MODELLI ORGANIZZATIVI APPROPRIATI PER LA GESTIONE DELLA CRONICITÀ NELL'AMBITO DELL'IPERCOLESTEROLEMIA CON I NUOVI ANTICORPI MONOCLONALI ANTI PCSK9

Ancona, 21 aprile 2017

Epidemiologia della Ipercolesterolemia nella Regione Marche

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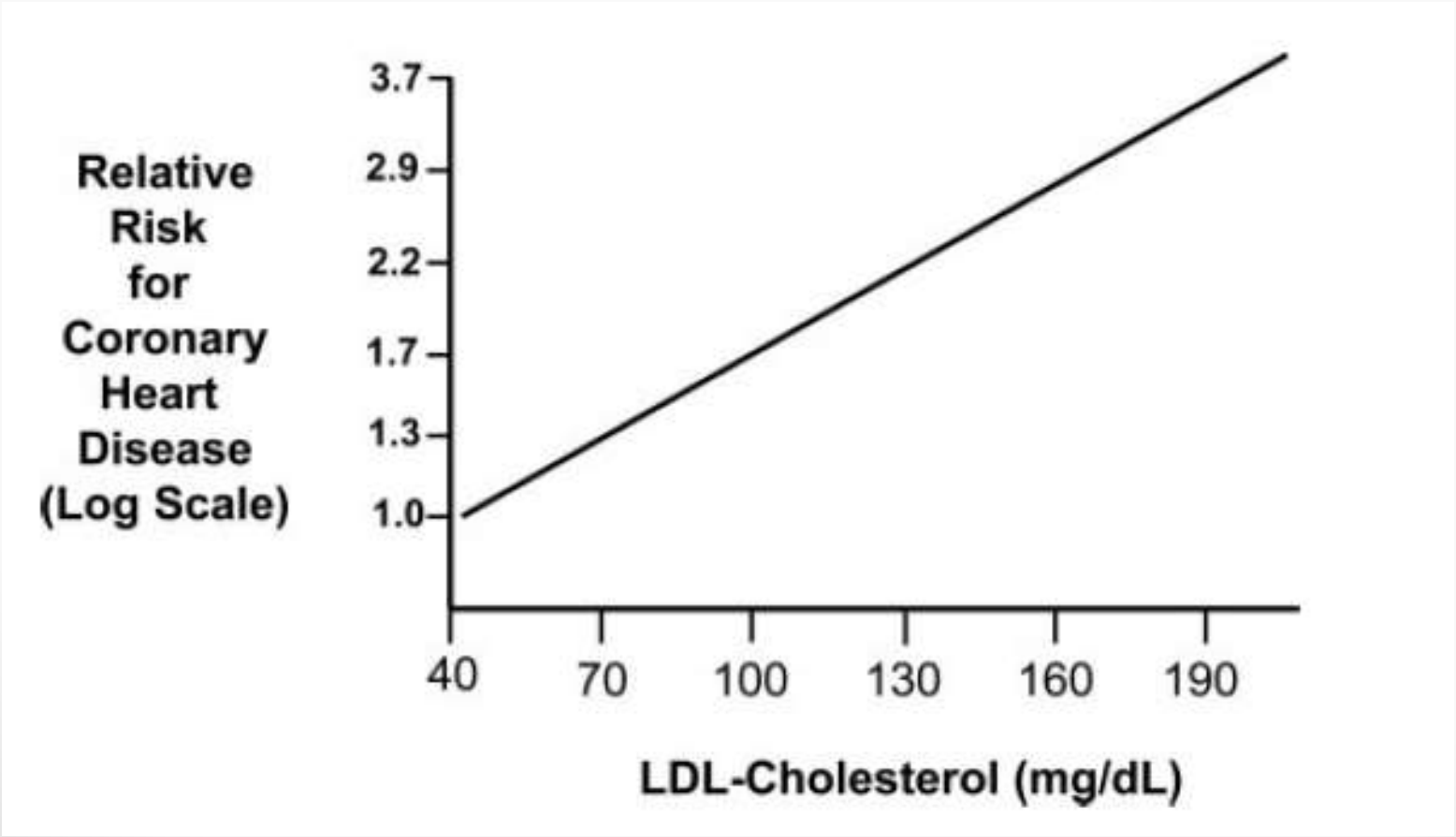
Mediche e Chirurgiche A. O. U. Ospedali Riuniti Ancona

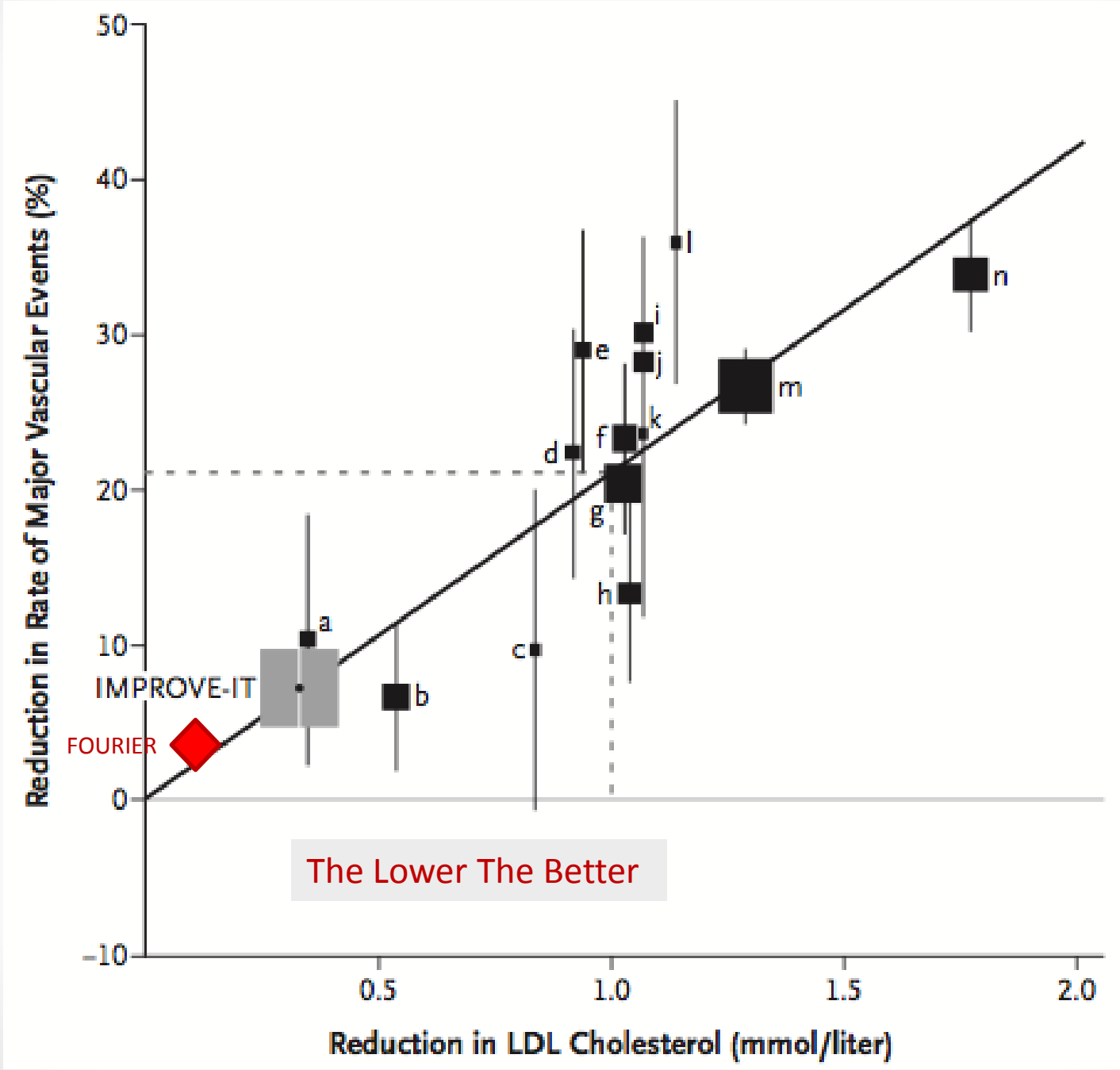
Lipid control

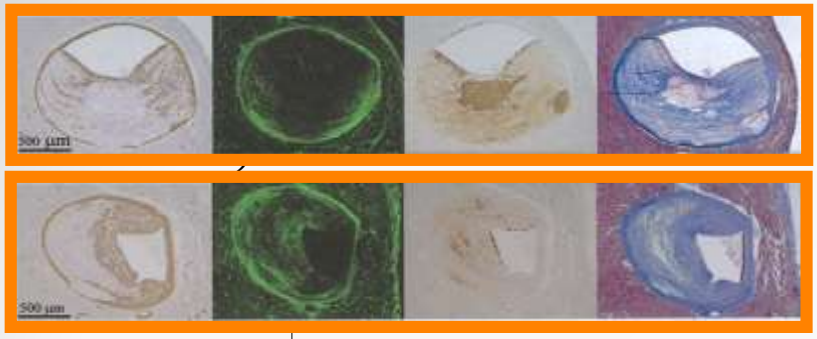
Key messages

- Elevated levels of plasma LDL-C are causal to atherosclerosis.
- Reduction of LDL-C decreases CV events.



