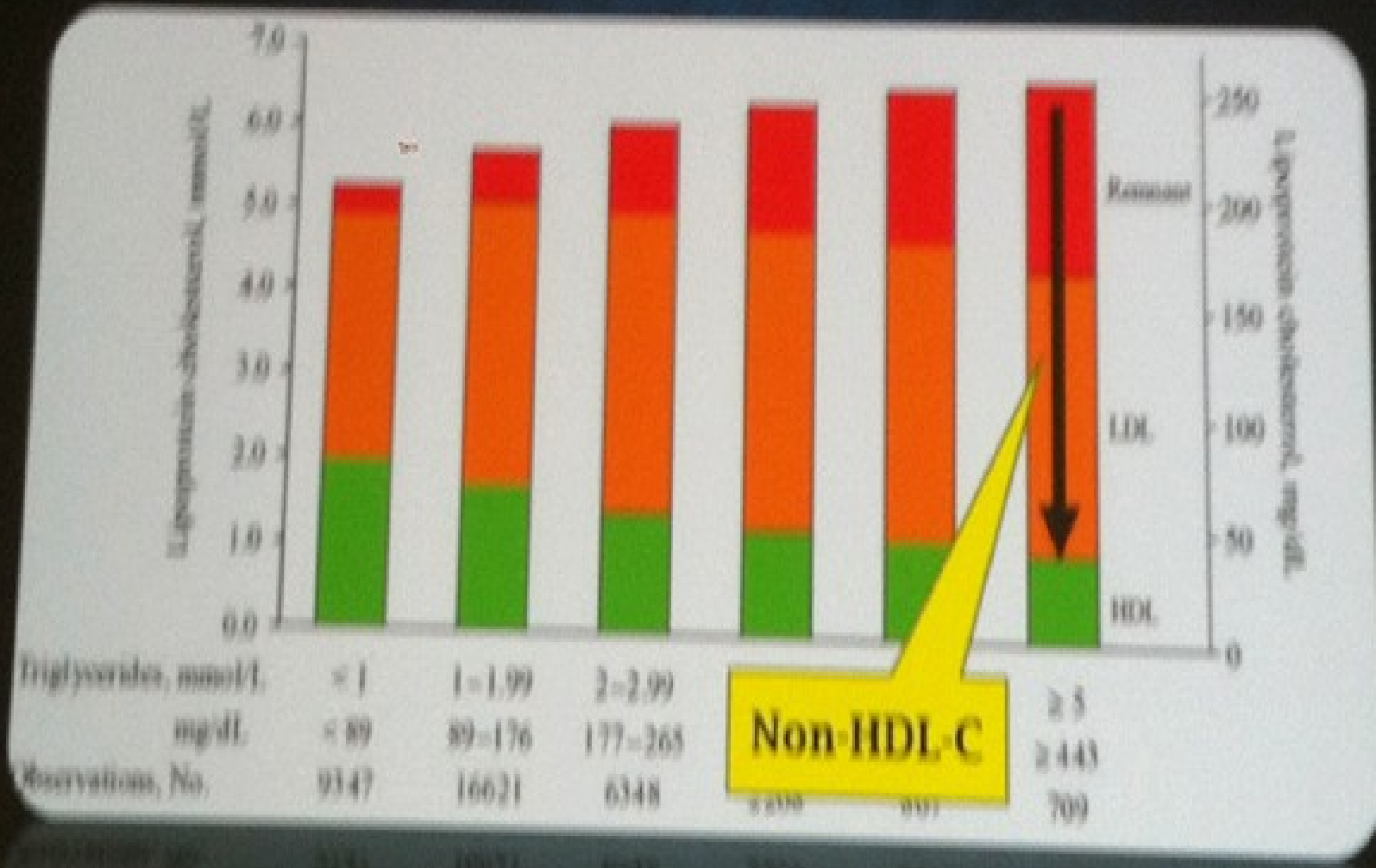
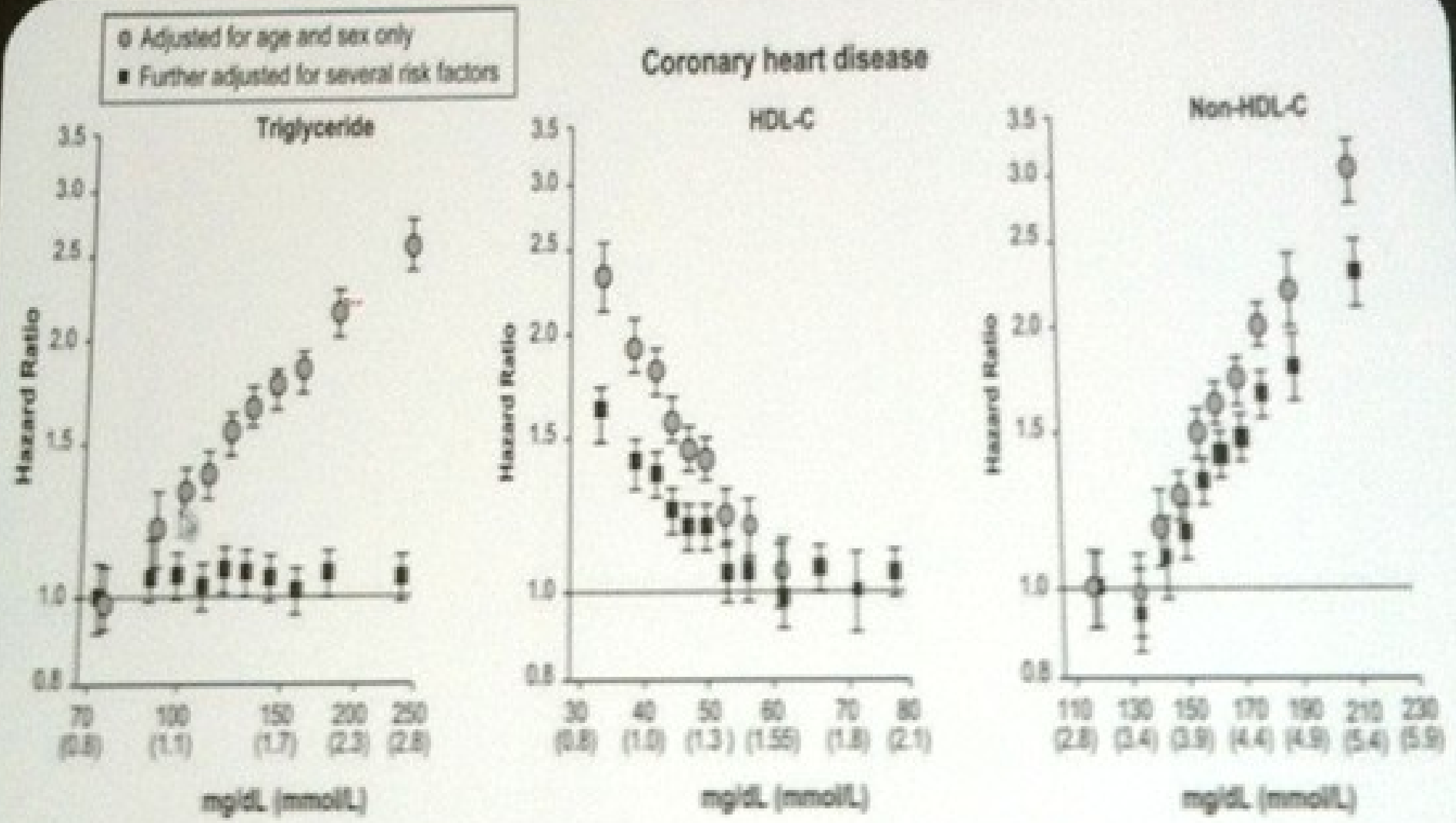
Fasting triglycerides > 150 mg/dl - HDL-C < 40 mg/dl



European Heart Journal (2011) 32, 1345–1361

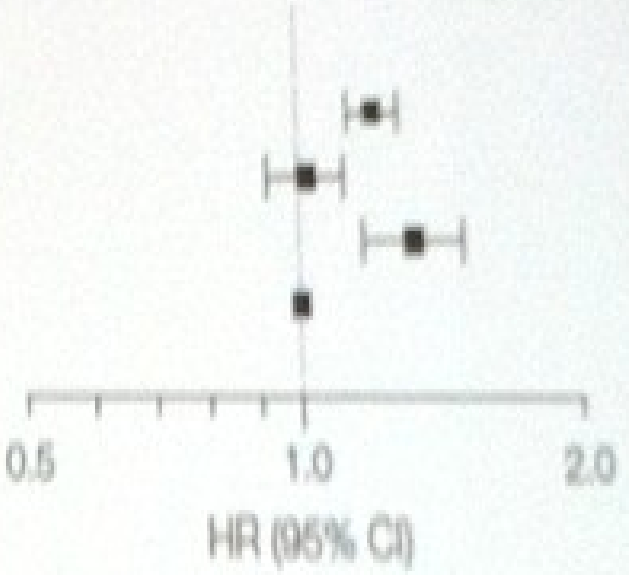
J Am Coll Cardiol 2013;61:427–36

The Emerging Risk Factors Collaboration. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* 2009;**302**:1993–2000.

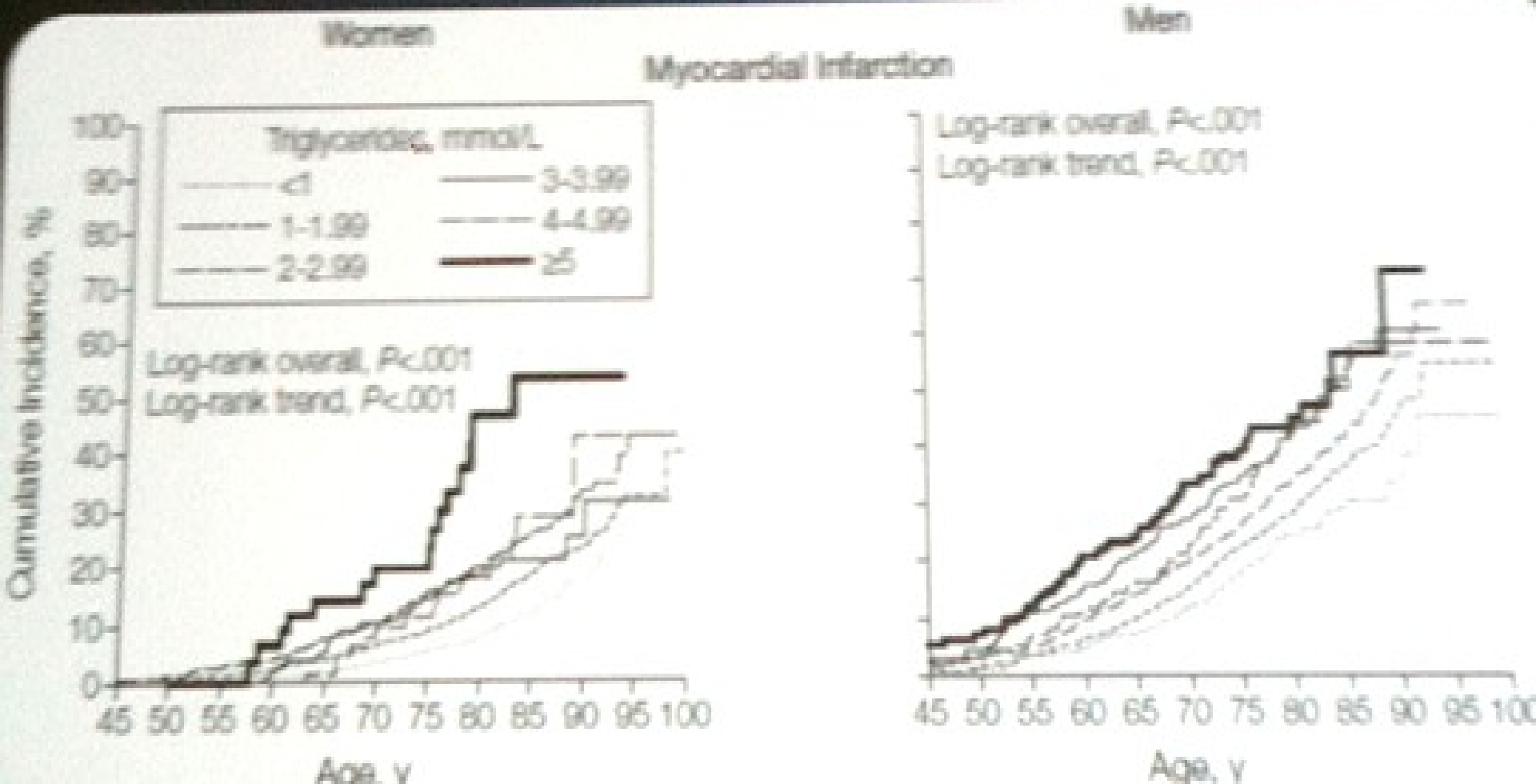


Association of LDL Cholesterol, Non–HDL Cholesterol, and Apolipoprotein B Levels With Risk of Cardiovascular Events Among Patients Treated With Statins

Target Level		No. of Major Cardiovascular Events	Total No. of Participants	HR (95% CI)
LDL-C	Non-HDL-C			
≥100 mg/dL	≥130 mg/dL	1877	10419	1.21 (1.13-1.29)
≥100 mg/dL	<130 mg/dL	467	2873	1.02 (0.92-1.12)
<100 mg/dL	≥130 mg/dL	283	1436	1.32 (1.17-1.50)
<100 mg/dL	<130 mg/dL	2760	23426	1.00 [Reference]



Nonfasting Triglycerides and Risk of Myocardial Infarction, Ischemic Heart Disease, and Death in Men and Women



Increased VLDL cholesterol-rich remnants

Low HDL-C

Small, dense LDL

Хипертриглицеридемия

Coagulation changes

Increased chylomicron remnants

Miller M. Eur Heart J. 1998;19 (Suppl H):H18-H22.

