

**Медицински университет- София
Катедра по Вътрешни болести
“Проф. д-р Ст. Киркович”**

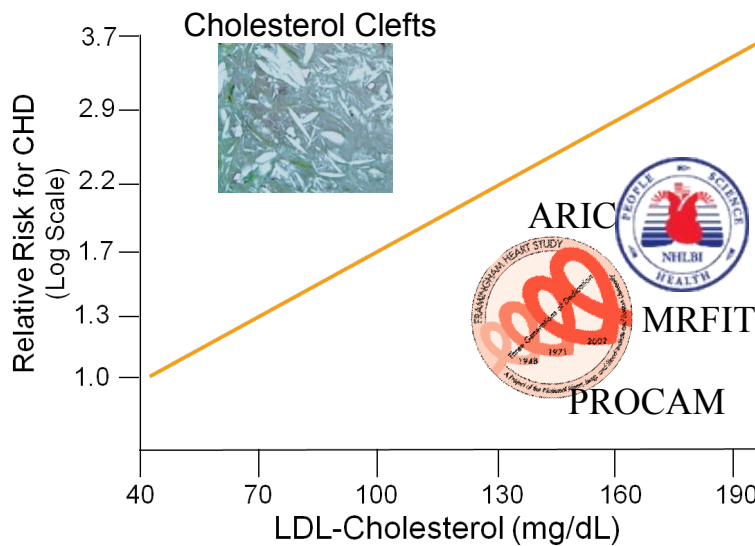


ИНХИБИТОРИ НА PCSK9

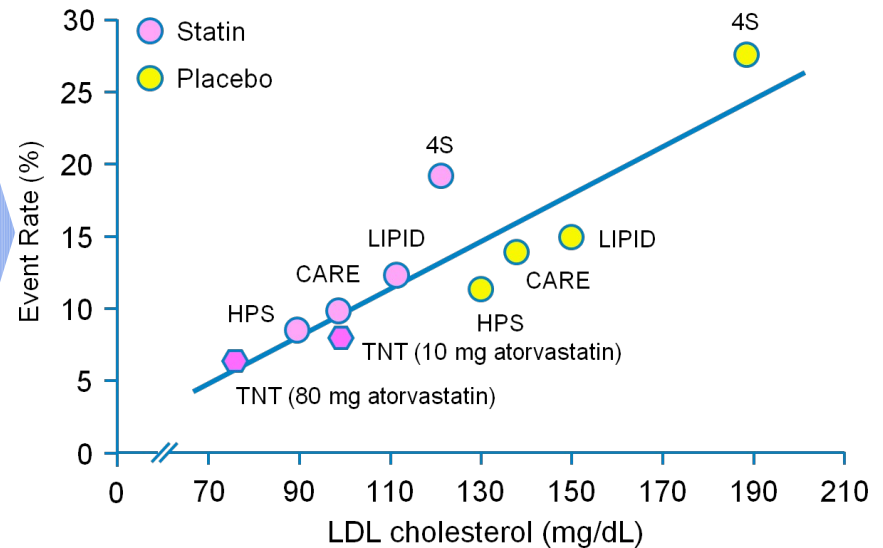
Д-р Светлин Цонев, д.м.

Нивата на холестерола са пряко свързани с коронарната артериална болест (КАБ)

Холестеролова хипотеза



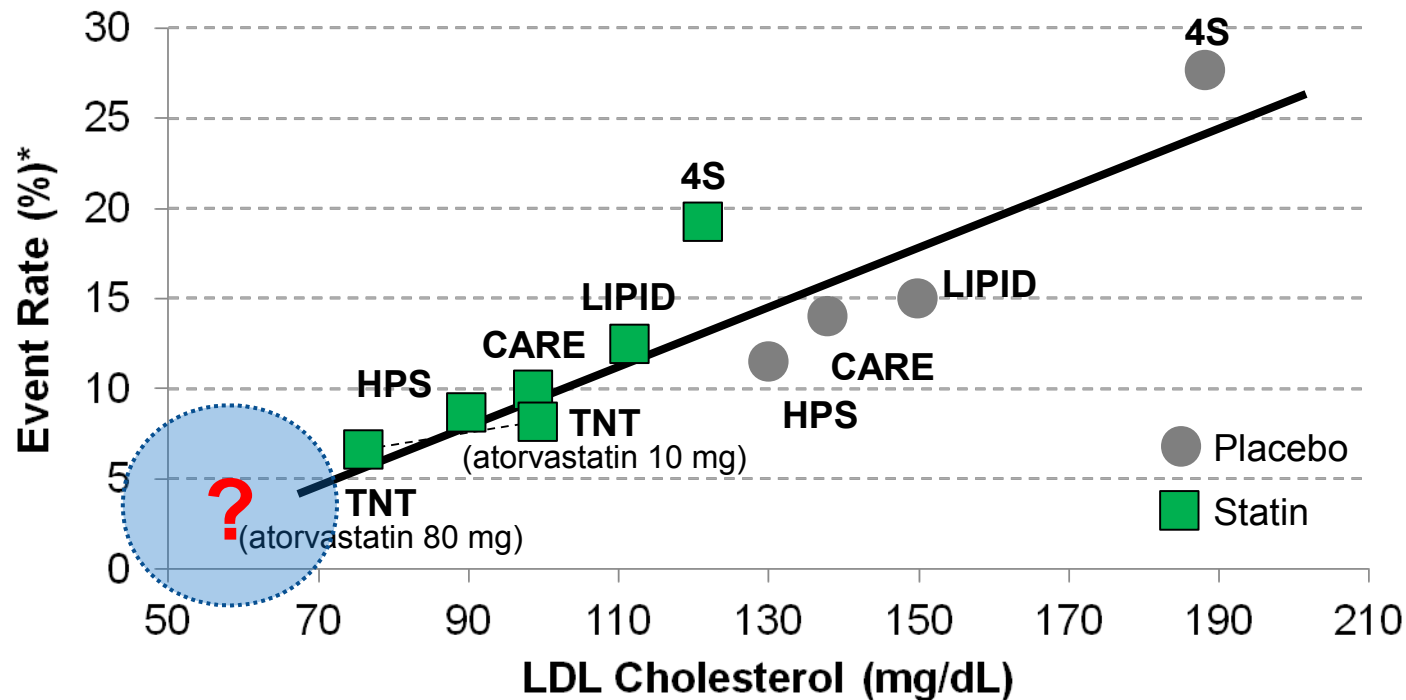
Статините потвърждават хипотезата



Event rates for HPS, CARE, and LIPID are for death and nonfatal MI; event rates for 4S, TNT also include resuscitated SCD. LaRosa JC, et al. N Engl J Med 2005;352:1425-35.

Всеки 1 mg/dL намаление в LDL-C е свързан с редукция на релативния риск за КАБ с ~1-2%

Намалението на LDL-C е силно свързано с редуцията на коронарния риск¹



*Event rates for HPS, CARE, and LIPID were CHD death and nonfatal myocardial infarction (MI); event rates for 4S and TNT also included resuscitation after cardiac arrest.

4S = Scandinavian Simvastatin Survival Study; LIPID = Long-term Intervention with Pravastatin in Ischemic Disease; CARE = Cholesterol and Recurrent Events; HPS = Heart Protection Study; TNT = Treatment to New Target; MI = myocardial infarction

1. Adapted from: LaRosa JC, et al. *N Engl J Med*. 2005;352:1425-1435.

2. Grundy SM, et al. *Circulation*. 2004;110:227-239.

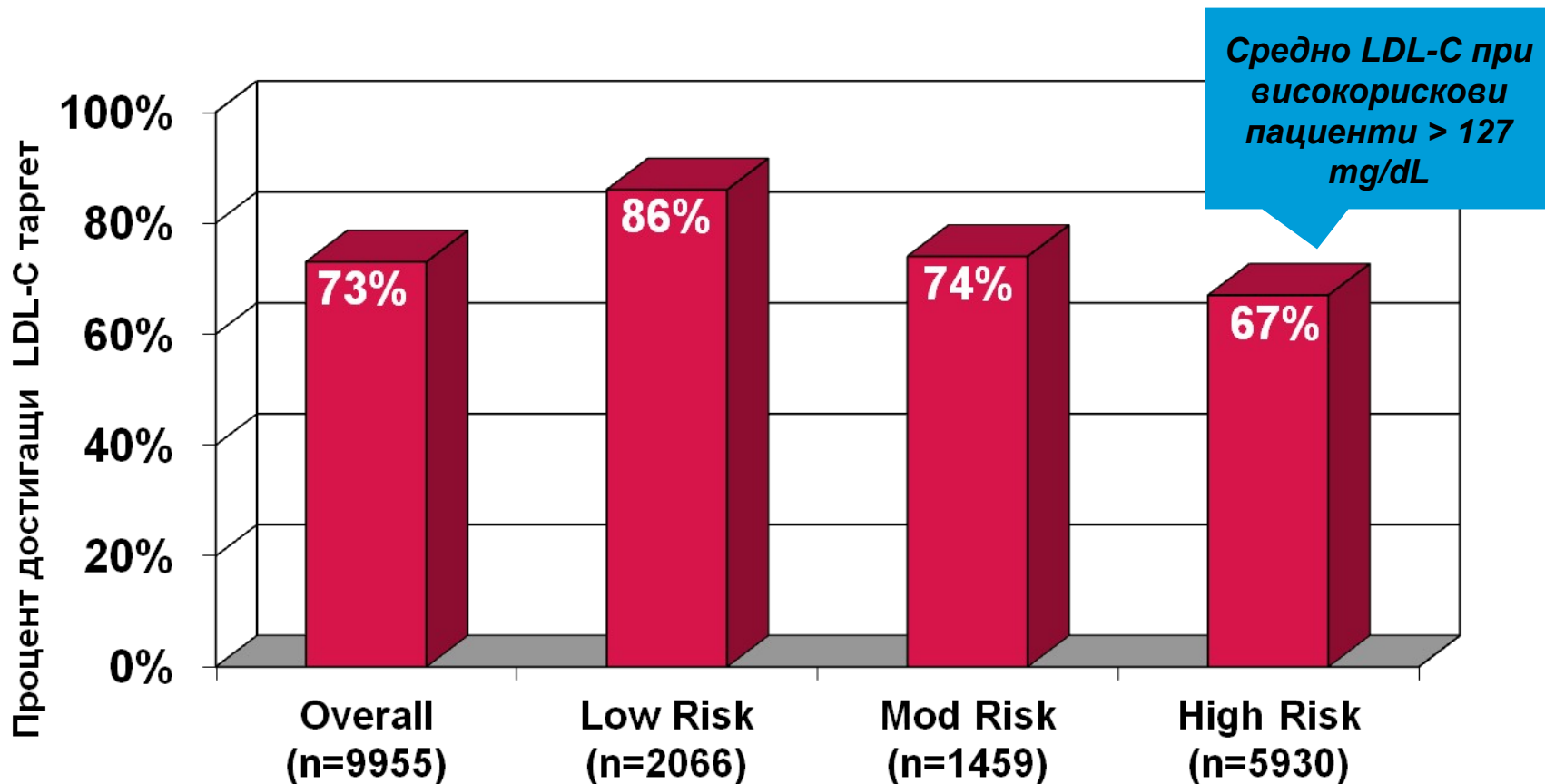
Медикаментозно лечение на дилипидемия

Меикамент	ТС	LDL-C	HDL-C	TG	Поносимост
Статини	↓19 – 37%	↓25 – 50%	↑4 – 12%	↓14 – 29%	добра
Ezetimibe	↓ 13%	↓ 18%	↑ 1%	↓ 9%	добра
Деривати на жл. К-ни	↓ 7 – 10%	↓10 – 18%	↑ 3%	Neutral or ↑	лоша
Никотинова к-на	↓10 – 20%	↓10 – 20%	↑14 – 35%	↓30 – 70%	Приемлива до лоша
Фибрати	↓19%	↓ 4 – 8%	↑11 – 13%	↓ 30%	добра

Yeshurun D et al. *South Med J* 1995;88:379–391. | NCEP. *Circulation* 1994;89:1333–1445. | Knopp RH. *N Engl J Med* 1999;341:498–511. | Gupta EK et al. *Heart Dis* 2002;4:399–409.



