Conoscere e Curare il Cuore 2015

NUOVI FARMACI IPOLIPEMIZZANTI: GLI INIBITORI DEL PCSK9. QUANDO E COME IMPIEGARLI

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DICHIARAZIONE CONFLITTO DI INTERESSI

Dichiaro che negli ultimi due anni ho avuto i seguenti rapporti anche di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

Onorari per presentazioni scientifiche a Congressi Internazionali:

Astra Zeneca
Sanofi
Amgen
Abbott
MSD
Roche
Chiesi

Emerging lipid-lowering therapies

CURRENT LIPID LOWERING STRATEGIES (Statins±Ezetimibe) Targeting LDL-C

UNMET CLINICAL NEEDS

CETP, cholesteryl ester transfer protein; MTP, microsomal triglyceride transfer protein; PCSK9, proprotein convertase subtilisin/kexin type 9; SI, statin intolerant

1. Sullivan D et al. *J Am Coll Cardiol.* 2012;308:2497–2508; 2. Stroes E et al. *J Am Coll Cardiol.* 2014;63:2541–2548; 3. Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects -3 (GAUSS-3). available at: http://clinicaltrials.gov/ct2/show/NCT01984424?term=NCT01984424%20&rank=1, accessed October 2014;
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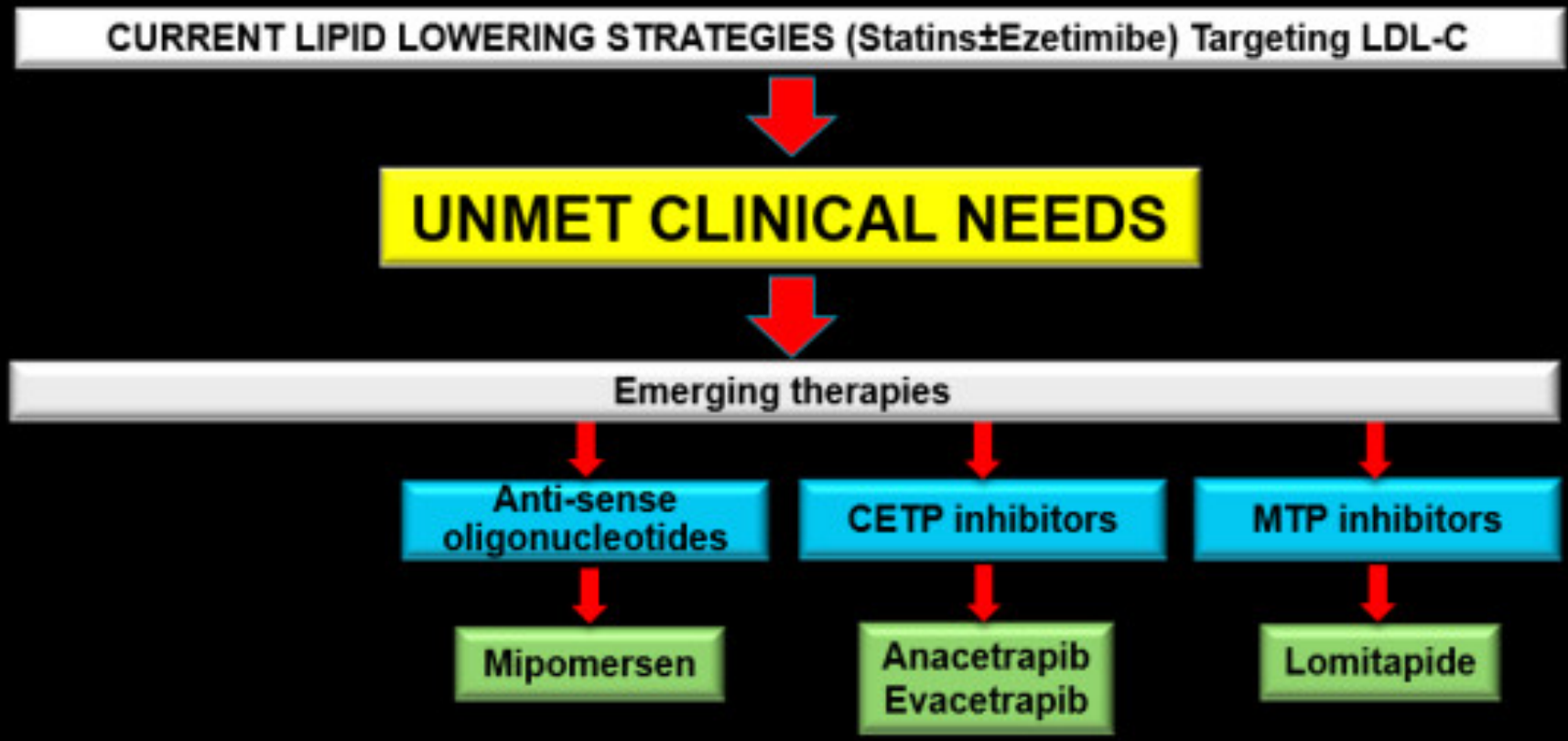
Emerging lipid-lowering therapies



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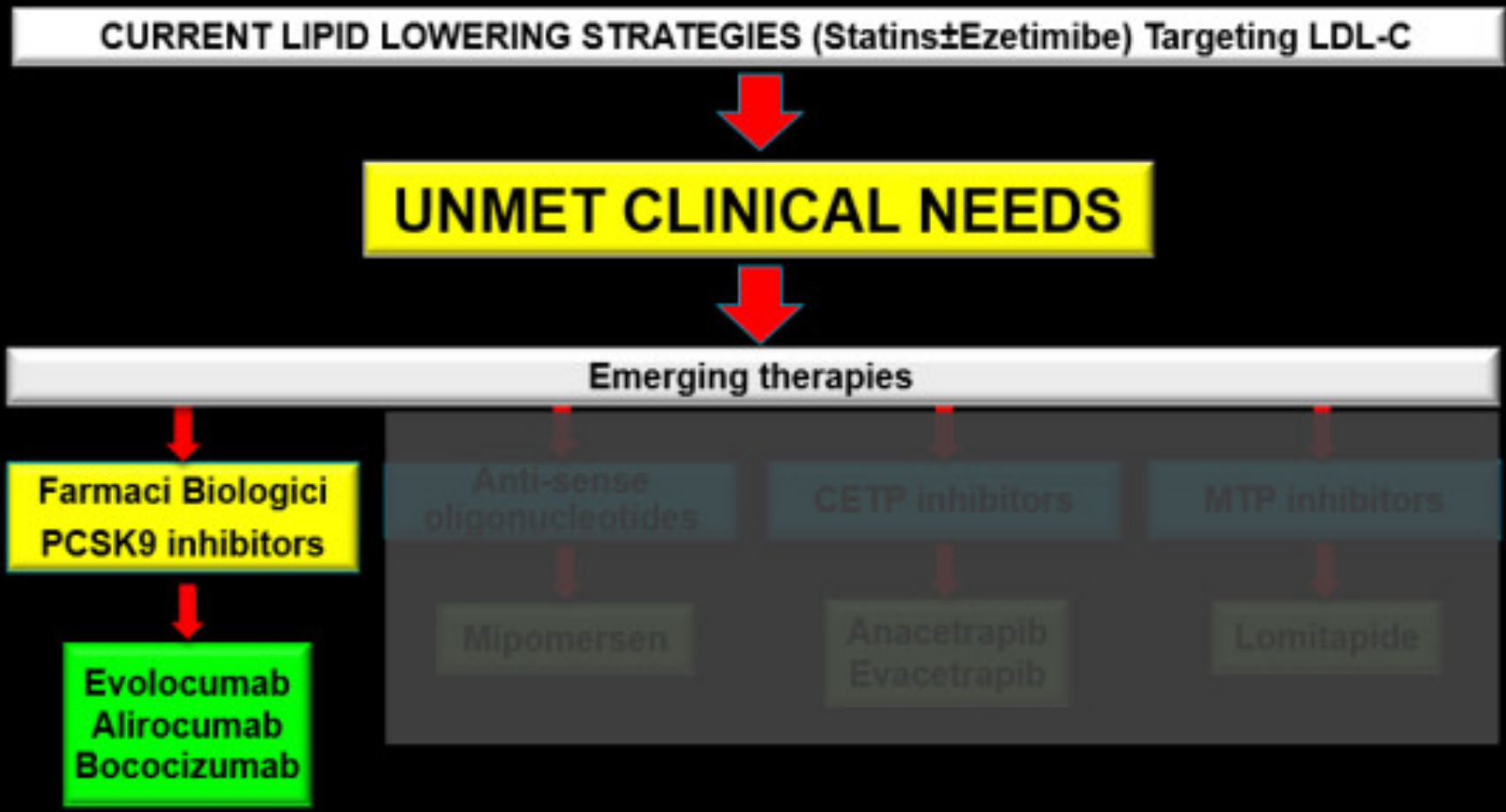

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GLI INIBITORI DELLA PCSK 9
QUANDO E COME IMPIEGARLI

- ✓ Cosa sono gli inibitori della PCSK9*
- ✓ Come agiscono
- ✓ Quando impiegarli (popolazioni Target)
- ✓ Come impiegarli (in associazione a max terapia tollerata)

* Proprotein Convertase Subtilisin/kexin Type 9 (PCSK9)

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✓ Cosa sono gli inibitori della PCSK9*

* Proprotein Convertase Subtilisin/kexin Type 9 (PCSK9)

Monoclonal Antibody Evolution

e.g. ibritum**omab**

Highly immunogenic
100% Mouse

Mouse variable
Mouse constant
Human variable
Human constant

Immunogenicity

Fully Mouse — Chimeric — Humanised — "Fully" Human

1st generation — 2nd generation — 3rd generation — 4th generation

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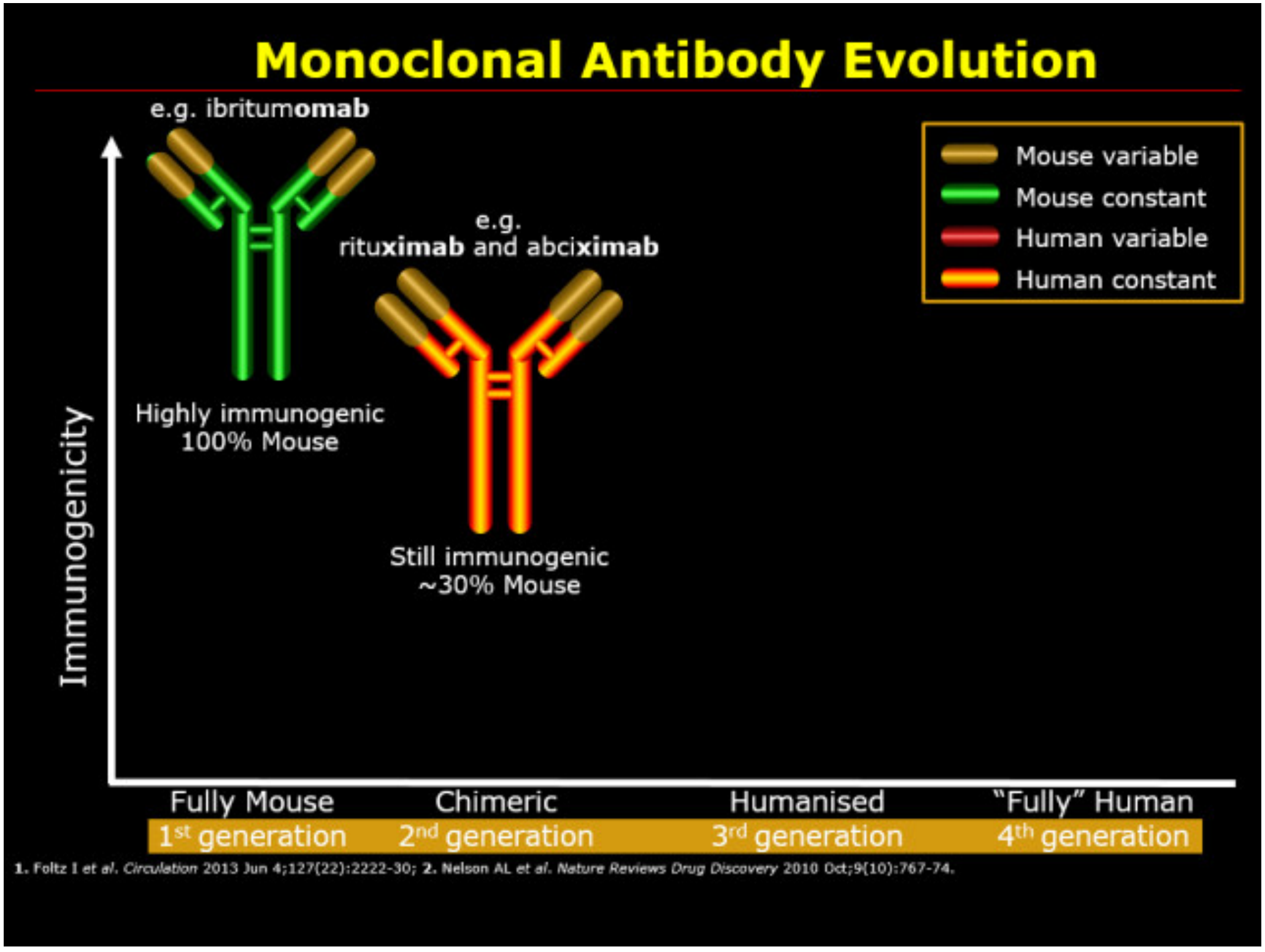
Monoclonal Antibody Evolution