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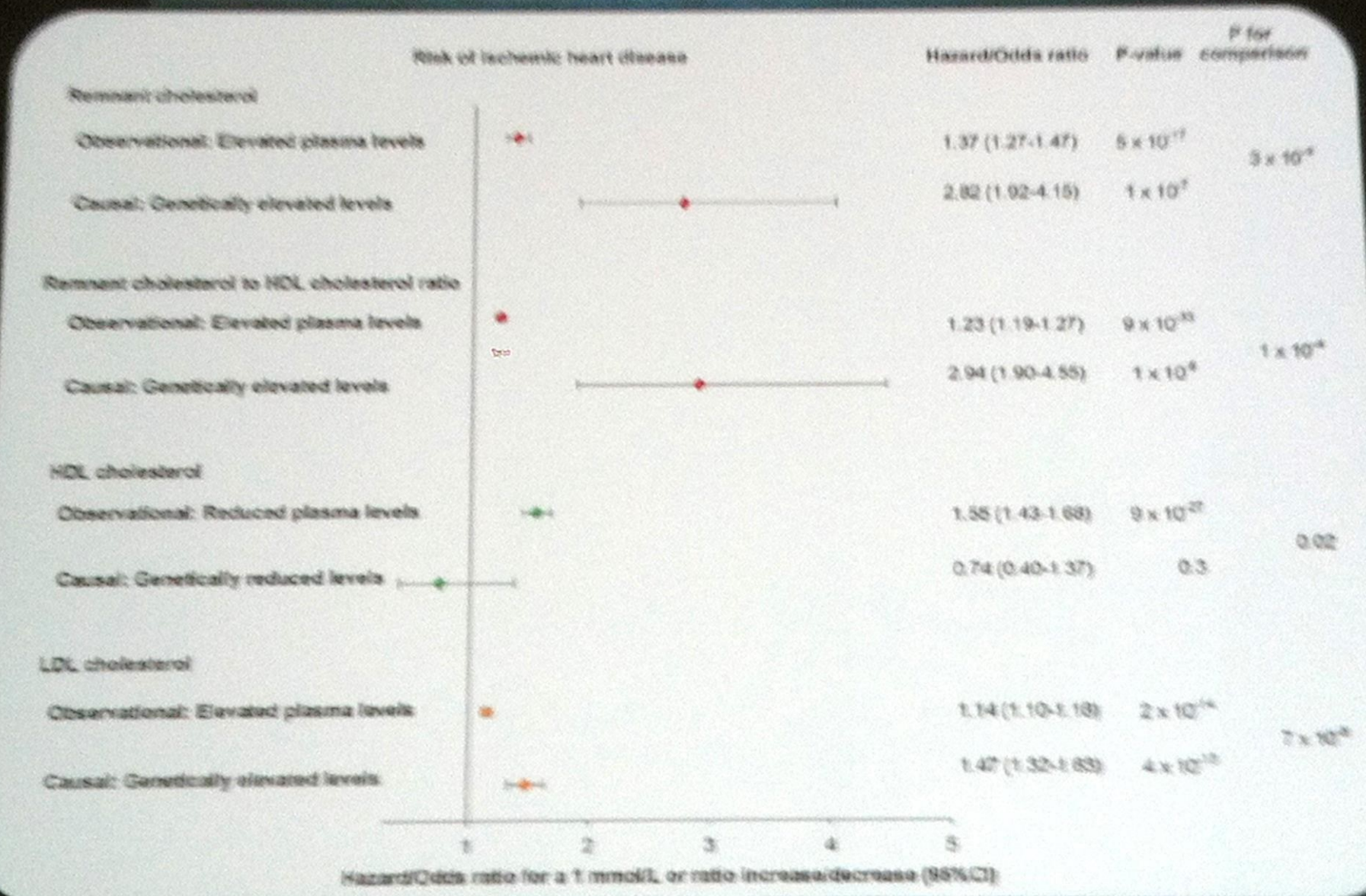
Remnant Cholesterol as a Causal Risk Factor for Ischemic Heart Disease



m Coll Cardiol 2013;61:427–36

REMNANT-C= (TC)-(HDL-C)-(LDL-C)

ОБОБЩЕНИЕ

- АТЕРОГЕННАТА ДИСЛИПИДЕМИЯ СЪЩЕСТВУВА
- НАРУШЕНИЯТА В VLDL СА КЛЮЧОВ ФАКТОР

- КАК ДА Е ИЗМЕРВАМЕ ?

1.NON-HDL

2. ниския HDL –под 0.9 високите TG –над 1.7

3.аполипопротеин-В

4. остатъчни холестеролови частици

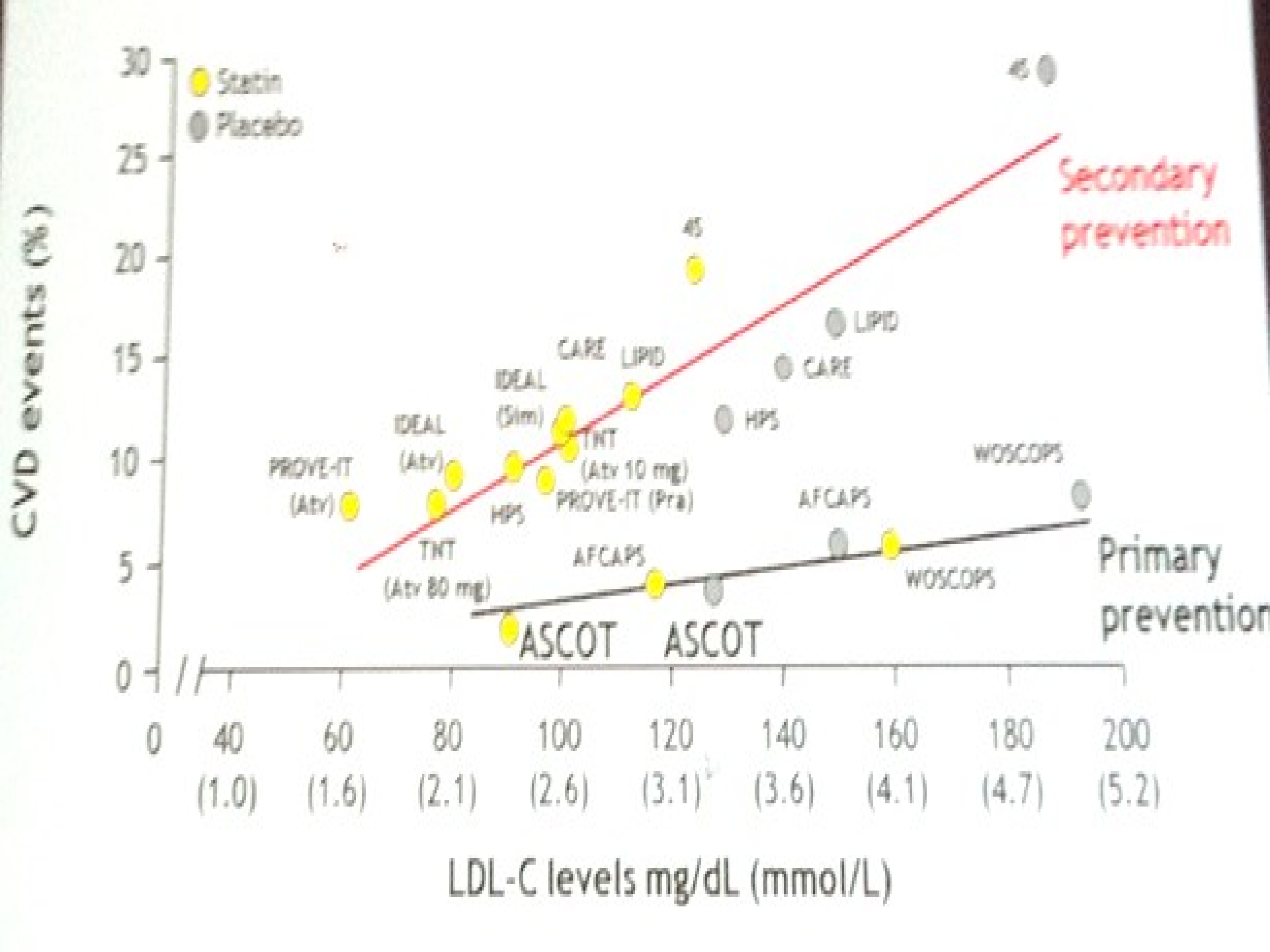
LDL-ПОНИЖАВАЩАТА ТЕРАПИЯ ДОСТАТЪЧНА ЛИ Е ЗА РЕГУЛИРАНЕ НА ССР, СВЪРЗАН С АТЕРОГЕННАТА ДИСЛИПИДЕМИЯ?

- **ЕФЕКТИВНИ ЛИ СА СТАТИНИТЕ?**

- **ИМА ЛИ ОСТАТЪЧЕН РИСК НА ФОНА НА СТАТИНИ?**

- **ЕФЕКТИВНО ЛИ Е ДОБАВЯНЕТО НА ТЕРАПИЯ ЗА**
- **ДОПЪЛНИТЕЛНО ПОНИЖАВАНЕ НА LDL- ХОЛЕСТЕРОЛА?**

- **ЕФЕКТИВНА ЛИ Е ДОПЪЛНИТЕЛНАТА ТЕРАПИЯ ЗА**
- **РЕГУЛИРАНЕ НА ТРИГЛИЦЕРИДИТЕ И HDL-ХОЛЕСТЕРОЛА?**


Statin
Placebo
CVD events (%)
30
25
20
15
10
5
0
4S
LIPID
CARE
HPS
WOSCOPS
AFCAPS
IDEAL (Sim)
IDEAL (Atv)
TNT (Atv 10 mg)
PROVE-IT (Pra)
PROVE-IT (Atv)
TNT (Atv 80 mg)
ASCOT
ASCOT
Secondary prevention
Primary prevention
0
40 (1.0)
60 (1.6)
80 (2.1)
100 (2.6)
120 (3.1)
140 (3.6)
160 (4.1)
180 (4.7)
200 (5.2)
LDL-C levels mg/dL (mmol/L)

‘Statin-ology’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DAILY EXPRESS

STATINS SLASH RISK OF CANCER


DAILY EXPRESS

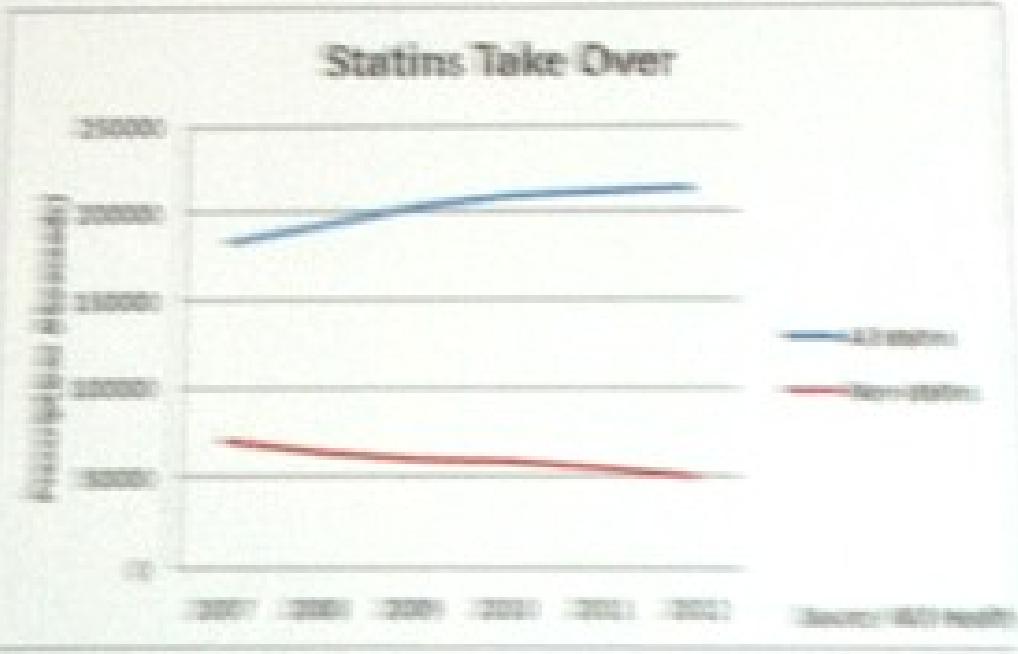
STATINS REALLY DO SAVE YOUR LIFE


DAILY EXPRESS

PILL TO PREVENT BREAST CANCER


DAILY EXPRESS

WONDER JAB TO FIGHT FAT



LDL-ПОНИЖАВАЩАТА ТЕРАПИЯ ДОСТАТЪЧНА ЛИ Е ЗА РЕГУЛИРАНЕ НА ССР, СВЪРЗАН С АТЕРОГЕННАТА ДИСЛИПИДЕМИЯ?

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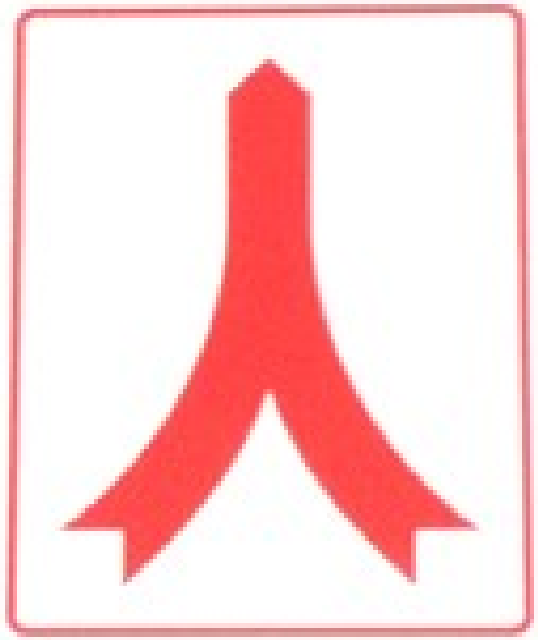
- ДОПЪЛНИТЕЛНО ПОНИЖАВАНЕ НА LDL- ХОЛЕСТЕРОЛА?

- ЕФЕКТИВНА ЛИ Е ДОПЪЛНИТЕЛНАТА ТЕРАПИЯ ЗА
- РЕГУЛИРАНЕ НА ТРИГЛИЦЕРИДИТЕ И HDL-ХОЛЕСТЕРОЛА?

