

VIII Convegno Nazionale Fondazione AMD



**Il rischio residuo nella persona con diabete:
come individuarlo e come trattarlo?**

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DISCLOSURE - CONFLICT OF INTEREST

Prof. A. Zambon reports having received grants, consulting fees and/or honoraria and delivering lectures for:

- Abbott
- Merck Sharp & Dohme
- Amgen
- Sanofi
- Lilly
- Mylan
- Chiesi

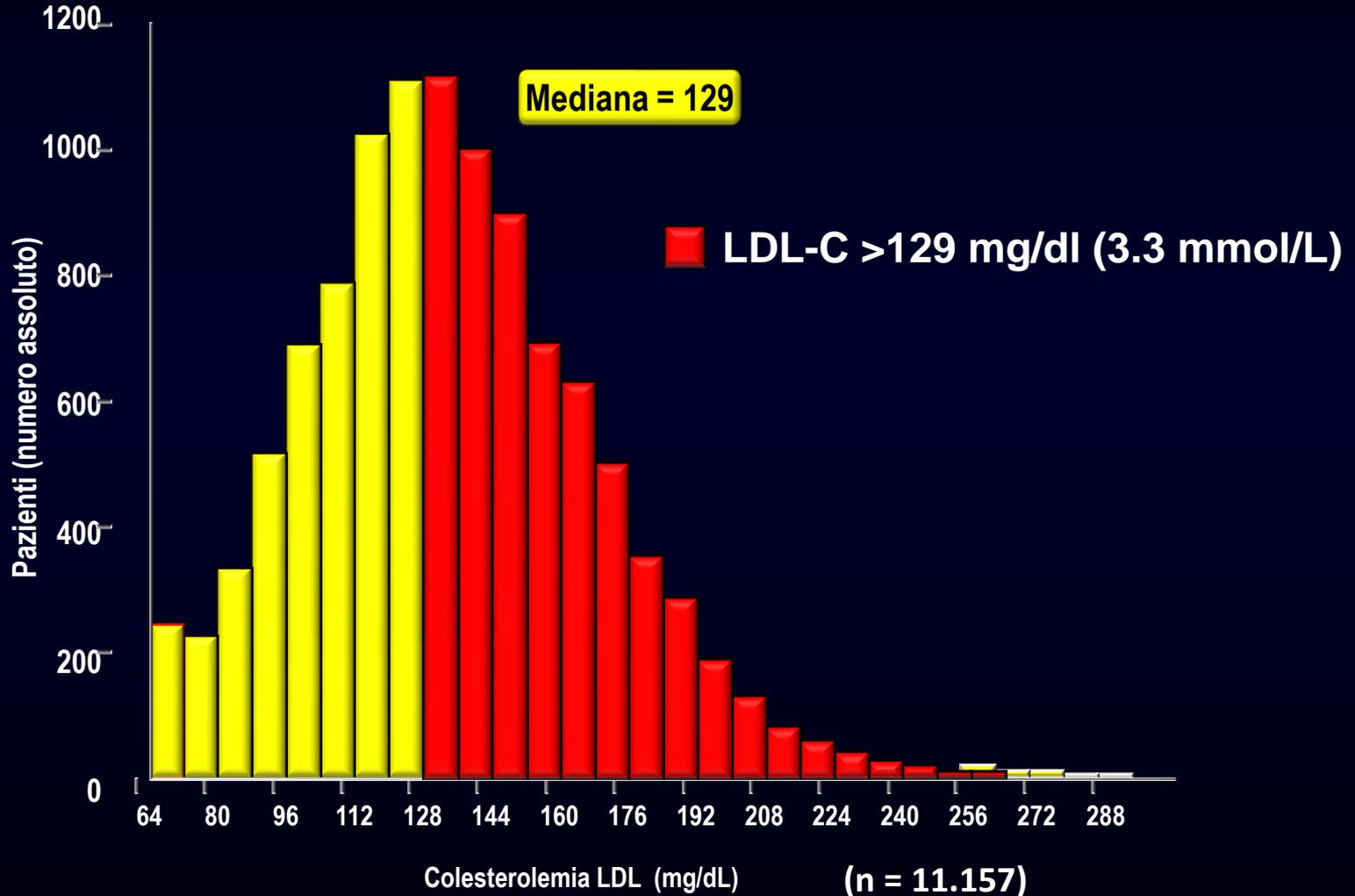
Rischio CV Residuo: Marker e Target Terapeutici

FOCUS SU LIPIDI E RISCHIO CV RESIDUO

- ✓ **Non solo LDL**
- ✓ Perché focus su lipidi e rischio CV residuo?
- ✓ Sicurezze consolidate: target LDL pros and cons
- ✓ I soliti sospetti (*a livelli ottimali di LDL-C*)
- ✓ Rischio CV residuo nel diabetico: tempi maturi per un nuovo approccio
 - *Marker migliore di rischio CV*
 - *Target più sensibile di riduzione del rischio CV in corso di terapia ipolipemizzante*
 - *In combinazione con LDL-C, predittore di risposta a terapia di associazione*