Cholesterol Treatment Trialists Collaboration (CTTC)





M. liscio Collagene Macrofagi Core lipidiico

Change in Percent Atheroma Volume* (%)

1
0.5
0
-0.5
-1

50 60 70 80 90 100 110 120

Mean LDL-C (mg/dL)

REVERSAL[5] pravastatin

CAMELOT[4] placebo

ACTIVATE[1] placebo

A-Plus[2] placebo

REVERSAL[5] atorvastatin

ASTEROID[3] rosuvastatin

GLAGOV Evolocumab

Progression

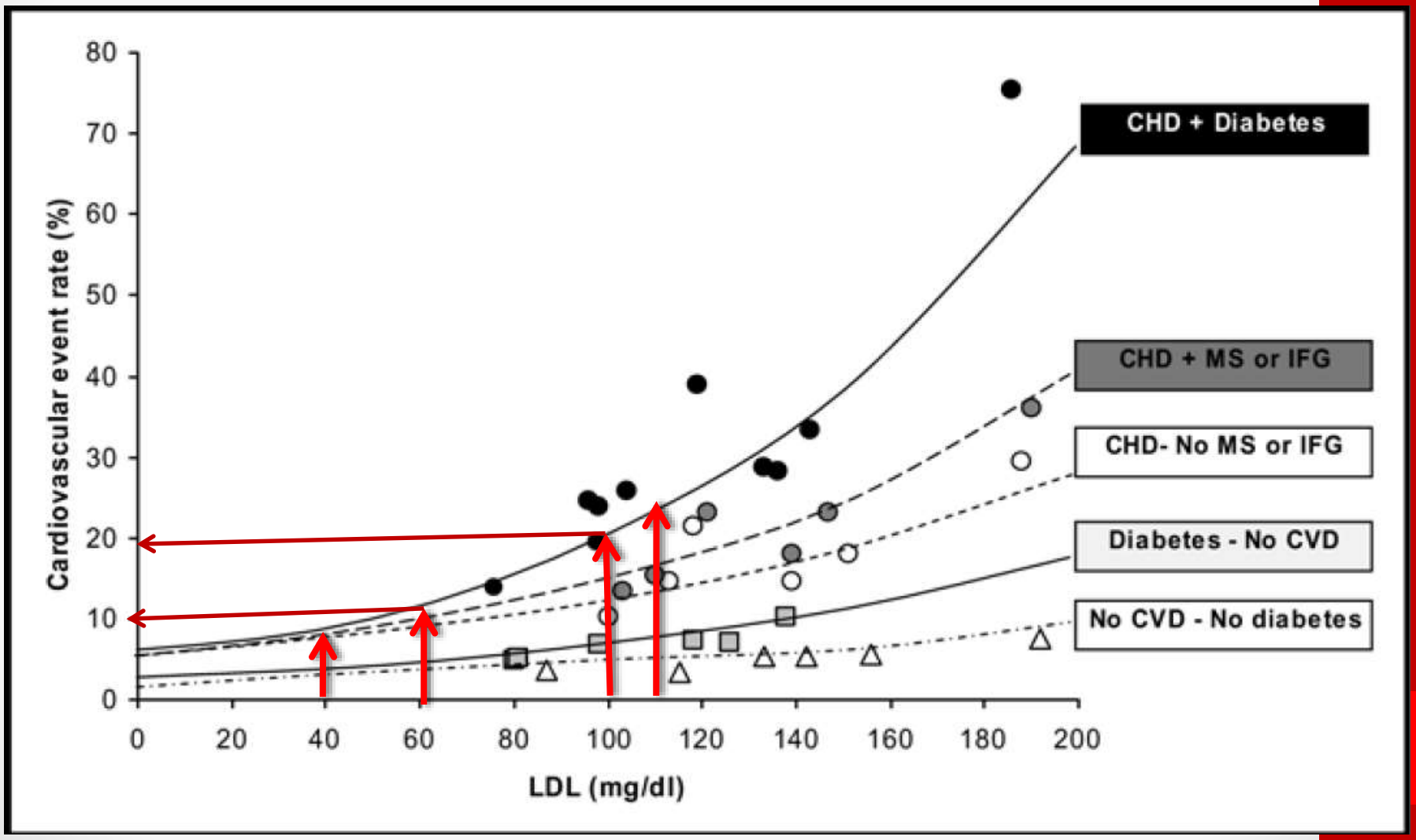
Regression

†ASTEROID and REVERSAL investigated active statin treatment; A-PLUS, ACTIVATE AND CAMELOT investigated non-statin therapies but included placebo arms who received background statin therapy (62%, 80% and 84% respectively).

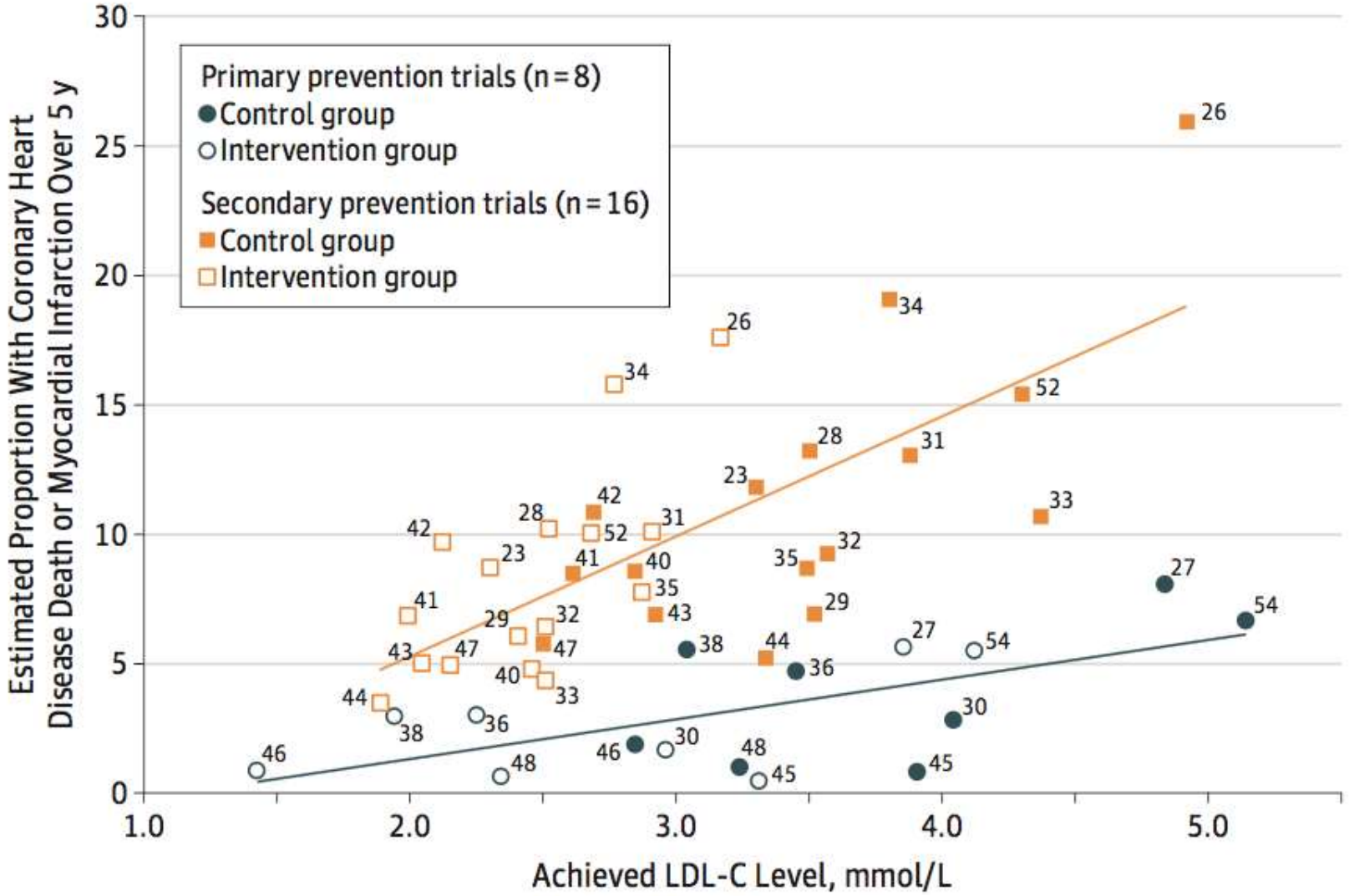
*Median change in PAV from ASTEROID and REVERSAL; LS mean change in PAV from A-PLUS, ACTIVATE AND CAMELOT

1 Nissen S et al. N Engl J Med 2006;354:1253-1263. 2 Tardif J et al. Circulation 2004;110:3372-3377. 3 Nissen S et al. JAMA 2006;295 (13):1556-1565 4 Nissen S et al. JAMA 2004;292: 2217–2225. 5 Nissen S et al. JAMA 2004; 291:1071–1080

LDL-C level and the Risk of CV Events



Robinson JG et al., Am J Cardiol 2006



JAMA. 2016;316(12):1289-1297.