Residual CV risk in LDL-lowering with statins

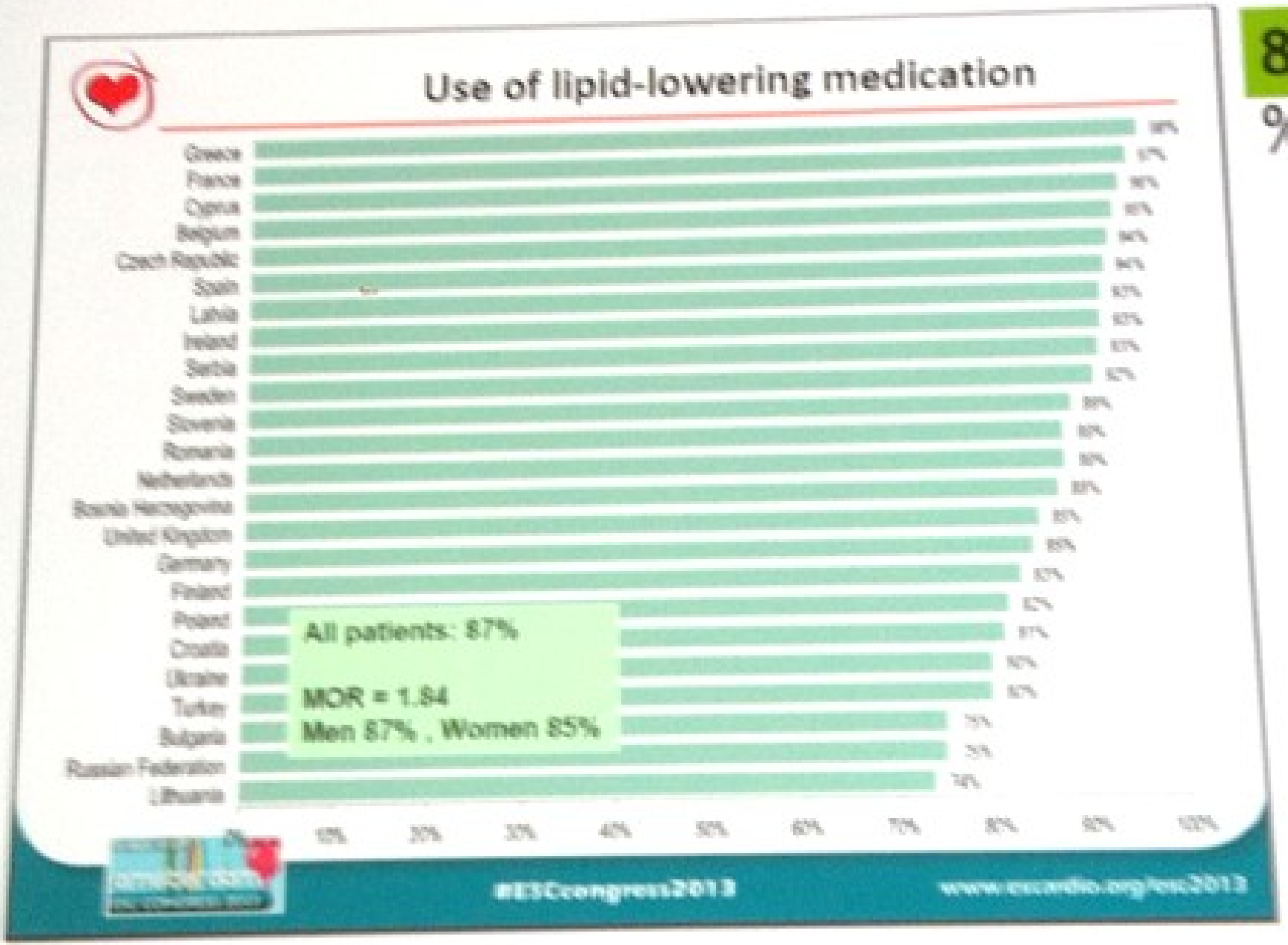


- Suboptimal adherence
- Not "unlimited" potential of statins

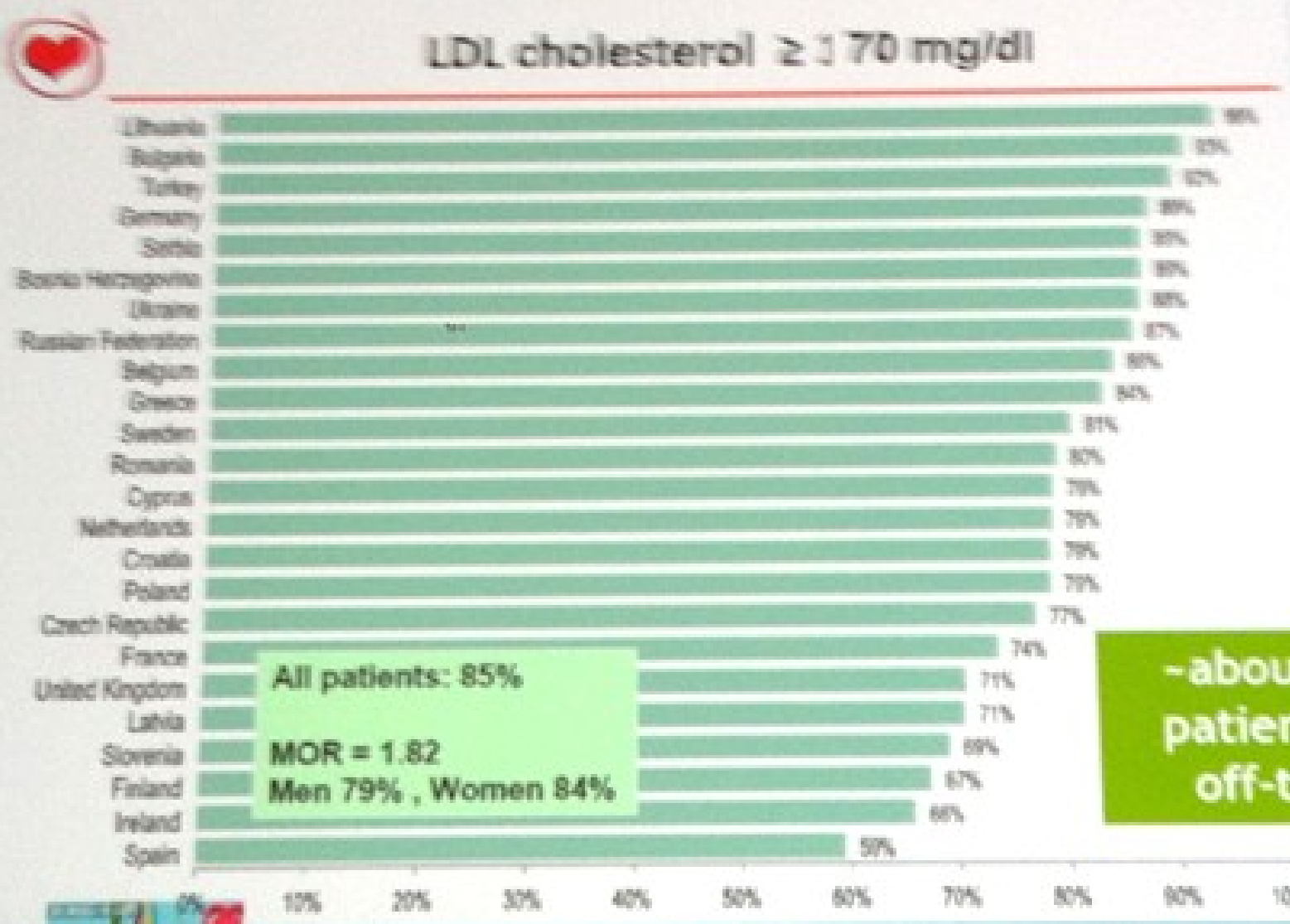
CV risk attributed to parameters other than LDL

EUROASPIRE IV

87 %

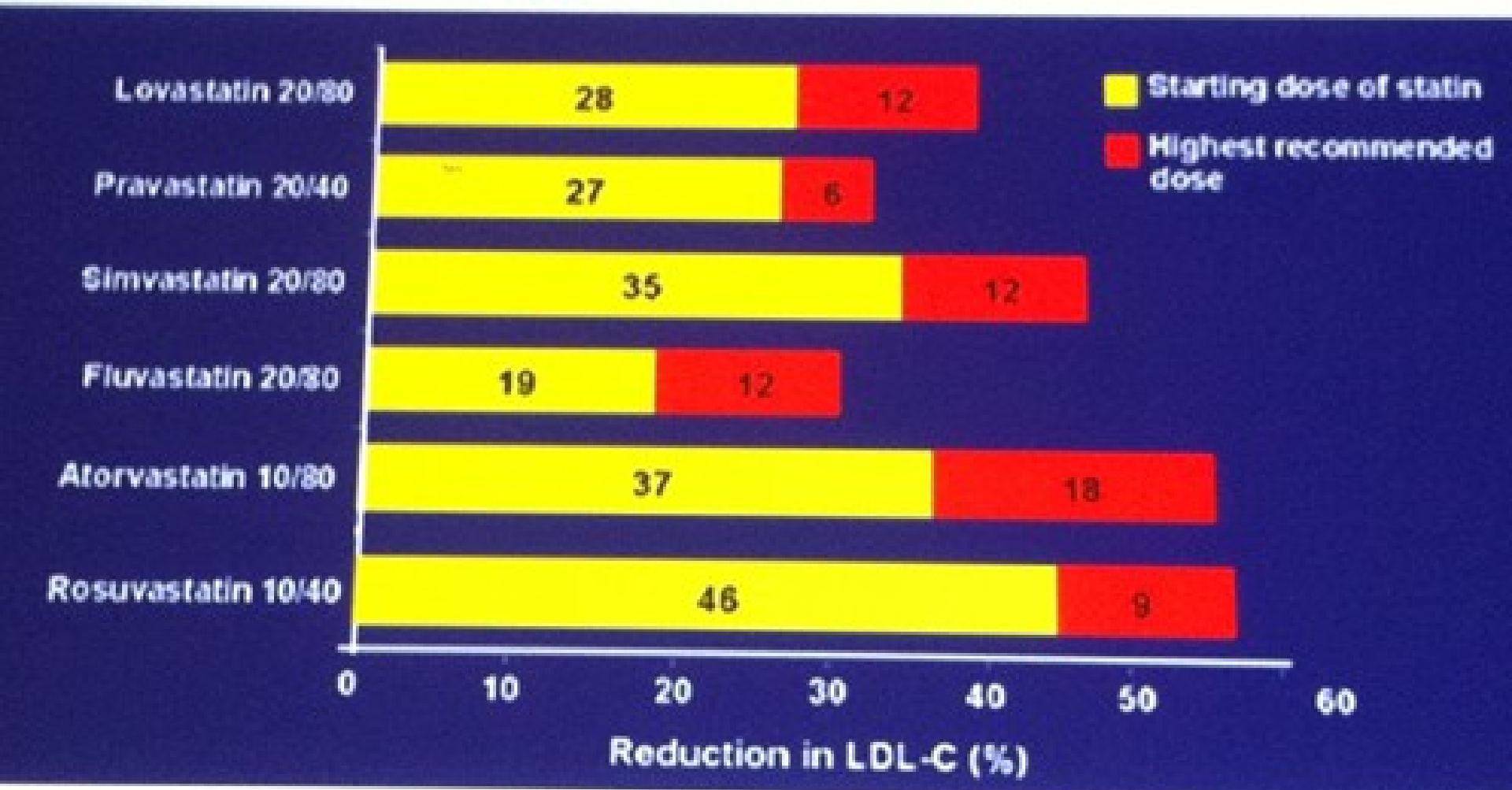


EUROASPIRE IV



~about 8/10 patients are off-target

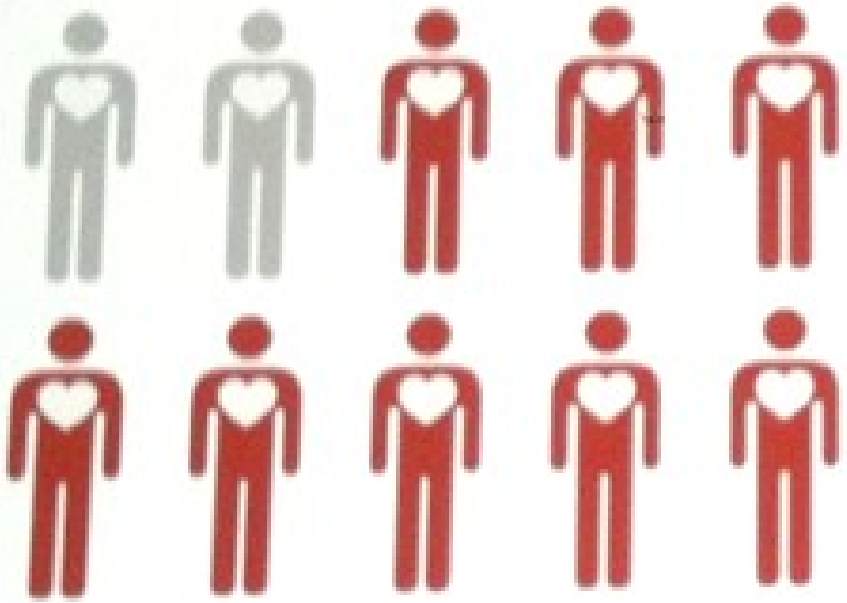
Effect of Statin Therapy on LDL-c Levels: the "rule of 6"



Adapted from Illingworth DR. Med Clin North Am.

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

*Cholesterol Treatment Trialists' (CTT) Collaboration**

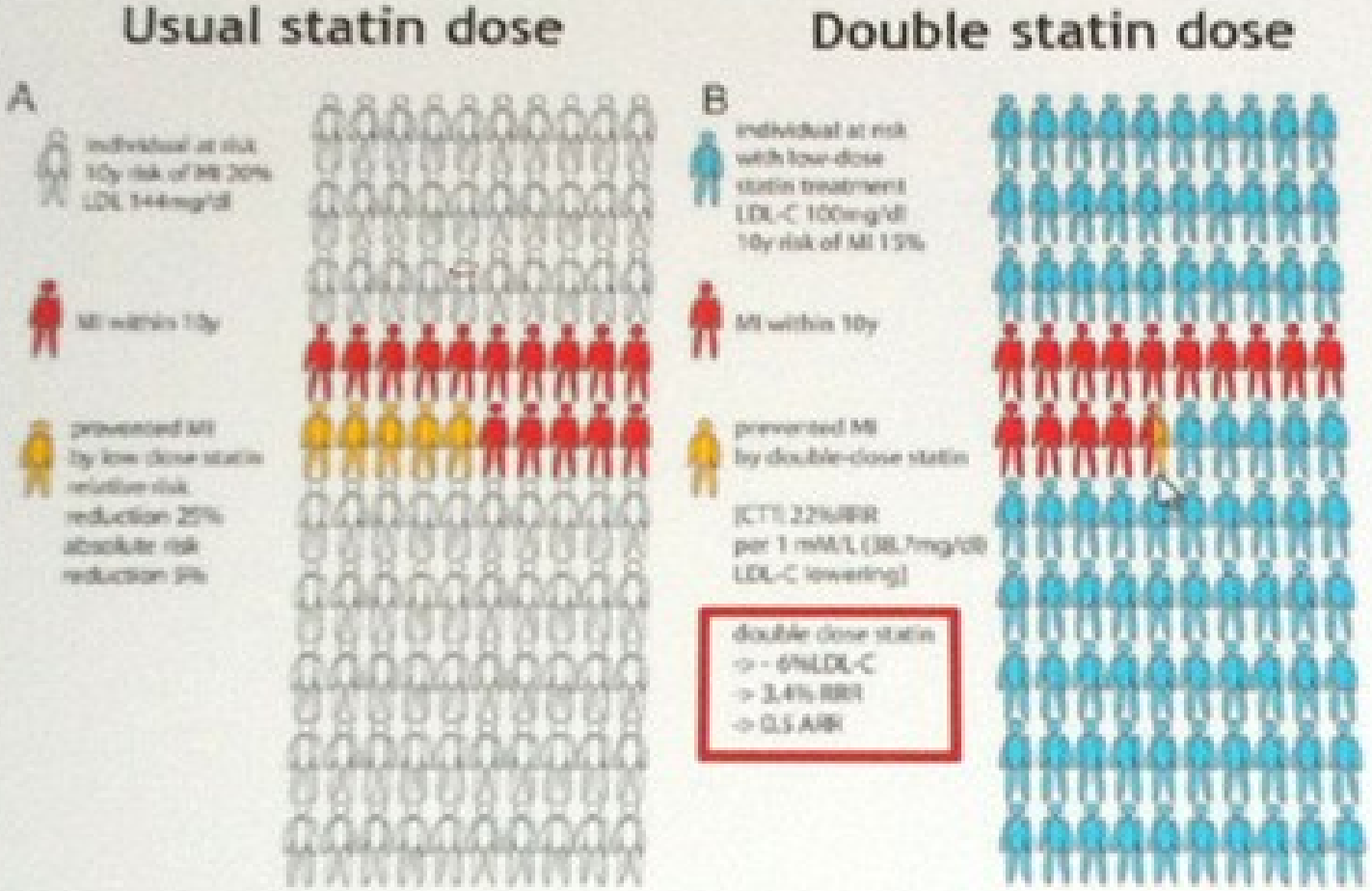


Approximately 2 out of 10 events are prevented with statins per 1 mmol/L reduction

.... suggesting that reduction of LDL cholesterol by 2-3 mmol/L would reduce risk by about 40-50%