Около 1/3 от високорисковите пациенти не достигат таргетни нива на LDL-C Goal*

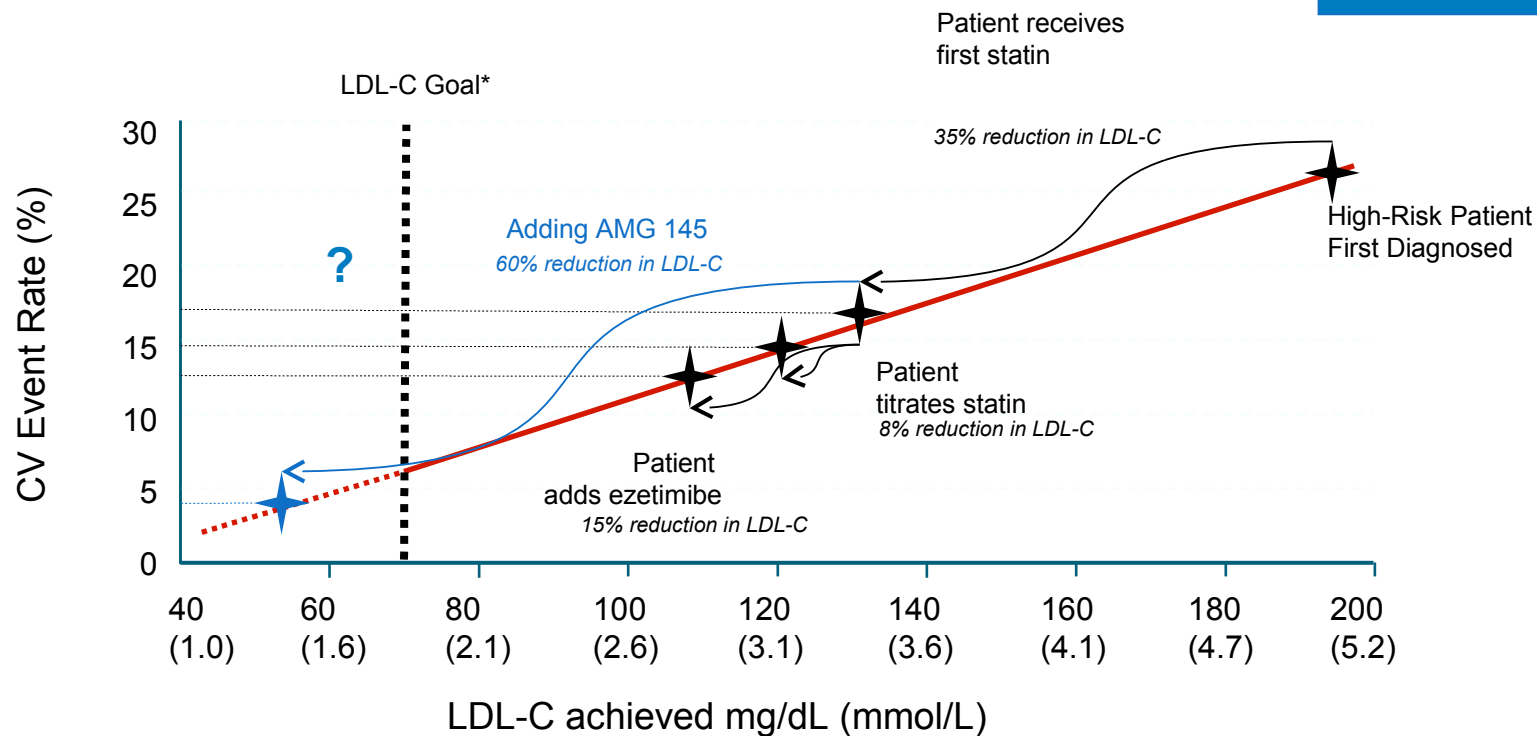


* 100 mg/dL LDL-C target based on NCEP ATP III for US, Lat Am and Asia; Joint European guidelines for Europe

Waters DD, et al *Circulation*. 2009;120:28-34.

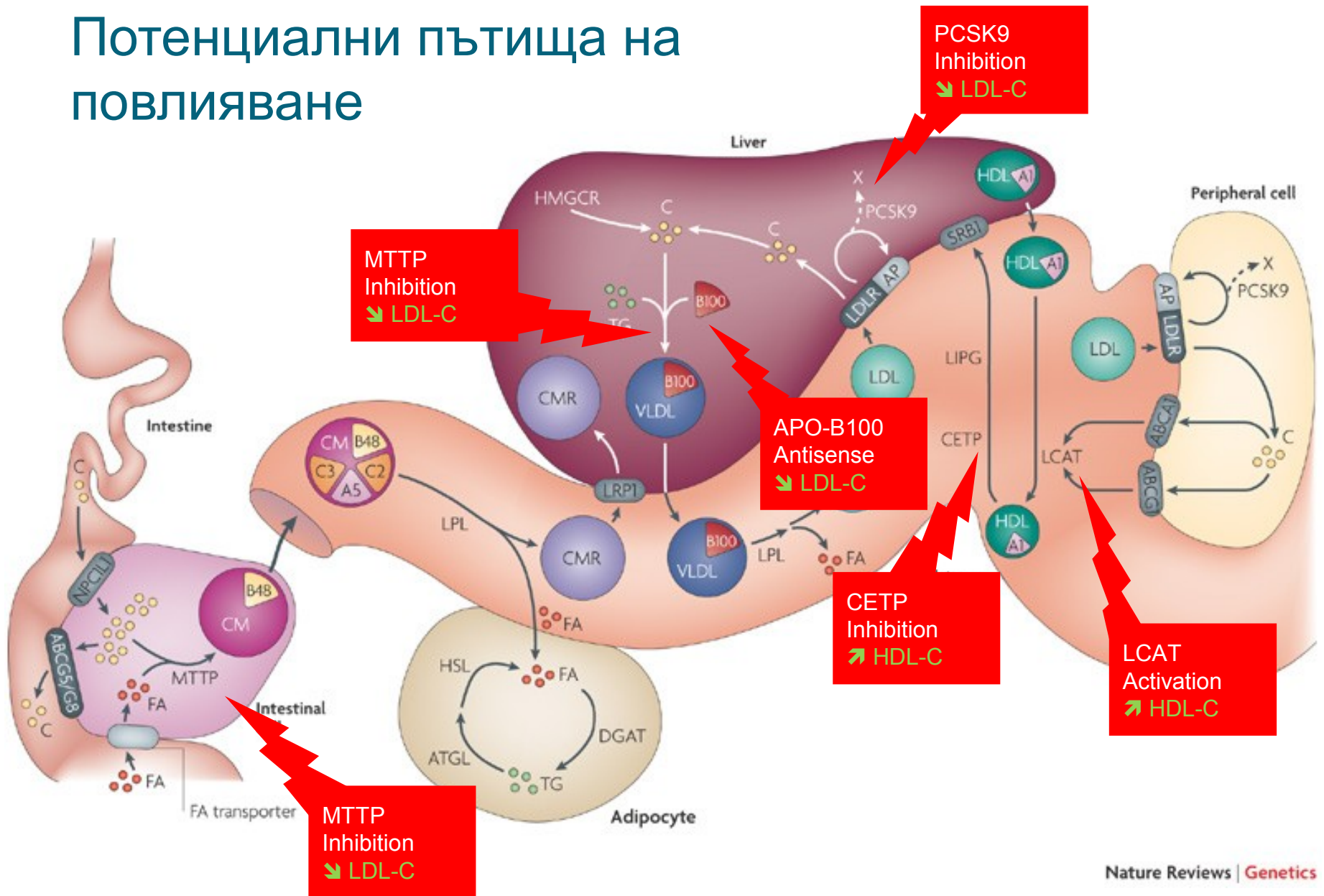
Колко ефективни можем да бъдем в редуцията на ССР?

ILLUSTRATIVE

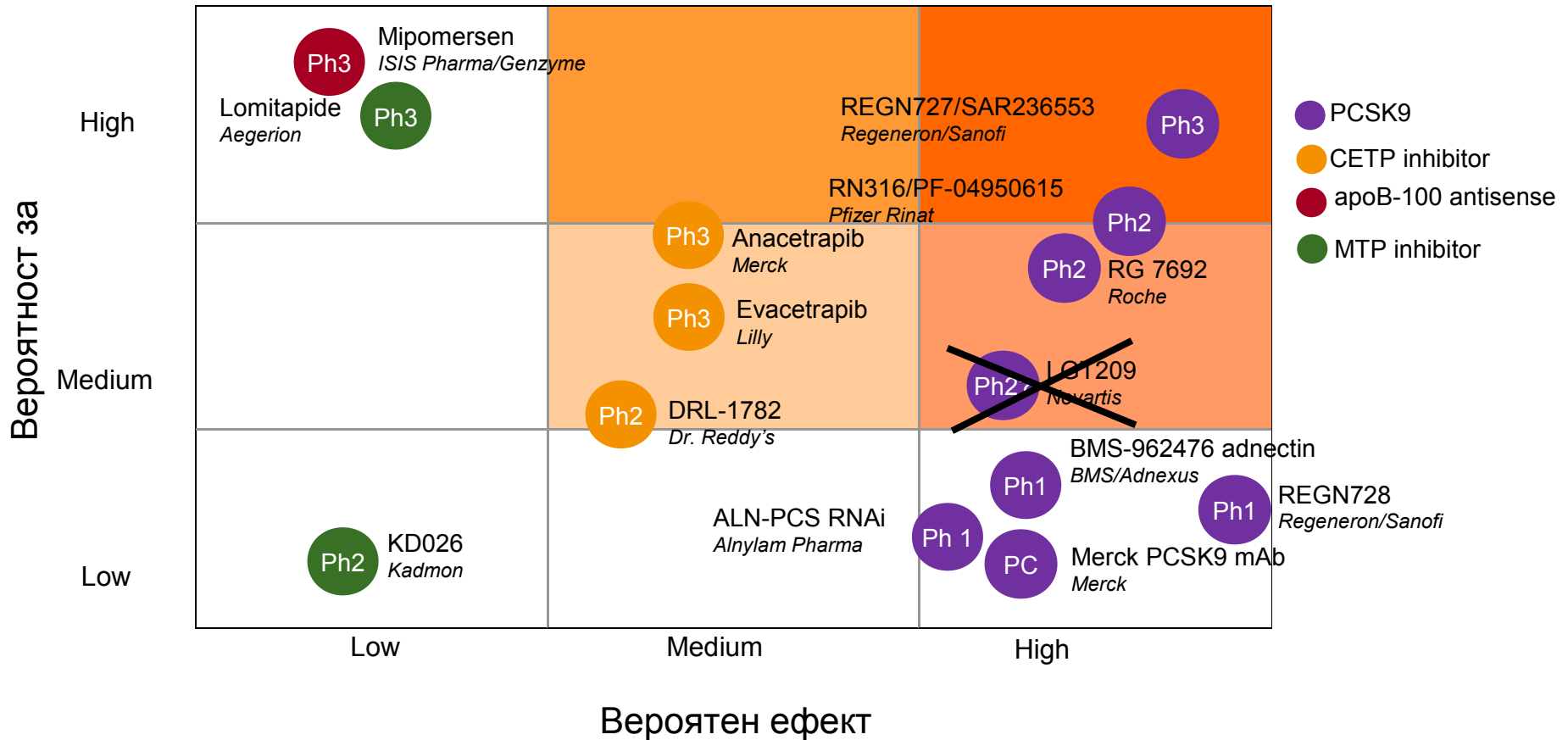


*LDL-Cholesterol goal for High Risk and Very High Risk patients as defined by ESC/EAS Guidelines for the management of dyslipidaemias. Adapted from Reiner Z et al. *Eur Heart J* 2011;32:1769-1818.