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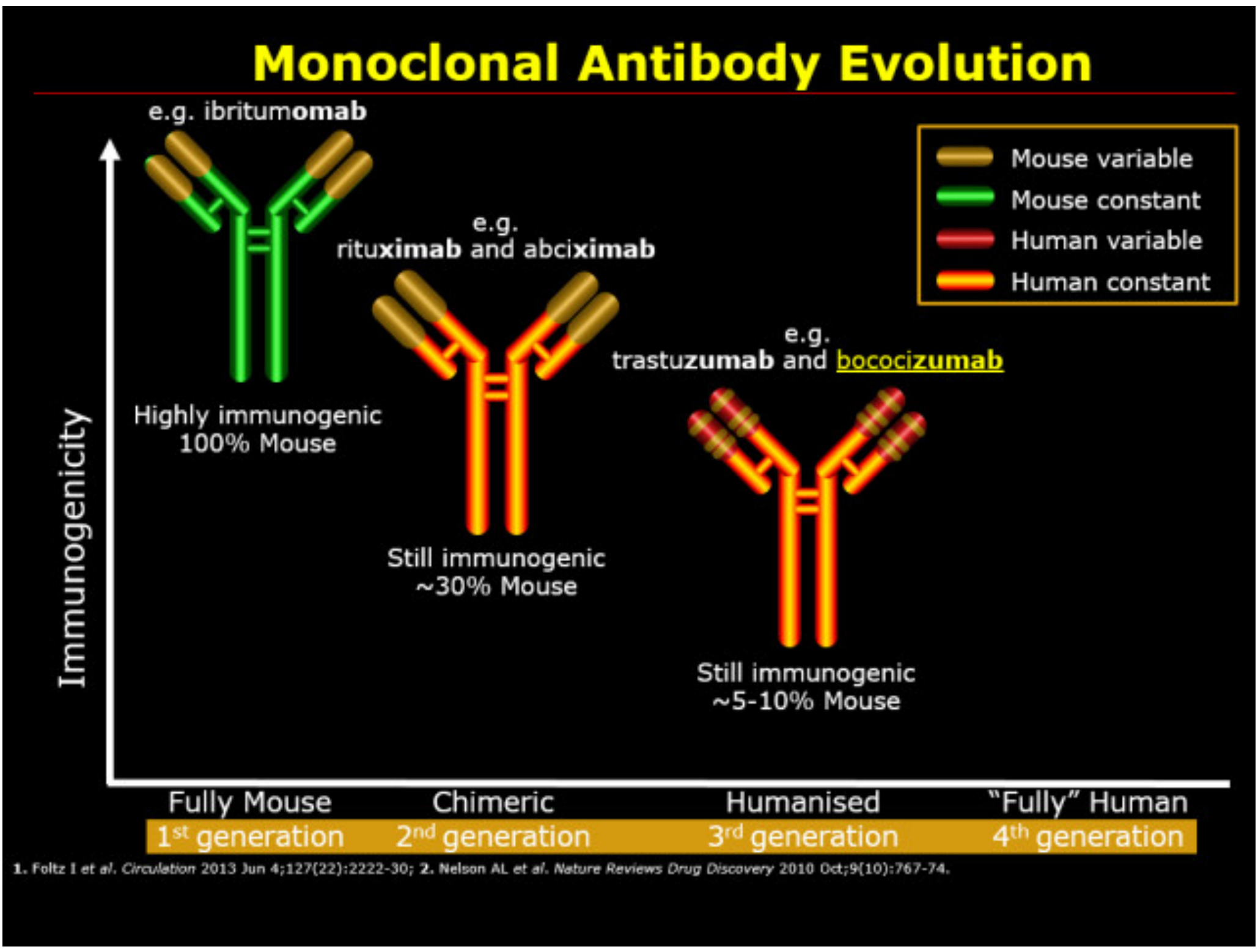

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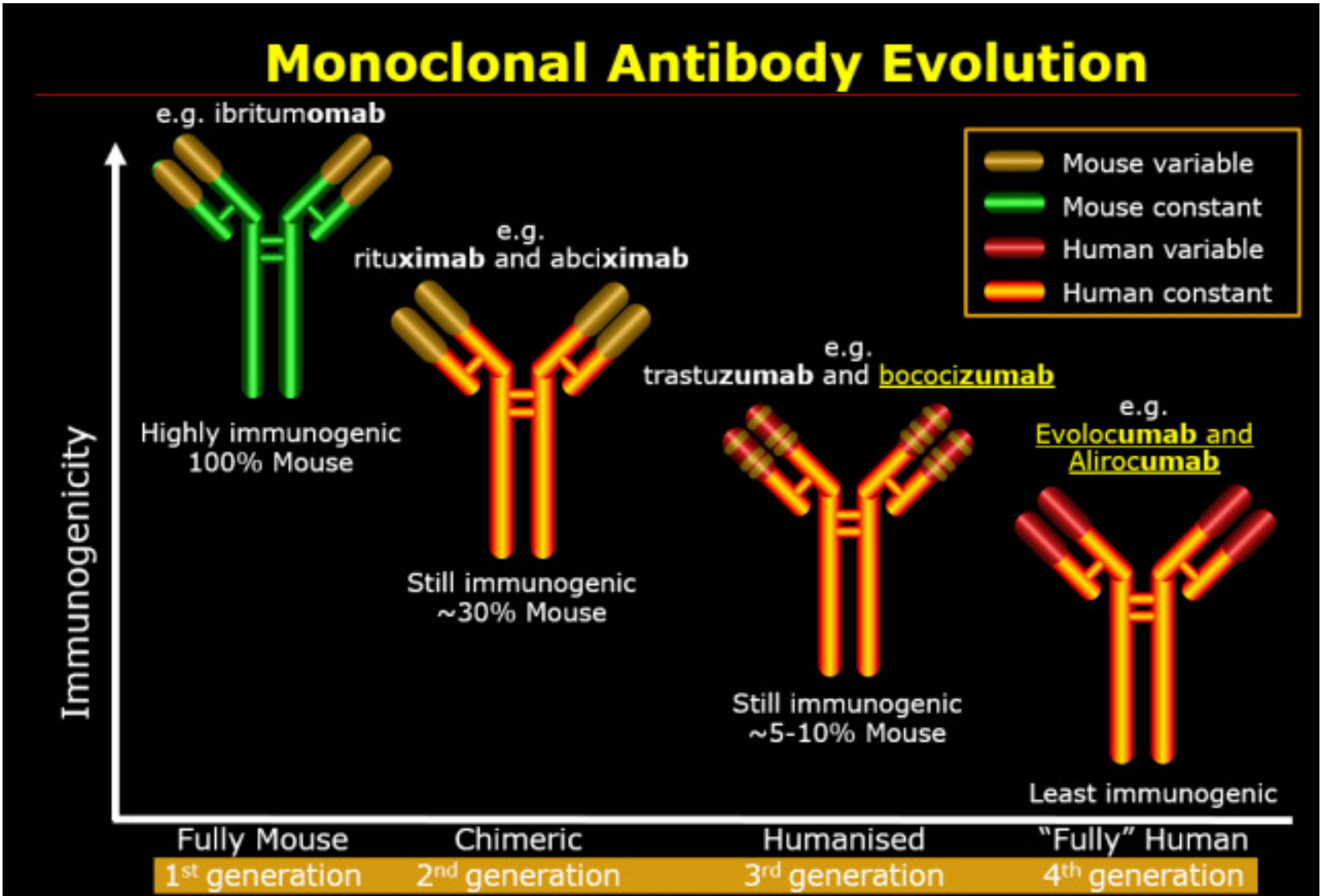

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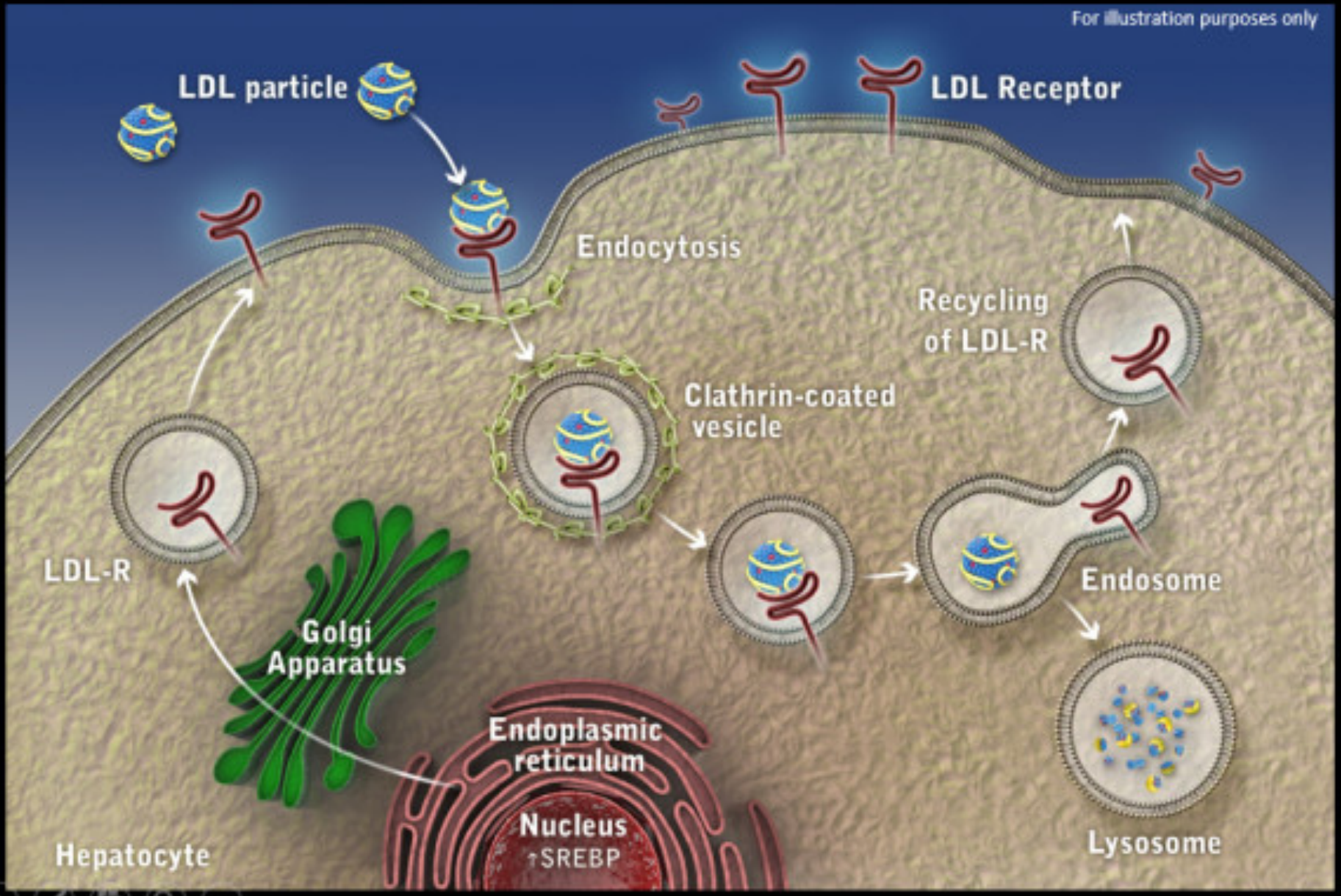
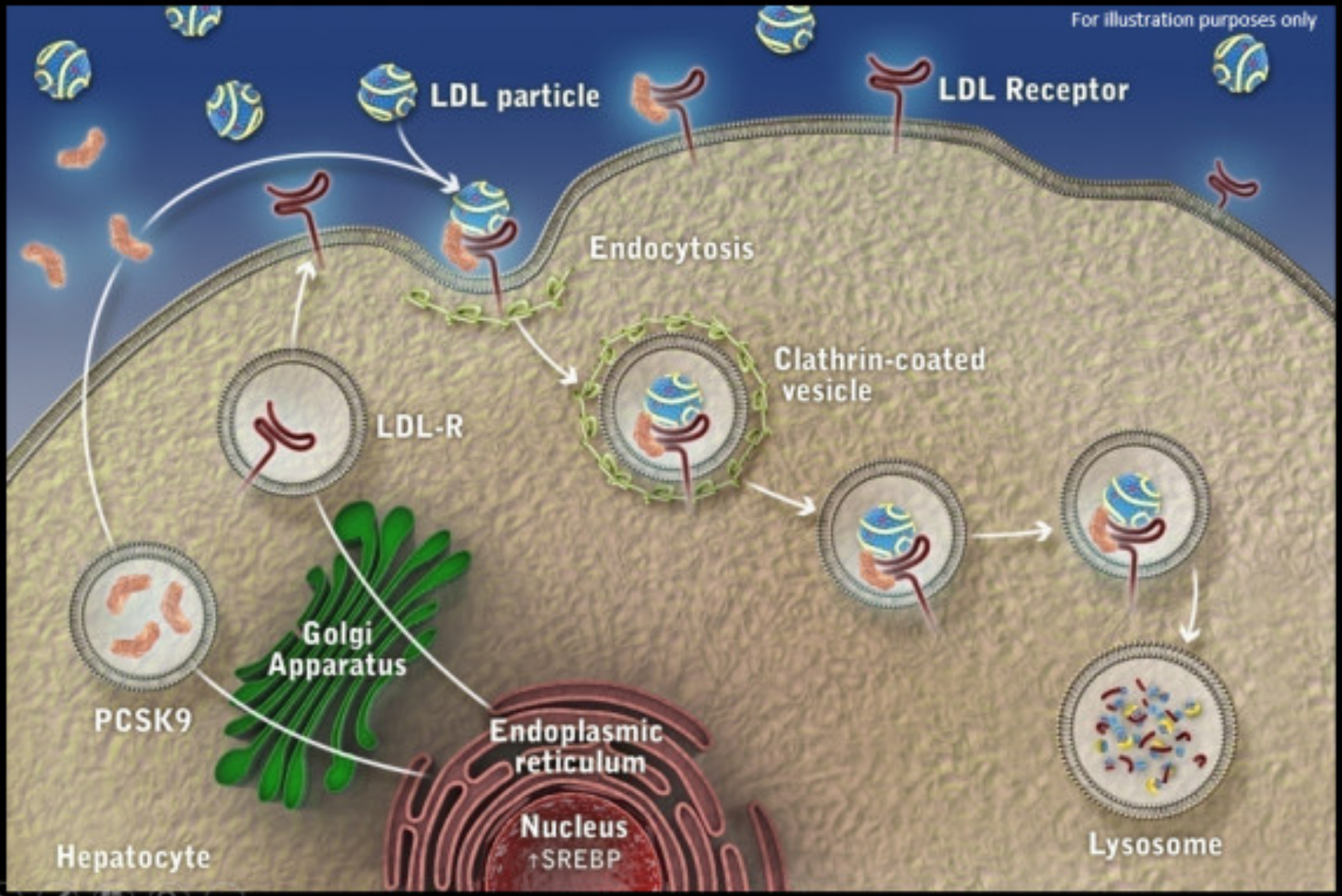
- ✓ Cosa sono: Anticorpi Monoclonali anti-PCSK9 - FARMACI BIOLOGICI
- ✓ Come agiscono