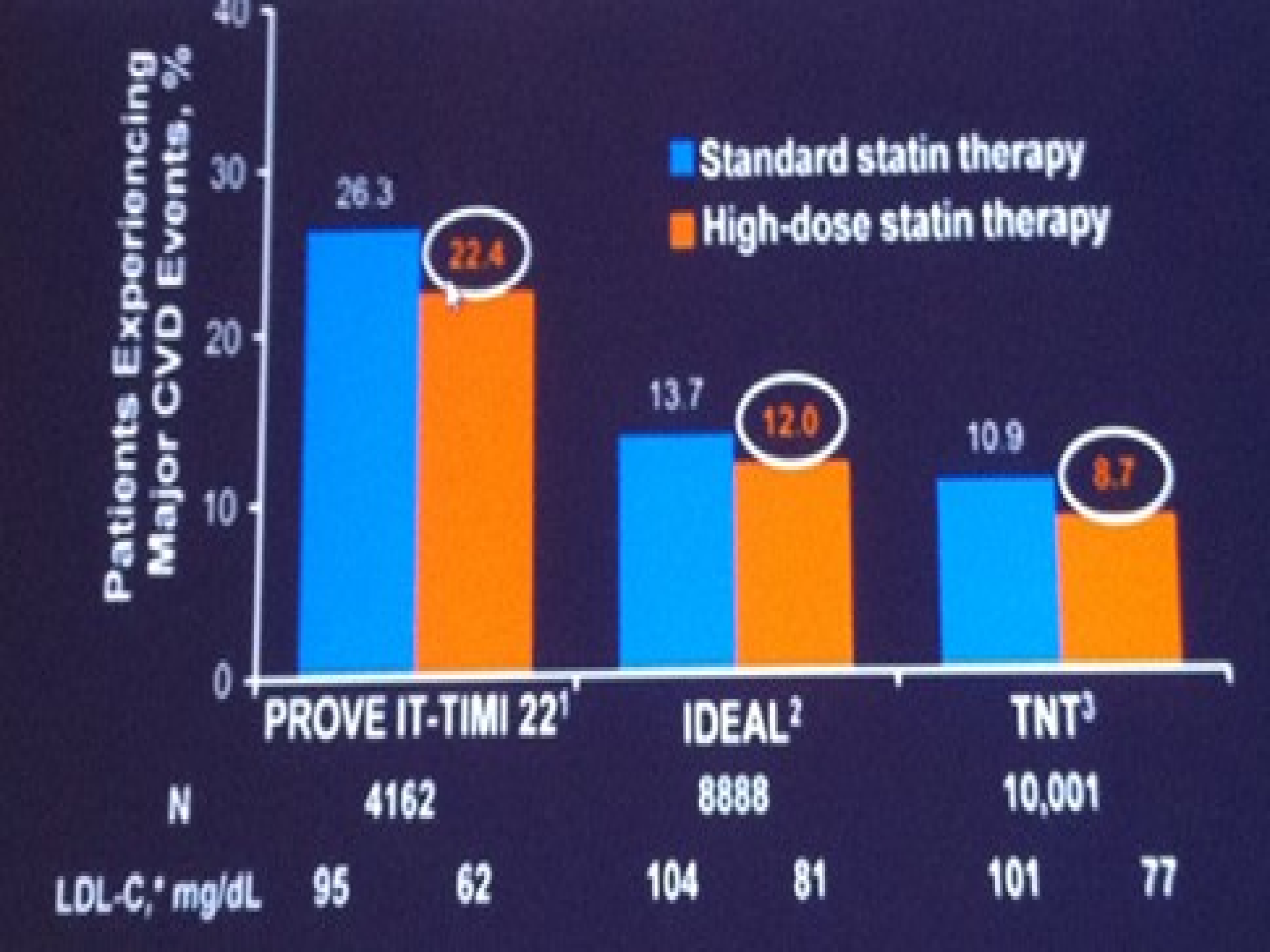
Lancet

Are statins enough on their own?



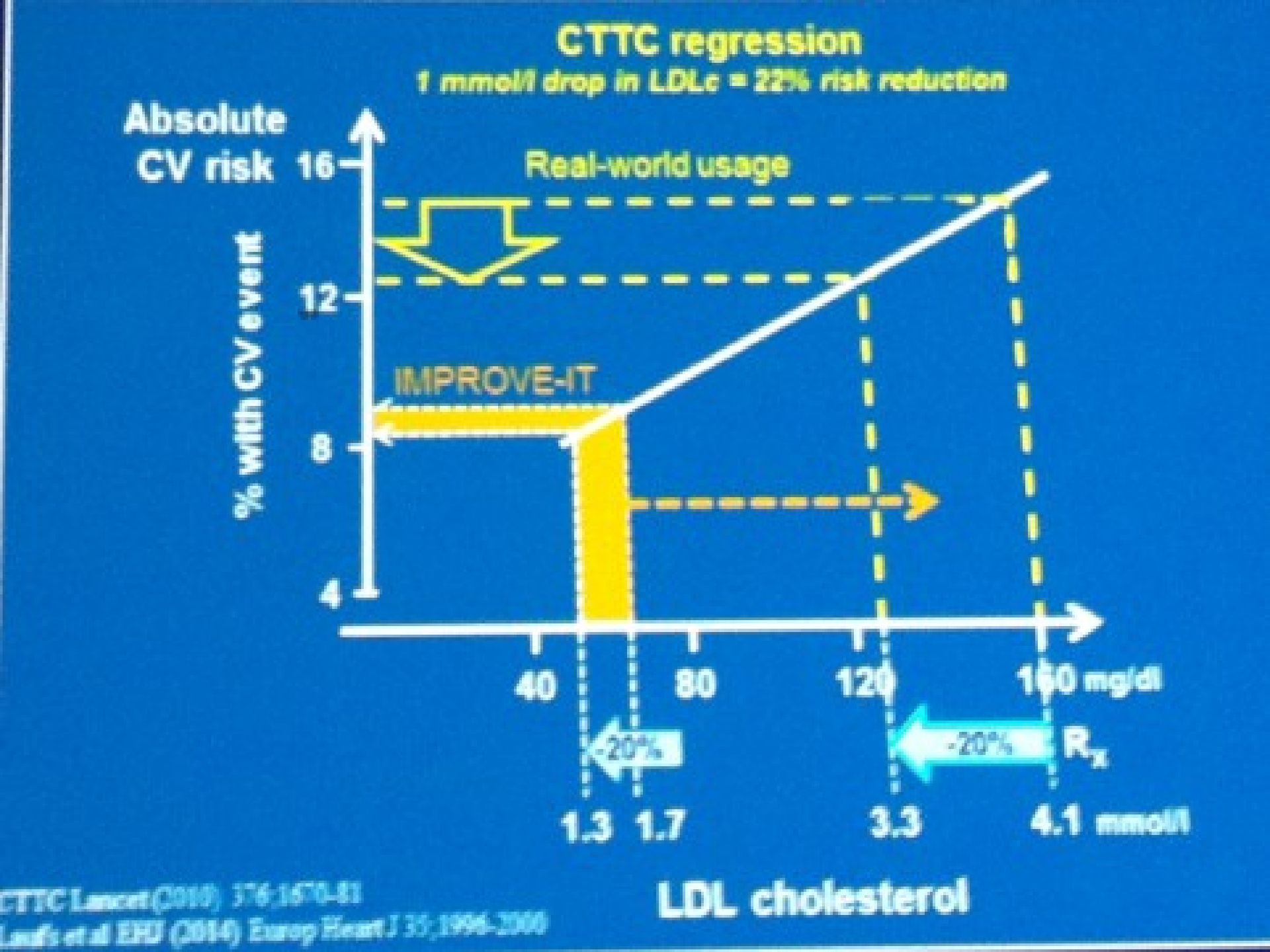
Laufs U, et al. Eur Heart J 2013


Patients Experiencing 1st Major CHD Event (%)
40
30
20
10
0
Placebo
Statin
28.0
19.4
15.9
12.3
13.2
10.2
11.8
8.7
10.9
6.8
4S[1]
LIPID[2]
CARE[3]
HPS[4]
WOSCOPS[5]
AFCAPS/TexCAPS[6]
N
4444
9014
4159
20,536
6595
5605
Δ LDL
-35%
-25%
-28%
-20%
-26%
-25%
Secondary
High Risk
Primary


Patients Experiencing Major CVD Events, %
40
30
20
10
0
Standard statin therapy
High-dose statin therapy
26.3
22.4
13.7
12.0
10.9
8.7
PROVE IT-TIMI 22[1]
IDEAL[2]
TNT[3]
N
4162
8888
10,001
LDL-C,* mg/dL
95
62
104
81
101
77

LDL-ПОНИЖАВАЩАТА ТЕРАПИЯ ДОСТАТЪЧНА ЛИ Е ЗА РЕГУЛИРАНЕ НА ССР, СВЪРЗАН С АТЕРОГЕННАТА ДИСЛИПИДЕМИЯ?

- ЕФЕКТИВНИ ЛИ СА СТАТИНИТЕ?
- ИМА ЛИ ОСТАТЪЧЕН РИСК НА ФОНА НА СТАТИНИ?
- ЕФЕКТИВНО ЛИ Е ДОБАВЯНЕТО НА ТЕРАПИЯ ЗА ДОПЪЛНИТЕЛНО ПОНИЖАВАНЕ НА LDL- ХОЛЕСТЕРОЛА?
- ЕФЕКТИВНА ЛИ Е ДОПЪЛНИТЕЛНАТА ТЕРАПИЯ ЗА
- РЕГУЛИРАНЕ НА ТРИГЛИЦЕРИДИТЕ И HDL-ХОЛЕСТЕРОЛА?


CTTC regression
1 mmol/l drop in LDLc = 22% risk reduction
Absolute CV risk
16
12
8
4
% with CV event
Real-world usage
IMPROVE-IT
40
80
120
160 mg/dl
-20%
-20%
Rx
1.3
1.7
3.3
4.1 mmol/l
LDL cholesterol
CTTC Lancet (2010) 376:1670-81
Landis et al EHJ (2014) Europ Heart J 35;1996-2000

LDL-ПОНИЖАВАЩАТА ТЕРАПИЯ ДОСТАТЪЧНА ЛИ Е ЗА РЕГУЛИРАНЕ НА ССР, СВЪРЗАН С АТЕРОГЕННАТА ДИСЛИПИДЕМИЯ?

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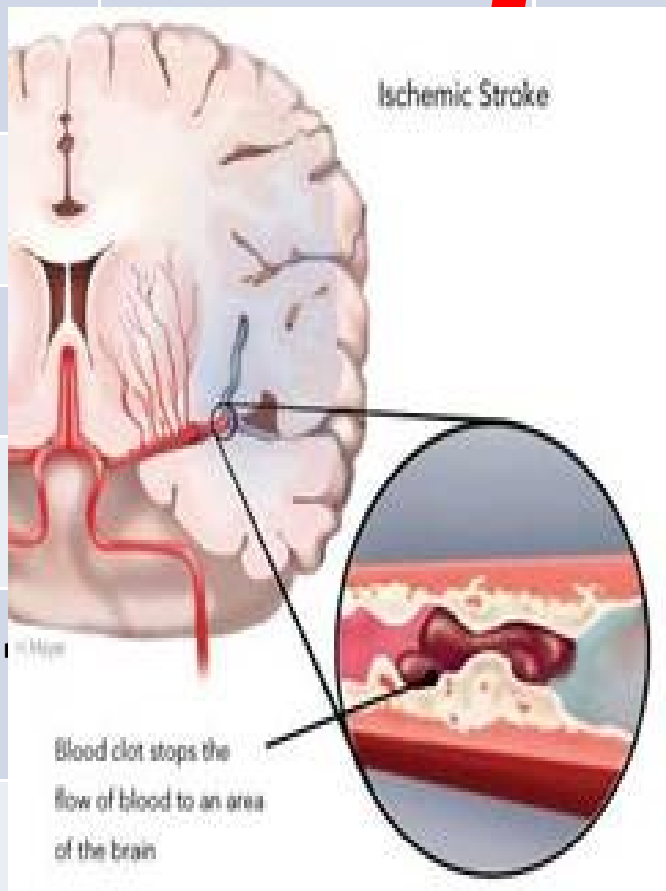
- ЕФЕКТИВНО ЛИ Е ДОБАВЯНЕТО НА ТЕРАПИЯ ЗА ДОПЪЛНИТЕЛНО ПОНИЖАВАНЕ НА LDL- ХОЛЕСТЕРОЛА?
- ЕФЕКТИВНА ЛИ Е ДОПЪЛНИТЕЛНАТА ТЕРАПИЯ ЗА РЕГУЛИРАНЕ НА ТРИГЛИЦЕРИДИТЕ И HDL-ХОЛЕСТЕРОЛА?

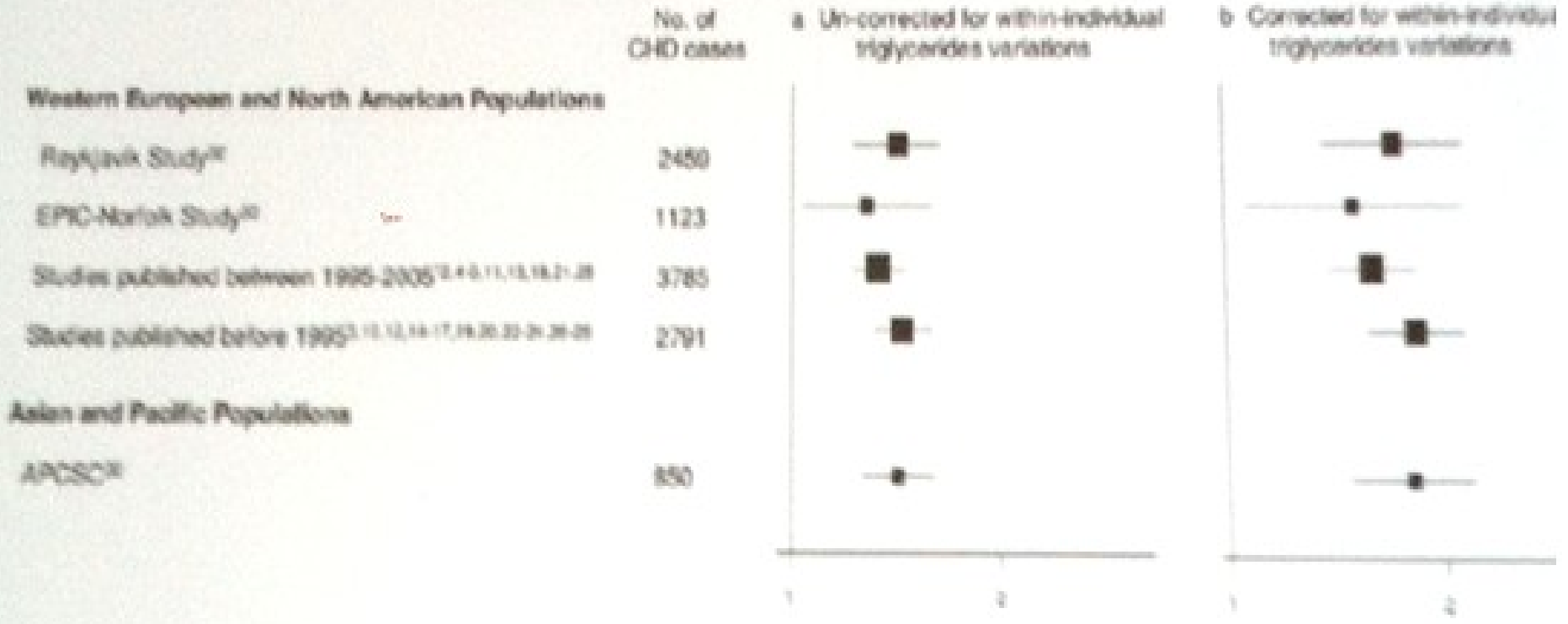
ЛИПОПРОТЕИНИ

ДЖОН ГОФМАН ЛИПОПРОТЕИНОВ СПЕКТЪР

	Повишени ЛП	Ниво на холестерола	Ниво на триглицери-дите	атерогенност
I	Хиломикрони	↑↑		-
II a	LDL	↑↑↑↑		+++
II b	LDL, VLDL	↑↑		+++
III	IDL	↑↑		+++
IV	VLDL	Нормални ↑		+
V	VLDL,	↑ до ↑↑		+