Потенциални пътища на повлияване



Молекули в разработка

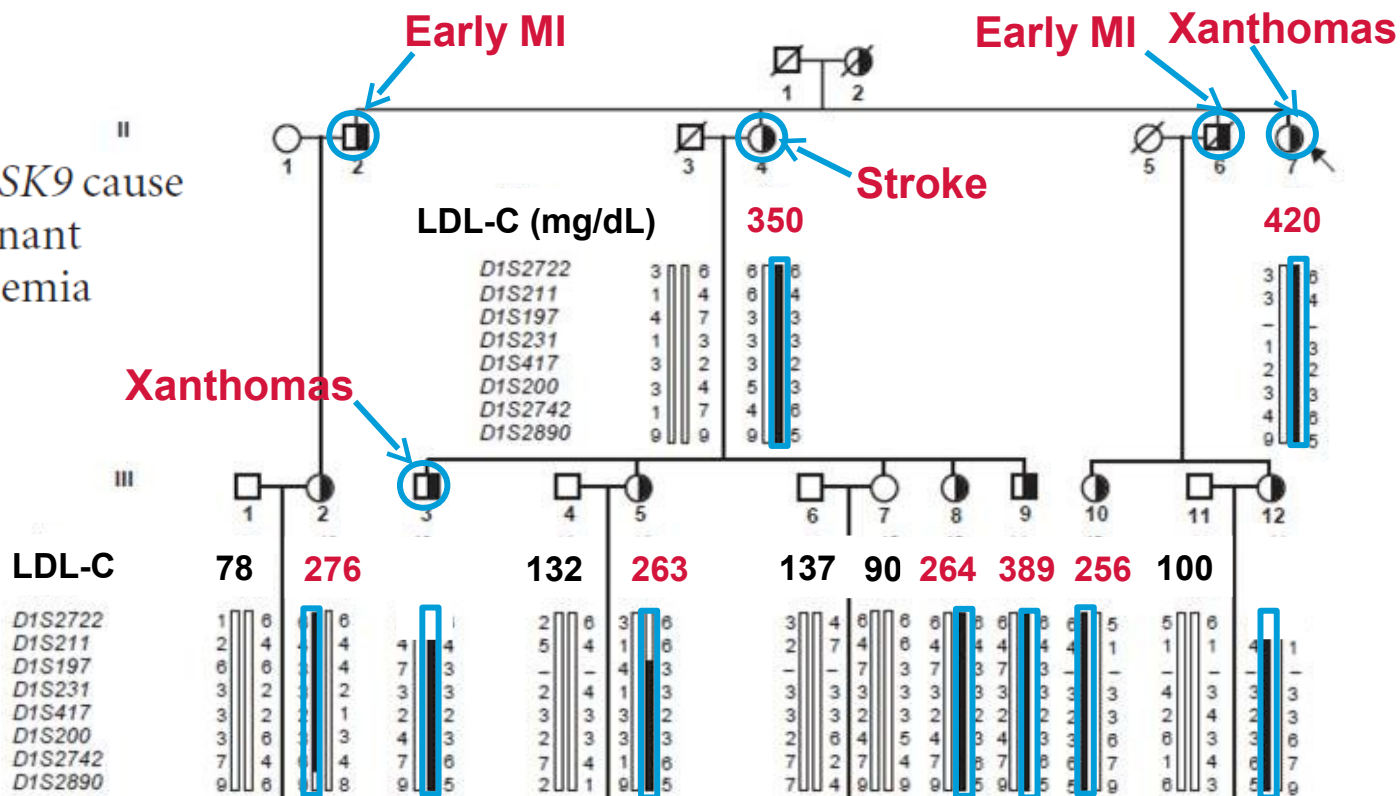


Sources: www.clinicaltrials.gov; Company WebSites and financial reports

Откриване на протеин конвертаза субтилизин кексин тип 9 (*PCSK9*)

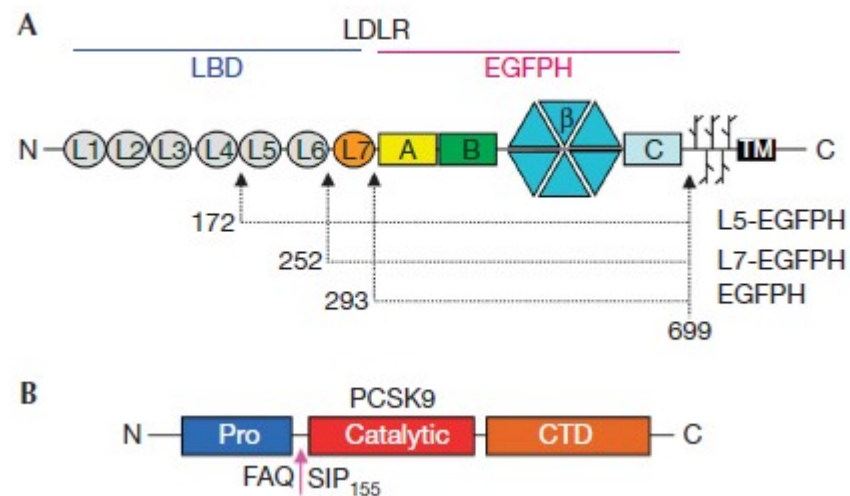
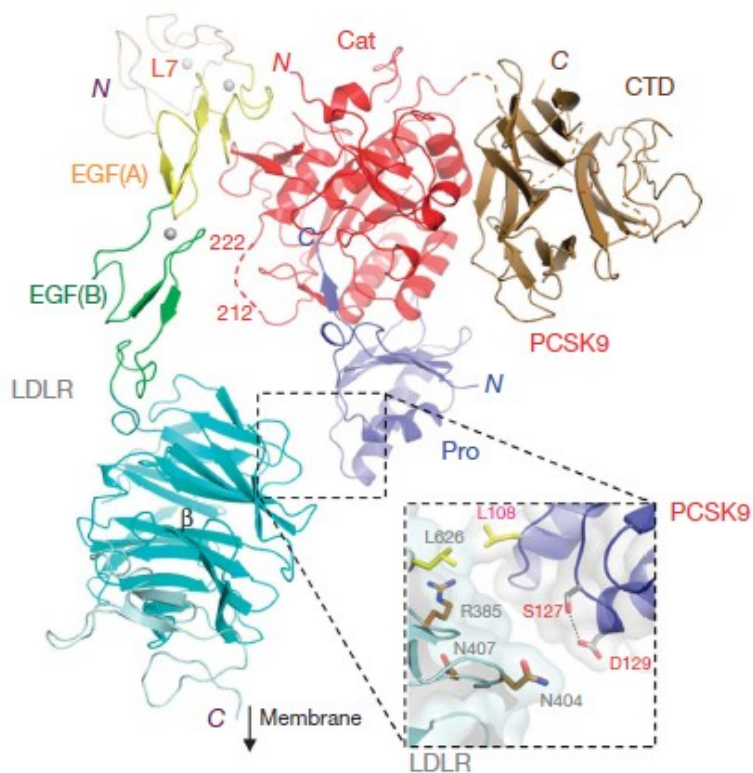
nature

Mutations in *PCSK9* cause autosomal dominant hypercholesterolemia



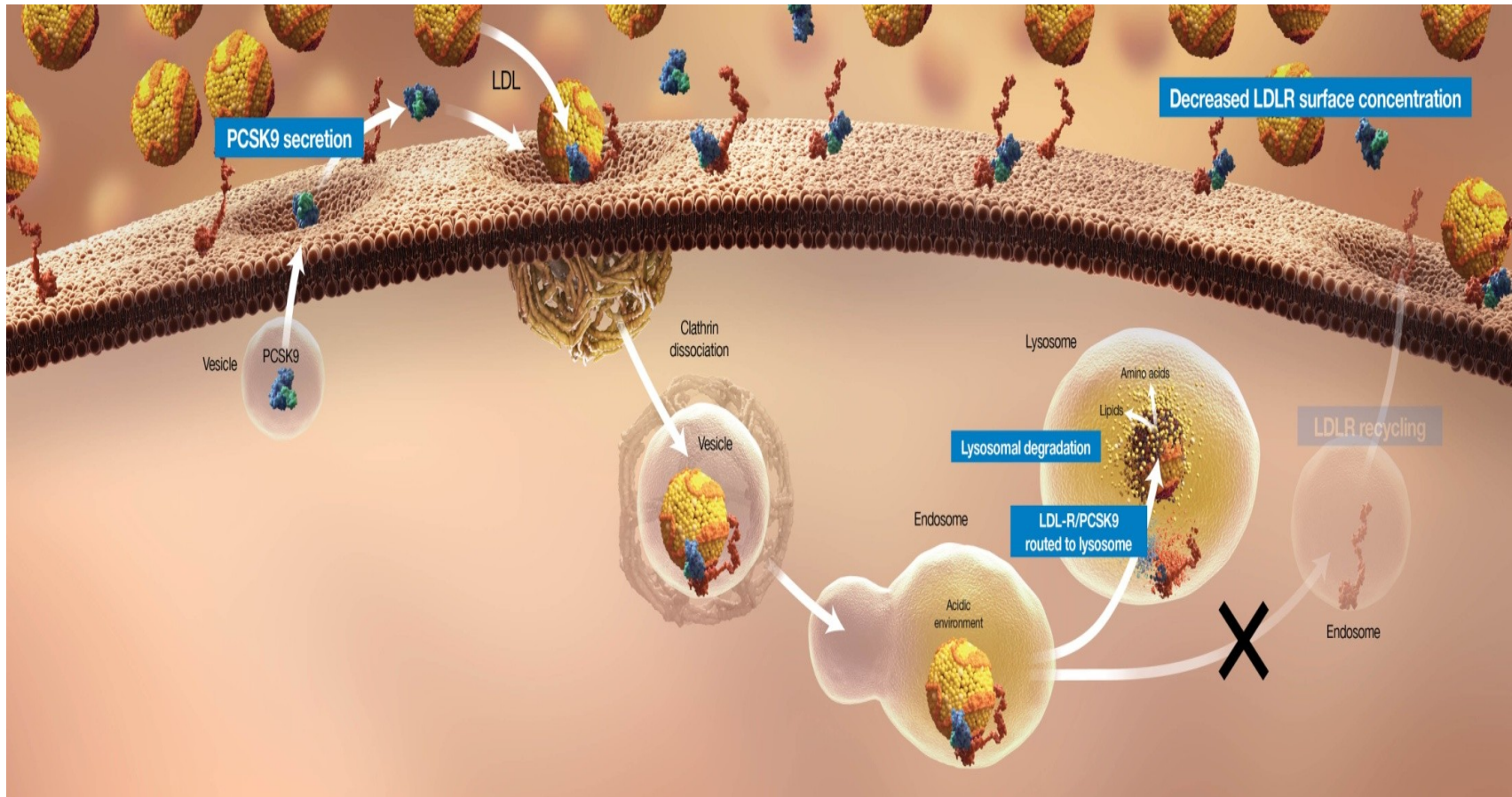
PCSK9 е трети локус за аштозомно доминантна хиперхолестеролемия (ADH): Gain-of-Function мутации в *PCSK9*