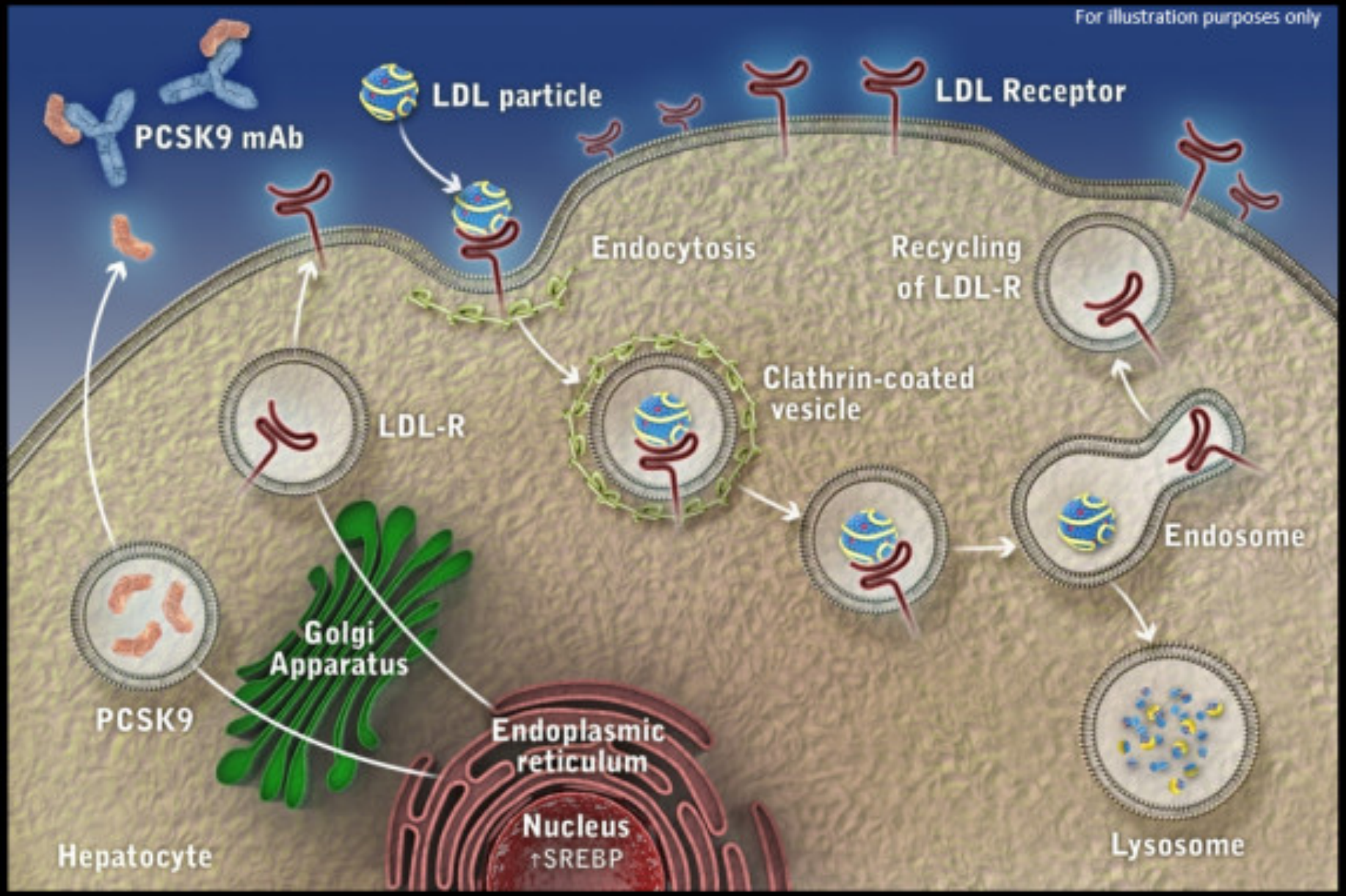
Funzione e Ciclo Biologico del Recettore LDL



Il Ruolo di PCSK9 nella Regolazione dell'Espressione del Recettore per le LDL



Impatto dell'Anticorpo contro PCSK9 sull'Espressione del Recettore delle LDL



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✓ Come agiscono: Interagiscono con PCSK9 contrastando la distruzione intracellulare del recettore LDL che può riciclarsi sulla superficie cellulare

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- ✓ Quando impiegarli (popolazioni Target)

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Trattamento ipocolesterolemizzante in Italia sulla base del target di LDL-C, tra i soggetti ad alto o altissimo rischio CV di età compresa tra 40 e 79 anni (n=7,047 milioni di soggetti*)

- 25% della popolazione italiana è a rischio CV alto o molto alto
- Nei pazienti ad alto o altissimo rischio, i farmaci a maggiore efficacia (Rosuva o Atorvastatina ± Ezetimibe) sono necessari per portare a target 6 pazienti su 10
- Quasi 3 su 10, in particolare, necessitano farmaci in grado di ridurre LDL-C almeno del 50%
- La grande maggioranza dei pazienti **NON** a target è a rischio CV alto o molto alto

* Estrapolazione dallo studio CHECK

Poli A. et al. Pharmacol Res. 2011 Oct;64(4):393-6
Poli A. Et al. Nutr Metab Cardiovasc Dis. 2012 Apr;22(4):327-36

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	LDL target SI	LDL target NO
Pazienti con diabete tipo 2:	**20.1%**	**79.9%**
Pazienti in prevenzione secondaria:	**14.7%**	**85.3%**

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QUANDO IMPIEGARE GLI Ab ANTI-PCSK9:

Farmaci Biologici: PCSK9 inhibitors

Evolocumab, Alirocumab, *Bococizumab*

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?	**<u>Ipercolesterolemia in pazienti a rischio CV alto</u>** (**<u>non controllati</u>** con dosi massime tollerate di statine ± Eze)	?

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Original Investigation

Effect of Evolocumab or Ezetimibe Added to Moderate- or High-Intensity Statin Therapy on LDL-C Lowering in Patients With Hypercholesterolemia
The LAPLACE-2 Randomized Clinical Trial

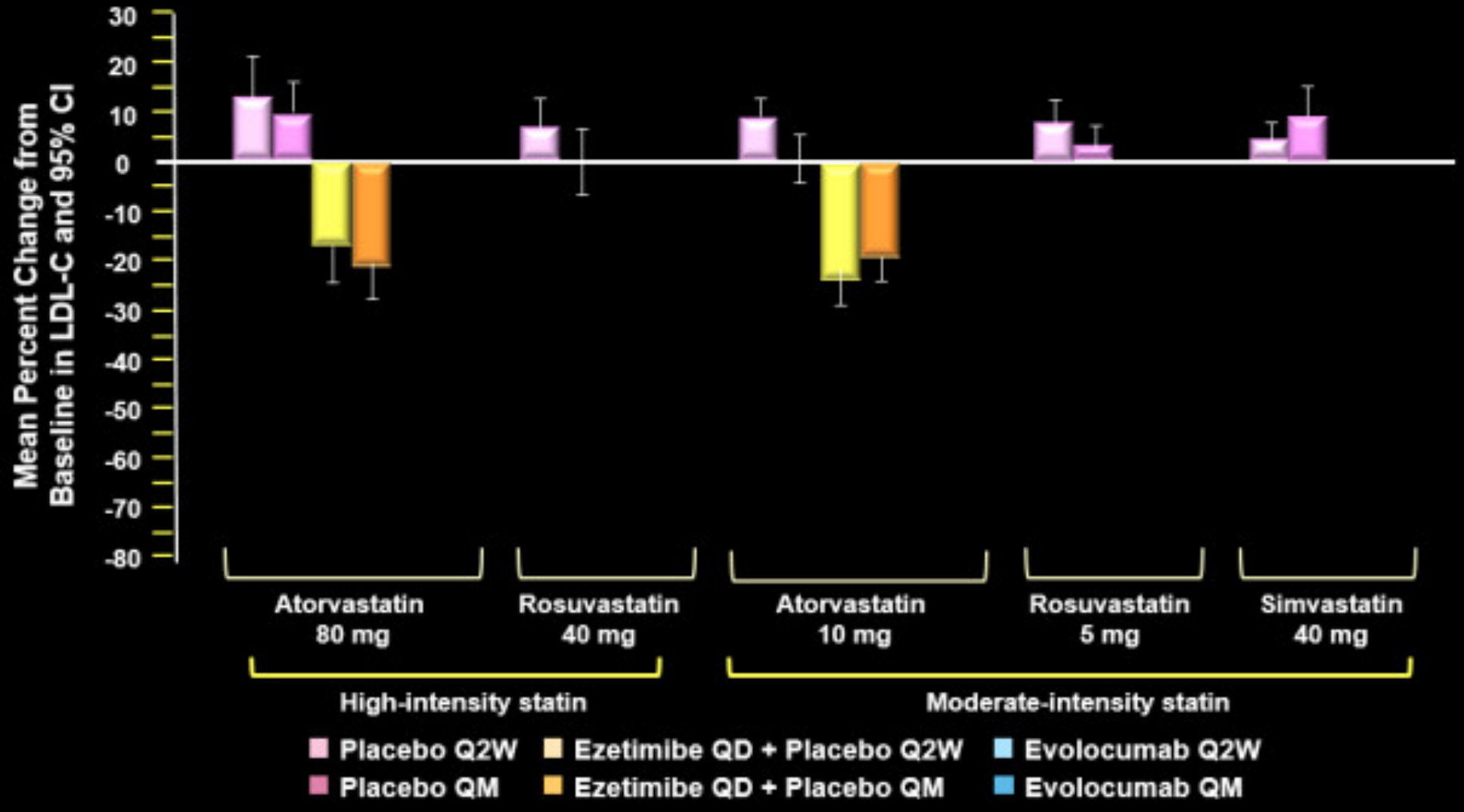
Jennifer G. Robinson, MD, MPH; Bettina S. Nedergaard, MD, PhD; William J. Rogers, MD; Jonathan Fialkow, MD; Joel M. Neutel, MD; David Ramstad, MD, MPH; Ransi Somaratne, MD, MBA; Jason C. Legg, PhD; Patric Nelson, MPH, MBA; Rob Scott, MD; Scott M. Wasserman, MD; Robert Weiss, MD; for the LAPLACE-2 Investigators

PATIENTS (N=2067): primary hypercholesterolemia and mixed dyslipidemia, 198 sites, 17 countries

Q2W: 140 mg sc ogni 2 settimane; QM: 420 mg sc ogni 4 settimane

LAPLACE-2

LDL-C Response at Mean of Weeks 10 and 12



All treatment differences versus placebo and ezetimibe were statistically significant ($P < 0.001$). Vertical lines represent 95% CIs.
No notable differences were observed between the mean of weeks 10 and 12 and week 12 alone.
LDL-C, low-density lipoprotein cholesterol; Q2W, biweekly; QM, monthly.