Cardiovascular risk factors and metabolic control in type 2 diabetic subjects attending outpatient clinics in Italy

The SFIDA (survey of risk factors in Italian diabetic subjects by AMD) study



Diabetic Dyslipidemia

LDL-C:

- Normal/moderate increase in LDL-C levels
- Increase in sd LDL

TG:

- Increase in total Triglycerides
- Increase in VLDL Triglycerides

± ↑ LDL-C
 ↑ Small, dense LDL

↑ TG-rich Lp(TRLs)
 (fasting and PP)
 ↑ Large VLDL particles

Visceral obesity
 Type 2 diabetes
 FCHL
 Chronic kidney disease
 POS

HDL-C:

- Decrease in HDL-C levels
- Increase in sd HDL

↓ HDL-C
 ↓ Small, dense HDL

PP=postprandial

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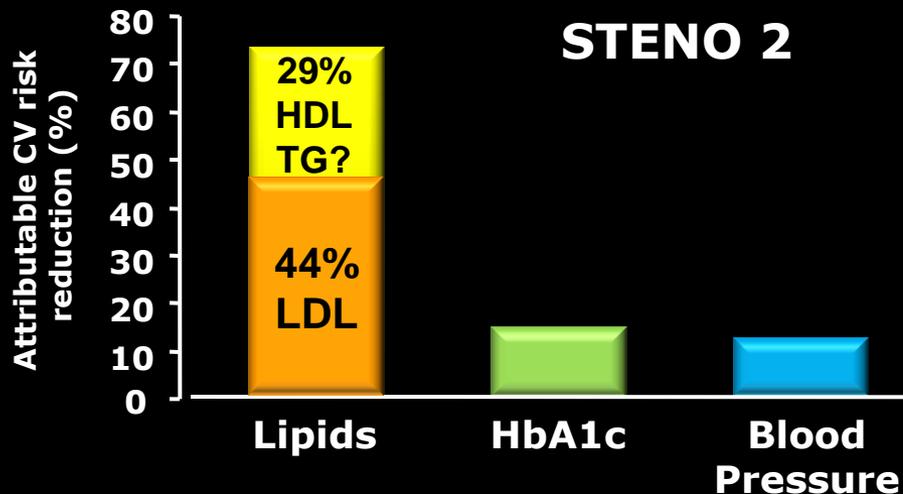
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UKPDS –STENO 2: Cardiovascular Risk Reduction as it is Accounted for by Changes in Risk Factors on Therapy (Patients with Type 2 Diabetes)

UKPDS – Coronary Events (n=280)

Ranking in the model	Variable	P Value
→ First	LDL Cholesterol	<0.0001
→ Second	HDL Cholesterol	0.0001
Third	Glycated Hemoglobin (HbA _{1c})	0.0022
Fourth	Systolic blood pressure	0.0065
Fifth	Cigarette smoking	0.056



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2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

Recommendations for the treatment of dyslipidaemia in diabetes

Recommendations	Class ^a	Level ^b	Ref ^c
Prescribe <u>statin up to the highest recommended dose or highest tolerable dose</u> to reach the goal.	I	A	62, 64, 68
In the case of statin intolerance, ezetimibe or bile acid sequestrants, or these combined, should be considered.	IIa	C	239, 256, 257
If the goal is not reached, statin combination with a cholesterol absorption inhibitor should be considered.	IIa	B	63

Treatment Recommended

 **Statin high dose**



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Table 11 Recommendations for treatment goals for low-density lipoprotein-cholesterol

Recommendations	Class ^a	Level ^b	Ref ^c
In patients at VERY HIGH CV risk ^d , an LDL-C goal of <u><1.8 mmol/L (70 mg/dL)</u> or a reduction of at least 50% if the baseline LDL-C ^e is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) is recommended.	I	B	61, 62, 65, 68, 69, 128
In patients at HIGH CV risk ^d , an LDL-C goal of <u><2.6 mmol/L (100 mg/dL)</u> , or a reduction of at least 50% if the baseline LDL-C ^e is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL) is recommended.	I	B	65, 129
In subjects at LOW or MODERATE risk ^d an LDL-C goal of <3.0 mmol/L (<115 mg/dL) should be considered.	IIa	C	-

Differences vs 2011 ESC/EAS Guidelines

-or a reduction of at least 50% if the baseline LDL-C is between **70 and 135 mg/dL** (1.8 and 3.5 mmol/L) is recommended.
-or a reduction of at least 50% if the baseline LDL-C is between **100 and 200 mg/dL** (2,6 and 5,2 mmol/L) is recommended.