Взаимодействие на PCSK9 с LDL-R



- Каталитияния домейн на PCSK9 се свързва с EGF(A) домейна на LDL R

PCSK9 регулира експресията на LDLRs чрез разграждане в лизозомите¹⁻³



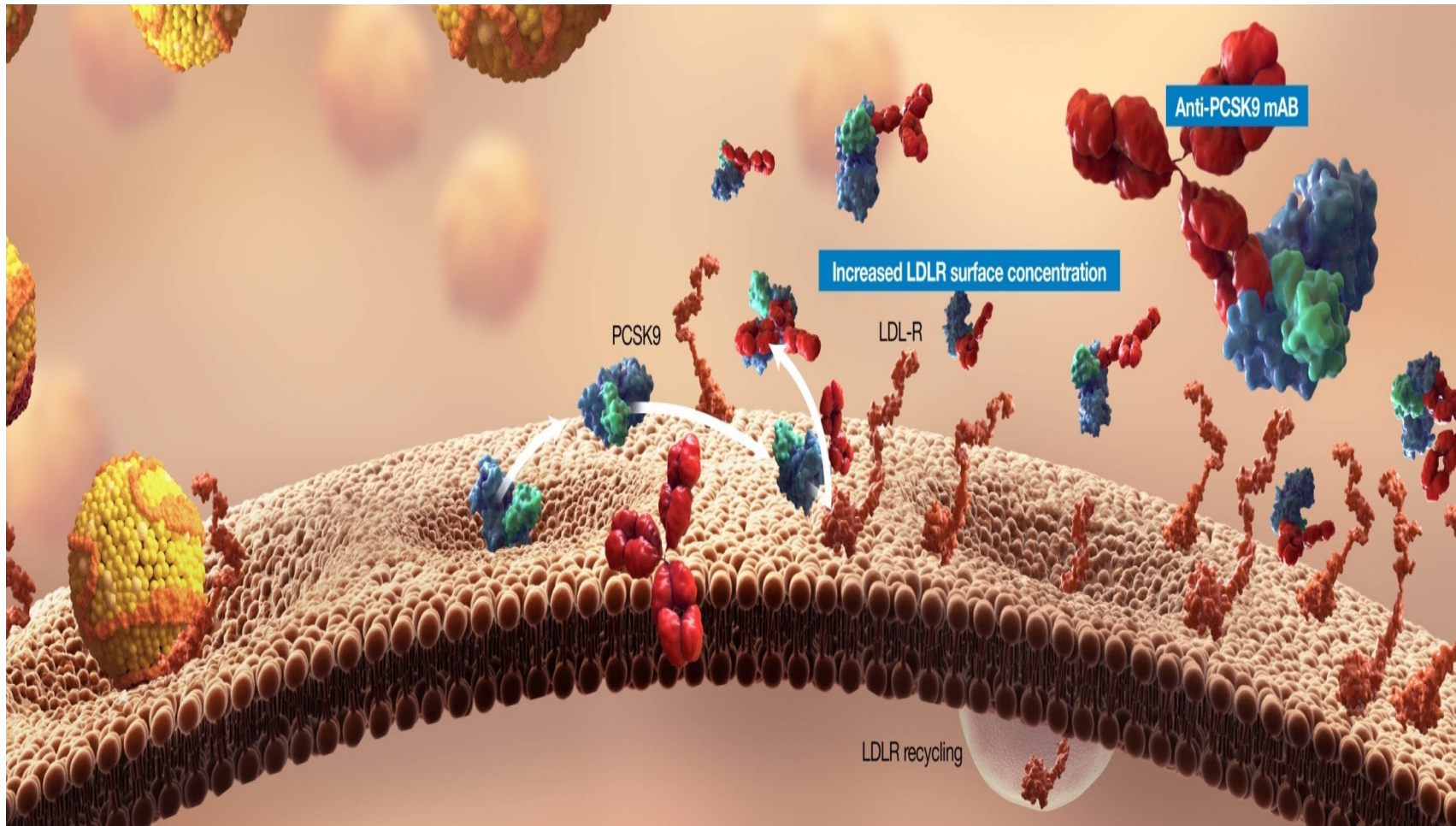
PCSK9 = proprotein convertase subtilisin-like/kexin type 9; LDLR = low-density lipoprotein receptor.

1. Horton JD, et al. *J Lipid Res.* 2009;50(suppl):S172-S177.

2. Zhang DW, et al. *J Biol Chem.* 2007;282:18602-18612.

3. Qian YW, et al. *J Lipid Res.* 2007;48:1488-1498.

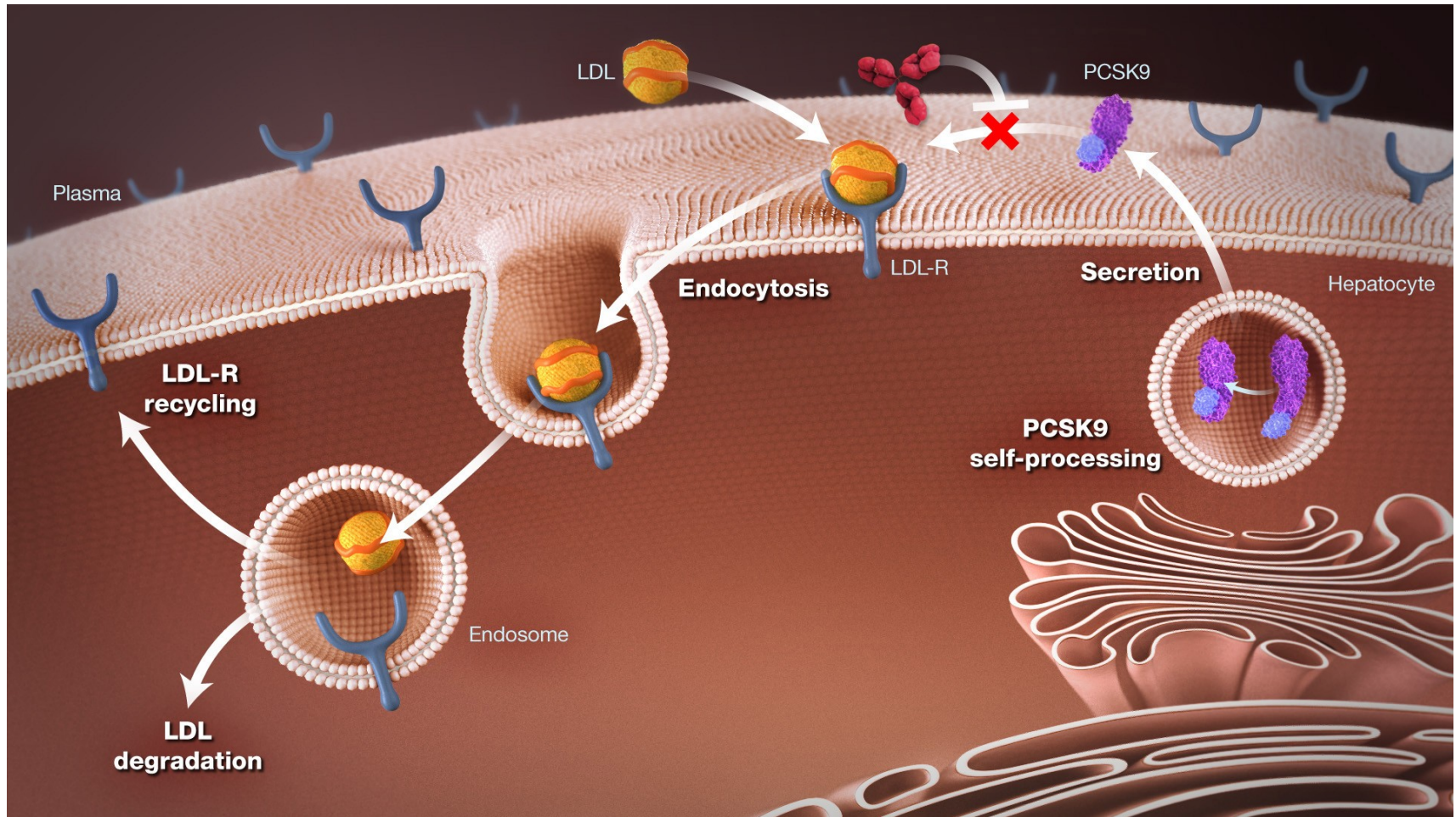
Инхибирането на PCSK9/LDLR свързването може да понижи нивата на LDLc¹