JAMA 2014; 311(18):1870-1882

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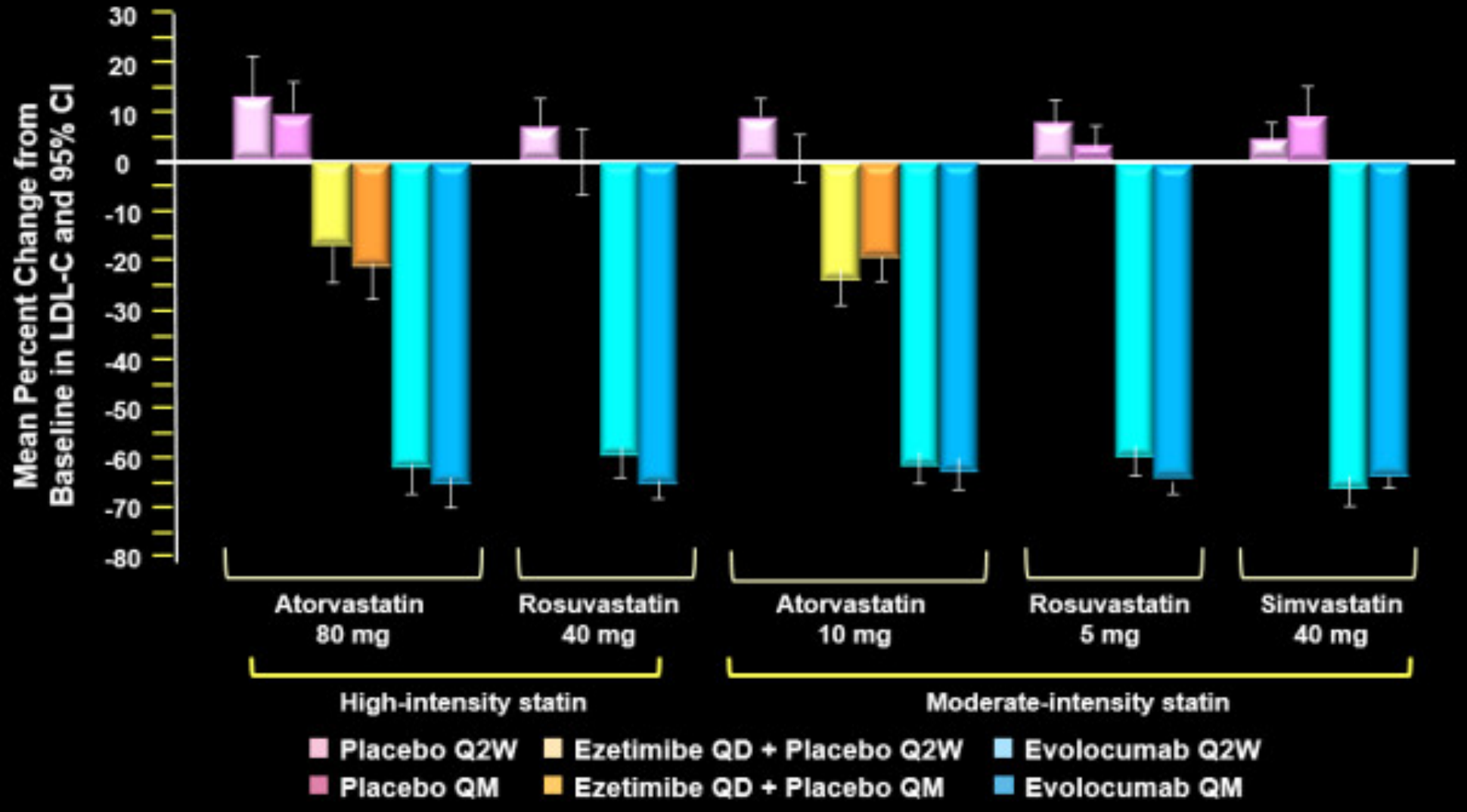

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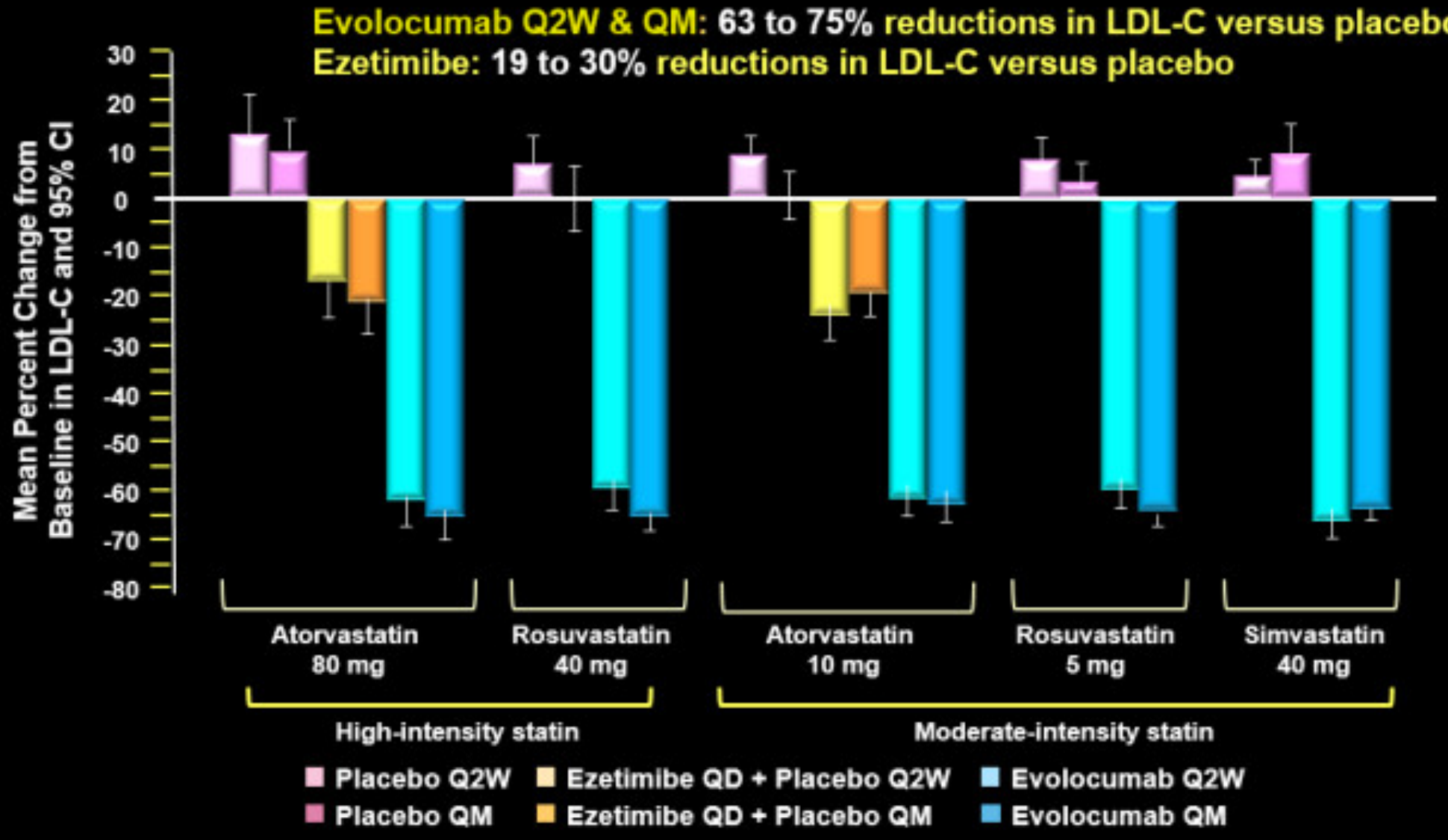

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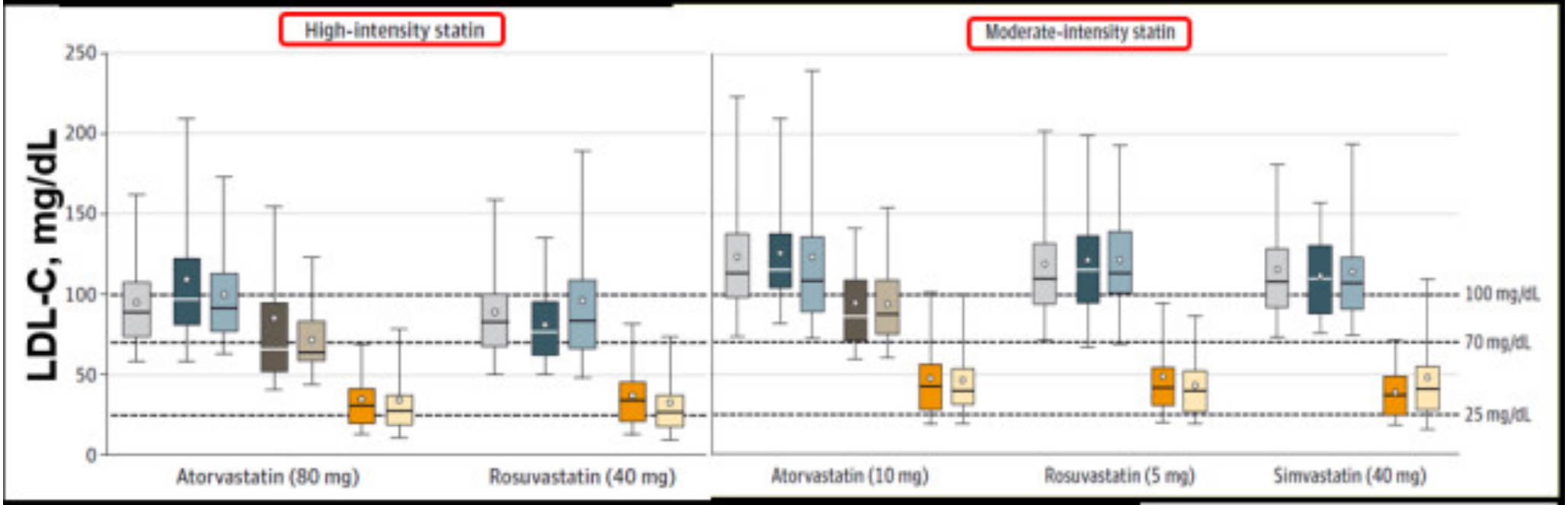
LAPLACE-2:
Baseline, and On-treatment LDL-C

JAMA 2014; 311(18):1870-1882



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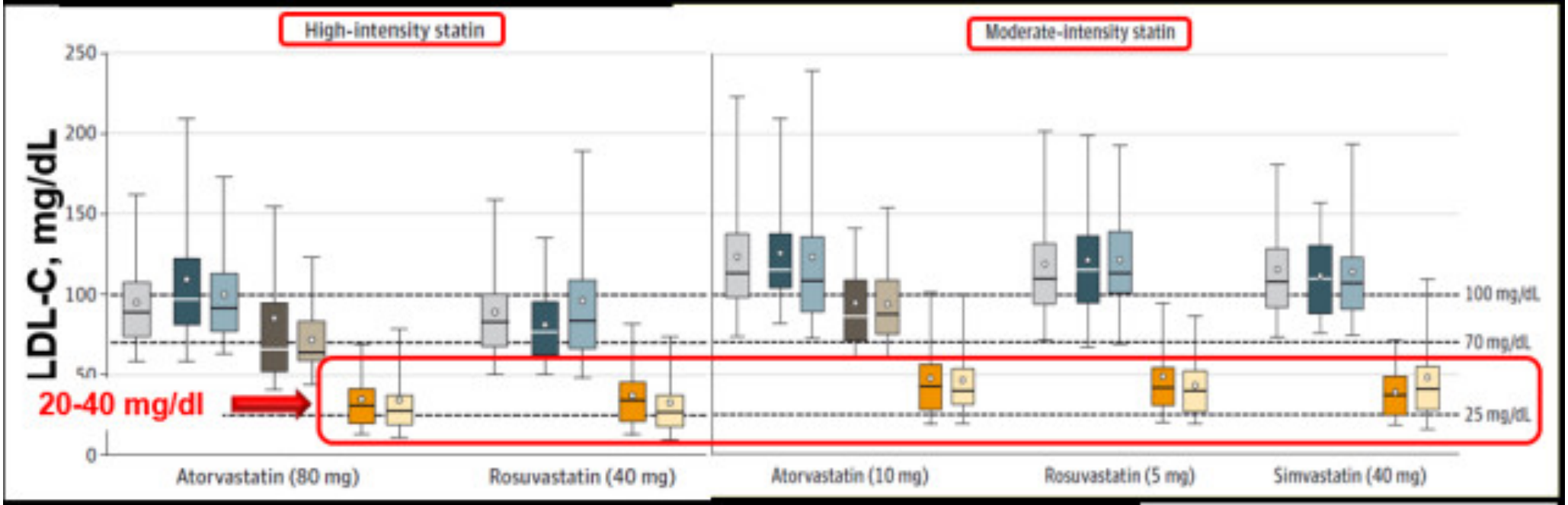

Baseline (after lipid stabilization phase)
Placebo (every 2 wk)
Placebo (monthly)
Ezetimibe (daily) + placebo (every 2 wk)
Ezetimibe (daily) + placebo (monthy)
Evolocumab (every 2 wk)
Evolocumab (monthly)