Patients With Diabetes Have Particularly High Residual CVD Risk After Statin Treatment

	Event Rate (No Diabetes)		Event Rate (Diabetes)	
	On Statin	On Placebo	On Statin	On Placebo
HPS^{1*} (CHD patients)	19.8%	25.7%	↔ 33.4%	37.8%
CARE^{2†}	19.4%	24.6%	↔ 28.7%	36.8%
LIPID^{3‡}	11.7%	15.2%	↔ 19.2%	22.8%
PROSPER^{4§}	13.1%	16.0%	↔ 23.1%	18.4%
ASCOT-LLA^{5‡}	4.9%	8.7%	↔ 9.6%	11.4%
TNT⁶	7.8%	9.7%	↔ 13.8%	17.9%

*CHD death, nonfatal MI, stroke, revascularizations

†CHD death, nonfatal MI, CABG, PTCA

‡CHD death and nonfatal MI

§CHD death, nonfatal MI, stroke

|CHD death, nonfatal MI, resuscitated cardiac arrest, stroke (80 mg versus 10mg atorvastatin)

¹HPS Collaborative Group. *Lancet*. 2003;361:2005-2016.

²Sacks FM, et al. *N Engl J Med*. 1996;335:1001-1009.

³LIPID Study Group. *N Engl J Med*. 1998;339:1349-1357.

⁴Shepherd J, et al. *Lancet*. 2002;360:1623-1630.

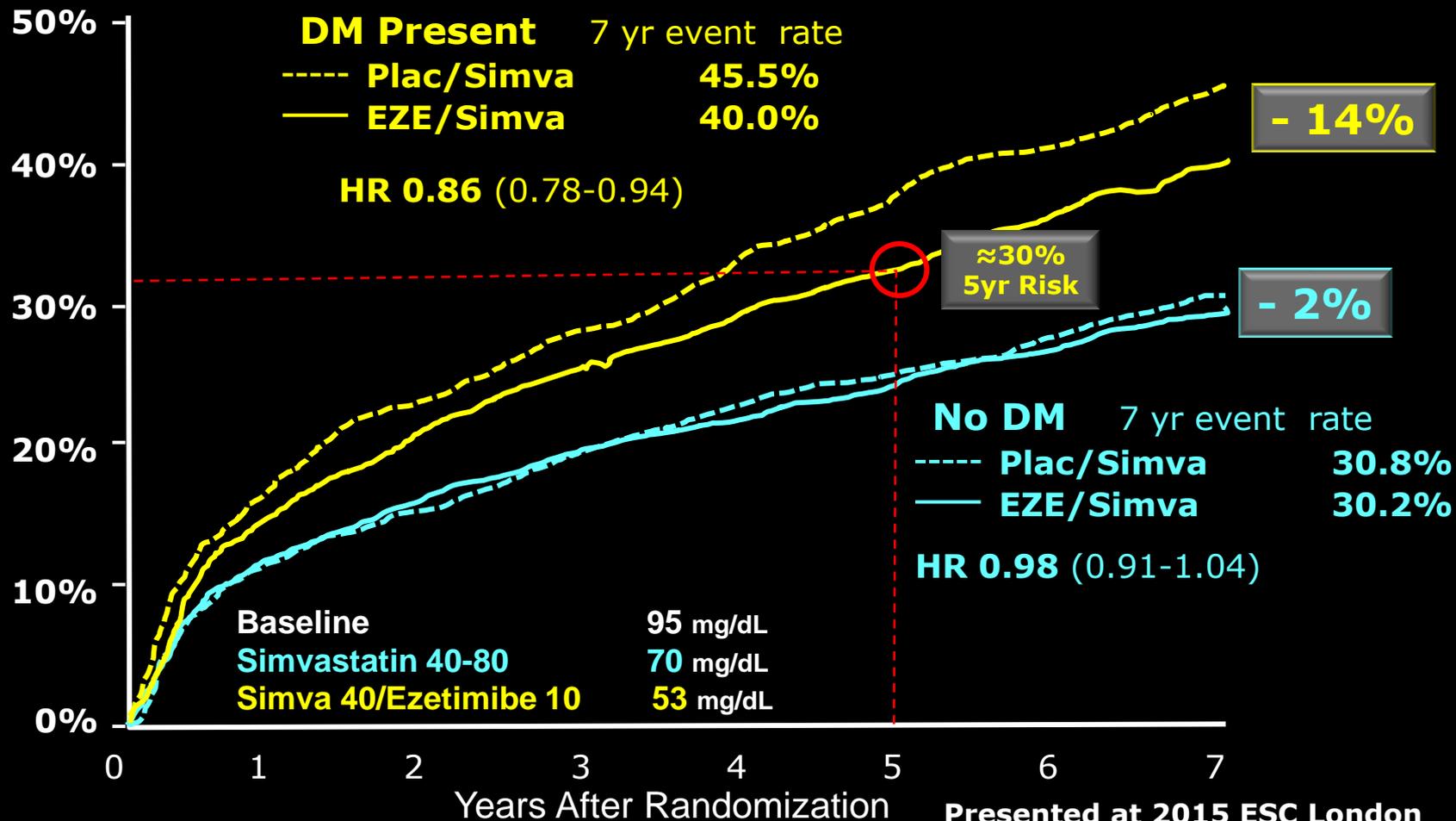
⁵Sever PS, et al. *Lancet*. 2003;361:1149-1158.

⁶Shepherd J, et al. *Diabetes Care*. 2006;29:1220-1226.