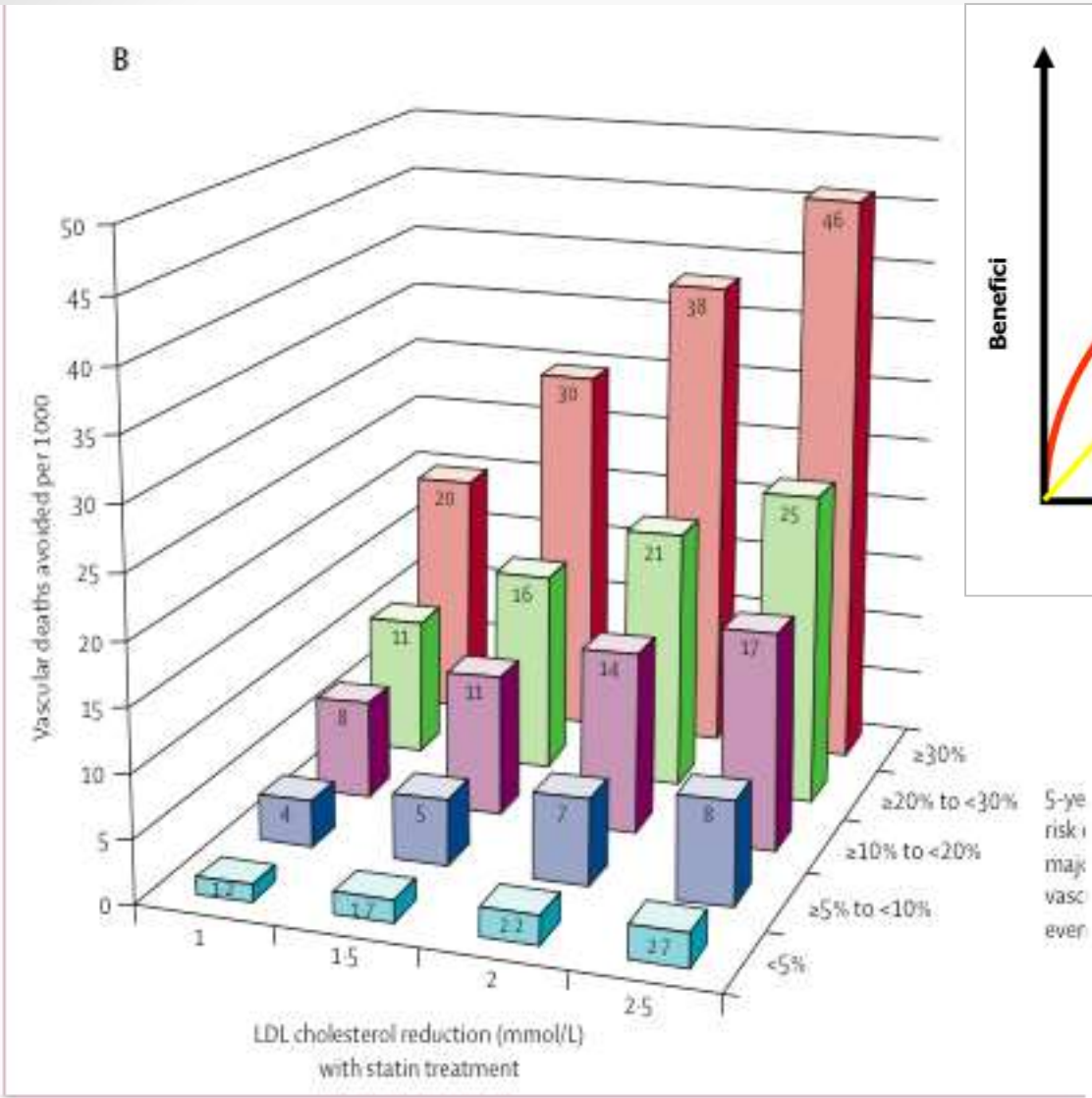
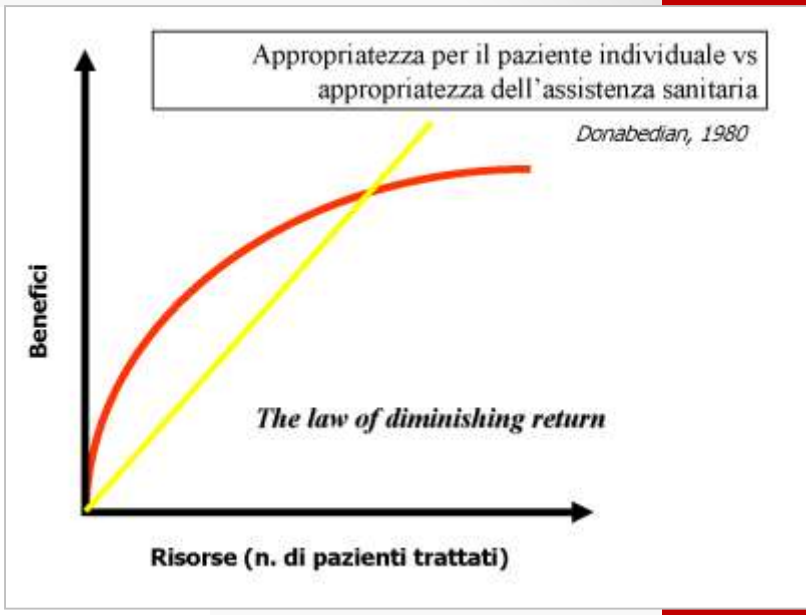


Figure 5: **Predicted 5-year benefits of LDL cholesterol reductions with statin treatment at different levels c**
(A) Major vascular events and (B) vascular deaths. Lifetable estimates using major vascular event risk or vascu
death risk in the respective risk categories and overall treatment effects per 1·0 mmol/L reduction in LDL
cholesterol with statin.



NNT ↓

NNH =

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Lipid Control – Recommendations for LDL-C targets 1

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 <1.8 mmol/L (70 mg/dL) 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 <2.6 mmol/L (100 mg/dL), 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	-

CV = cardiovascular; LDL-C = low-density lipoprotein-cholesterol.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.
[d]For definitions see section 2.2.
[e]The term "baseline LDL-C" refers to the level in a subject not taking any lipid lowering medication.

Specific situations where **achievements of a LDL-C reduction ≥ 50% is the primary objective** :

- Very High Risk patients with baseline LDL-C between 1.8 and 3.5 mmol/L (70 and 135 mg/dL)*
- High Risk patients with baseline LDL-C between 2.6 and 5.2 mmol/L (100 and 200 mg/dL)

A. Catapano al. Eur Heart J. 2016; doi:10.1093/eurheartj/ehw272

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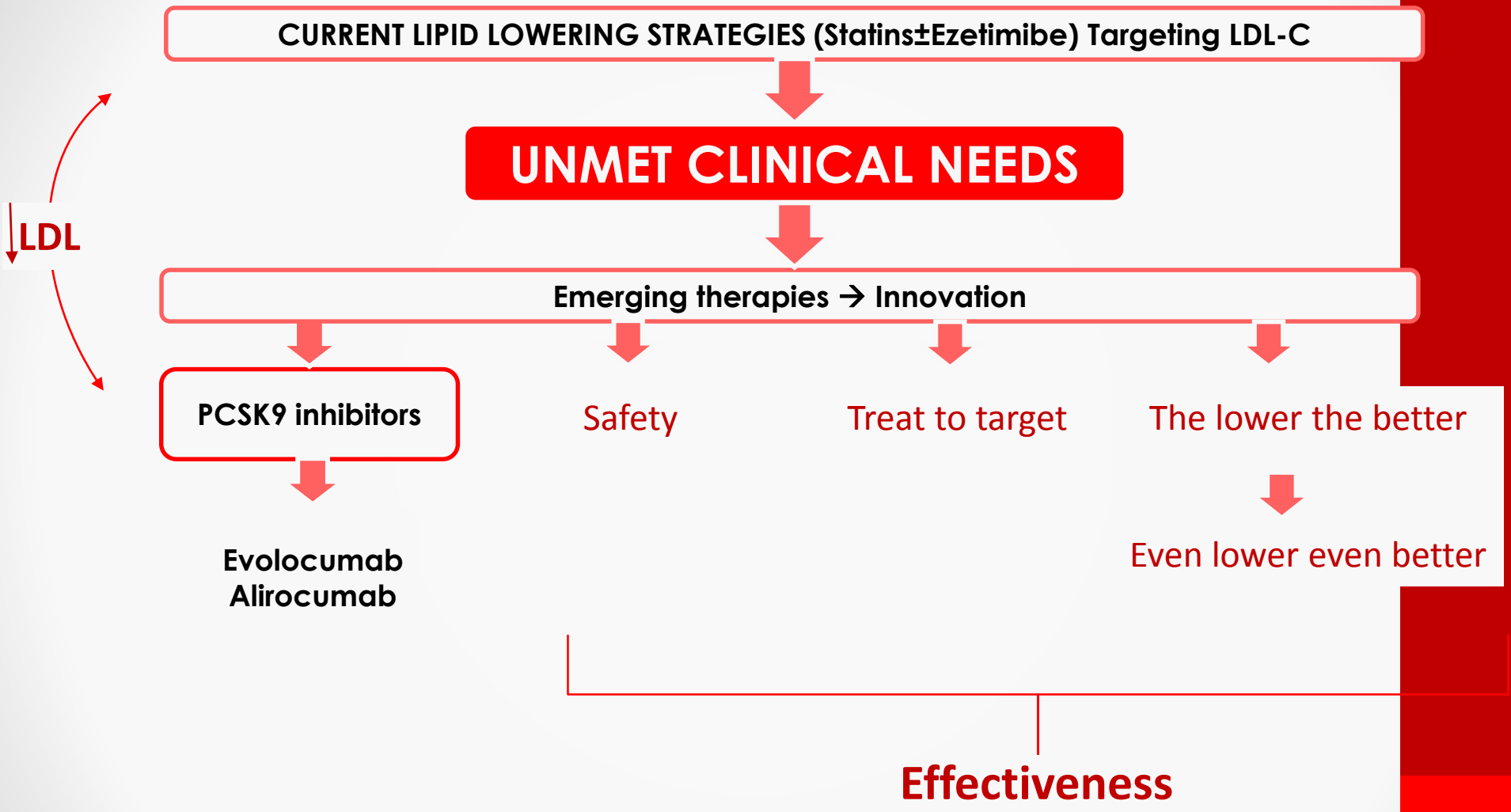
Lipid Control – Recommendations for LDL-C targets 2