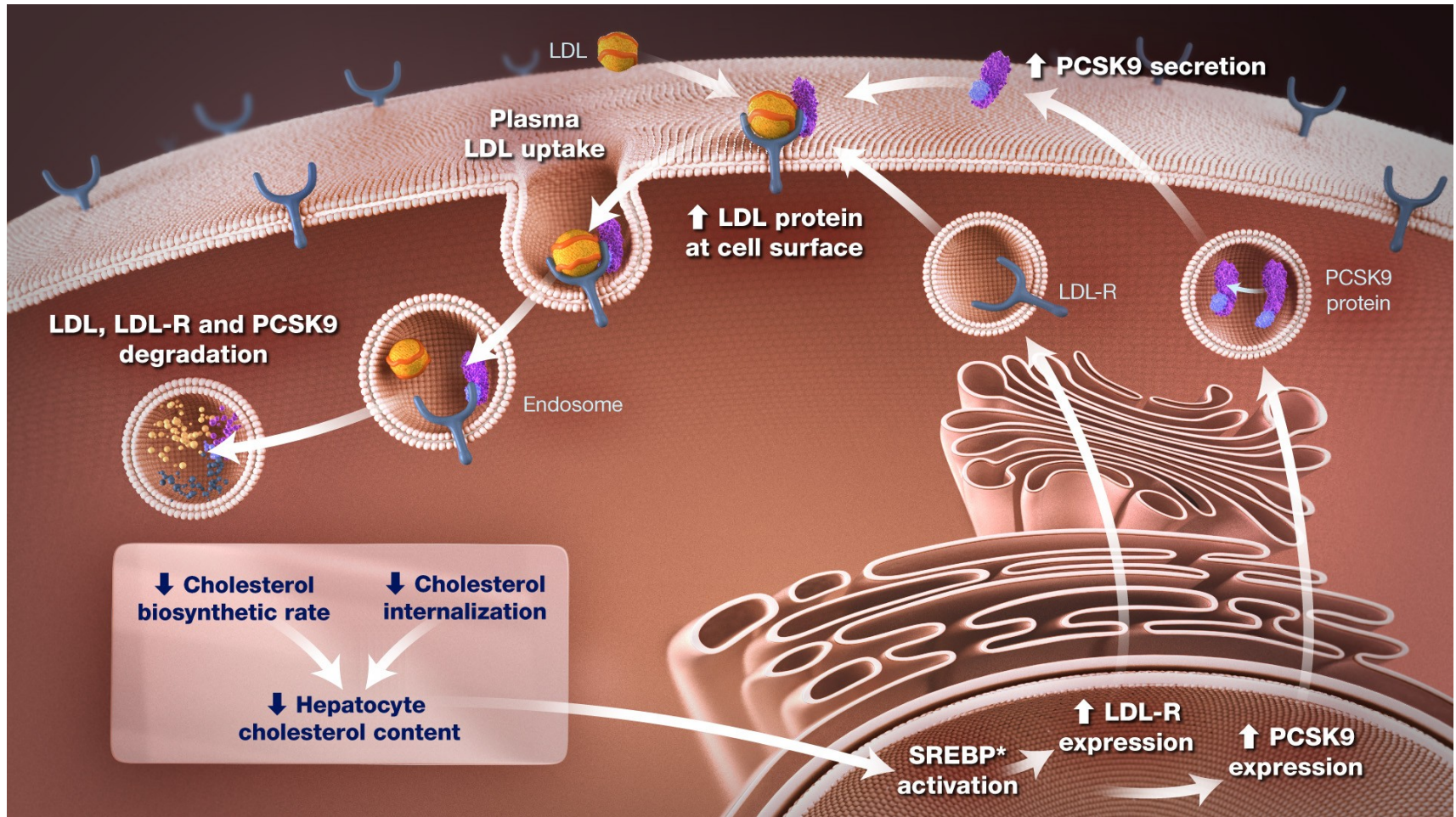
mAb = monoclonal antibody

1.Chan JC, et al. *Proc Natl Acad Sci U S A*. 2009;106:9820-9825.

Анти-PCSK9 Моноклонални антитела (mABs) блокират PCSK9/LDL-R взаимодействие и могат да намалят LDL-С нива



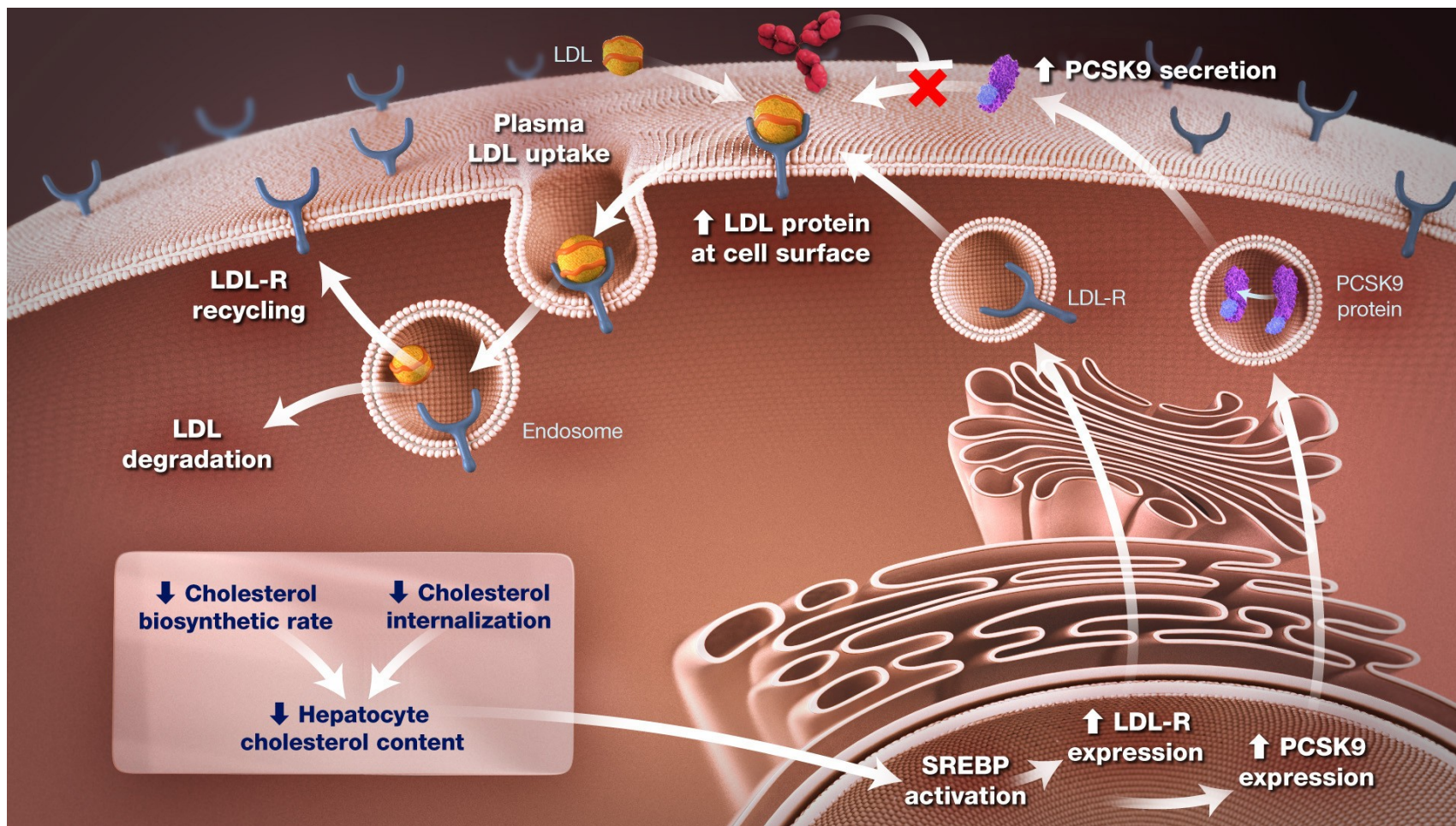
LDL-R и PCSK9 експресијата се засилва, когато нивата на интрацелуларниот холестерол се ниски



*[SREBP] = sterol regulatory element-binding protein

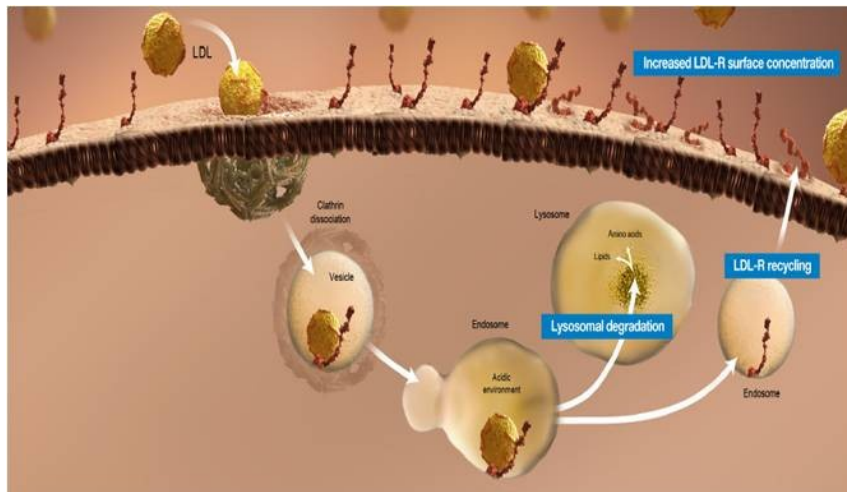
1. Goldstein JL, Brown MS. *Arterioscler Thromb Vasc Biol.* 2009;29:431-438.
2. Dubuc G, Chamberland A, Wassef H, et al. *Arterioscler Thromb Vasc Biol.* 2004;24:1454-1459.

Анти-PCSK9 mAbs може да намали LDL-C нива при тези условия



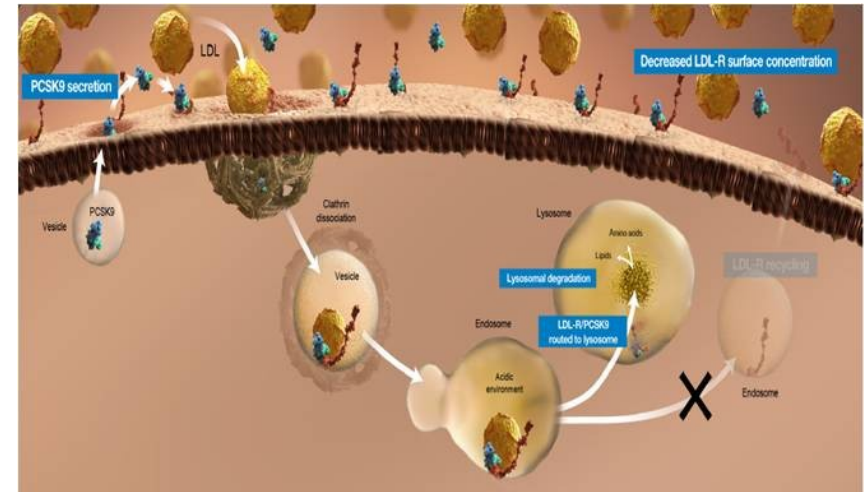
PCSK9 е нов регулатор на хепаталната експресия на LDL R