IMPROVE-IT: Primary Endpoint

Diabetes YES vs Diabetes NO

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary rivascularization (≥ 30 days), stroke



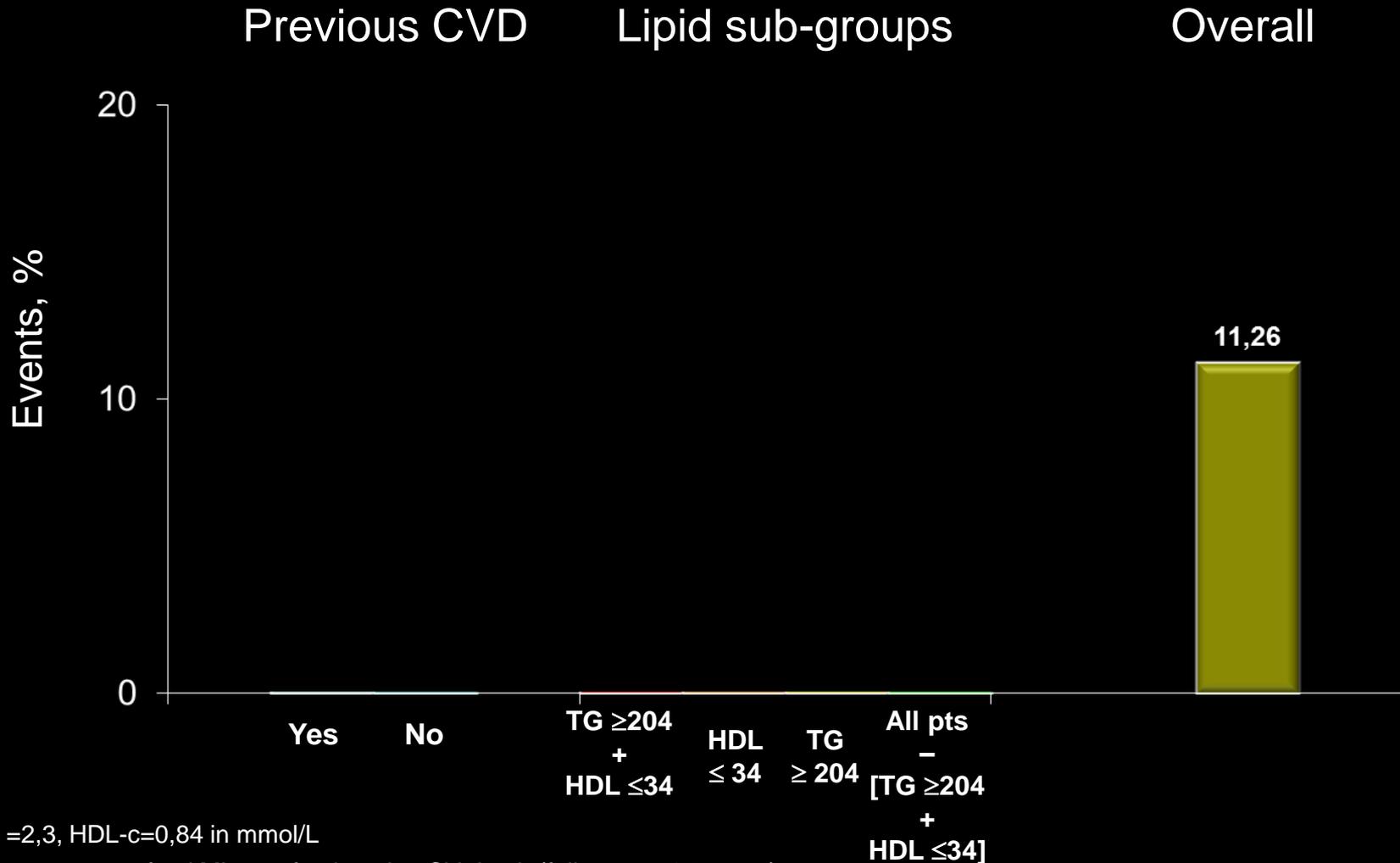
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ACCORD-Lipid Study

Diabetes and Residual Risk on Statin* (placebo group)



TG =2,3, HDL-c=0,84 in mmol/L

% events = non-fatal MI, non-fatal stroke, CV death (follow-up : 4.7 years)