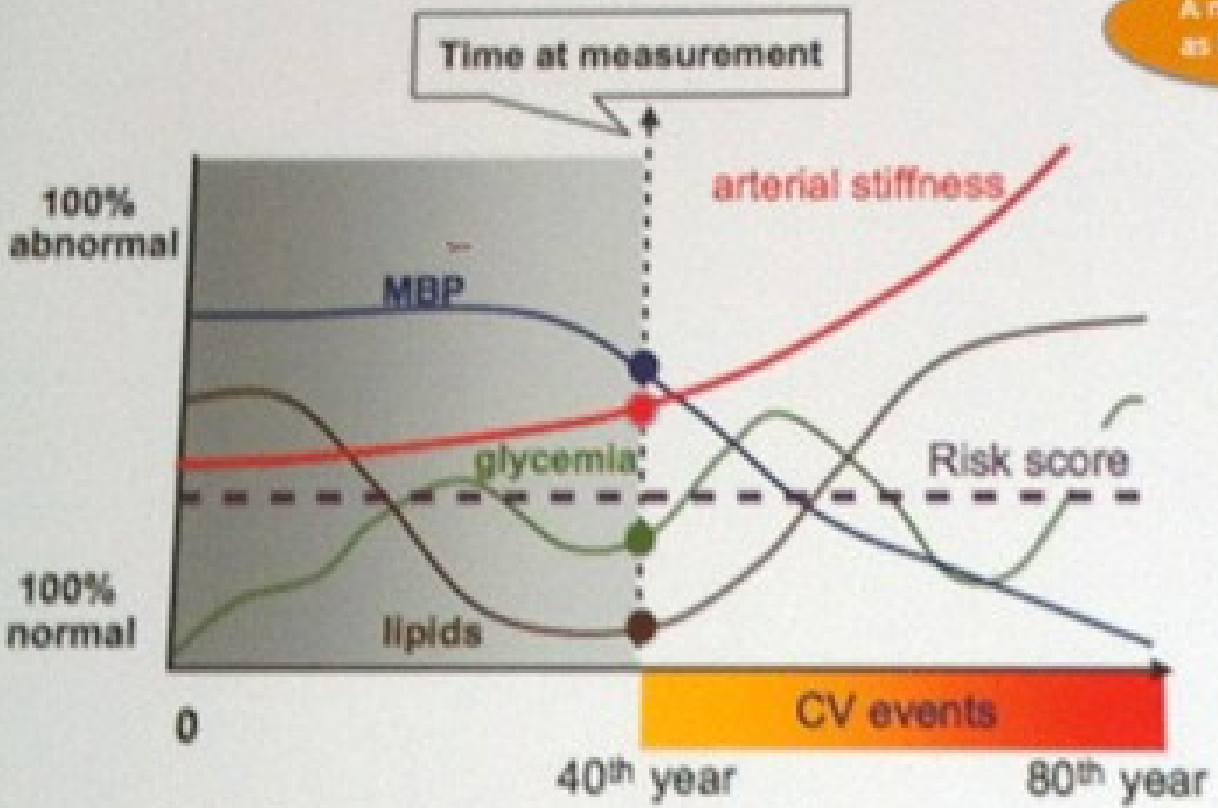


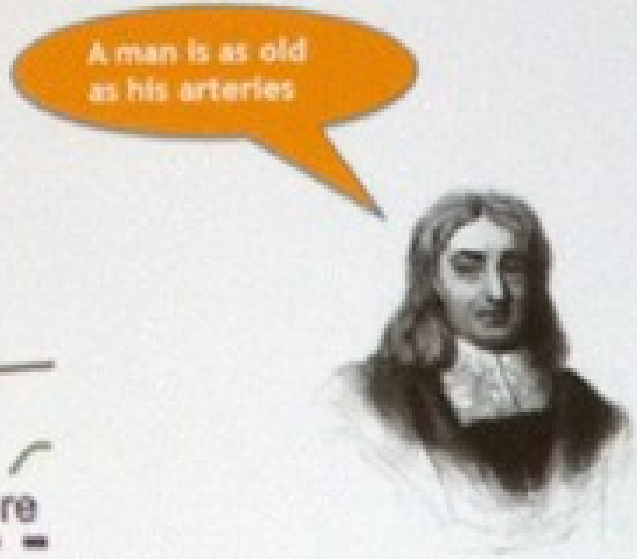
Do high triglycerides represent high CV risk?



In Western populations, people with the highest TG levels showed a **72%** increased risk of CHD compared to those with the lowest TG levels

Arterial Aging





Thomas Sydenham (1624-1689)

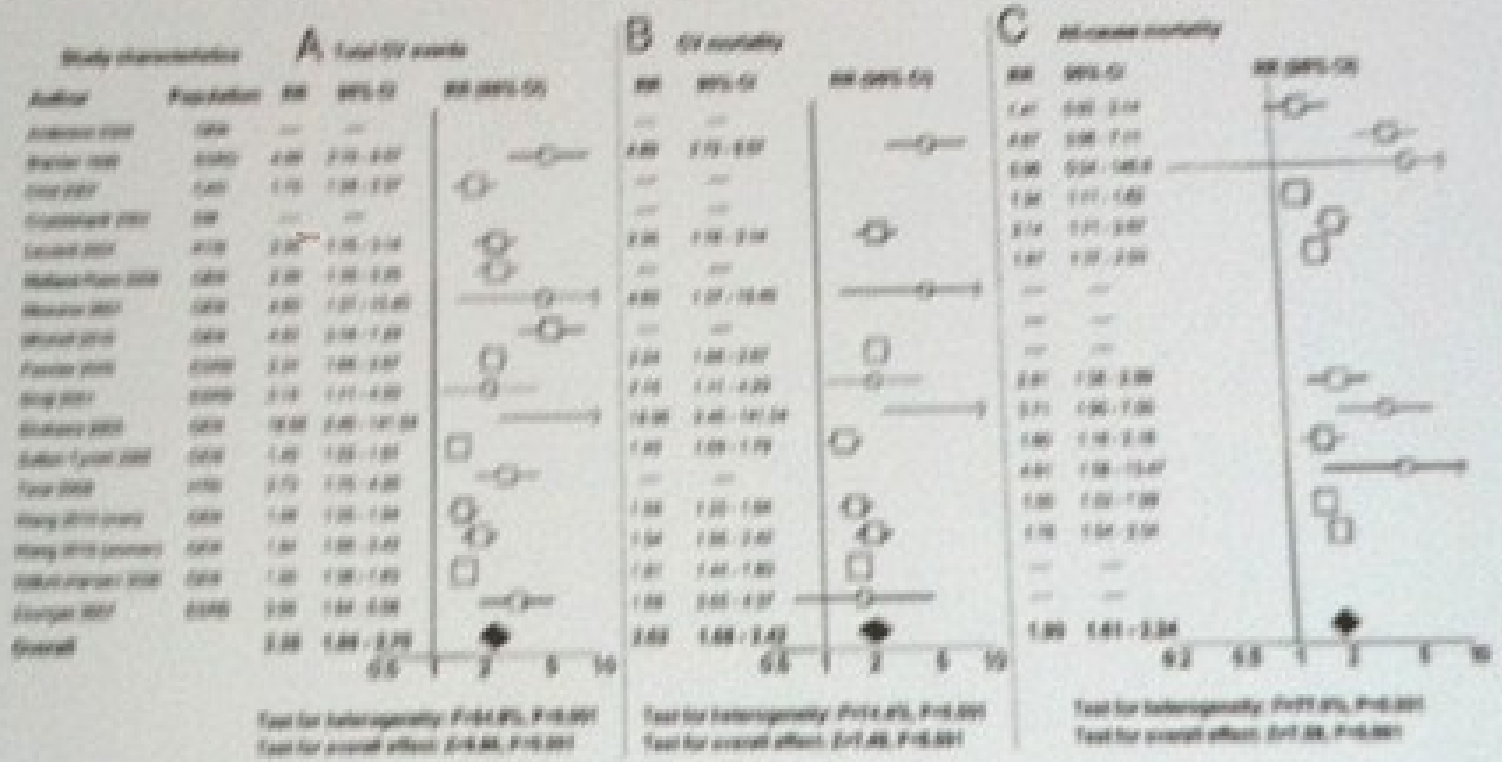
EVA (Early Vascular Aging): a cumulative measure of the impact of CV risk factors

Nilsson P et al. Hypertension 2009

Aortic Stiffness: gauging vascular age and predicting CV events

Vlachopoulos C / Aznaouridis K., et al, J Am Coll Cardiol 2010

Vlachopoulos C / Aznaouridis K., et al, J Am Coll Cardiol 2014



15,877 patients / follow up 7.7 years

Increased arterial stiffness is linked to a **twofold** increase in CV events and mortality, as well as all-cause mortality

DIABETES, LIPIDS AND METABOLISM

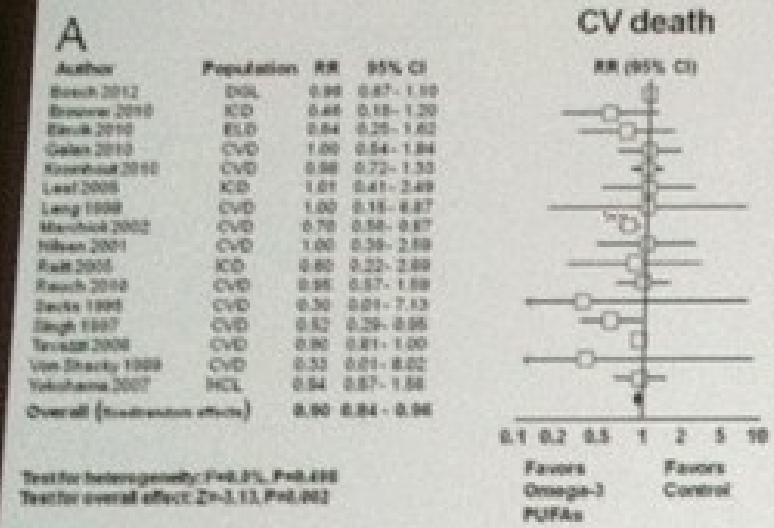
Triglyceride level is associated with wave reflections and arterial stiffness in apparently healthy middle-aged men

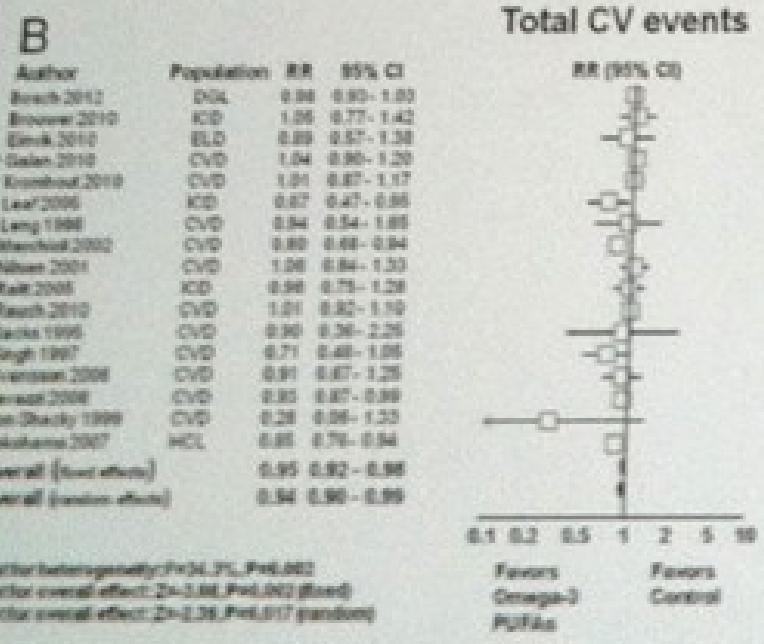
Konstantinos Aznaouridis, Charalambos Vlachopoulos, Ioanna Dima, Nikolaos Ioakeimidis, Christodoulos Stefanadis

Heart 2007;93:613–614. doi: 10.1136/hrt.2006.095554

In healthy men, serum triglyceride levels increase arterial stiffness

Does lowering TG levels decrease CV risk?



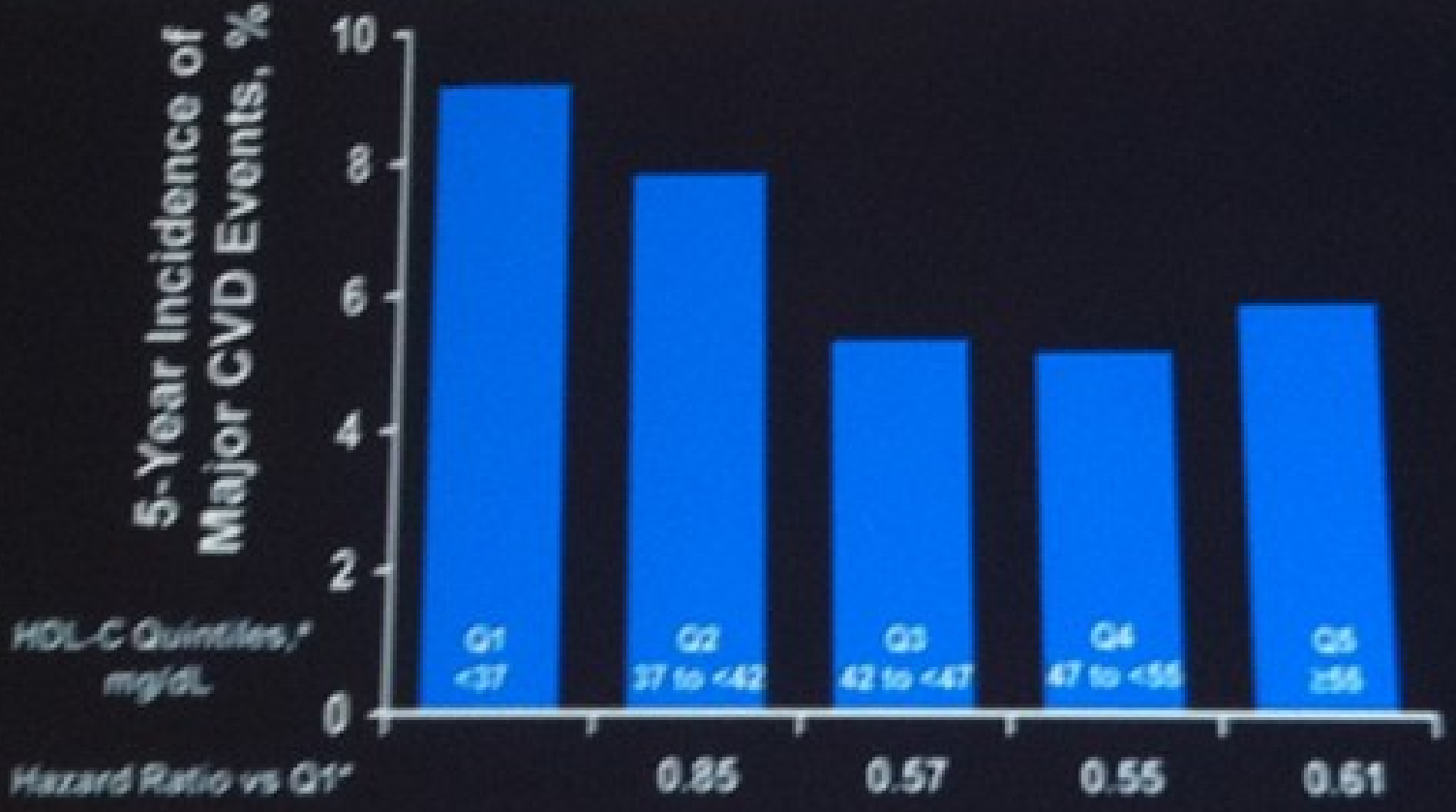


Therapy for lowering triglycerides is associated with decreased risk of CV events