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LAPLACE-2:
Baseline, and On-treatment LDL-C

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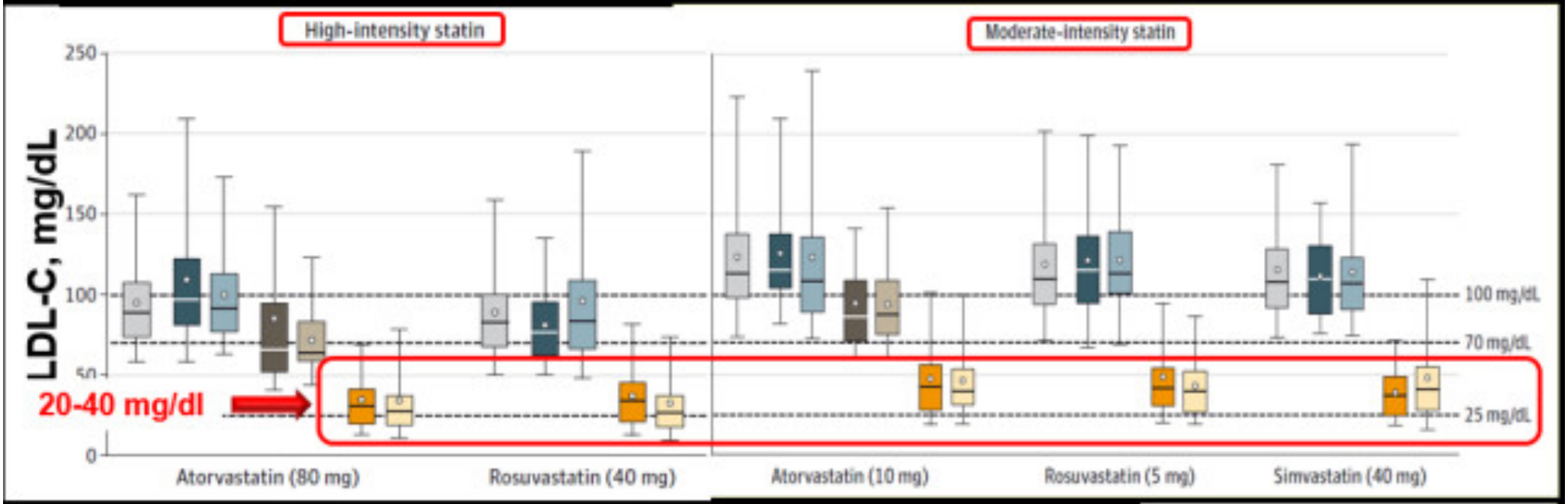
LDL-C < 70 mg/dL: High-intensity statin Q2W 94%; QM 93 to 95%

LDL-C < 70 mg/dL: Moderate-intensity statin Q2W 88 to 94%; QM 86 to 90%



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LAPLACE-2: Safety and Tolerability

n (%)	Any Statin + Placebo (N = 558)	Atorvastatin + Ezetimibe (N = 221)	Any Statin + Evolocumab (N = 1117)
Treatment-emergent AEs	219 (39)	89 (40)	406 (36)
Most common AEs[a]			
Back pain	14 (3)	7 (3)	20 (2)
Arthralgia	9 (2)	4 (2)	19 (2)
Headache	15 (3)	5 (2)	19 (2)
Muscle spasms	6 (1)	6 (3)	17 (2)
Pain in extremity	7 (1)	3 (1)	17 (2)
Serious AEs	13 (2)	2 (1)	23 (2)
AEs leading to study drug discontinuation	12 (2)	4 (2)	21 (2)
Positively adjudicated CV events	2 (0.4)	2 (0.9)	5 (0.4)
CK > 5 x ULN	2 (0.4)	0 (0)	1 (0.1)
ALT or AST > 3 x ULN	6 (1)	3 (1)	4 (0.4)
Potential injection site reactions[b]	8 (1)	2 (1)	15 (1)
Neurocognitive AEs[c]			
Disturbance in attention	0 (0)	1 (0.5)	0 (0)
Cognitive disorder	0 (0)	1 (0.5)	0 (0)
Disorientation	0 (0)	1 (0.5)	1 (0.1)
Post-baseline binding antibodies	NA	NA	1 (0.1)[d]

[a] Top 5 in evolocumab treatment group. [b] Reported using high-level term groupings including IS - rash, inflammation, pruritus, reaction, urticaria. [c] Searched HLGT terms: Deliria (incl confusion); Cognitive and attention disorders and disturbances; dementia and amnestic conditions; disturbances in thinking and perception; mental impairment disorders. [d] Binding antibody was present at baseline and at the end of study. No neutralizing antibodies were detected. NA: Not applicable

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Farmaci Biologici: PCSK9 inhibitors

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Evolocumab, Alirocumab, *Bococizumab*

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Inibitori PCSK9 come Add-on a massima dose tollerata statine (± altri LLT)

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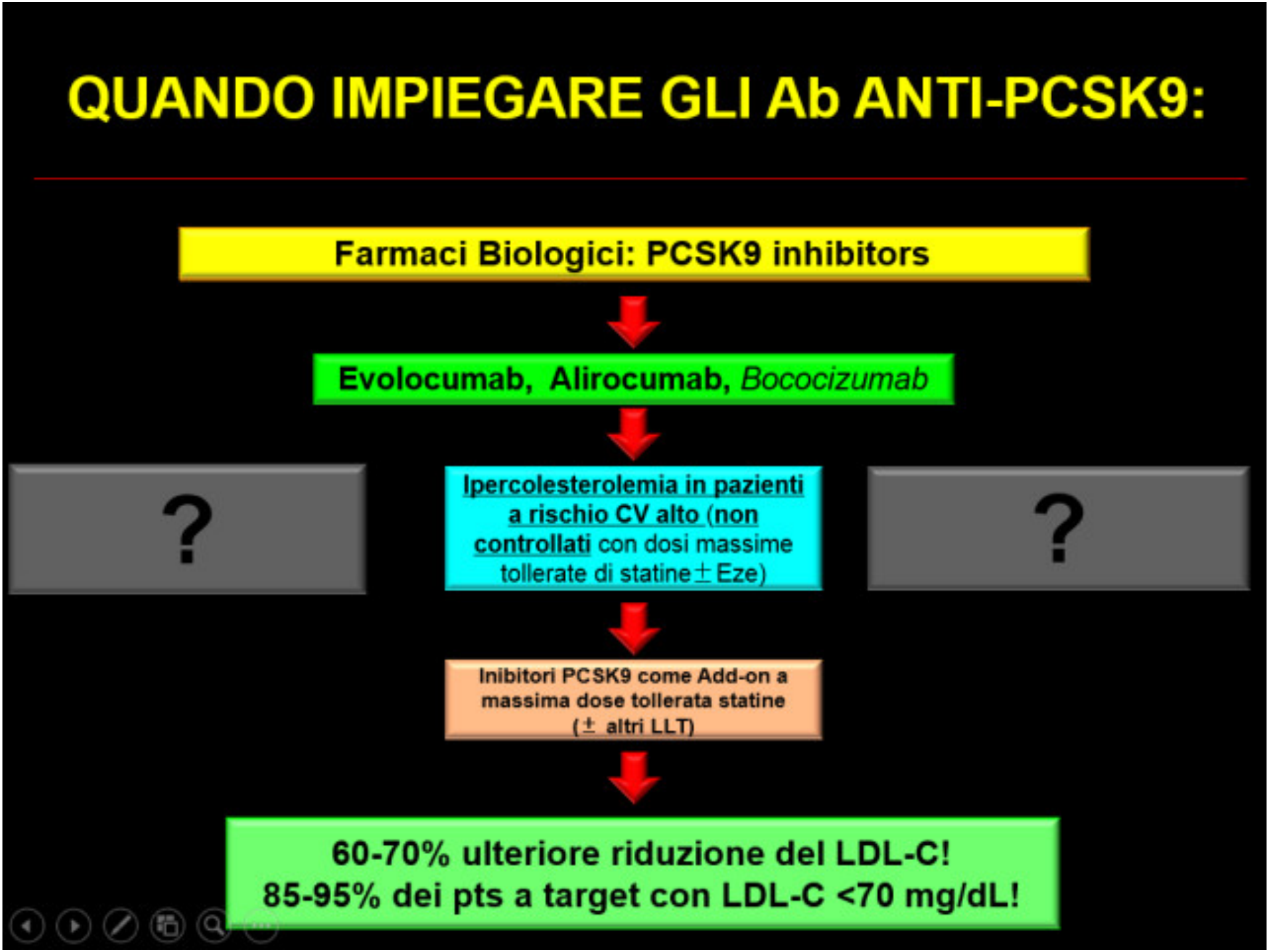

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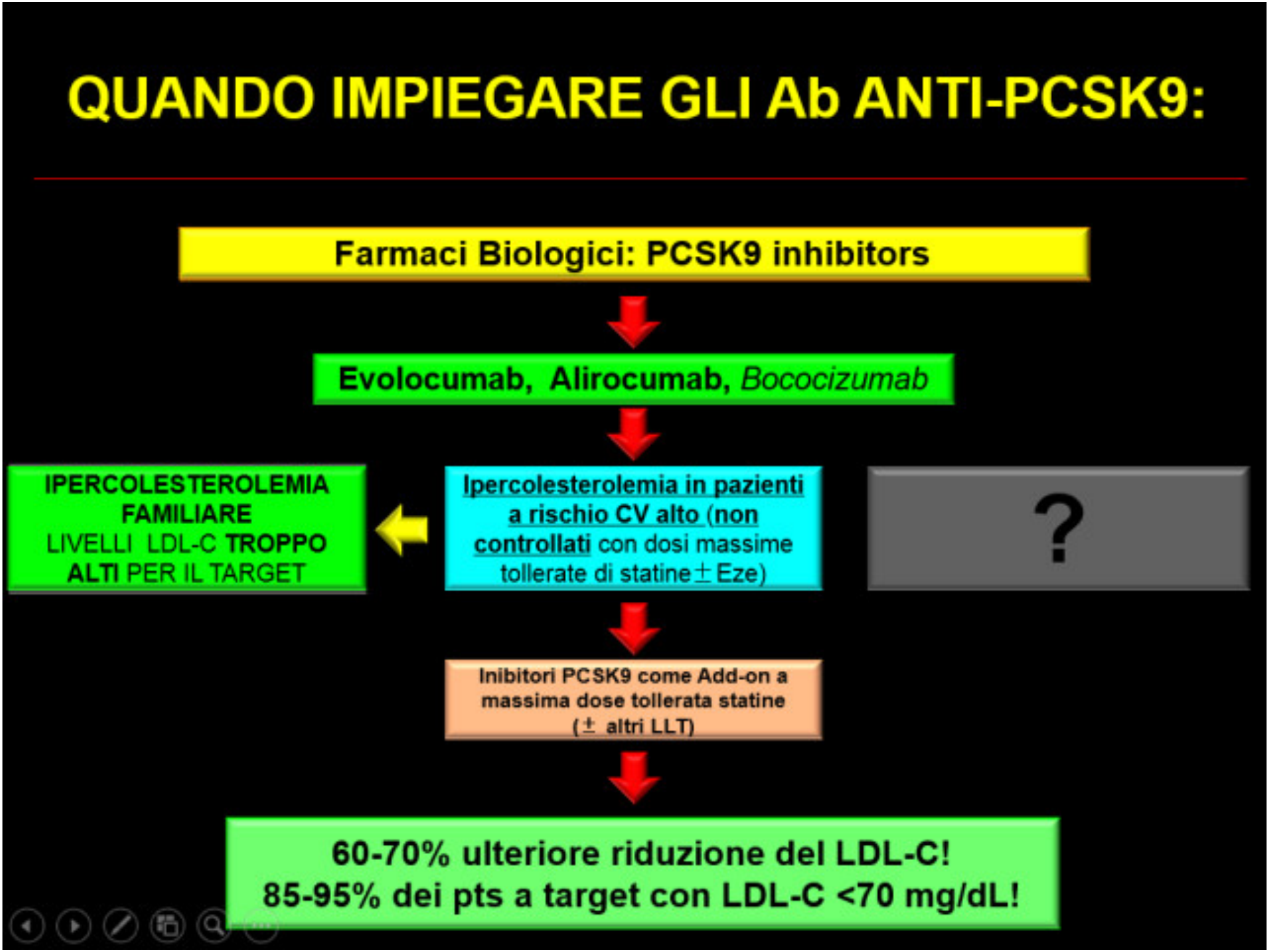

Ipercolesterolemia Familiare: Sotto-diagnosticata e sottotrattata

LDL-C

FH Target #1 in tutte le Linee Guida

Colesterolo Plasmatico	Forme PRIMITIVE
300-580 mg/dl	Ipercolesterolemia Familiare Eterozigote*
480-1000 mg/dl	Ipercolesterolemia Familiare Omozigote*

*Ipercolesterolemia Familiare (FH) monogenica

Heart Journal (2011,32:1769-1818)

Ipercolesterolemia Familiare: Sotto-diagnosticata e sottotrattata

FH Target #1 in tutte le Linee Guida

ESC/EAS Guidelines - European Heart Journal (2011,32:1769-1818)