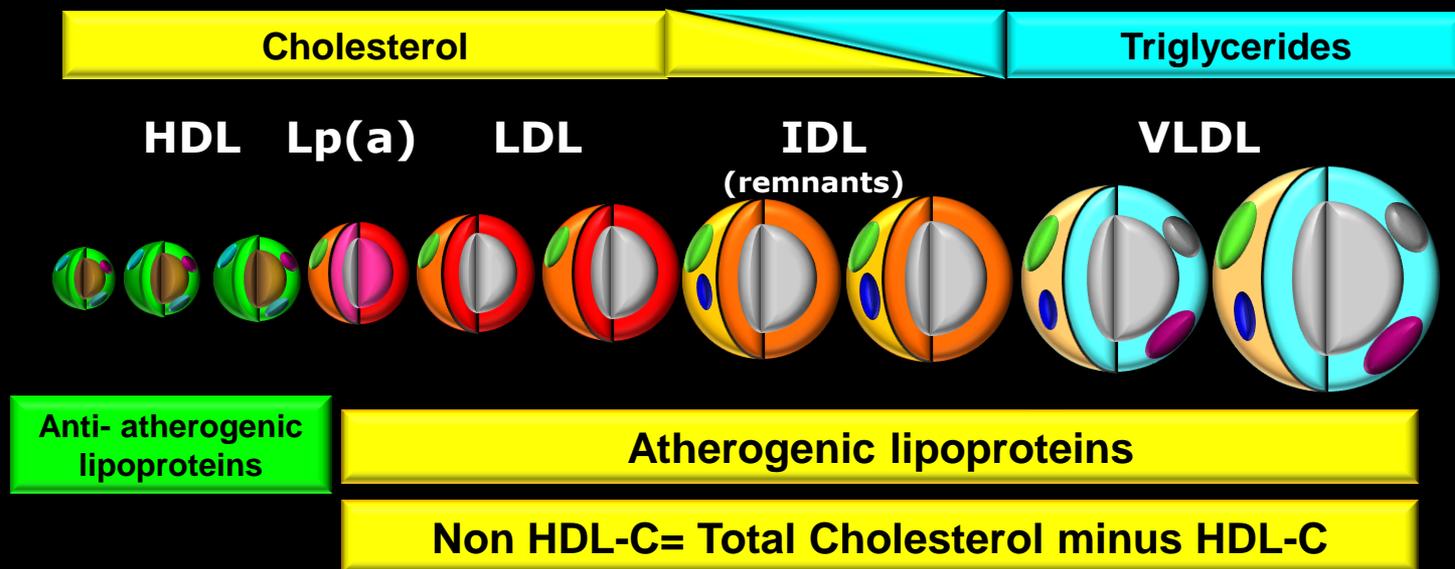
* LDL-c ≈ 2.0 mmol/L (80 mg/dL) on simvastatin

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Non-HDL Cholesterol: Emerging Target for the Treatment of (Residual) CV Risk



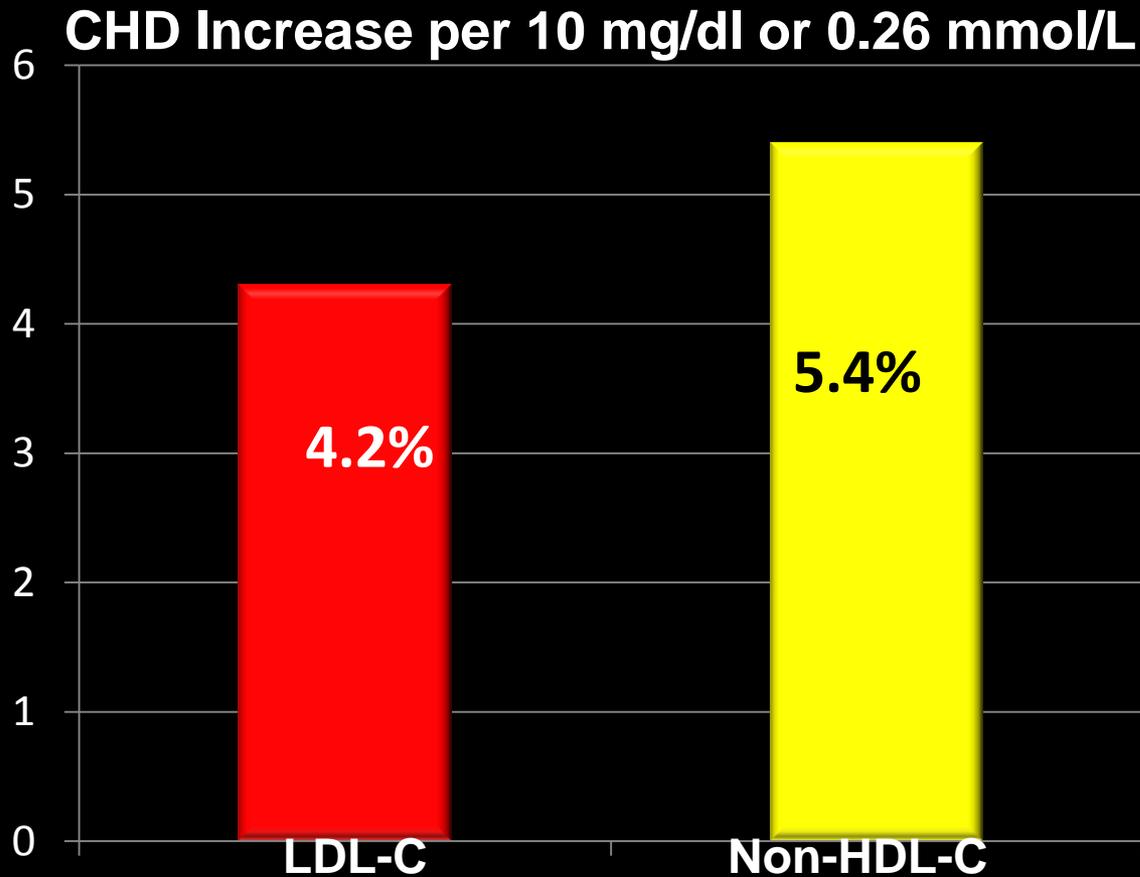
- ✓ **Accounts for all atherogenic lipoproteins;** improved estimate of CV risk in patients with diabetes, metabolic syndrome or chronic kidney disease
- ✓ **Fasting Not Required**
- ✓ Recommended as **secondary target** by national/international guidelines
- ✓ Target levels= **LDL-C goal + 30 mg/dl** (0.8 mmol/L)
- ✓ **Easy to calculate:** Total cholesterol minus HDL-C