Липса на PCSK9



- Повече LDL-R
- Ниски плазмени нива на LDL-C

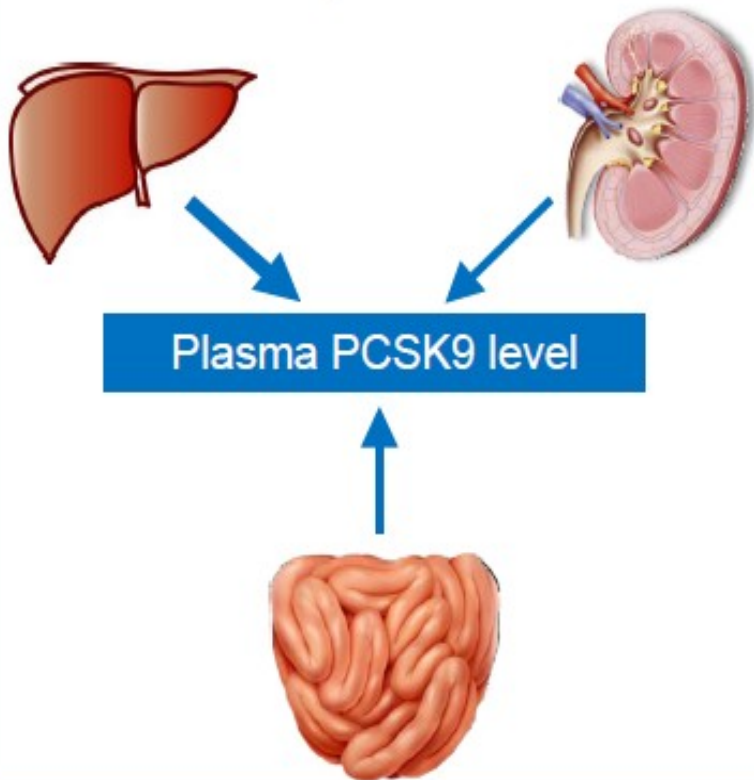
Наличие на PCSK9



- По-малко LDL-R
- Високи плазмени нива на LDL-C

Синтеза на PCSK9

PCSK9 is produced primarily by the liver, kidney, and intestines¹



Upregulates PCSK9

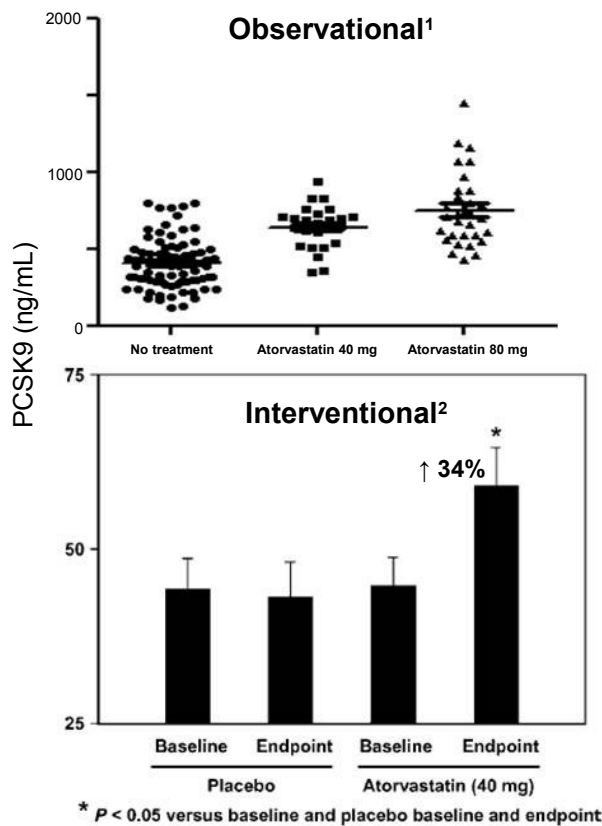
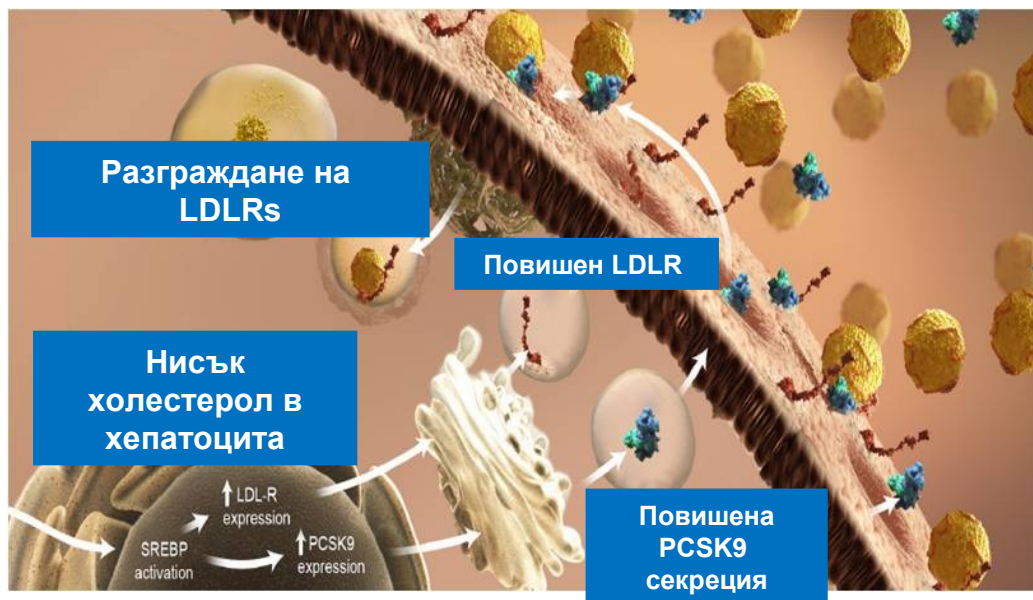
- Cholesterol depletion^{2,3}
- Cholestyramine²
- Sterol regulatory element-binding protein 2^{1,3,4}
- Statins^{3,4}

Downregulates PCSK9

- Dietary and cellular cholesterol⁴
- Long-term fasting¹
- Bile acids^{3,4}

Намаляването на хепаталния холестерол води до повишаване на LDL-R експресия и плазмената PCSK9

LDL-R и PCSK9 се повишават, когато има много ниски нива на вътреклетъчния холестерол



¹ Amgen, data on file.

² Careskey HE, Davis RA, et al. *J Lipid Res.* 2008;49:394–398

Lost-of-Function мутации

PCSK9 Genotype	Mutation Type	Biochemical Phenotype	Clinical Phenotype
R46L	Missense Polymorphism	No effect on processing or secretion ¹	11%–16% reduction in LDL-C ⁵ ; 30% reduction in IHD ⁵ ; reduced risk of early onset MI ⁶ ; 47% reduction of CHD ¹
G106R	Missense	Defective protein that is not secreted ¹	Reduced LDL-C ¹
Y142X	Nonsense	Disrupted protein synthesis resulting in no detectable protein ³	40% reduction in LDL-C; 88% reduction in CHD ^{1,2}
Q152H	Missense	Defective autocatalytic cleavage and secretion ⁴	48% decrease in LDL-C; 79% decrease in plasma PCSK9 ⁴
L253F	Missense	Poorly cleaved and secreted ¹	30% reduction in LDL-C ^{2,3} ; Reduced risk of CHD ³
A443T	Missense Polymorphism	Normally cleaved and secreted; higher susceptibility to cleavage ¹	Modest (2%) reduction in LDL-C ⁷
Q554E	Missense	Poorly cleaved and secreted ¹	Reduced LDL-C ⁸
C679X	Nonsense	Disrupted protein folding; impaired protein secretion ^{1,2}	40% reduction in LDL-C; 88% reduction in CHD ^{1,2}

Please refer to Lopez et al. (2008) and Abifadel et al. (2009) for comprehensive lists of PCSK9 mutations and variants.



Мутации водещи до загуба на функция на човешки PCSK9 са свързани с ниски нива на LDL-C

PCSK9 вариант	Популация	LDL-C	КАБ
R46L	ARIC, DHS	↓ 15% ¹	↓ 47% ¹
Y142X or C679X	ARIC, DHS	↓ 28-40% ^{1,2}	↓ 88% ¹
R46L	CGPS	↓ 11% ³	↓ 46% ³

- Открити в 1% до 3% от популацията¹
- Свързани със
 - По-нисък LDL-C¹
 - По-ниска честота на КАБ¹
- Инхибиране на LDL-R / PCSK9 взаимодействието може да намали плазмените нива на LDL-C ⁴

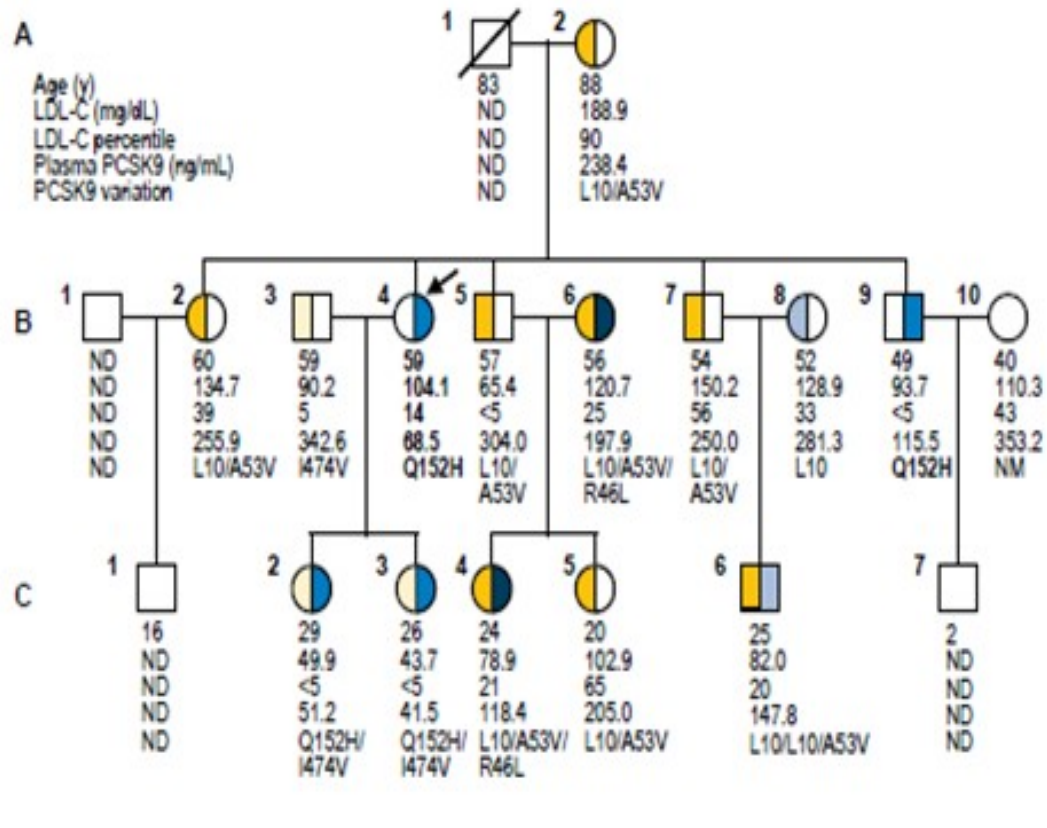
1. Cohen JC, Boerwinkle E, Mosley TH, Hobbs HH., *N Engl J Med.* 2006; 354:1264-1272.

2. Cohen J, Pertsemlidis A, Kotowski IK, et al., *Nat Genet.* 2005, 37:161-165.

3. Benn M, Nordestgaard BG, Grande P, Schnohr P, Tybjaerg-Hansen A. *J. Am. Coll. Cardiol.* 2010;55:2833-2842.

4. Steinberg D, Witztum JL. *Proc Natl Acad Sci U S A.* 2009;106:9546-9547.

Френско-Канадско семейство с LOF мутация в синтеза на PCSK9



- PCSK9^{Q152H} associated with a 79% decrease in plasma PCSK9 and 48% decreased LDL-C level in heterozygotes compared to unrelated noncarriers (n = 210)