Box 8 Recommendations for treatment goals for lowdensity lipoprotein-cholesterol (LDL-C)–examples

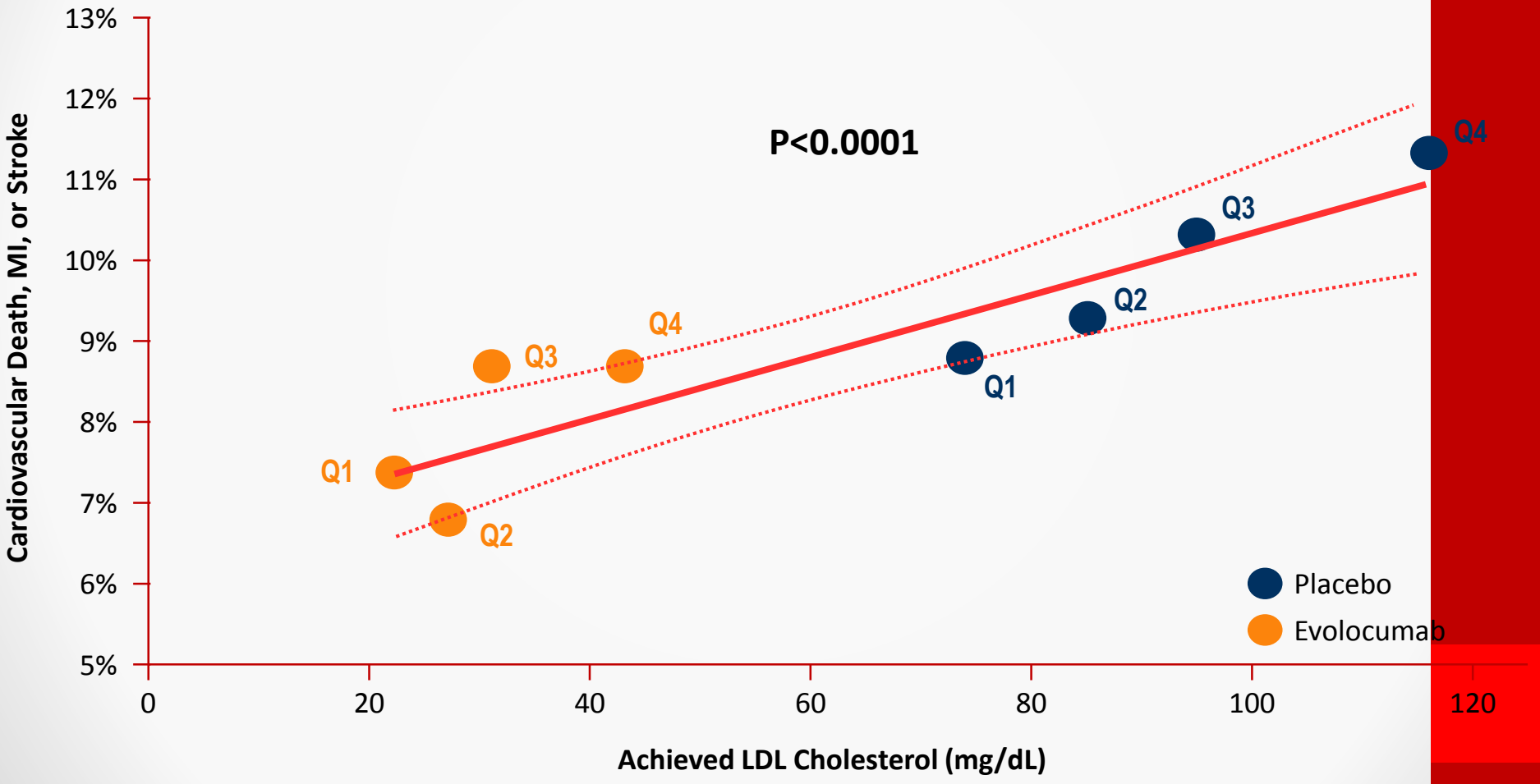
Patient A	Very high-risk, LDL-C >1.8 mmol/L (>70 mg/dL) on statin: the goal is still <1.8 mmol/L (70 mg/dL).
Patient B	High-risk, LDL-C >2.6 mmol/L (>100 mg/dL) on statin: the goal is still <2.6 mmol/L (100 mg/dL).
Patient C	Very high-risk, LDL-C 1.8–3.5 mmol/L (70–135 mg/dL) not on pharmacological therapy: the goal is at least a 50% reduction.
Patient D	High-risk, LDL-C 2.6–5.2 mmol/L (100–200 mg/dL) not on pharmacological therapy: the goal is at least a 50% reduction.
Patient E	Very high-risk, LDL-C >3.5 mmol/L (135 mg/dL) not in pharmacological therapy: the goal is <1.8 mmol/L (70 mg/dL).
Patient F	High-risk LDL-C >5.2 mmol/L (200 mg/dL) not in pharmacological therapy: the goal is <2.6 mmol/L (100 mg/dL).

A. Catapano al. Eur Heart J. 2016; doi:10.1093/eurheartj/ehw272


CURRENT LIPID LOWERING STRATEGIES (Statins±Ezetimibe) Targeting LDL-C
UNMET CLINICAL NEEDS
LDL
Emerging therapies → Innovation
PCSK9 inhibitors
Safety
Treat to target
The lower the better
Evolocumab
Alirocumab
Even lower even better
Effectiveness

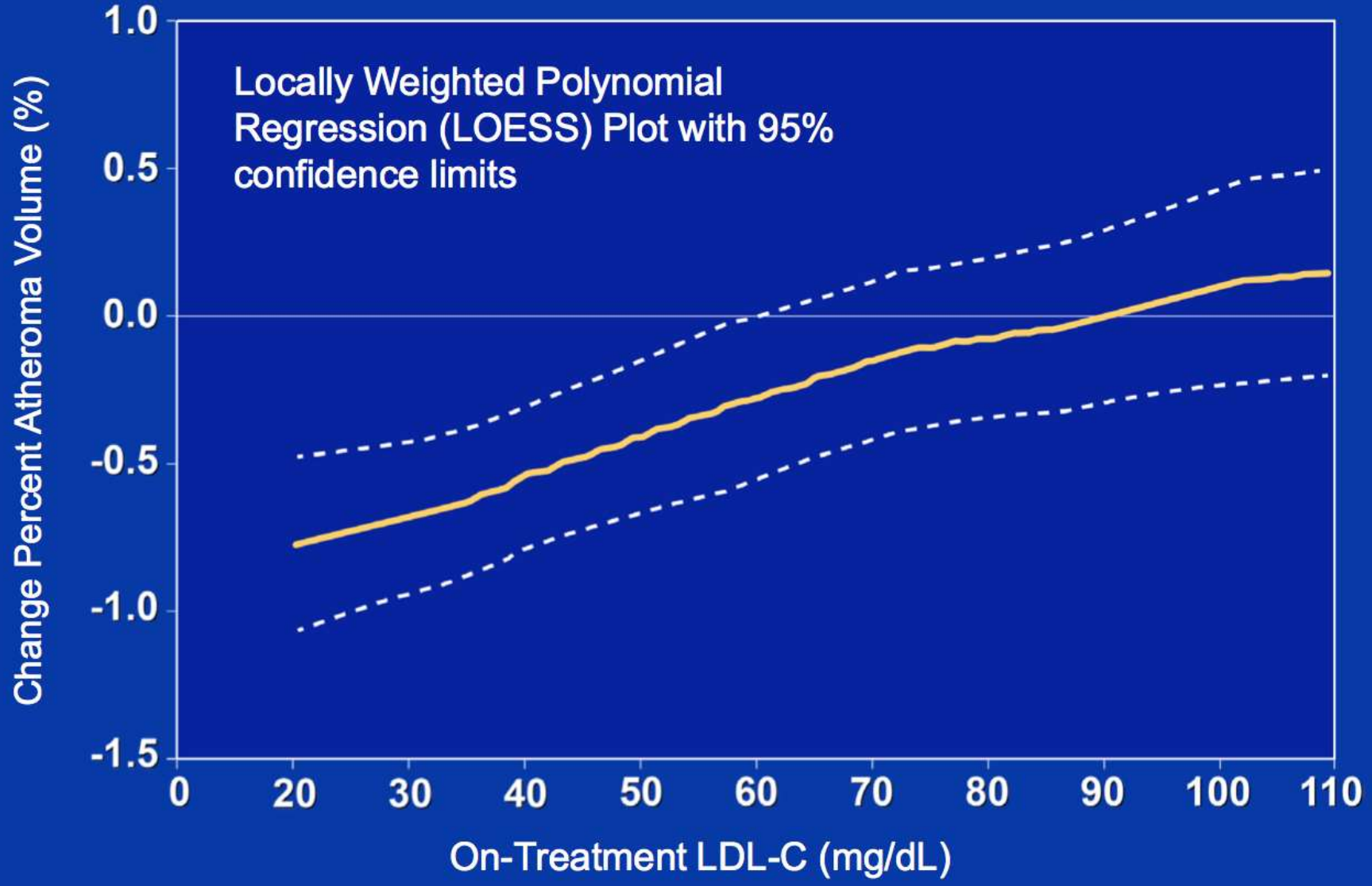
Association of LDL-C Levels and CV Events

Patients divided by quartile of baseline LDL-C and by treatment arm



Sabatine MS, et al. *American College of Cardiology – 66th Annual Scientific Session Late-Breaking Clinical Trial*. Washington, D.C. March 17, 2017.