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 - In combinazione con LDL-C, **predittore di risposta** a terapia di associazione

Non HDL-C a better marker of the risk of vascular disease than LDL-C

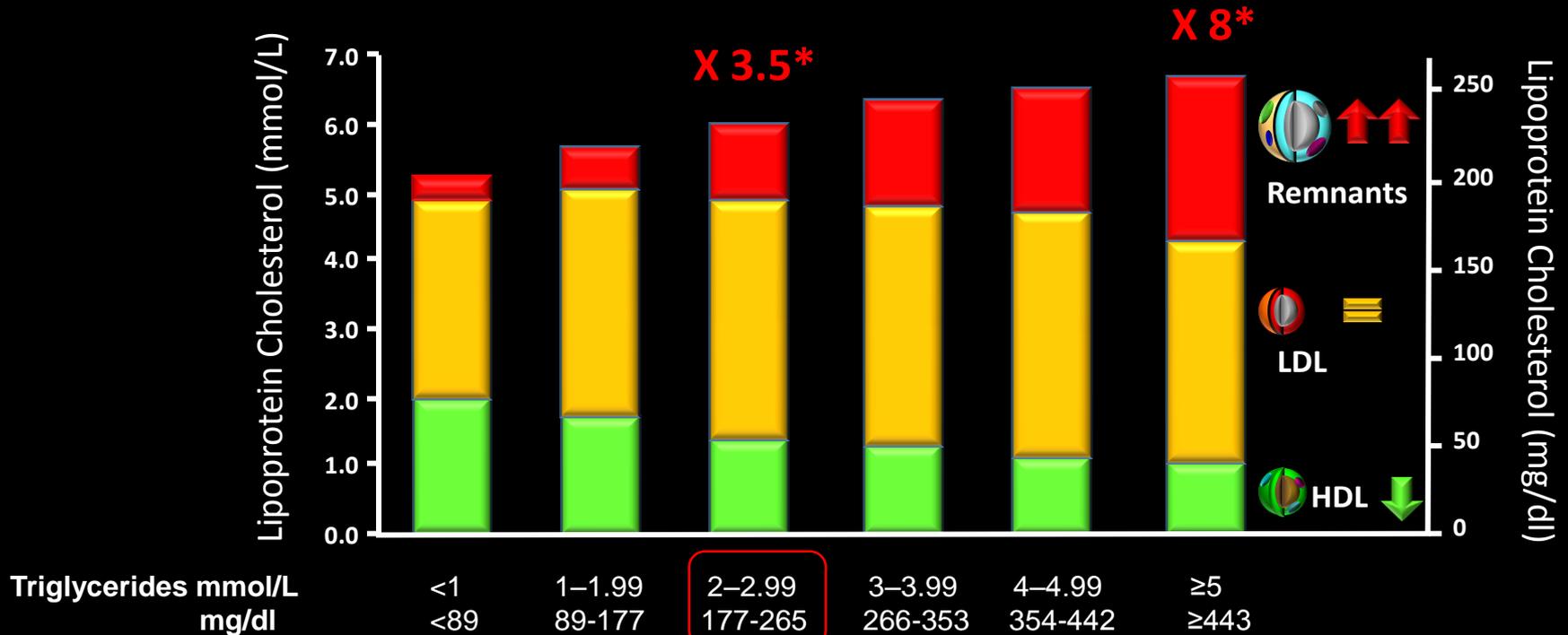


CHD risk per 10 mg/dl of Non-HDL-C relative to LDL-C:  **26%**

U.S. population from National Health and Nutrition Examination Survey 2005 to 2006 accounting for complex sample design.

Sniderman A et al. Journal of Clinical Lipidology (2010) 4, 152–155

Lipoprotein cholesterol as a function of increasing levels of non-fasting triglycerides in the general population



- * 3.5 and 8 fold increased cholesterol vs subjects with TG<1 mmol/L or 89 mg/dl
- Based on non-fasting samples from **36 160 men and women from the Copenhagen General Population Study** collected over the period 2003–2007
- Remnant cholesterol is calculated from a non-fasting lipid profile as total cholesterol minus HDL cholesterol minus LDL cholesterol; under these conditions, remnant cholesterol represents the total cholesterol transported in IDL, VLDL, and chylomicron remnants.