Vlachopoulos et al (letter). JAMA 20

CVD events across on-treatment HDL-C Quintiles: Treating to new Targets (TNT study)

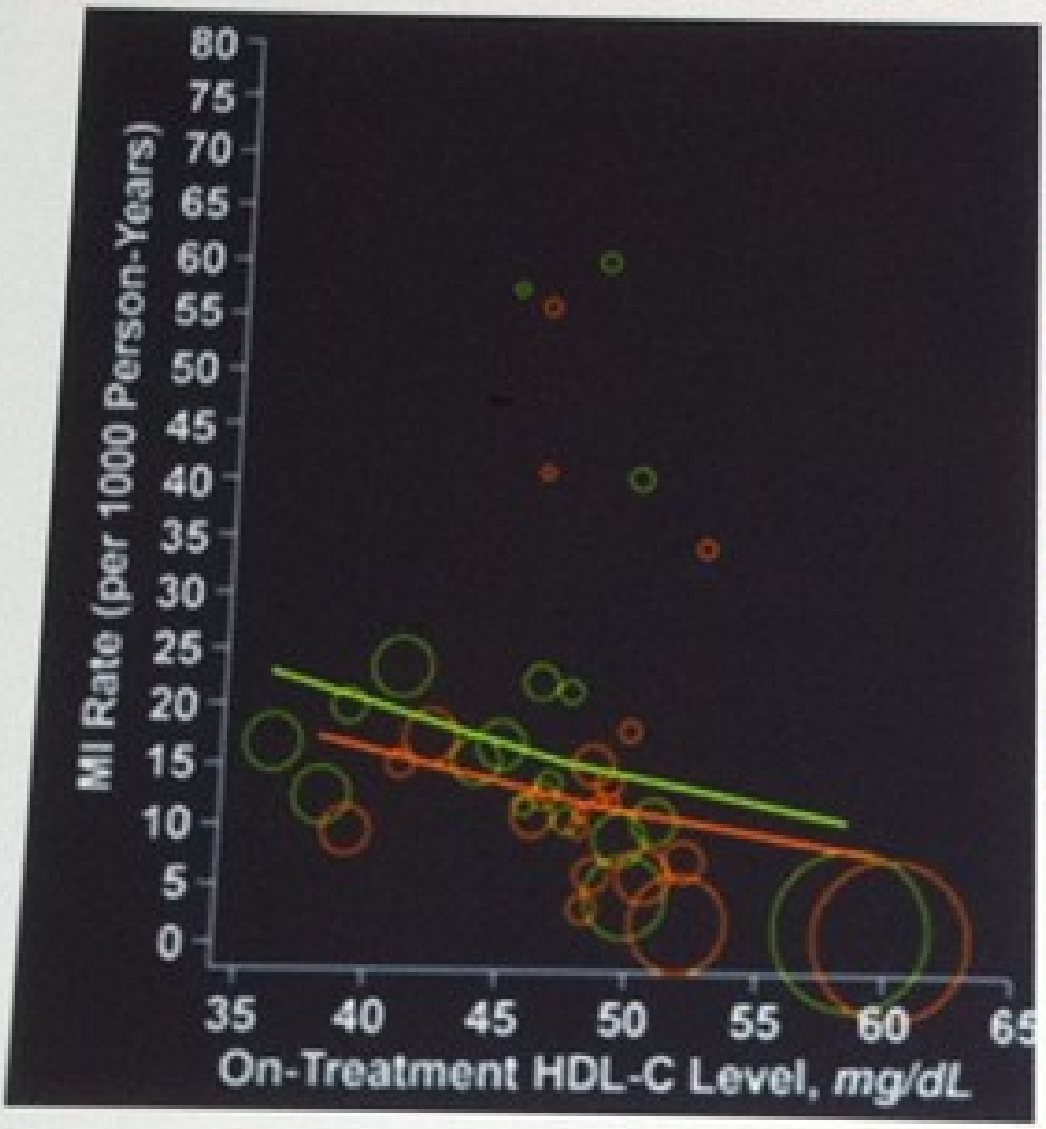
Patients with LDL-C ≤ 70 mg on statin [a,b]



*On-treatment level (3 months statin therapy); n = 3661
[a]Mean LDL-C = 98 mg/dL, mean TG = 128 mg/dL
[b]P = 0.03 for differences among quintiles of HDL-C

Barter P, et al. New Engl J Med 2007;357(13):1301-1310

Association Between HDL-C and CV Outcomes: Statin Treatment does not alter inverse relationship

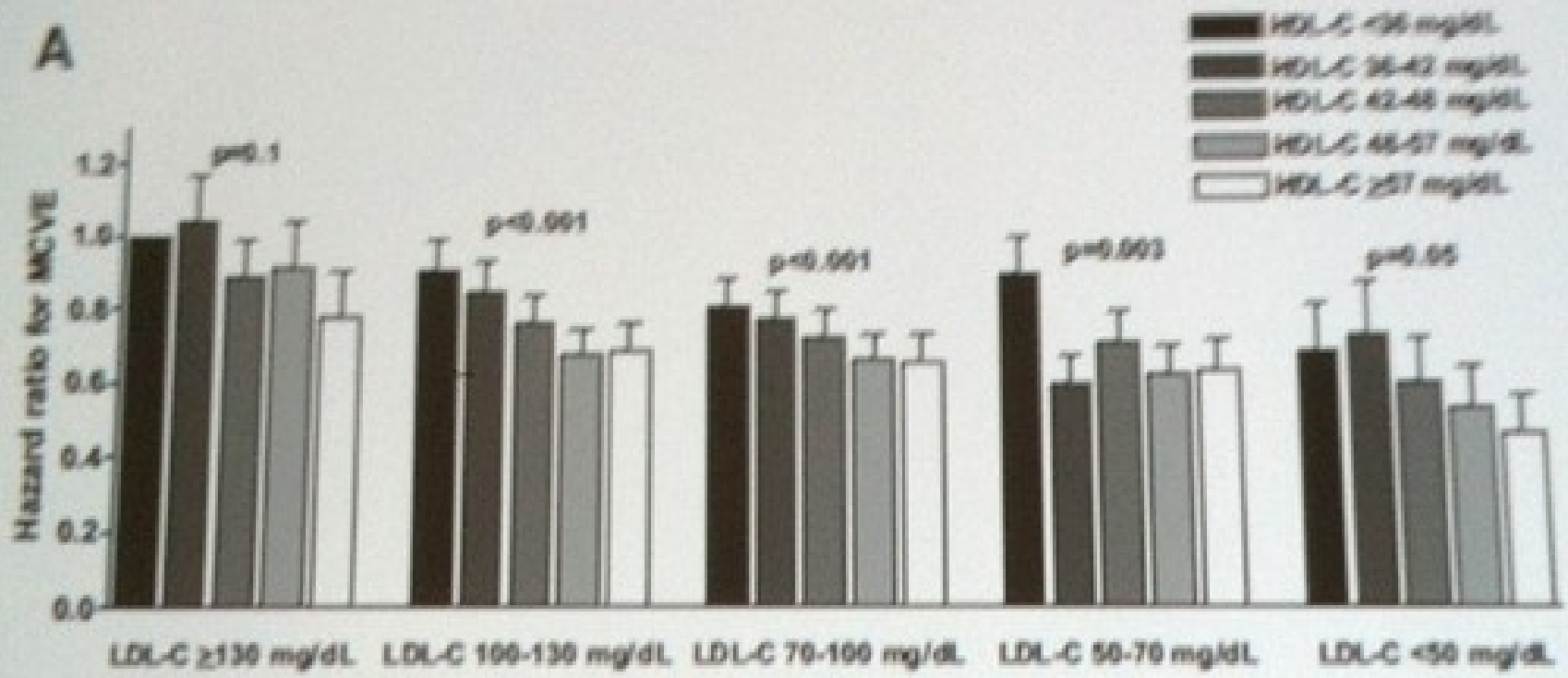


Orange circles:
Pts who are on statins

Green circles:
Pts who are on a non-statin control

Jafri H, et al. Ann Intern Med 2010

Do low HDL levels represent high CV risk?

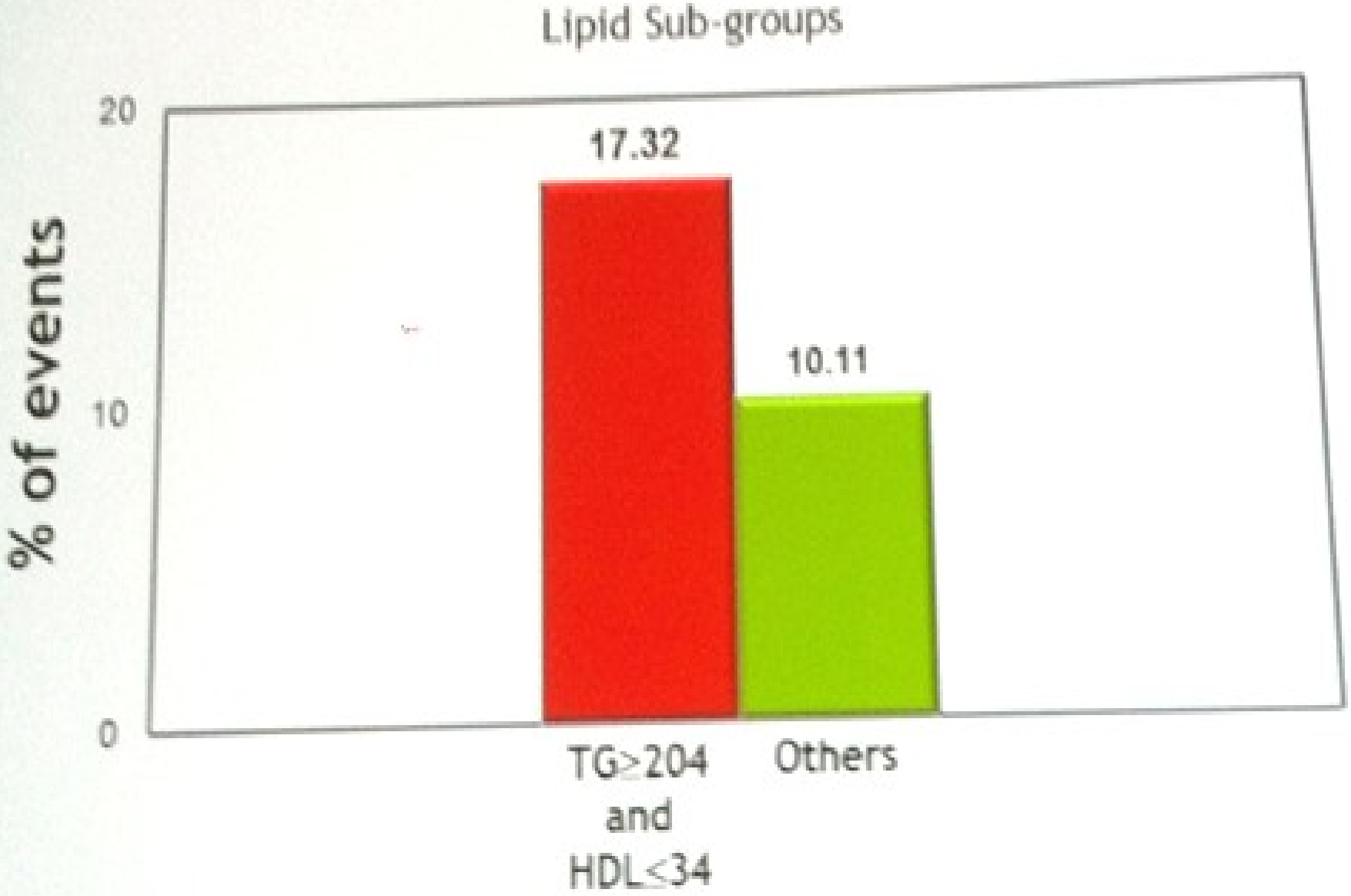


Among statin-treated patients, levels of HDL-C were strongly associated with the risk of major CV events (yet change in HDL-C was not associated with reduction of CV events)

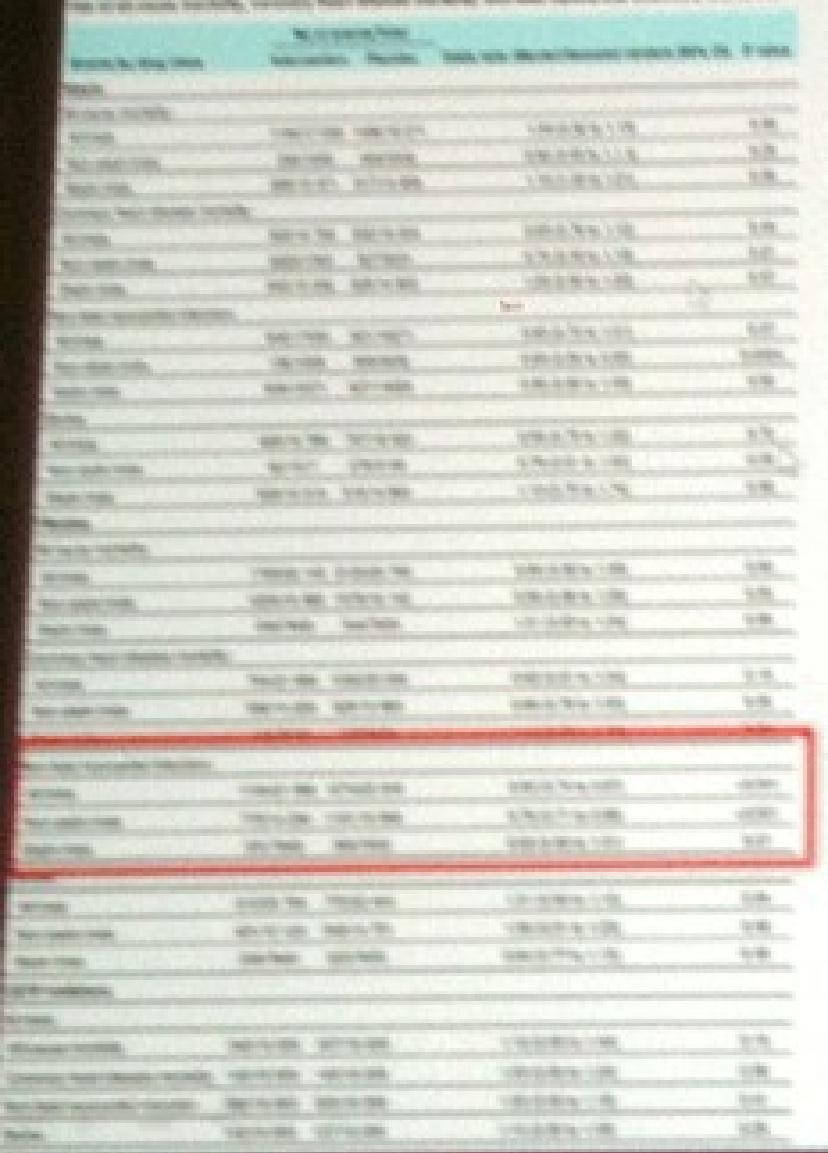
Boekholdt et al. Circulation 2013

ACCORD-Lipid Study

Residual Risk on Simvastatin* (placebo group)



Does modulation of HDL or TGs translate into reduction of CV risk?