Ipercolesterolemia Familiare: Sotto-diagnosticata e sottotrattata

FH Target #1 in tutte le Linee Guida

- ✓Solo 1 su 5 FH a target per LDL-C nelle casistiche dei migliori centri internazionali
- ✓La maggior parte dei pazienti FH necessita di ridurre il LDL-C di >60%!!! (Raramente ottenibile anche con le terapie più efficaci disponibili)

ESC/EAS Guidelines - European Heart Journal (2011,32:1769-1818)

PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial

Fredrick J Raal, Evan A Stein, Robert Dufour, Traci Turner, Fernando Civeira, Lesley Burgess, Gisle Langslet, Russell Scott, Anders G Olsson, David Sullivan, G Kees Hovingh, Bertrond Cariou, Joanne Gouni-Berthold, Rensi Somaratne, Ian Bridges, Rob Scott, Scott M Wasserman, Daniel Gaudet, for the RUTHERFORD-2 Investigators*

- 329 patients with heterozygous familial hypercholesterolaemia
- LDL-C≥ 100 mg/dl
- Evolocumab 140 mg every 2 weeks
- Evolocumab 420 mg monthly

The Lancet, 385:331-340, 2015

Efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolaemia (heFH) not adequately controlled with current lipid-lowering therapy: Results of ODYSSEY FH I and FH II studies

J.J.P. Kastelein, HN.Ginsberg, G Langslet, G.K Hovingh, R. Ceska, R. Dufour, D. Blom, F. Civeira, M. Krempf, M.Farnier

- 486 (FH I) e 249 (FH II) patients with heterozygous familial hypercholesterolaemia
- LDL-C≥ 100 mg/dl o ≥ 70 mg/dl se CVD
- Alirocumab 75 mg every 2 weeks
- Alirocumab 150 mg every two weeks*

* If LDL-C>70 mg/dl at 8 weeks

Presented ESC 2014, Barcelona

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- **LDL-C≥ 100 mg/dl**
- Evolocumab 140 mg every 2 weeks
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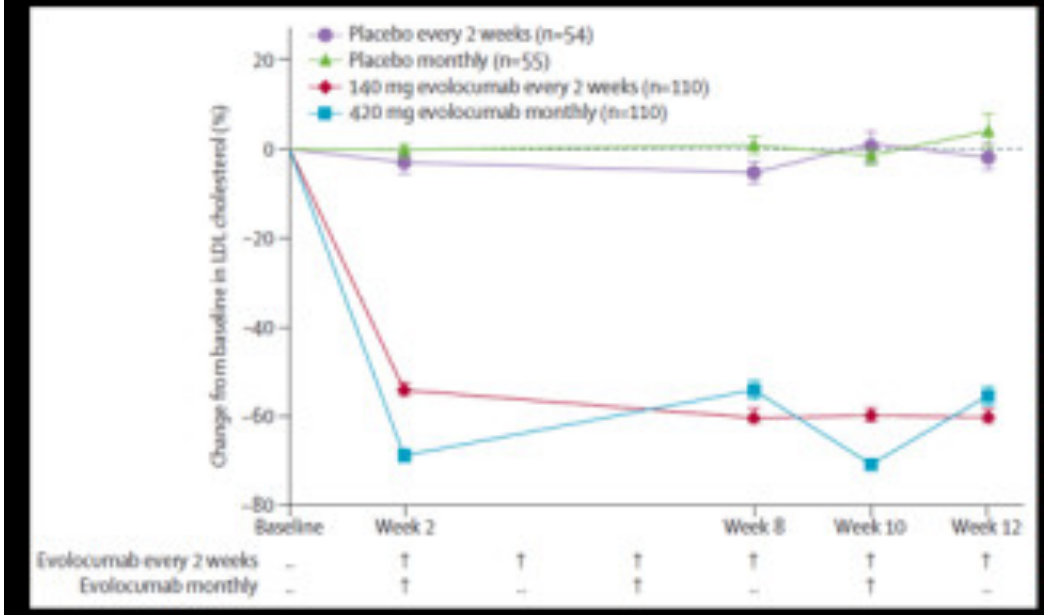
Mean % change from baseline in LDL-C



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- **486 (FH I) e 249 (FH II) patients** with heterozygous familial hypercholesterolaemia
- **LDL-C≥ 100 mg/dl o ≥ 70 mg/dl se CVD**
- Alirocumab 75 mg every 2 weeks
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* If LDL-C>70 mg/dl at 8 weeks

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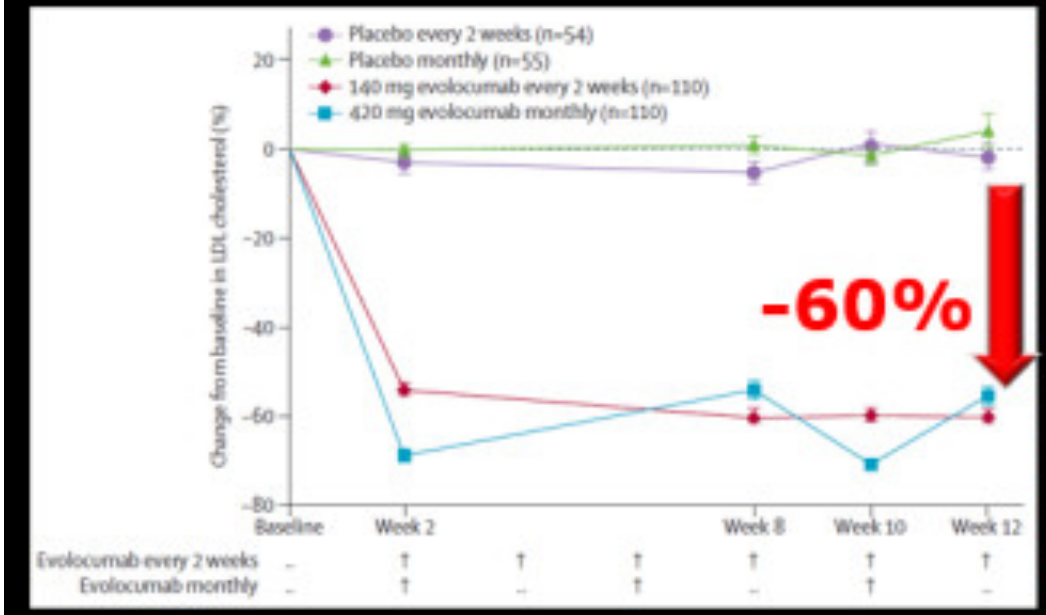
Mean % change from baseline in LDL-C



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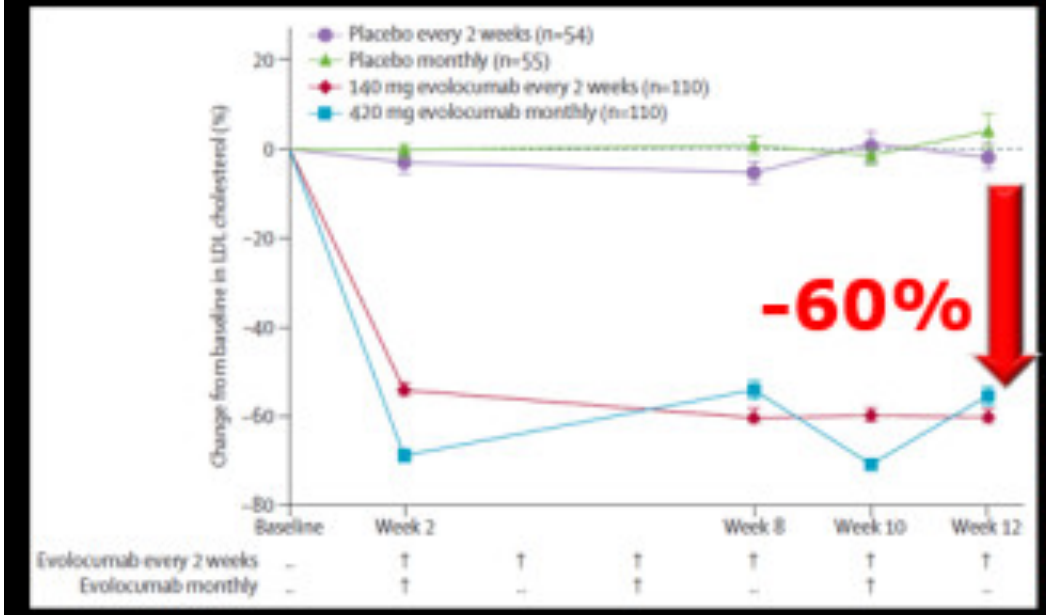

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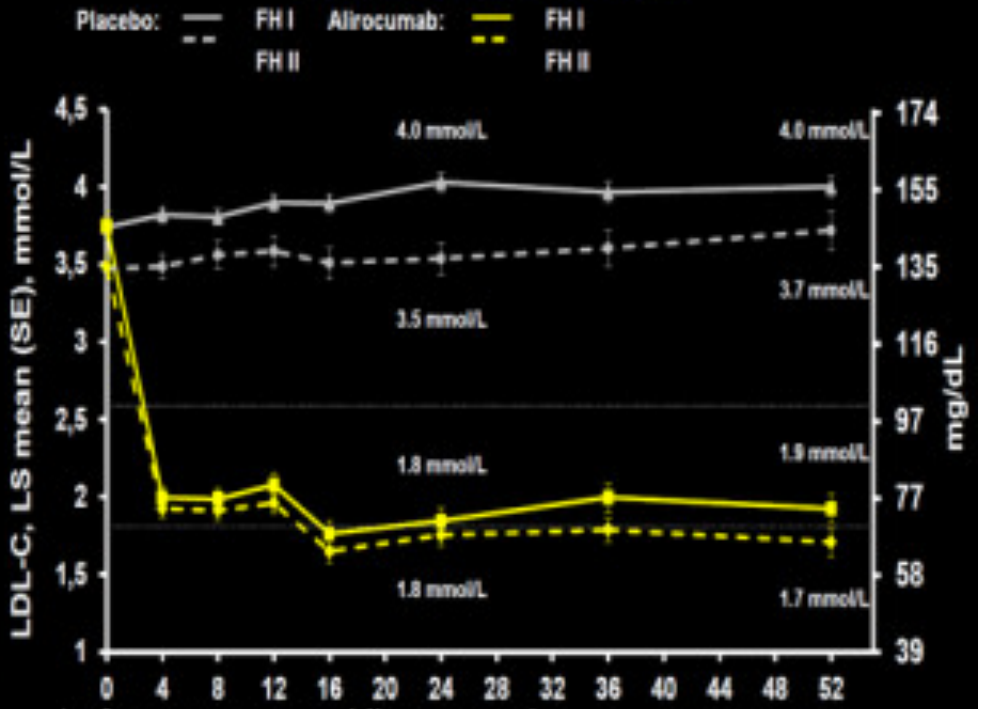
Achieved LDL-C Over Time on Background of Maximally-Tolerated Statin ±Other LLT



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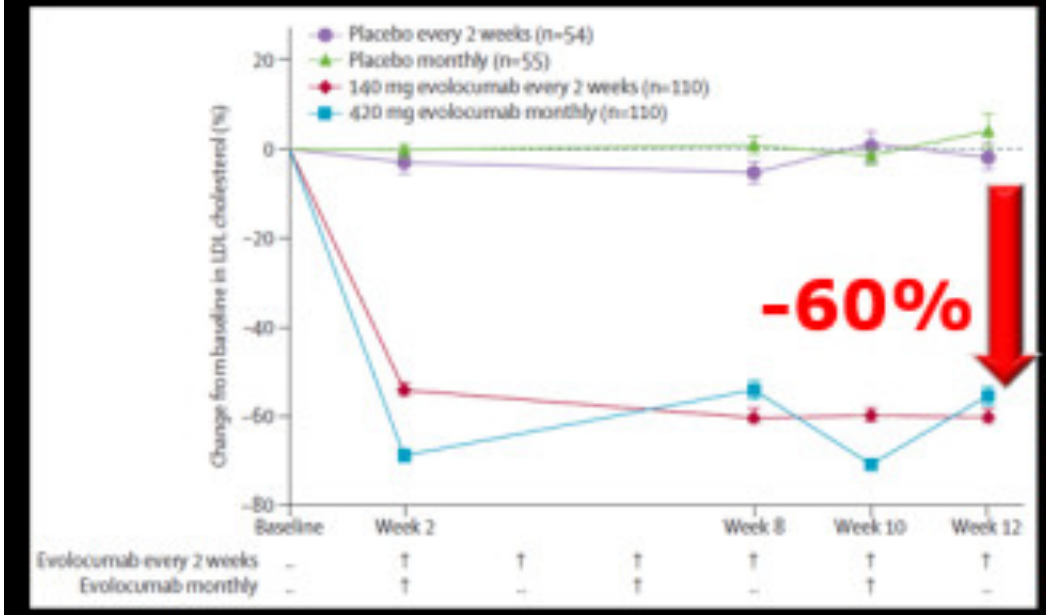