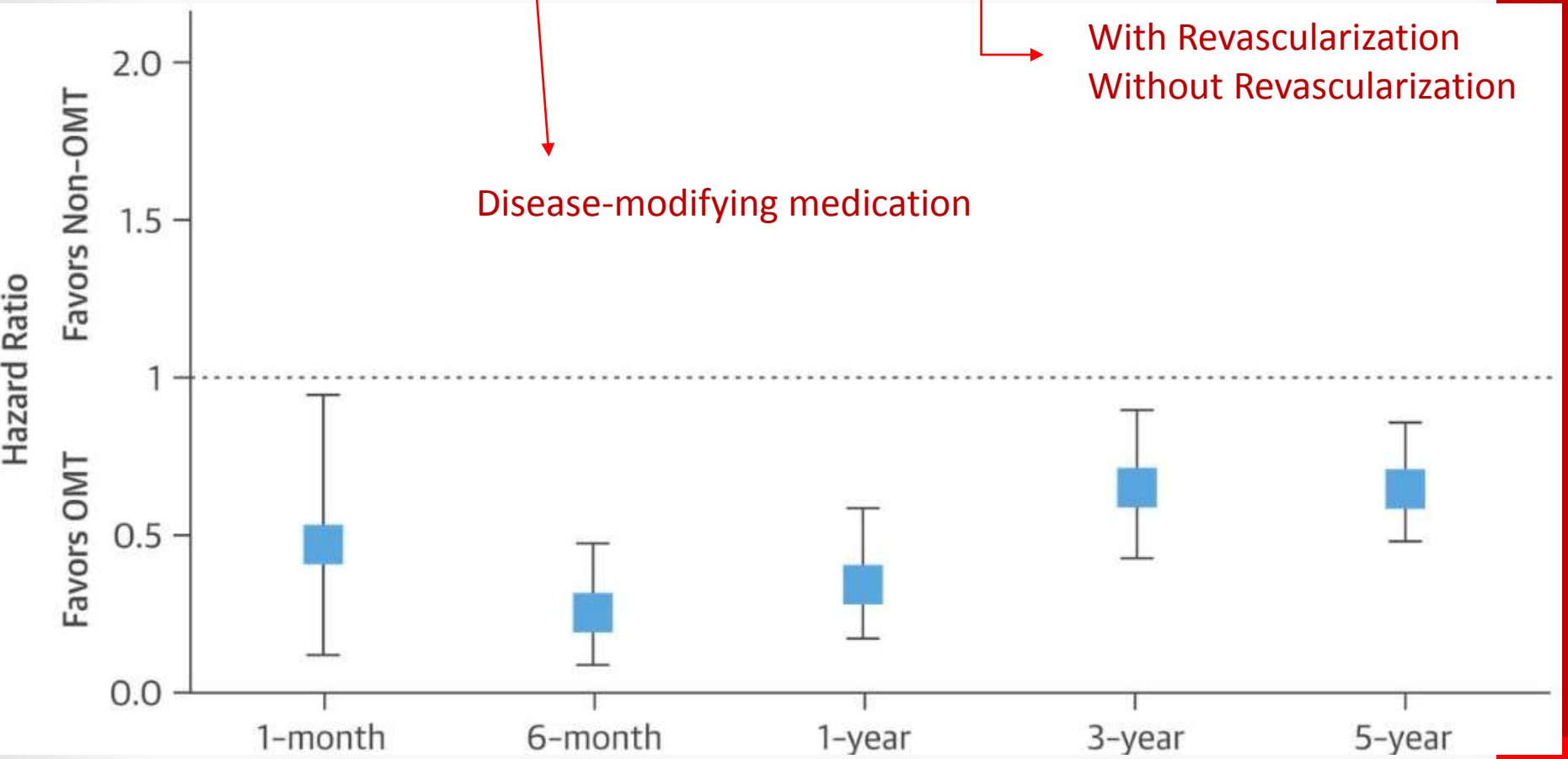
Mean On-Treatment LDL-C vs. Change in PAV



OMT : Lifestyle and pharmacological interventions that lower the risk of death , MACE and MI

With Revascularization
Without Revascularization

Disease-modifying medication



Syntax Study ; Iqbal et al , Circulation 2015

Patient Populations with an Unmet Need for LDL-C Lowering

Familial Hypercholesterolemia	High / Very High CV Risk Population	Statin-Intolerant Population
• Genetic disorder • High risk of early CHD • HeFH prevalence 1:200 to 1:250[1,2] • Untreated LDL-C of 200-400 mg/dL[3]	• Previous MI /stroke / CVD or multiple CV risk factors incl. T2DM • Difficult to achieve LDL-C goals, despite current therapies[5]	• 10-15% on high-intensity statins show intolerance[6] • Many discontinue due to muscle pain and/or weakness
79% with HeFH not at goal (<100 mg/dL [2.6 mmol/L])[4]	**• 20% with CHD not at goal (<100 mg/dL [2.6 mol/L])** **• 59% at very high CV risk not at goal (<70 mg/dL [1.8 mmol/L])**	**Nearly all patients who need considerable LDL-C reductions will not reach goal**

Nordestgaard et al. *Eur Heart J* 2013;34:3478-90. [2] Sjouke et al. *Eur Heart J.* 2015 Mar 1;36(9):560-5. [3] 2011 ESC/EAS Guidelines for the management of dyslipidaemias Eur Heart J. 2011;32(14):1769-818. [4] Pijlman et al. *Atherosclerosis* 2010;209:189-94. [5] Virani et al. *Am Heart J* 2011;161:1140-6. [6] Arca et al. *Diabetes Metab Syndr Obes* 2011;4:155-66.

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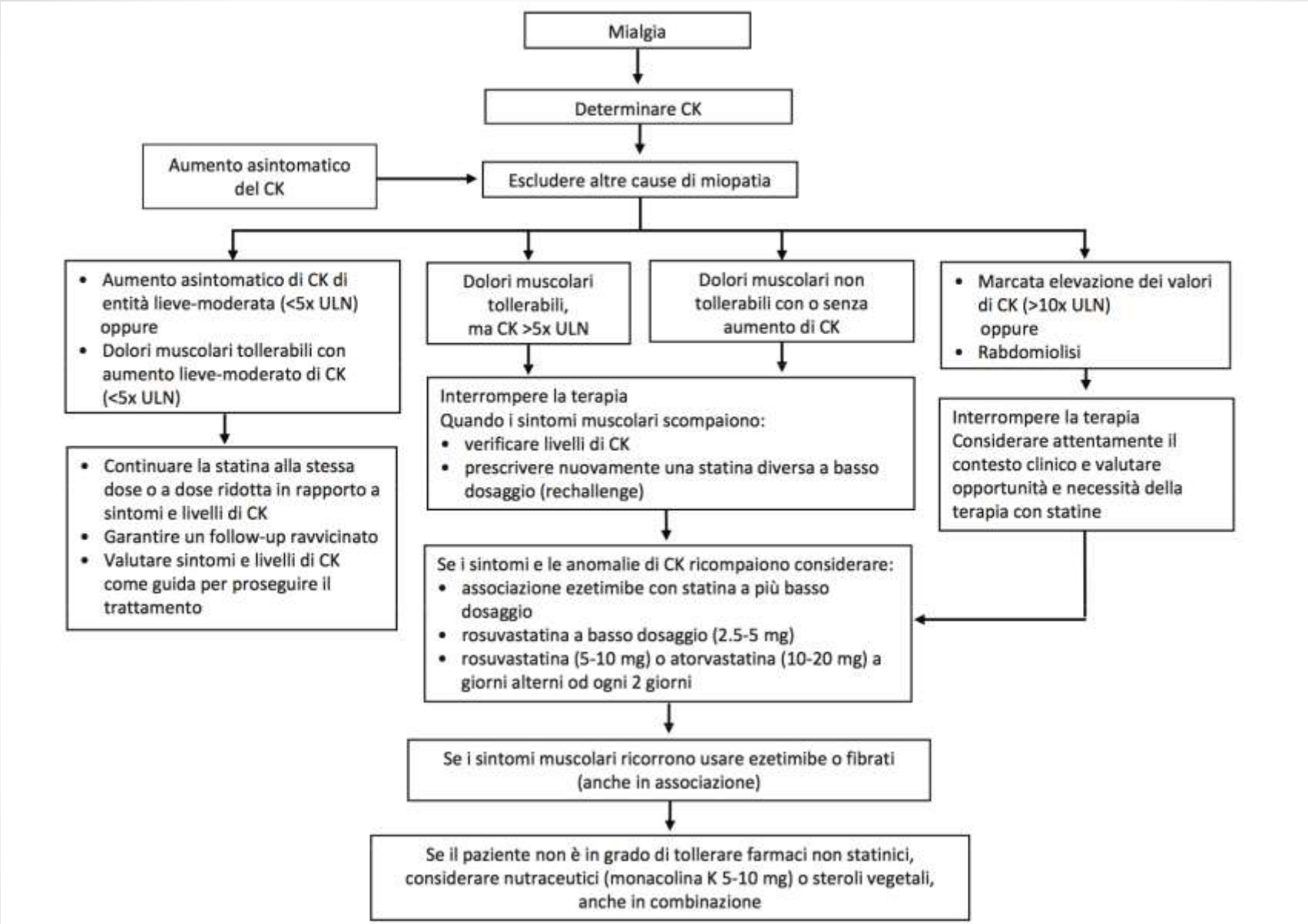
Recommendations for pharmacological treatment

CHD = coronary heart disease; CVD = cardiovascular disease; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein-cholesterol; Lp(a) = lipoprotein(a).
[a]Class of recommendation.
[b]Level of evidence.