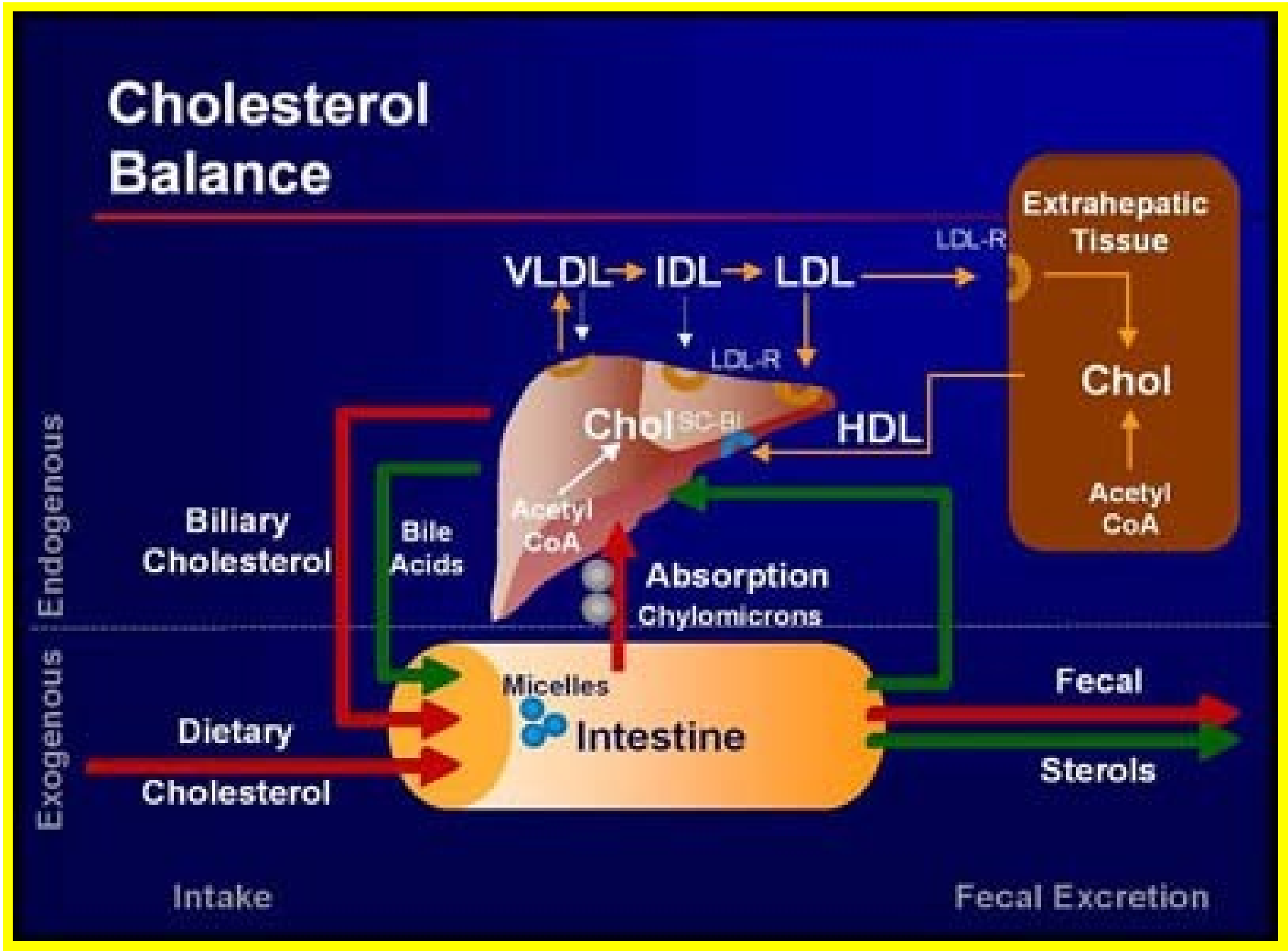
A trend for decrease in non-fatal MI was seen with fibrates on top of statin therapy

Keen D, et al. BMJ 2014

СИГНИФИКАНТЕН ОСТАТЪЧЕН ССР ИМА СЛЕД ОПТИМИЗИРАНЕ НА LDL-ХОЛЕСТЕРОЛА Е ДОКУМЕНТИРАНЕ В МНОГО СТАТИНОВИ, НЕСТАТИНОВИ И КОМБИНИРАНИ ПРОУЧВАНИЯ

НАЙ-ЗНАЧИМИТЕ ПАРАМЕТРИ ОТРАЗЯВАЩИ ОСТАТЪЧНИЯ РИСК СА HDL И ТРИГЛИЦЕРИДИТЕ

НА ТОЗИ ЕТАП Е ТРУДНО ДА СЕ ДЕФИНИРАТ ПРЕПОРЪЧИТЕЛНИ СТОЙНОСТИ НА СЪЩИТЕ ПРИ ВСИЧКИ ДИСЛИПИДЕМИЧНИ ПАЦИЕНТИ, НО СА ДОКАЗАНИ ТАРГЕТИ ПРИ АТЕРОГЕННА ДИСЛИПИДЕМИЯ


Cholesterol Balance
Extrahepatic Tissue
LDL-R
VLDL
IDL
LDL
LDL-R
Chol
SC-BI
HDL
Chol
Acetyl CoA
Acetyl CoA
Biliary Cholesterol
Bile Acids
Absorption
Chylomicrons
Micelles
Intestine
Dietary Cholesterol
Fecal Sterols
Endogenous
Exogenous
Intake
Fecal Excretion

КОМБИНИРАНО ЛЕЧЕНИЕ

СТАТИН С НИАЦИН

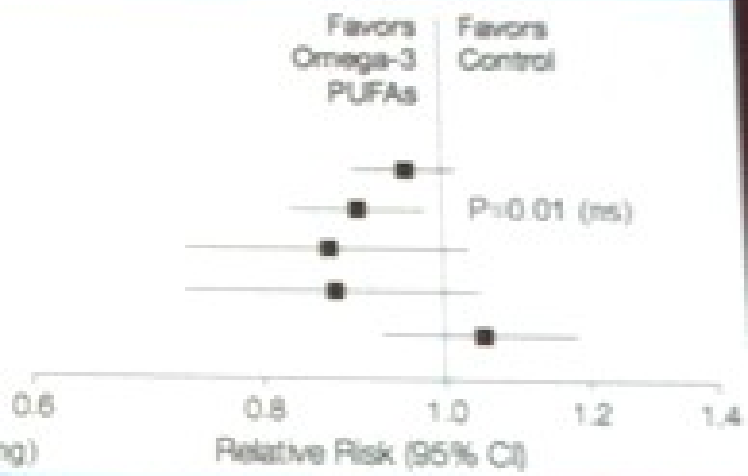
ДОБАВЯНЕТО НА ERN / Laropiprant КЪМ СТАТИНОВАТА ТЕРАПИЯ НЕ ВОДИ ДО РЕДУКЦИЯ НА

ГОЛЕМИТЕ ВАСКУЛАРНИ СЪБИТИЯ

n-3 Fatty Acids

Meta-Analysis of 20 Randomized Controlled Trials

Outcome	No. Studies	No. Events	No. Participants	RR (95% CI)
All-cause mortality	17	6295	69279	0.96 (0.91-1.02)
Cardiac death	13	3480	56407	0.91 (0.85-0.98)
Sudden death	7	1030	41751	0.87 (0.75-1.01)
Myocardial infarction	13	1755	53875	0.89 (0.78-1.04)
Stroke	9	1490	52589	1.05 (0.93-1.18)



Statistical significance at a P value threshold of 0.0063 (multiple comparisons testing)

- n-3 PUFA supplementation was **not associated with lower risk of all-cause mortality, cardiac death, sudden death, MI, or stroke**, regardless of clinical context, blinding and n-3 dose
- **Results question antiarrhythmic effect and potential advantages of higher (TG-lowering) doses** of n-3 PUFA

13 secondary prevention studies, 4 primary and secondary prevention studies, 3 ICD studies.
Mean n-3 PUFA dose 1.51 g/day. Median treatment duration 2 years (max 6.2 years).

Rizos EC et al. JAMA **2012**; 308: 1024

Atherogenic Dyslipidaemia

Role of Combination Therapy

Therapy	TChol	LDL-C	HDL-C	TG	Tolerability
Resins	↓10-25%	↓15-30%	↑3-5%	↑10%	Weak
Niacin	↓25%	↓15-25%	↑15-35%	↓20-40%	Weak/Fair
Fibrates	↓15%	↓5-20%	↑10-35%	↓20-50%	Good
Probucol	↓25%	↓10-15%	↓20-30%	neutral	Fair
Statins	↓19-37%	↓18-55%	↑5-15%	↓7-30%	Good
Ezetimibe		↓18%	↑1%	↓8%	Good
n-3 PUFA	neutral	neutral	↑<5%	↓25-30%	Good
Phytosterols	↓7-10%	↓7-10%	neutral	neutral	Good

Fenofibrate

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Effects Mediated by PPAR-α Activation

LIPID-MODIFYING

- ↑ Lipolysis of TG-rich particles (↑ LPL, ↓ apo C-III)
- ↑ β-oxidation of fatty acids in liver (↑ acyl-CoA synthase)
- ↓ VLDL synthesis and secretion (↓ apo B)
- ↑ apo A-I and ↑ apo A-II synthesis in the liver
- ↓ SR-B1 expression in the liver
- ↓ CETP-mediated transfer of cholesterol from HDL to VLDL
- ↑ Reverse cholesterol transport (↑ ABCA1)

MACROVASCULAR

- ↓ TG
- ↑ HDL
- ↓ small dense LDL

PLEIOTROPIC

- ↓ Fibrinogen, ↓ PAI-1, ↓ TF expression by monocytes
- ↓ CRP, IL-6, IL-2, IFNγ, VCAM-1
- ↓ Endothelin-1

MICROVASCULAR

- ↓ Inflammation
- ↓ Thrombosis
- ↑ Endothelial function

McKeage K et al. *Drugs* **2011**; 71:

Fenofibrate

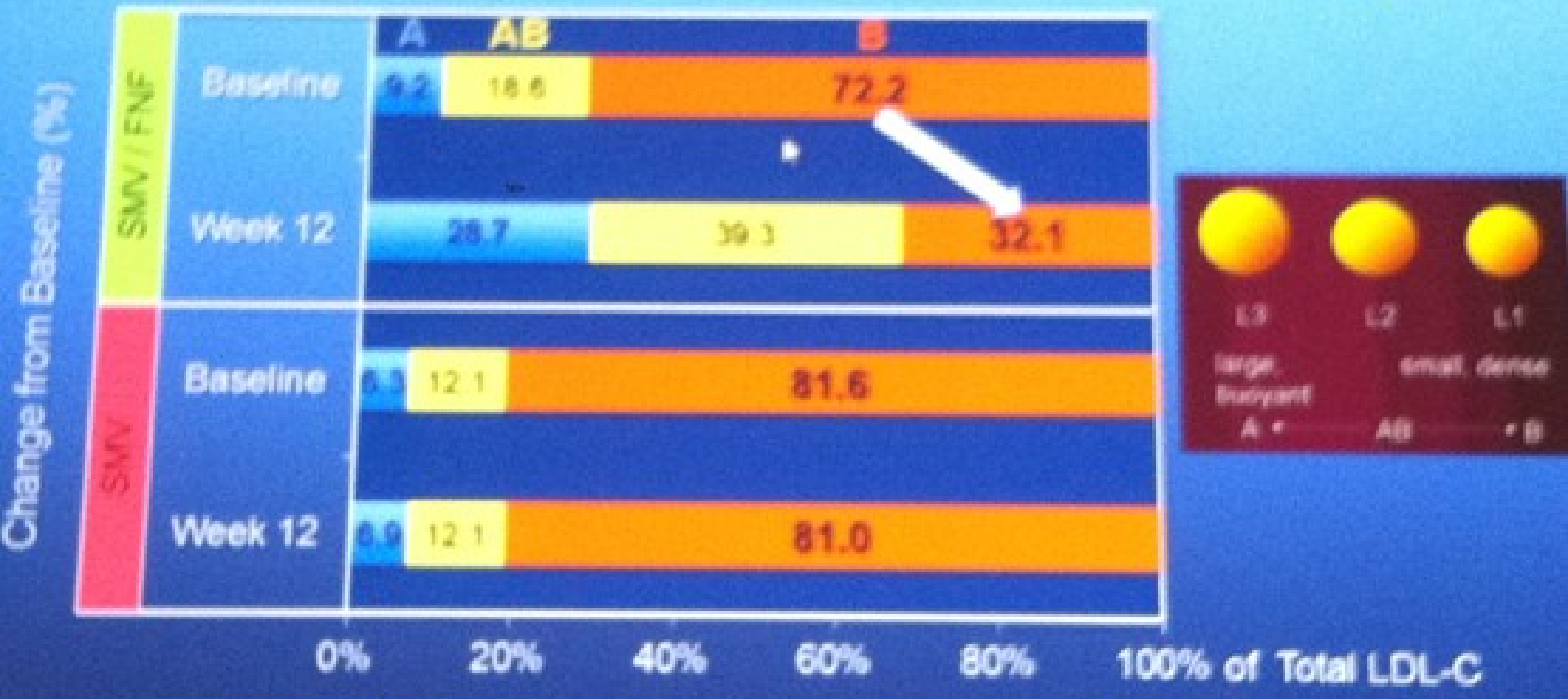
Lipid Effects with Combination Therapy

SAFARI: 618 Pts, age 21-68 years, TG 150-500 and LDL >130 mg/dL; 17% DM, 16% CVD
SMV20 vs SMV20/FNF160 for 12 weeks
P<0.001 for all comparisons between SMW and SMW/FNF

Grundy SM et al. *Am J Cardiol* **2005**;

Fenofibrate

LDL-C Effects with Combination Therapy



P<0.001 for difference in LDL phenotype between SMV and SMV/FNF

Grundy SM et al. Am J Cardiol 2005; 95: 4

Fenofibrate

Outcomes Evidence for Combination Therapy

FIELD	9795 Pts, age 50-75, T2DM, 22% w/ CVD, Statin 19% in FNF, Statin 36% in placebo	11% RRR CHD death or nonfatal MI (P=ns) TG >200 + HDL ≤40/50: 27% RRR **CV death, MI, stroke, revasc** ***NNT$_5$=23***
ACCORD-LIPID	5518 Pts, T2DM, SMV 20-40, LDL =80, 37% w/ CVD	8% RRR CV death, MI, stroke (P=ns) TG ≥204 + HDL ≤34: 31% RRR **CV death, MI or stroke** ***NNT$_5$=20***