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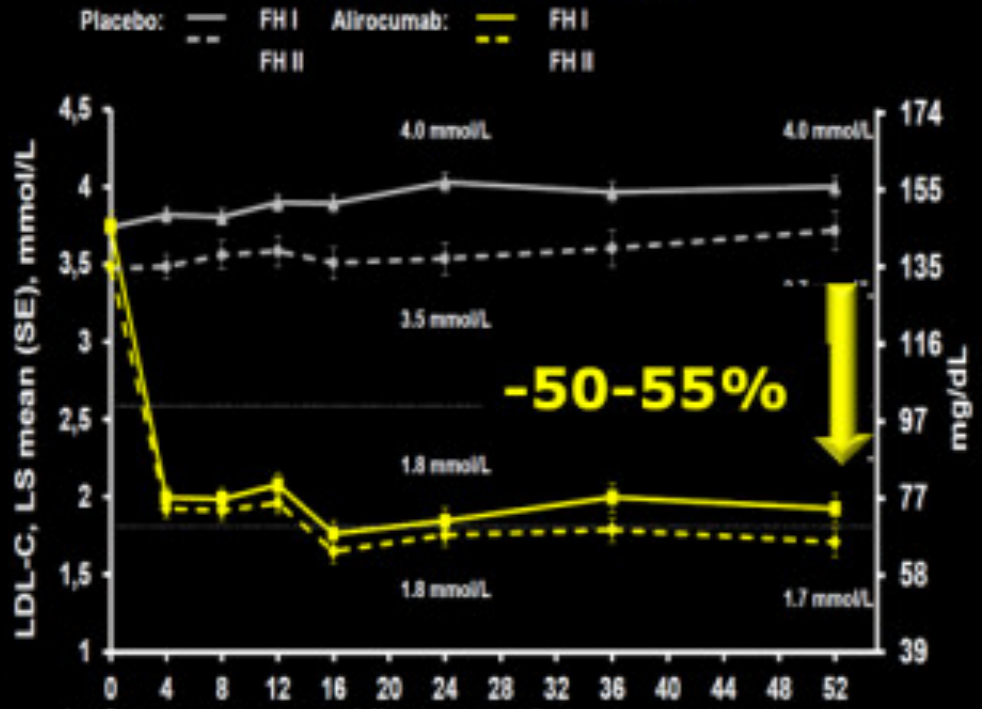

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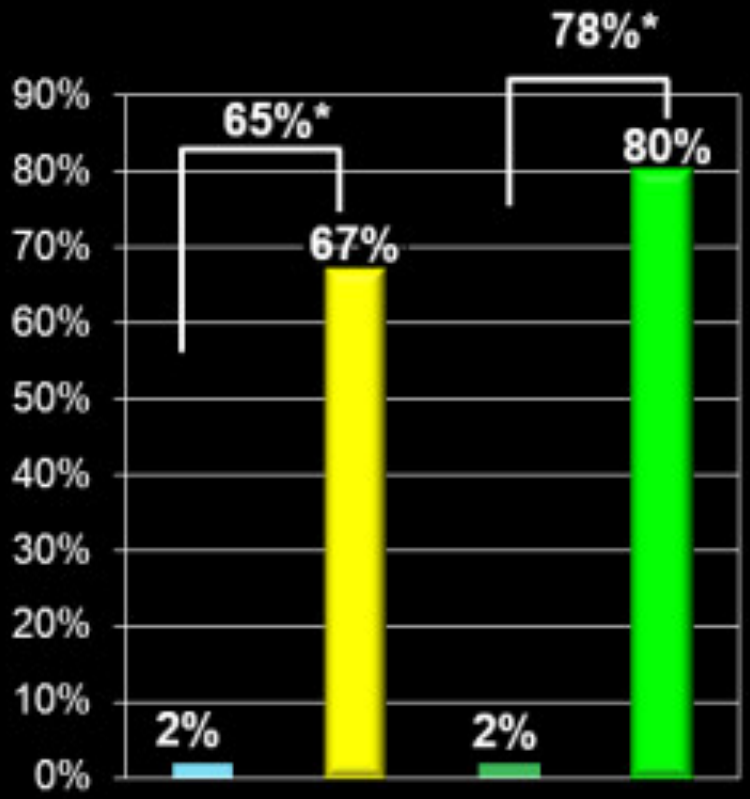
LDL-C Goal Achievement < 70 mg/dL
Weeks 10 and 12



Placebo Q2W (N = 54)
Evolocumab 140 mg Q2W (N = 110)
Placebo QM (N = 55)
Evolocumab 420 mg QM (N = 110)

*P<0.0001 evolocumab treatment difference vs placebo

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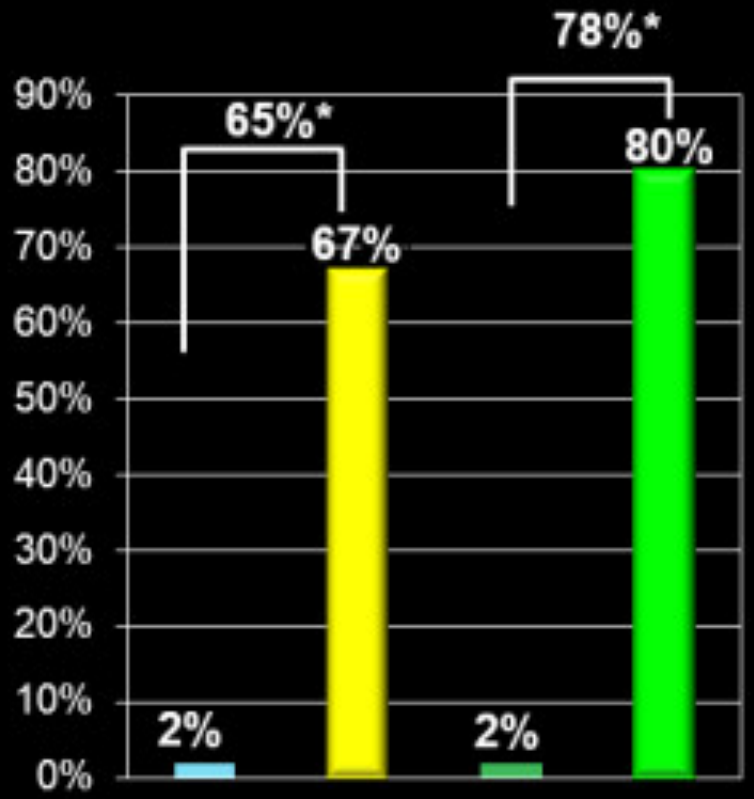

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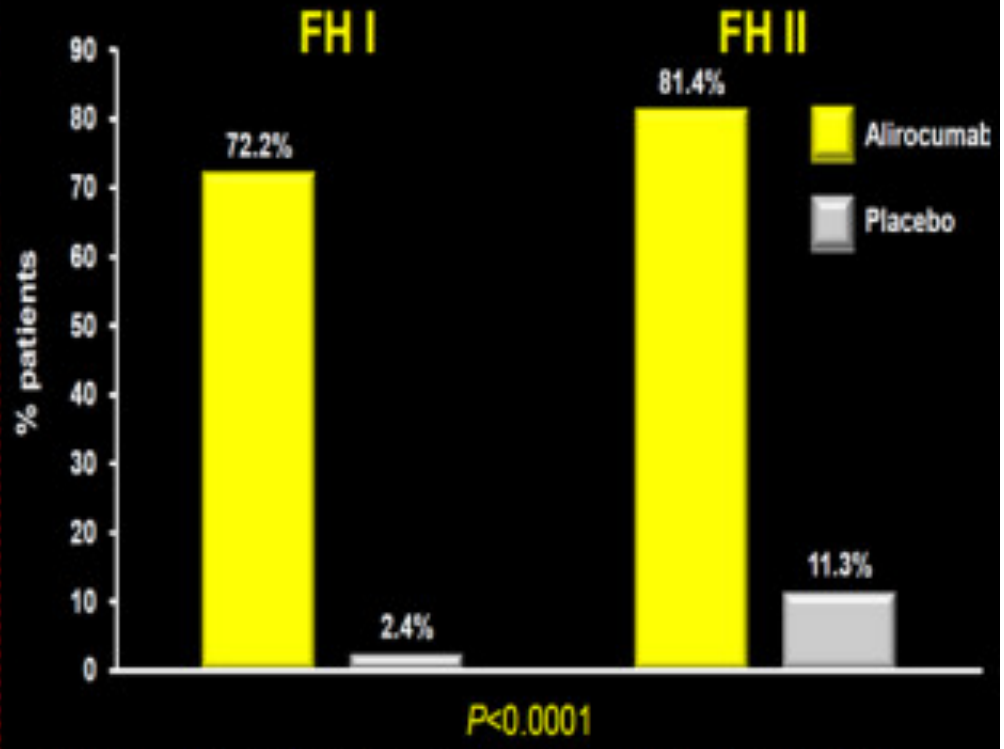
Proportion of patients reaching LDL-C goal† at Week 24



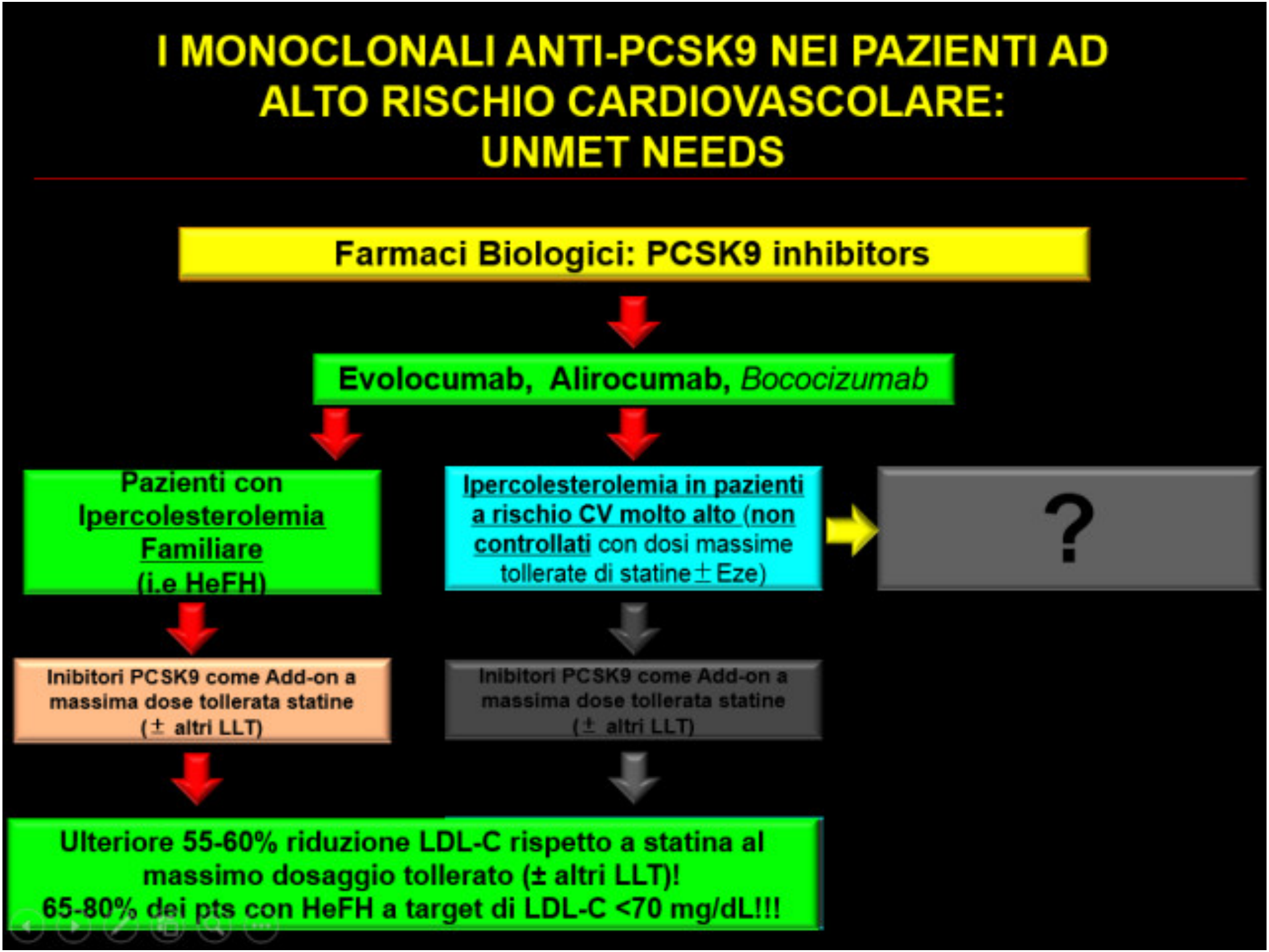
P<0.0001

†Very high-risk: <1.81 mmol/L (70 mg/dL); high-risk: <2.59 mmol/L (100 mg/dL). LLT = lipid-lowering therapy.