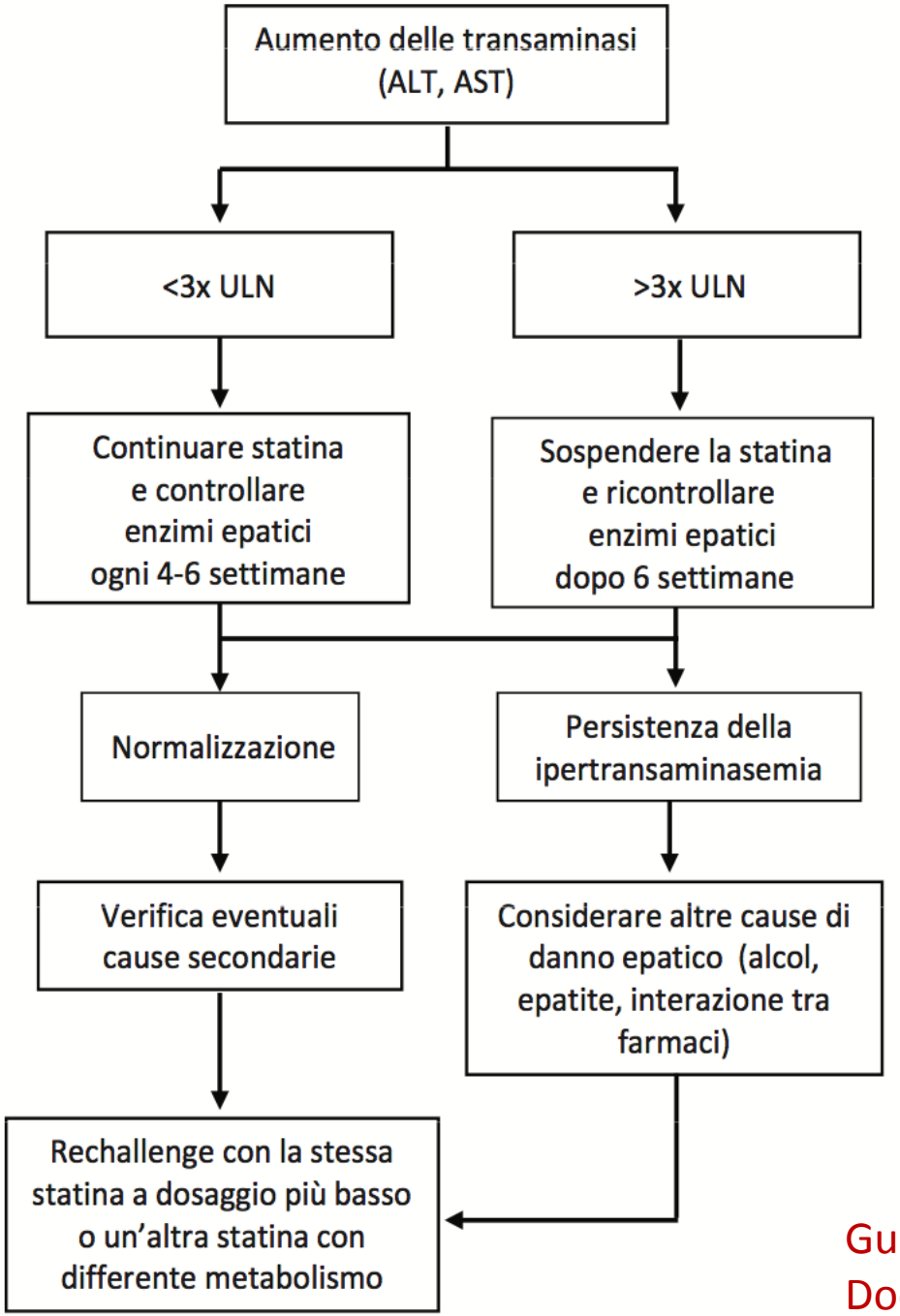
Recommendations	Class [a]	Level [b]
FH is recommended to be suspected in patients with CHD before the age of 55 years for men and 60 years for women, in subjects with relatives with premature fatal or non-fatal CVD, in subjects with relatives having tendon xanthomas, and in subjects with severely elevated LDL-C [in adults >5 mmol/L (190 mg/dL), in children >4 mmol/L (150 mg/dL)].	I	C
Diagnosis is recommended to be confirmed with clinical criteria and, when available, with DNA analysis.	I	C
Family cascade screening is recommended to be performed when an index case of FH is diagnosed.	I	C
FH patients are recommended to be treated with intense-dose statin, often in combination with ezetimibe.	I	C
Treatment should be considered to aim at reaching an LDL-C <2.6 mmol/L (100 mg/dL) or in the presence of CVD <1.8 mmol/L (70 mg/dL). If targets cannot be reached, maximal reduction of LDL-C should be considered using appropriate drug combinations.	IIa	C
Treatment with a PCSK9 antibody should be considered in FH patients with CVD or with other factors putting them at very high-risk for CHD, such as other CV risk factors, family history, high Lp(a) or statin intolerance.	IIa	C
In children, testing is recommended from age 5 years, or earlier if homozygous FH is suspected.	I	C
Children with FH should be educated to adopt a proper diet and treated with statin from 8–10 years of age. Targets for treatment should be LDL-C <3.5 mmol/L (135 mg/dL) at >10 years of age.	IIa	C

Table 22 **Recommendations for the detection and treatment of patients with heterozygous familial hypercholesterolaemia**

A. Catapano al. Eur Heart J. 2016; doi:10.1093/eurheartj/ehw272



Gulizia MM, Colivicchi F, Perna GP et al : Documento di consenso ANMCO 2016



Intolleranza "completa" :
< 5% muscolare
< 1% epatica

Gulizia MM, Colivicchi F, Perna GP et al :
Documento di consenso ANMCO 2016

ESC/EAS guidelines 2016 the Management of dyslipidemias

Recommendations for pharmacological treatment

Table 16 Recommendations for the pharmacological treatment of hypercholesterolaemia

Recommendations	Class [a]	Level [b]	Ref [c]
Prescribe statin up to the highest recommended dose or highest tolerable dose 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
If the goal is not reached, statin combination with a bile acid sequestrant may be considered.	IIb	C	
In patients at very high-risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimibe or in patients with statin intolerance, a PCSK9 inhibitor may be considered.	IIa	A	115, 116

LDL-C = low-density lipoprotein-cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Statina ad alta dose

↓ -50%

Statina HD + Ezetimibe

↓ -70%

Dieta + Attività Fisica
- 15- 20% (-90%)

↓

PCSK-9 Inibitori
-60% (-150%)