Fenofibrate

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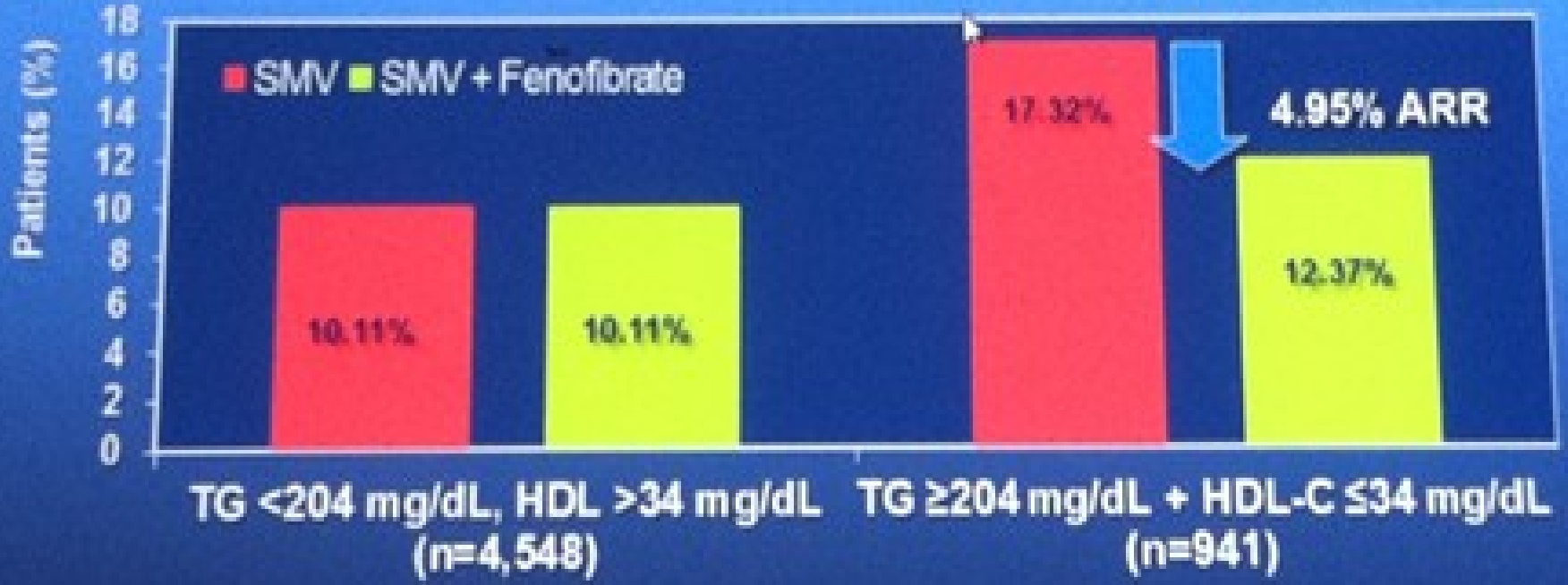
Outcomes Evidence for Combination Therapy

ACCORD-LIPID: 5518 Pts with T2DM, SMV 20-40 mg, LDL 80 mg/dL

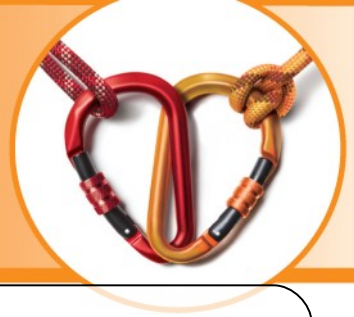
Atherogenic dyslipidaemia: ↑ 70% risk of major CV events



Pre-specified analysis. Major CV event (1° endpoint): CV death, nonfatal MI or nonfatal stroke. Mean follow-up 4.7 years.

P=0.057 for interaction. Benefit in atherogenic dyslipidaemia was present regardless of gender.

STATIN-FENOFIBRATE КОМБИНИРАНАТА ТЕРАПИЯ: ФАРМАКОЛОГИЧЕН ПОДХОД ЗА ПО-МАЛКО РАБДОМИОЛИЗА



Gemfibrozil		Fenofibrate
Atorvastatin	↑ in C_{max} (expected)	Няма взаимодействие с клинична значимост
Simvastatin	↑ in C_{max} с 2-пъти	
Pravastatin	↑ in C_{max} с 2-пъти	
Rosuvastatin	↑ in C_{max} с 2-пъти	
Fluvastatin	No effect	
Cerivastatin	↑ in C_{max} с 2 до 3 пъти	
Lovastatin	↑ in C_{max} с 2,8-пъти	Няма данни

Pan WJ et al. *J Clin Pharmacol* 2000; 40:316-23.
Backman JT et al. *Clin Pharmacol Ther* 2000; 68:122-9.
Kyrklund C et al. *Clin Pharmacol Ther* 2001; 69:340-5.
Backman JT et al. *Clin Pharmacol Ther* 2002; 72:685-91.
Davidson MH et al. *Am J Cardiol* 2002; 90 (suppl):50K-60K.
Prueksaritanont T et al. *Drug Metab Dispos* 2002; 30:1280-7.
Martin PD et al. *Clin Ther* 2003; 25:459-71.

Cholib® Fenofibrate/Simvastatin FORCES COMBINED

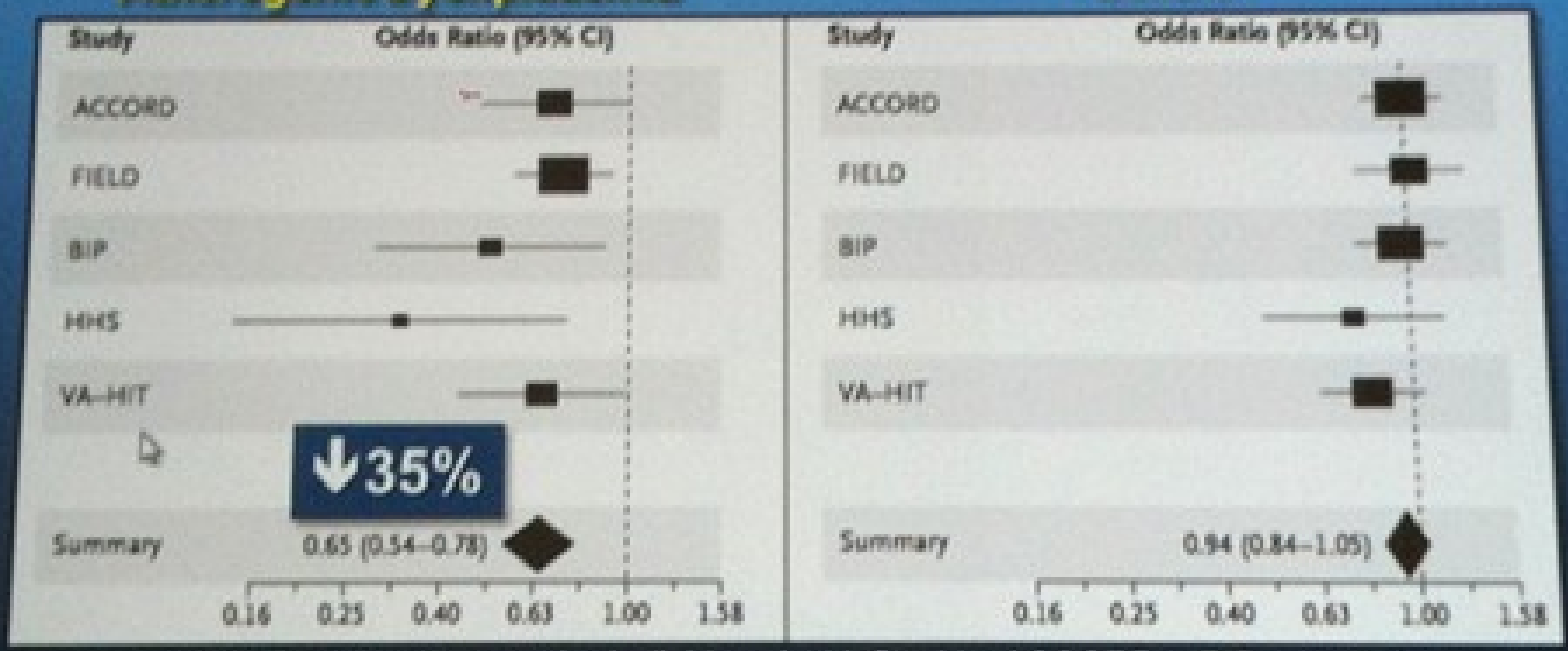
Fenofibrate

15

Outcomes Evidence for Combination Therapy

Metanalysis of Clinical Trials of Fibrates

Reduction of Coronary Events in Atherogenic Dyslipidaemia



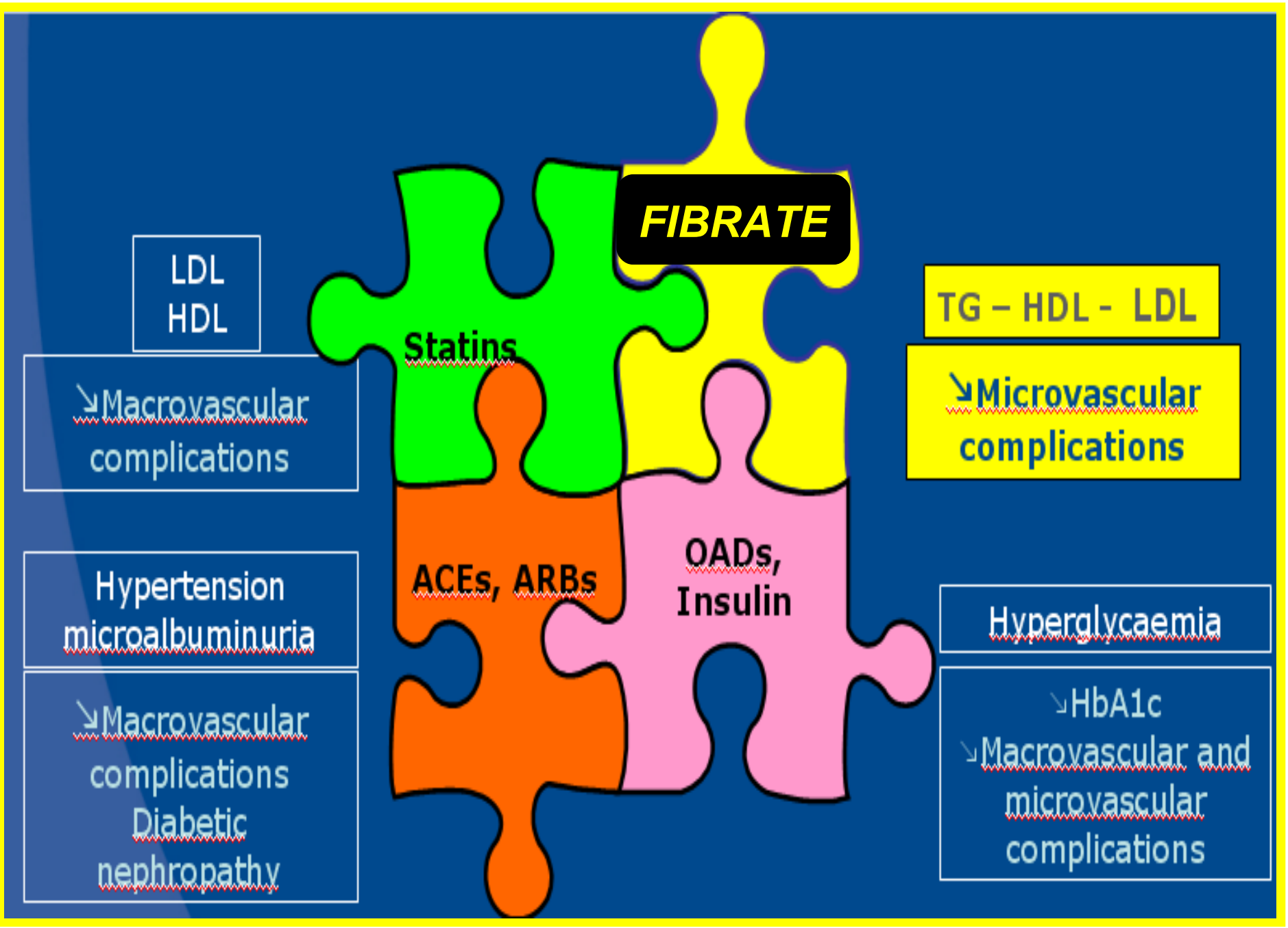
4726 Pts with atherogenic dyslipidaemia (defined by ACCORD-LIPID criteria)

СТАТИНИ И ФИБРАТИ: ДОПЪЛВАЩИ СЕ ЛИПИДНИ ЕФЕКТИ

	Статини	Фибрати
Намаляване на LDL	+++	+
Намаляване на TG	+	+++
Увеличаване на HDL	+	++
Намаляване на пост-прандиалната липемия	+	++
Подобрение в профила на LDL	±	++
Профилактика окислението на липопротеините	++	±

Cholib® Fenofibrate/Simvastatin FORCES COMBINED

Farnier M. *Am J Cardiovasc Drugs* 2003;3:169-78.


FIBRATE
Statins
ACEs, ARBs
OADs, Insulin
LDL
HDL
↘Macrovascular complications
Hypertension microalbuminuria
↘Macrovascular complications Diabetic nephropathy
TG – HDL - LDL
↘Microvascular complications
Hyperglycaemia
↘HbA1c
↘Macrovascular and microvascular complications

Combination Therapy

Muscle and Liver Safety in ACCORD-LIPID

Serious Adverse Event	Fenofibrate (n=2765)	Placebo (n=2753)
Muscle symptoms	1110 (40.1)	1115 (40.5)
Muscle symptoms + CPK >5X	7 (0.3)	8 (0.3)
Muscle symptoms + CPK >10x	1 (0.04)	2 (0.07)
Myopathy, myositis or rhabdo	4 (0.1)	3 (0.1)
Hepatitis	3 (0.1)	0 (0.0)
Laboratory Measures		
ALT ever >3x	52 (1.9)	40 (1.5)
ALT ever 5x	16 (0.6) *	6 (0.2)
CPK ever >5x	51 (1.9)	59 (2.2)
CPK ever >10x	10 (0.4)	9 (0.3)

* P=0.03

ACCORD Study Group. N Engl J Med 2010;

ESC Guidelines

Recommendations for Vascular Prevention

After LDL: Priority is Triglycerides

- Of every 3 adults, 1 has TG >150 mg/dL
- Investigate and treat underlying causes
  - Alcohol, diabetes, diet rich in simple carbohydrates, hypothyroidism, lupus, nephrotic syndrome, drug therapy

Diabetic Pts with atherogenic dyslipidaemia are at increased risk

Fibrate if TG >200 mg/dL (drug class with largest effect on TG)

Recommendation of the European Medicines Agency:

FENOFIBRATE is the only fibrate that may be added to a statin

ПОСЛАНИЕ ЗА ДОМА.....

1. ДОБАВЯНЕТО НА ФЕНОФИБРАТ ВОДИ ДО МОДИФИЦИРАНЕ НА АТЕРОГЕННАТА ДИСЛИПИДЕМИЯ И СЕ ТОЛЕРИРА ДОБРЕ КАКТО СТАТИНОВАТА МОНОТЕРАПИЯ

2. ФЕНОФИБРАТА ИМА ПЛЕЙОТРОПНИ ЕФЕКТИ, КОИТО ОПРЕДЕЛЯТ МИКРОВАСКУЛАРНАТА УСПЕШНОСТ ПРИ ДИАБЕТ 2 ТИП

3. ФЕНОФИБРАТА Е ЕДИНСТВЕНИЯ ФИБРАТ С ДОКАЗАТЕЛСТВЕН МАТЕРИАЛ ПРИ КОМБИНАЦИЯ СЪС СТАТИН

4. ФЕНОФИБРАТА Е ЕДИНСТВЕНИЯ ФИБРАТ С ИНДИКАЦИИ В ЕВРОПА ПРИ ПАЦИЕНТИ С ВИСОК РИСК И КОГАТО ТРИГЛИЦЕРИДИТЕ И НДЛ НЕ СА В ЦЕЛТА

MEDICAL TRICORDER

БЛАГОДАРЯ ЗА ВНИМАНИЕТО!