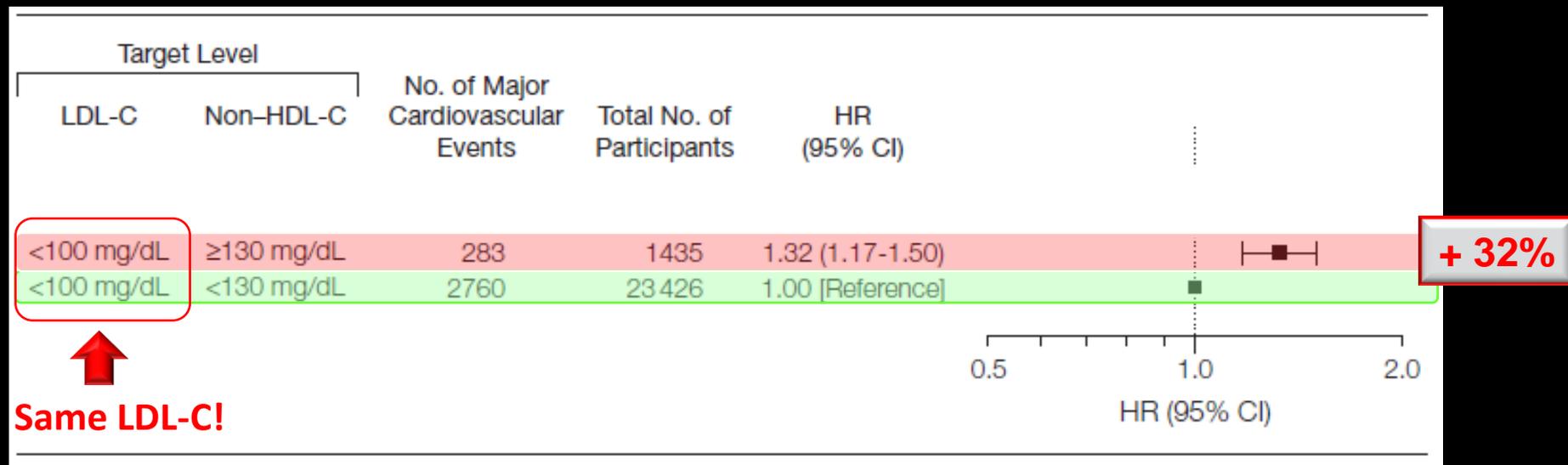
Association of LDL-C, Non-HDL cholesterol, and Apo B with risk of cardiovascular events among patients **treated with statins**

A meta-analysis

62 154 patients enrolled in 8 trials published between 1994 and 2008

Risk of major cardiovascular events by LDL and non-HDL cholesterol categories

Non-HDL cholesterol a better Target?



Data markers indicate hazard ratios (HRs) and 95% CIs for risk of major cardiovascular events. Results are shown for 4 categories of statin-treated patients based on whether or not they reached the LDL-c target of 100 mg/dL (2.6 mmol/L) and the non-HDL-C target of 130 mg/dL (3.4 mmol/L). HRs were adjusted for sex, age, smoking, diabetes, systolic blood pressure and trial

Non-HDL Cholesterol

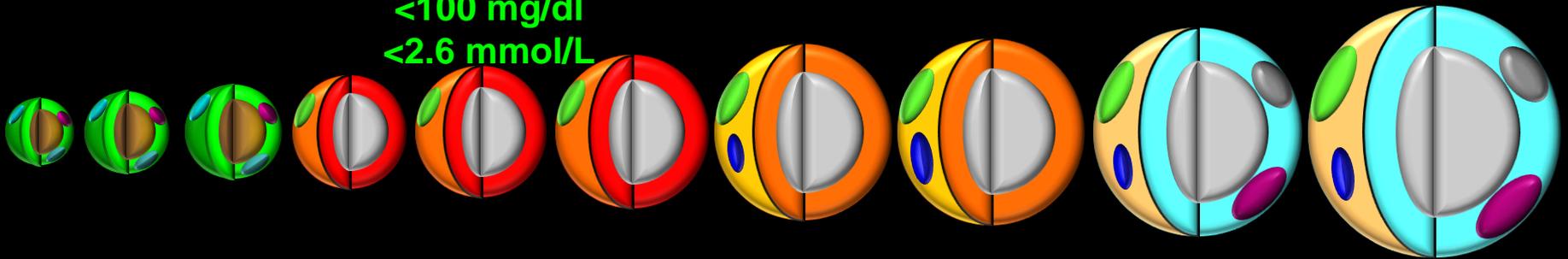
HDL ↓

LDL

AT TARGET
<100 mg/dl
<2.6 mmol/L

IDL ↑
(Remnants)