A. Catapano al. Eur Heart J. 2016; doi:10.1093/eurheartj/ehw272

Condizioni di rimborsabilità PCSK9-I

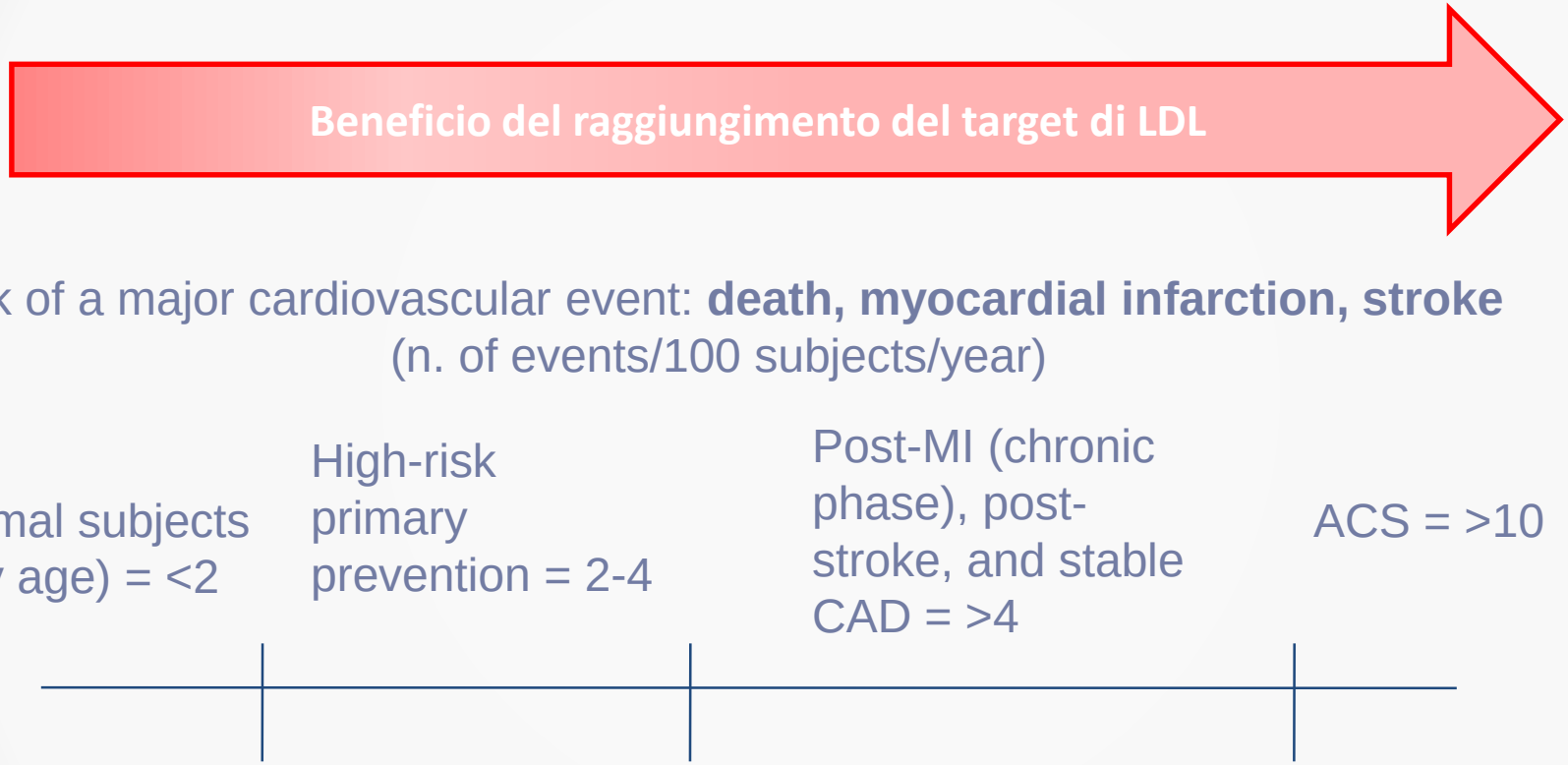
- Ipercolesterolemia Familiare Omozigote
- Ipercolesterolemia Familiare Eterozigote
- Ipercolesterolemia Non Familiare e Dislipidemia mista in pazienti ad alto rischio

In associazione a statine/LLT in pazienti che non raggiungono il target di LDL

In monoterapia o in associazione in pazienti con intolleranza o controindicazione a statina