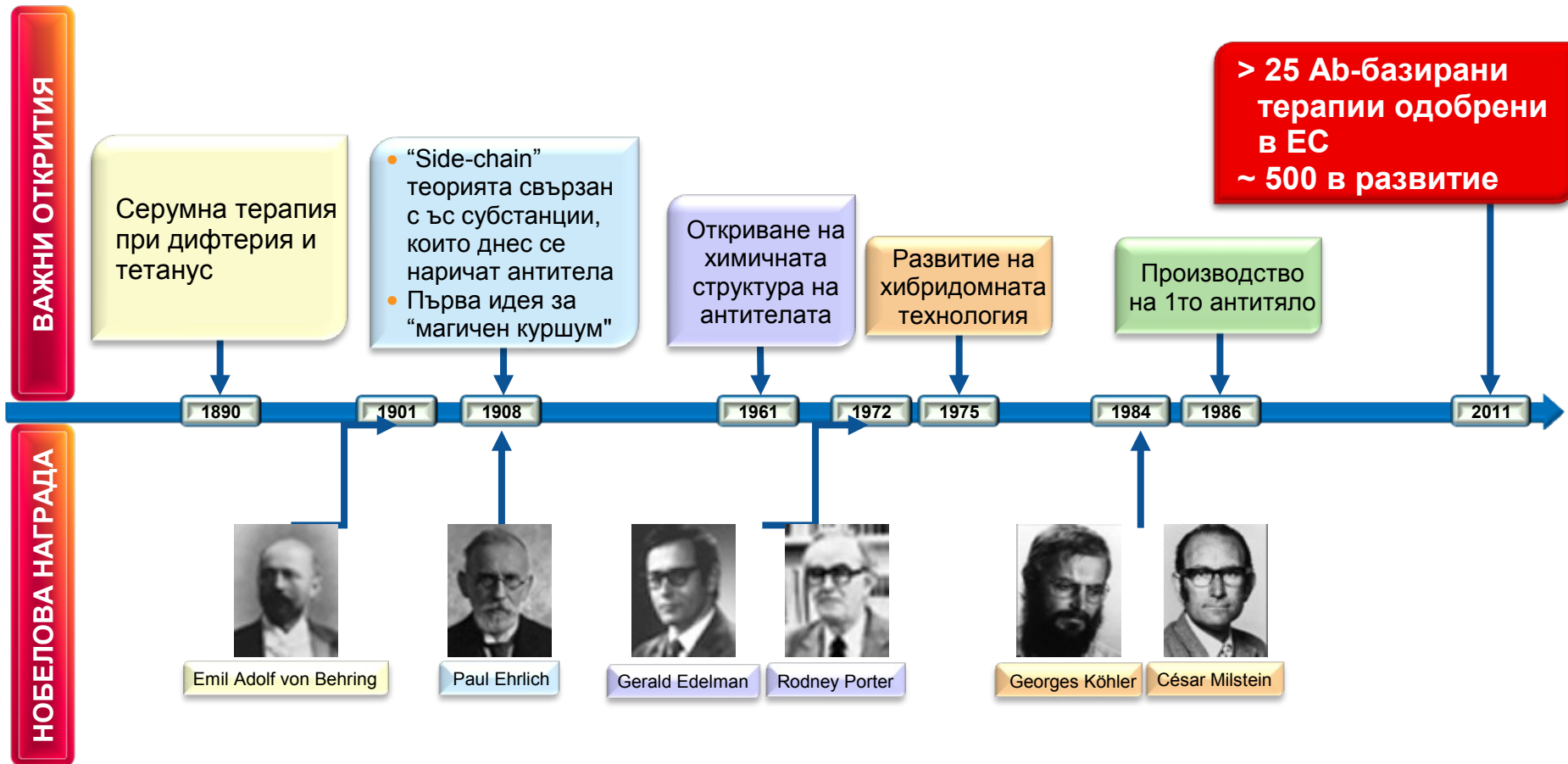
Gain-of-Function мутации

PCSK9 Genotype	Mutation Type	Biochemical Phenotype	Clinical Phenotype
S127R	Missense	5x higher affinity for LDL-R; decreased LDL-R expression and activity; may interfere with trafficking of LDL-R to the cell surface ^{1,2}	Cholesterol levels in 90th percentile; tendon xanthomas, CHD, early MI, and stroke ³
D129G	Missense	Leads to decreased LDL-R expression and activity ¹	Elevated LDL-C, identified in family with strong history of CV disease ²
F216L	Missense	Loss of PCSK9 activation; increased LDL-R degradation; may prolong PCSK9 half-life, causing higher circulating PCSK9 ^{2,3}	Premature CHD; Early MI ³
R218S	Missense	Normal processing and secretion but loss of PCSK9 enzymatic activity ¹	Tendon xanthomas, arcus corneae ⁴
D374Y	Missense	10–25x higher affinity for LDL-R; decreased LDL-R recycling and increased degradation ^{1,5}	Tendon xanthomas; premature atherosclerosis ⁴

Please refer to Lopez et al. (2008) and Abifadel et al. (2009) for comprehensive lists of PCSK9 mutations and variants.



Антитяло-базирано лечение: Важни открития



1. AGN. *Can Med Assoc J.* 1931;25:206.

2. Nobel Media AG. The Nobel Prize in Physiology or Medicine 1901. Available at: www.nobelprize.org. Accessed November 7, 2011.

3. The Nobel Prize in Physiology or Medicine 1908—speed read. Available at: www.nobelprize.org. November 7, 2011.

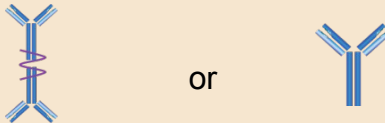




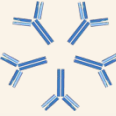
4. Zhou H, et al. *Annu Rev Pharmacol Toxicol.* 2011;51:359-372.

5. Edelman GM, et al. *Proc Natl Acad Sci U S A.* 1961;47:1751-1758.

6. The Nobel Prize in Physiology or Medicine 1972. Available at: www.nobelprize.org. Accessed February 1, 2012.

7. Beck A, et al. *Nat Rev Immunol.* 2010;10:345-352.

Класове имуноглобулини

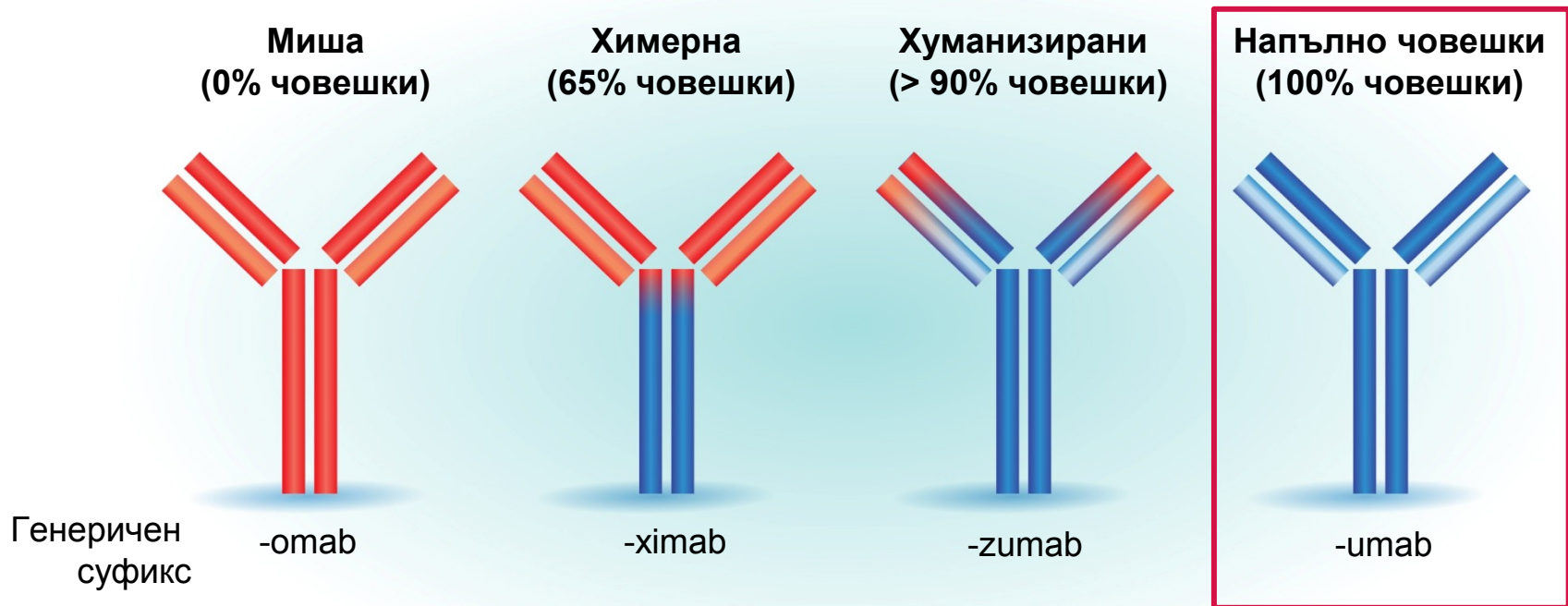
Имуноглобулин (Ig) Клас	Тежка верига	Диаграма	Разпределение
IgA	α	 or 	Външна секреция
IgD	δ		В-склетъчен повърхностен рецептор
IgE	ϵ		Важна роля при хиперсензитивност или алергични реакции
IgG*	γ		Главно Ab в серума Най-стабилно
IgM	μ		Първо Ab секретирано при първичен отговор

Ab изотипове

IgG1
IgG2
IgG3
IgG4

*IgG се използва най-често като структурна основа за терапевтичните Abs

Напълно човешките Abs имат намалена имуногенност



1. Weiner LM. *J Immunother.* 2006;29:1-9.
2. Yang XD, et al. *Crit Rev Oncol Hematol.* 2001;38:17-23.
3. Lonberg N. *Nat Biotechnol.* 2005;23:1117-1125.
4. Gerber DE. *Am Fam Physician.* 2008;77:311-319.

Амджен в сърдечно-съдовата област

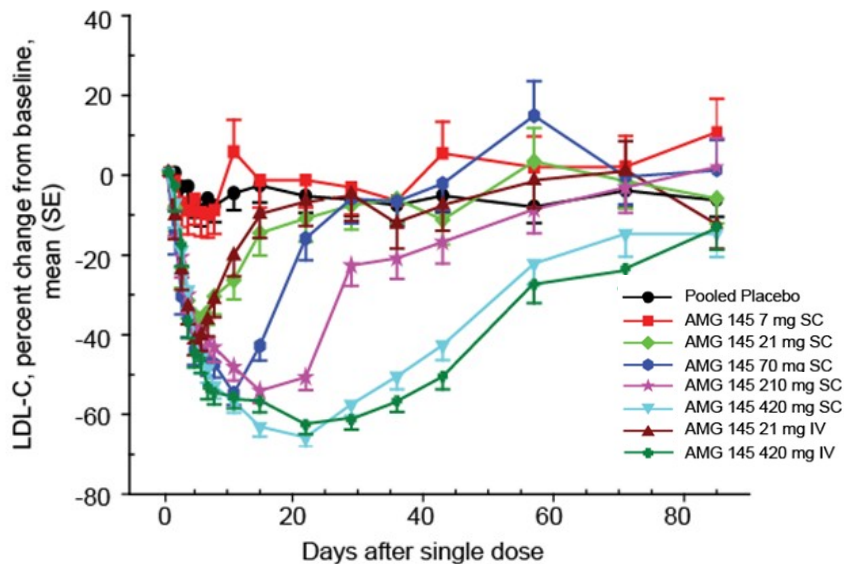
- ▶ През последните няколко години, Амджен направи ключови усилия за изясняване на ролята на PCSK9 в холестероловия метаболизъм³⁻⁵
- ▶ Амджен допринесе със разширен научен опит във откриването и разработването на антицяло лечението в сърдечно-съдовата област³⁻⁵

2003	2004	2007	2009	2010
Натрупването на функционални мутации в proprotein convertase subtilisin/kexin type 9 (PCSK9) свързани с автозомно-доминантна хиперхолестеролемия ¹	Свръхекспресията на PCSK9 при мишки води до LDL рецепторен блок фенотип ²	Амджен разкриват кристалната структура на PCSK9 ³  <small>Reprinted from Structure, vol 15, Piper DE, et al. The crystal structure of PCSK9: a regulator of plasma LDL-cholesterol, pp545-552, Copyright (2007), with permission from Elsevier.</small>	Докладва се, че Ab срещу PCSK9 може да намали холестерола при мишки и примати ⁴ Първи пример на PCSK9 неутрализиращо Ab, което намалява LDL-C in vivo	mAbs срещу PCSK9 влиза във фаза на тестване при хора ⁵