VLDL ↑
Triglycerides



Anti
Atherogenic
Lipoproteins

Non HDL-C ≥ 130 mg/dl or 3.4 mmol/L NOT AT TARGET

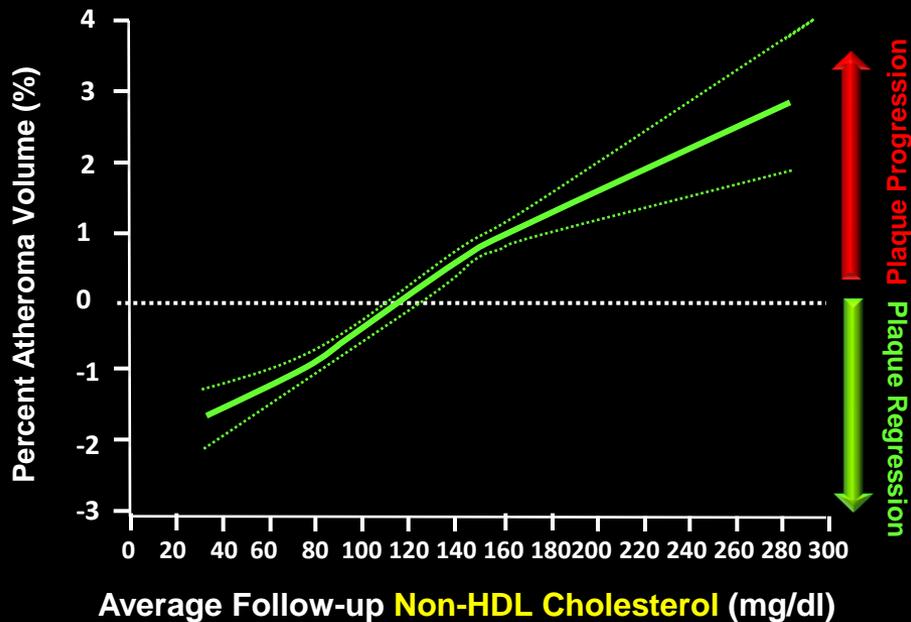
Atherogenic Lipoproteins

Non-HDL cholesterol: Emerging # 1 **TARGET** for
treatment of (Residual) **Cardiovascular Risk**

Non-HDL Cholesterol and Triglycerides

Implications for Coronary Atheroma Progression and Clinical Events

- 9 clinical trials involving 4957 patients with coronary disease undergoing serial intravascular ultrasonography to assess **changes in percent atheroma volume (Δ PAV)**.
- Follow-up 18-24 months
- Evaluated against on-treatment non-HDL C < 100 mg/dl (<2.6 mmol/L) vs >100 mg/dl (>2.6 mmol/L)



CONCLUSIONS—Coronary disease progression is more tightly linked with changes in non-HDL C compared with LDL C and on-treatment TG levels associate with coronary atheroma progression (and thus, cardiovascular risk), especially when these levels exceed 200 mg/dL.

**Full Lipid Profile
(Chol, LDL-C, HDL-C, TG)**

*PAD
Aortic aneurysm
Carotid Artery disease
CHD risk >10 (SCORE)

CHD or
CVD Equivalent*
Very High CVD Risk

NO

High CVD Risk

YES

CV risk evaluation and identification of #1 target LDL-C

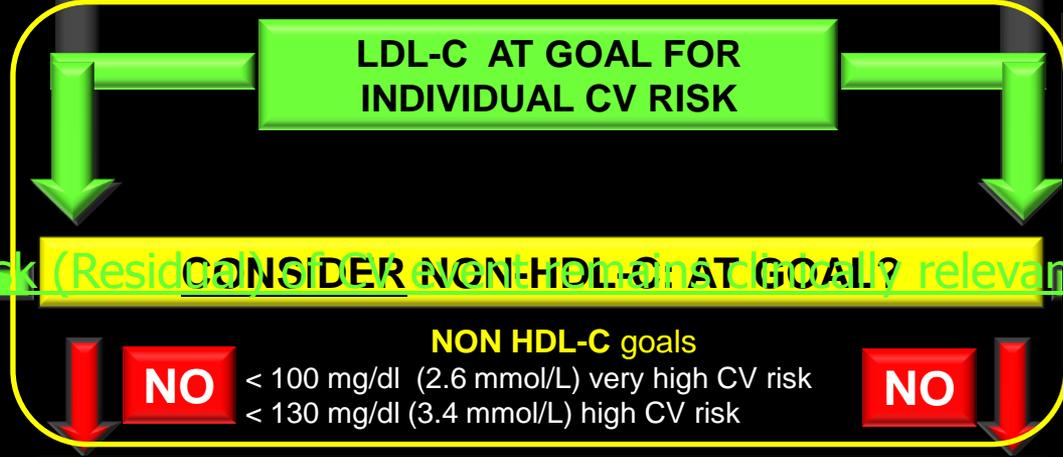
LDL-C Target
<70 mg/dl or
≥50% reduction

1 Approach
LifeStyle+high Intensity **STATIN**
or Statin-Ezetimibe (PCSK9 Mab)

LDL-C target
<100 mg/dl or
≥50% reduction

1 Approach
LifeStyle +high Intensity **STATIN**
or Statin-Ezetimibe

Statin (±ezetimibe) highly effective CV events reduction in diabetes



**YES
OK STOP**