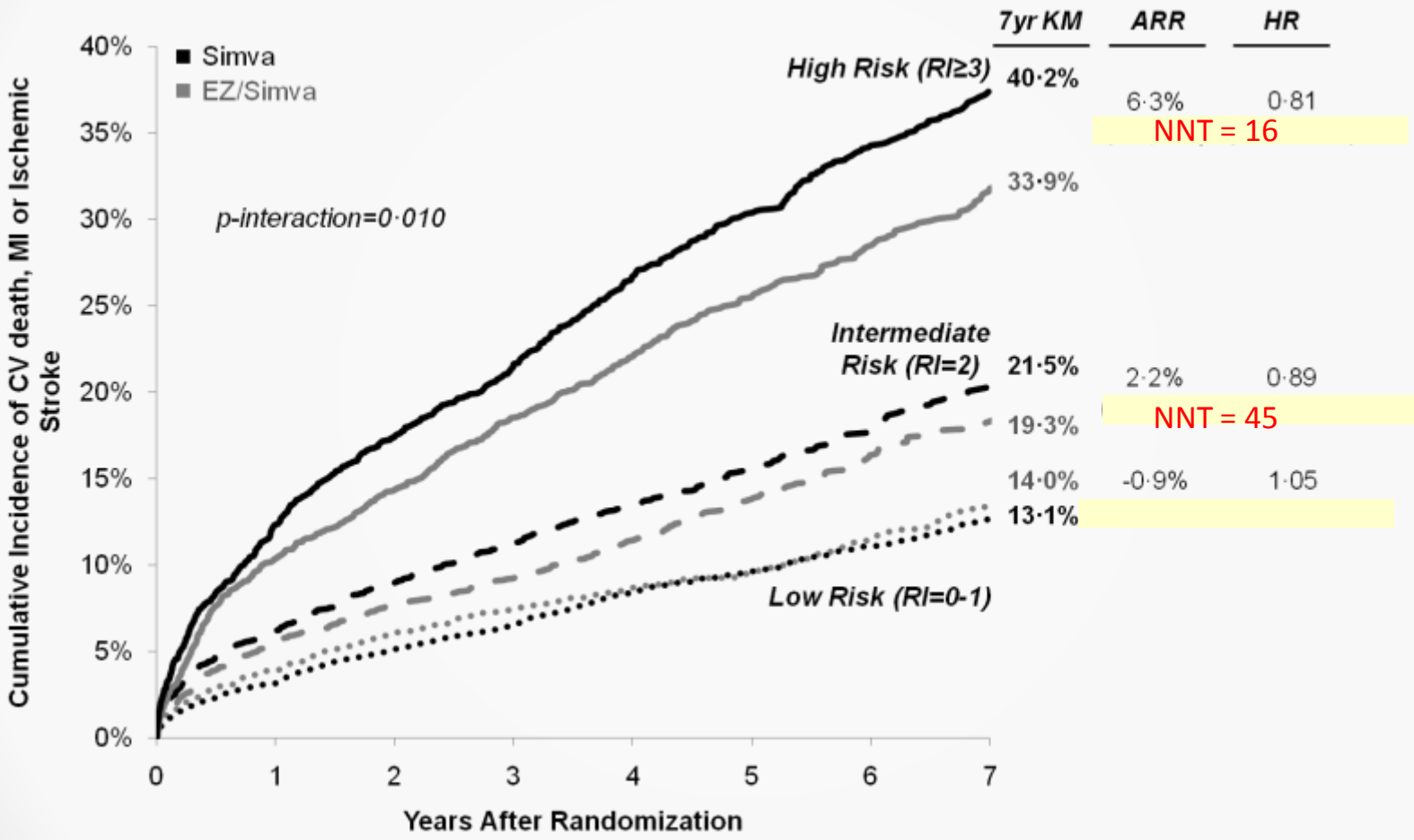
G.U. 7/2/2017

The spectrum of cardiovascular risk

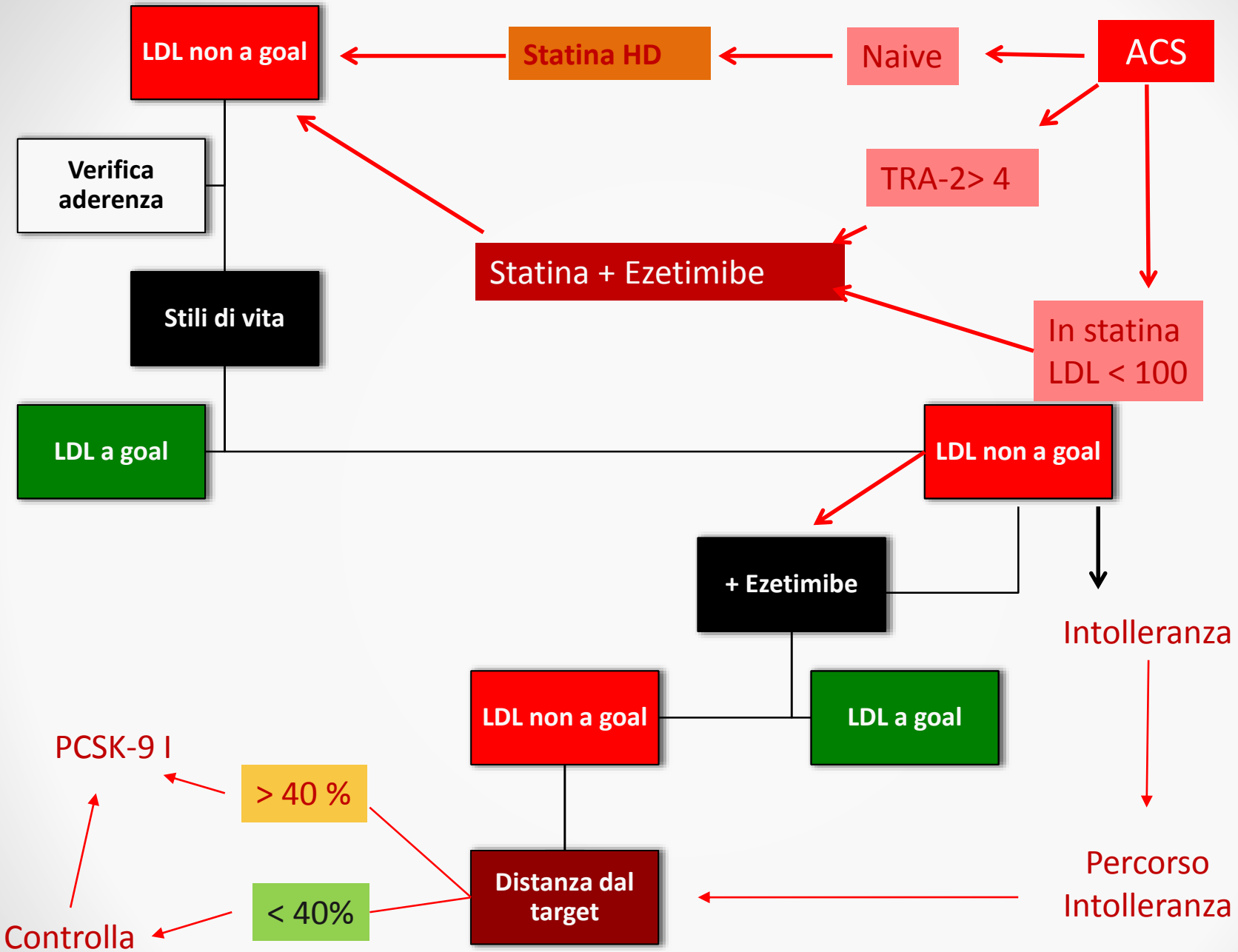


Redrawn from Halvorsen S et al., JACC 2014 64: 319–27

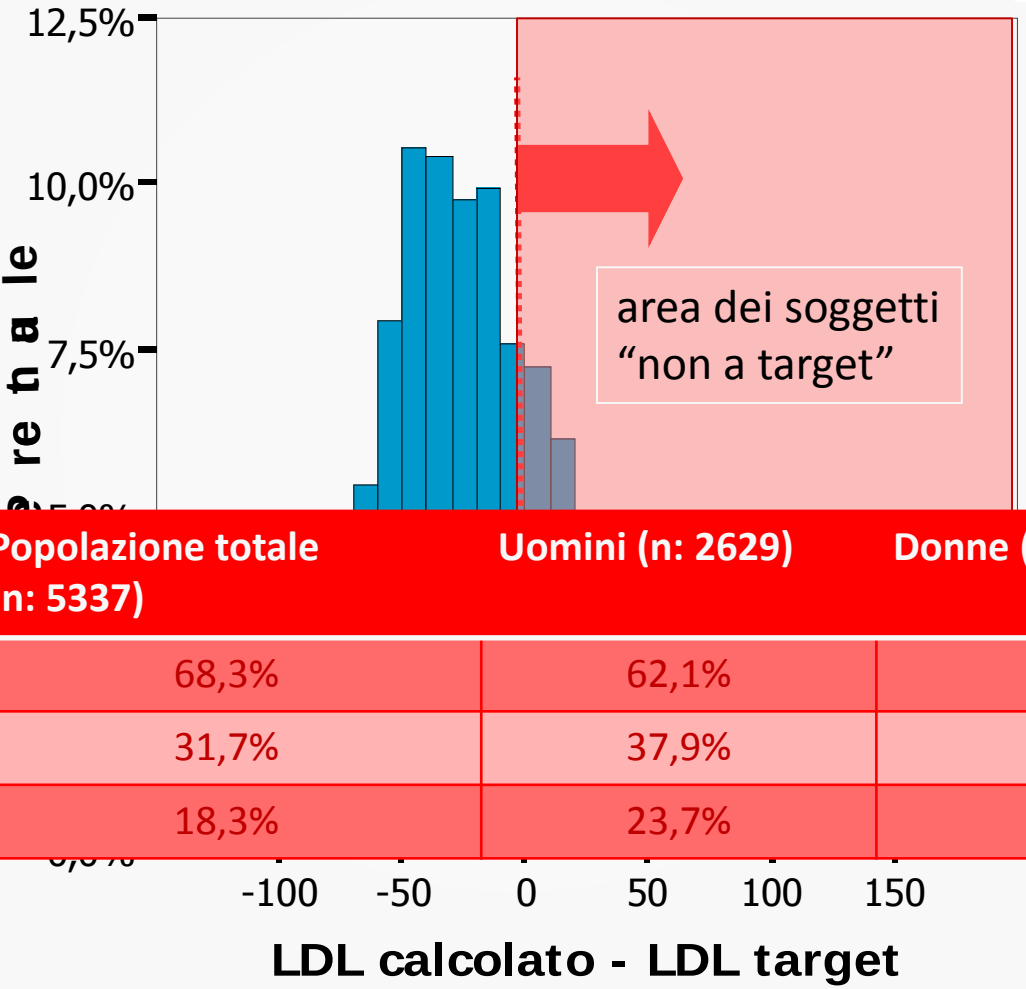
Effects of ezetimibe by TRAP 2P risk score in IMPROVE-IT



Bohula EA et al. (2016)


LDL non a goal
Statina HD
Naive
ACS
Verifica aderenza
TRA-2> 4
Statina + Ezetimibe
Stili di vita
In statina LDL < 100
LDL a goal
LDL non a goal
+ Ezetimibe
Intolleranza
LDL non a goal
LDL a goal
PCSK-9 I
> 40 %
Distanza dal target
Percorso Intolleranza
< 40%
Controlla

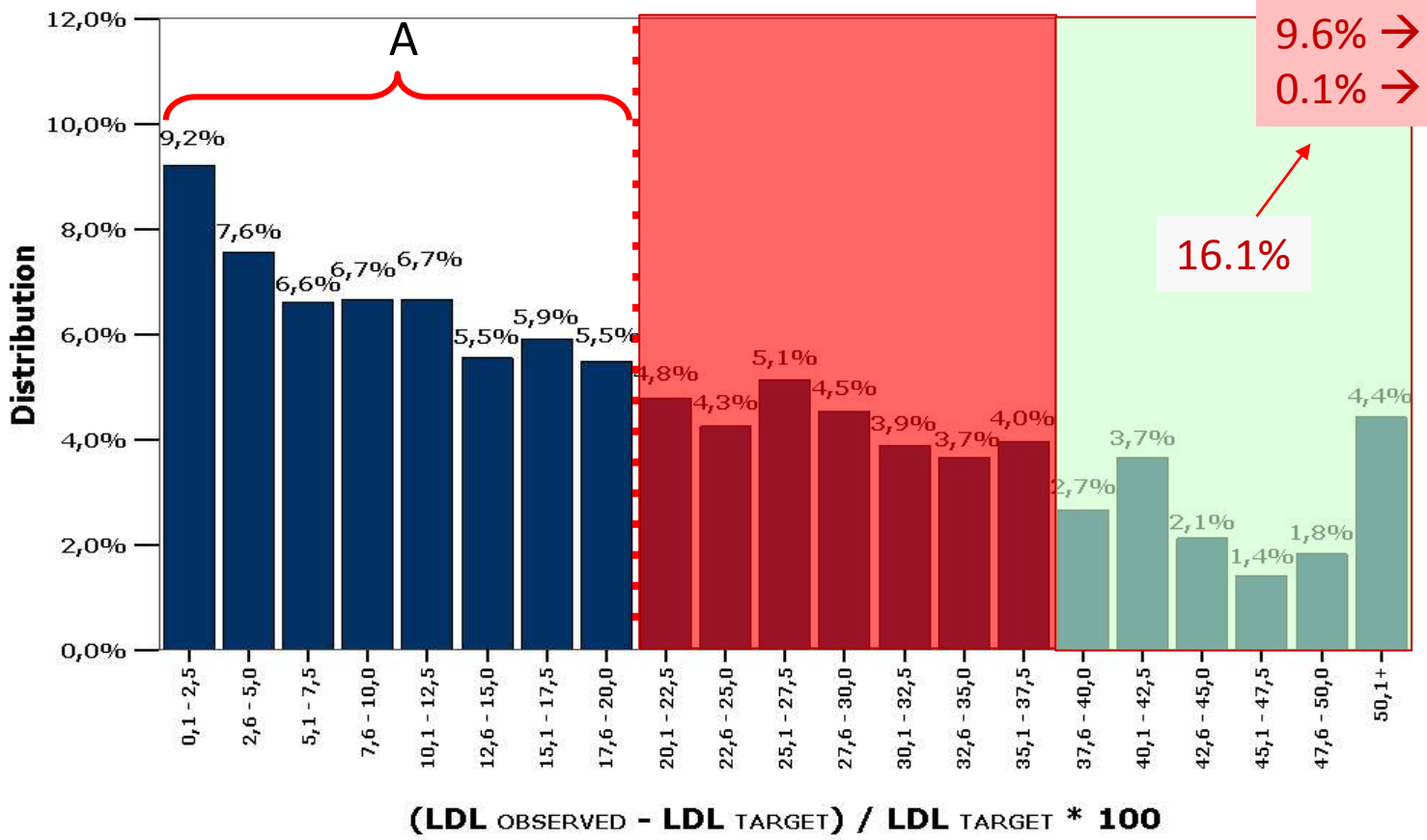
Distribuzione delle “distanze dal target” per LDL-c nel campione CHECK



	Popolazione totale (n: 5337)	Uomini (n: 2629)	Donne (n: 2708)
A target	68,3%	62,1%	74,2%
Non a target	31,7%	37,9%	25,8%
> 15% dal target	18,3%	23,7%	13,3%

Poli A et al., Pharm Res, 2011

Distanza dal proprio target (%) dei soggetti “non a target” del campione CHECK, e classificazione in gruppi di possibile intervento



Poli A et al., Pharm Res, 2011