* If LDL-C>70 mg/dl at 8 weeks

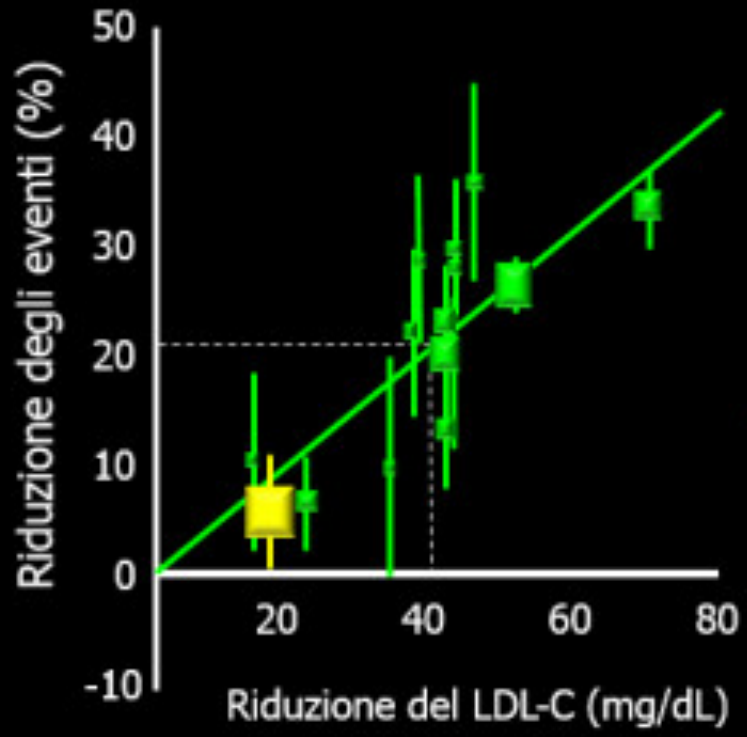
Presented ESC 2014, Barcelona

I MONOCLONALI ANTI-PCSK9 NEI PAZIENTI AD ALTO RISCHIO CARDIOVASCOLARE: UNMET NEEDS



Riduzione dell'incidenza degli **eventi cardiovascolari** maggiori e **riduzione media del LDL-C**

(Meta-analisi di 14 trials, n=90.056, pubblicati dal 1994 al2004)



-21% ogni 40 mg/dl LDL-C

Lancet 2005; 366:1267-1278

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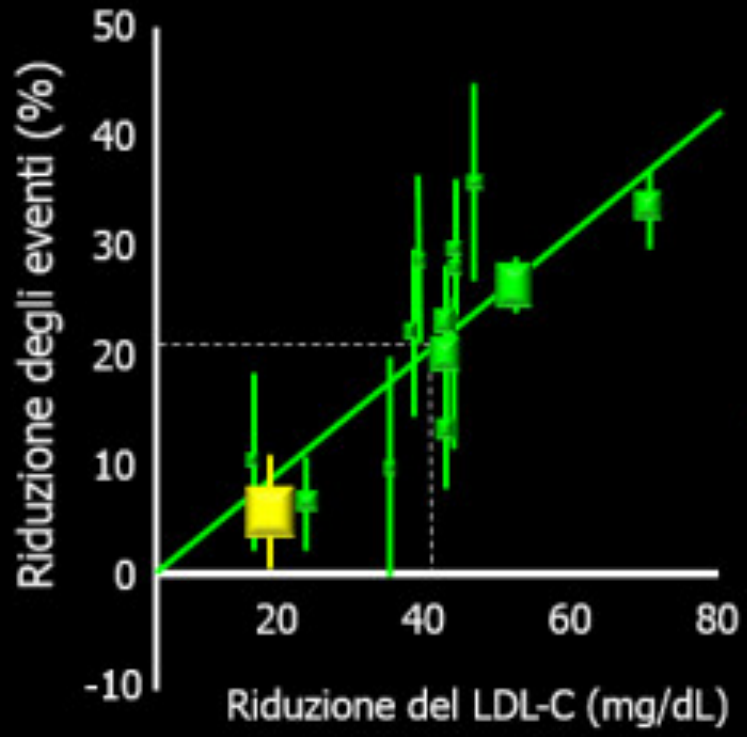

Ipercolesterolemici Familiari FH Eterozigoti già in statina+ Anti PCSK9:

1) Riduzione ulteriore LDL-C 70-100 mg/dl (1.8 -2.2 mmol/l)

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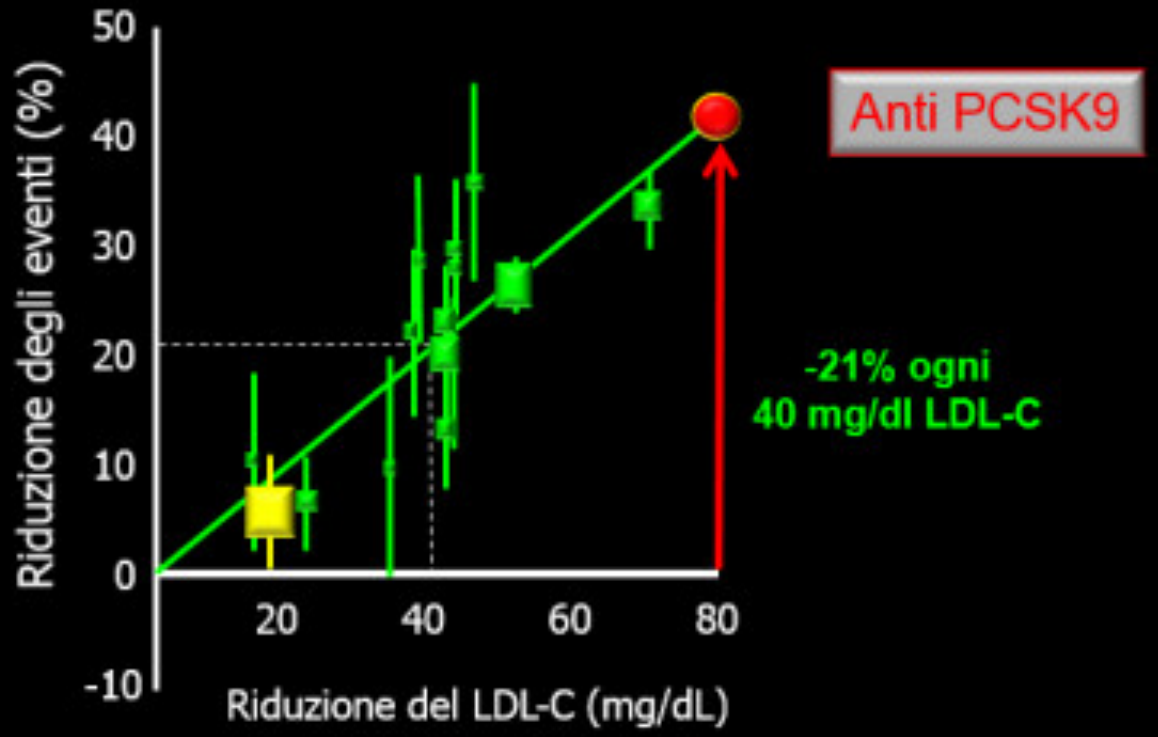

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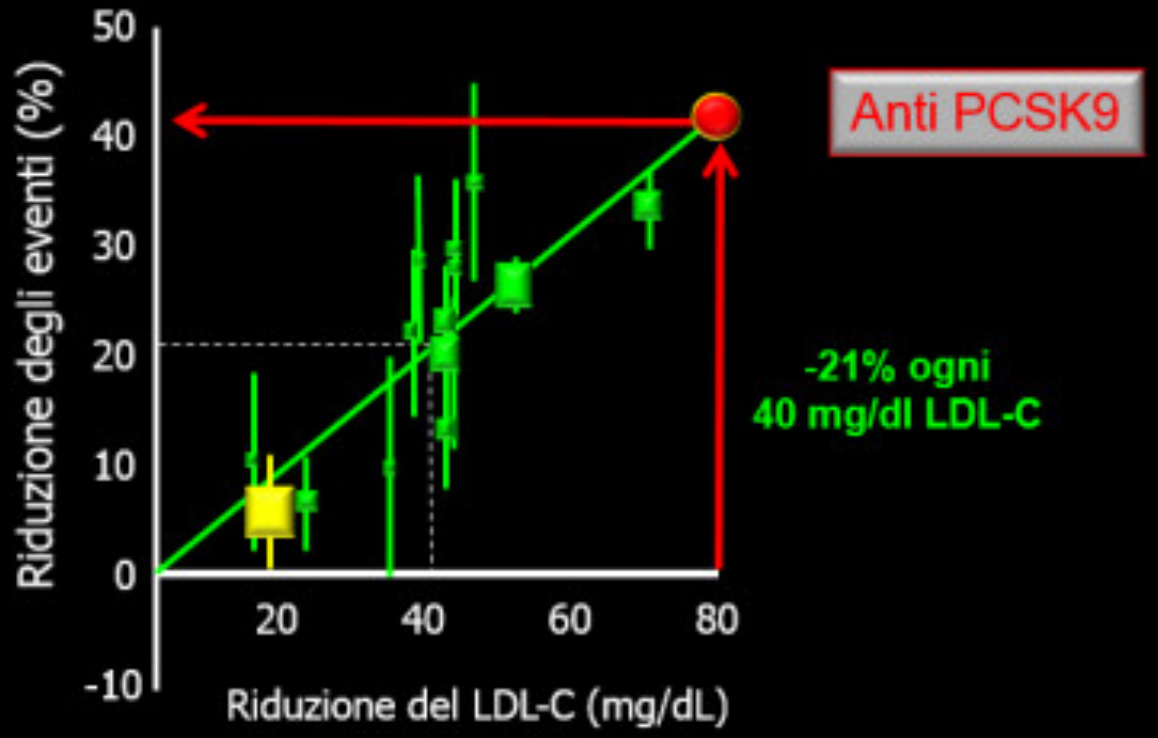

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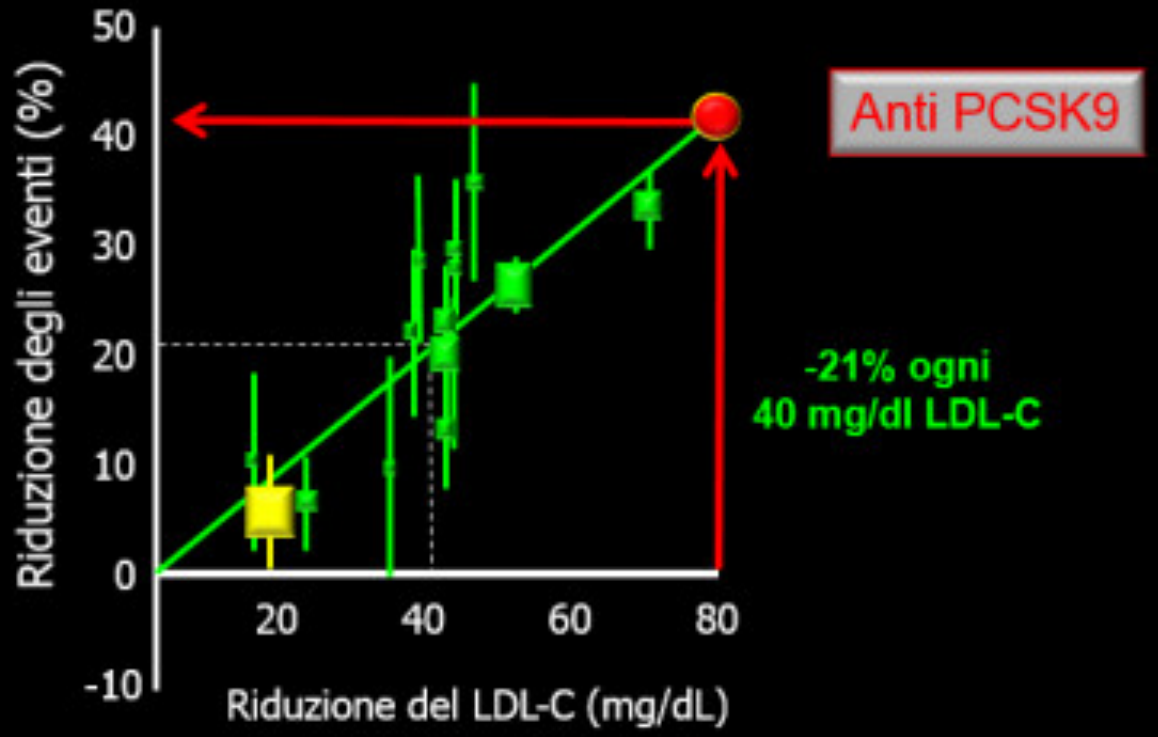

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1) Riduzione ulteriore LDL-C 70-100 mg/dl (1.8 -2.2 mmol/l)
2) ULTERIORE possibile RIDUZIONE EVENTI CHD/CVD di circa il 40%

?

Lancet 2005; 366:1267-1278

I MONOCLONALI ANTI-PCSK9 NEL CONTROLLO DEL COLESTEROLO LDL: TAKE HOME MESSAGE

Farmaci Biologici: PCSK9 inhibitors

UNMET CLINICAL NEED WITH CURRENT THERAPY

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Ipercolesterolemia in pazienti a richio CV molto alto (non controllati con max dose tollerata di statina ± Eze)

Pazienti con Intolleranza alle Statine

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COSTI ($) **CV BENEFICI**

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COSTI ($) **CV BENEFICI**

POPOLAZIONE AL TOP DEL COST/BENEFIT RATIO

Ipercolesterolemia Familiare Eterozigote

Rischio CV Molto Alto (con intolleranza alle statine?)