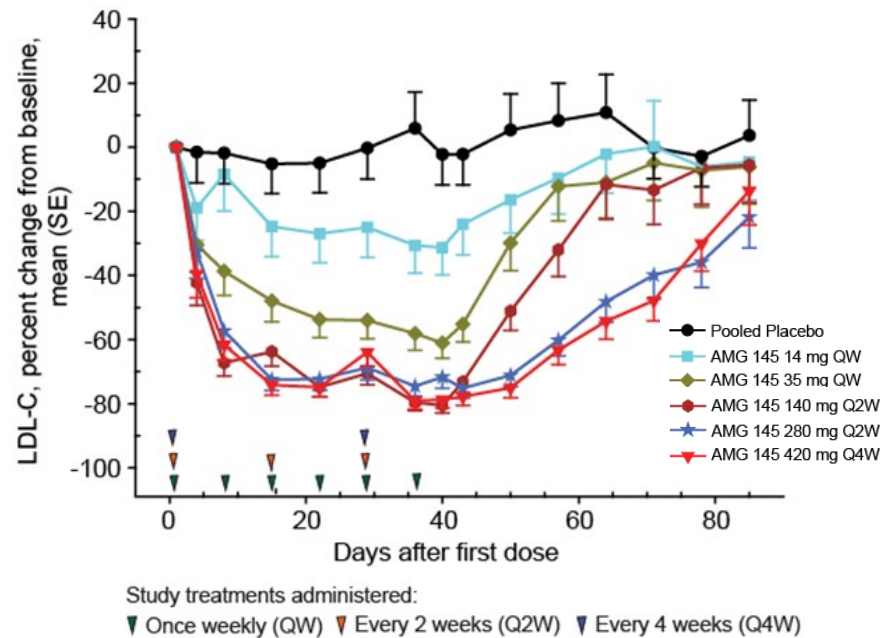
1. Abifadel M, et al. *Nat Genet.* 2003;34:154-156.
2. Maxwell KN, et al. *Proc Natl Acad Sci U S A.* 2004;101:7100-7105.
3. Piper DE, et al. *Structure.* 2007;15:545-552.
4. Chan JCY, et al. *Proc Natl Acad Sci U S A.* 2009;106:9820-9825.
5. Dias C, et al. *Circulation.* 2011;124:Abstract 10701.

AMG145: фаза 1а-в отчитане на първичната ефикасност

Phase 1a: Еднократна доза, Здрави доброволци



Phase 1b: дозови режими, пациенти на статини



- Мах 55% до 67% LDL-C редуция при еднократна ≥ 70 mg доза
- По-високи дози удължават ефекта

- Мах 63% до 75% LDL-C редуция при няколкократни дози ≥ 140 mg

SC = subcutaneous; IV = intravenous; QW = once weekly; Q2W = once every 2 weeks; QM = once a month

1. Das CS, et al. *J Am College Cardiol.* 2012;60:1888-1898.

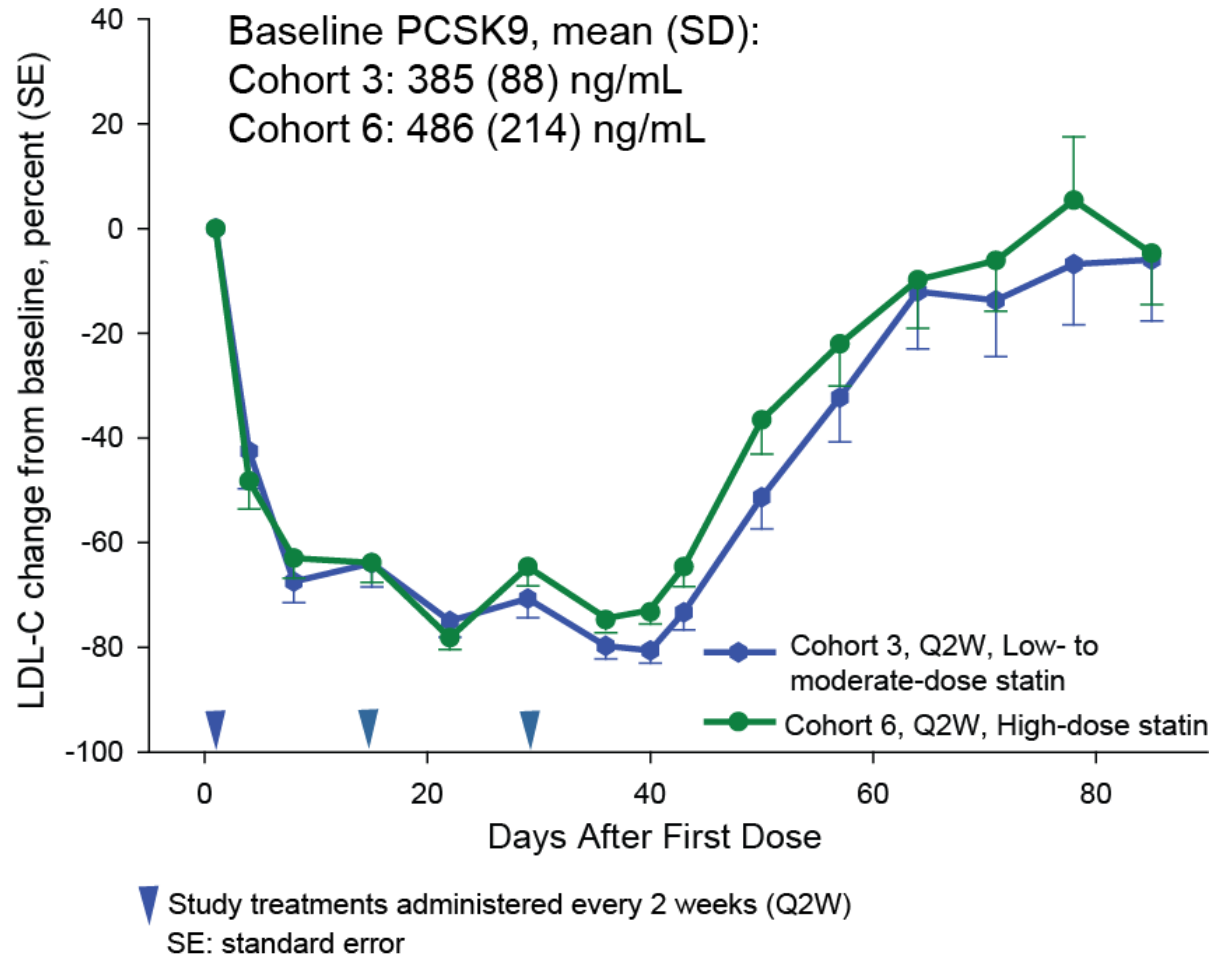
Индивиди на високи дози Atorvastatin или Rosuvastatin имат сравнимо намаление на LDL-C при ниски до средни дозови режими

Средно намаление на LDL-C в края на дозирания интервал:

- ▶ 63% vs плацебо ($p < 0.001$)
- ▶ 65% от изходните

Сравнение на индивиди на ниски до средни дози статини в края на дозирания интервал:

- ▶ 73% vs плацебо ($p < 0.001$)
- ▶ 73% от изходните



AMG 145 намалява ApoB Up to 59% vs плацебо

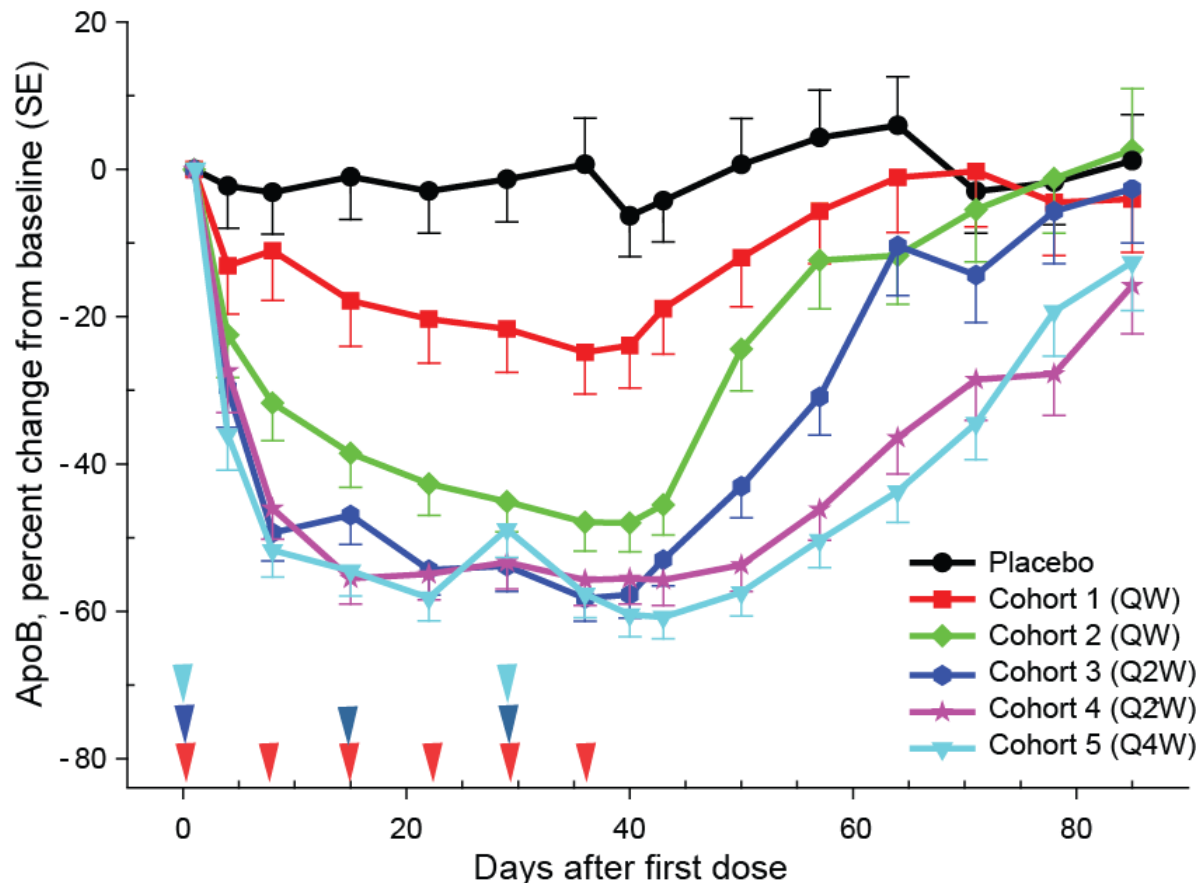
Средна редукция на ApoB в края на дозирания интервал:

- ▶ До 54% vs плацебо ($p < 0.001$)
- ▶ До 56% от изходните

Максимално намаление:

- ▶ 59% vs плацебо ($p < 0.001$)
- ▶ 61% от изходните

Сравними резултати във високодозовата кохорта



Study treatments administered:

- ▶ Once weekly (QW)
- ▶ Every 2 weeks (Q2W)
- ▶ Every 4 weeks (Q4W)

SE: standard error

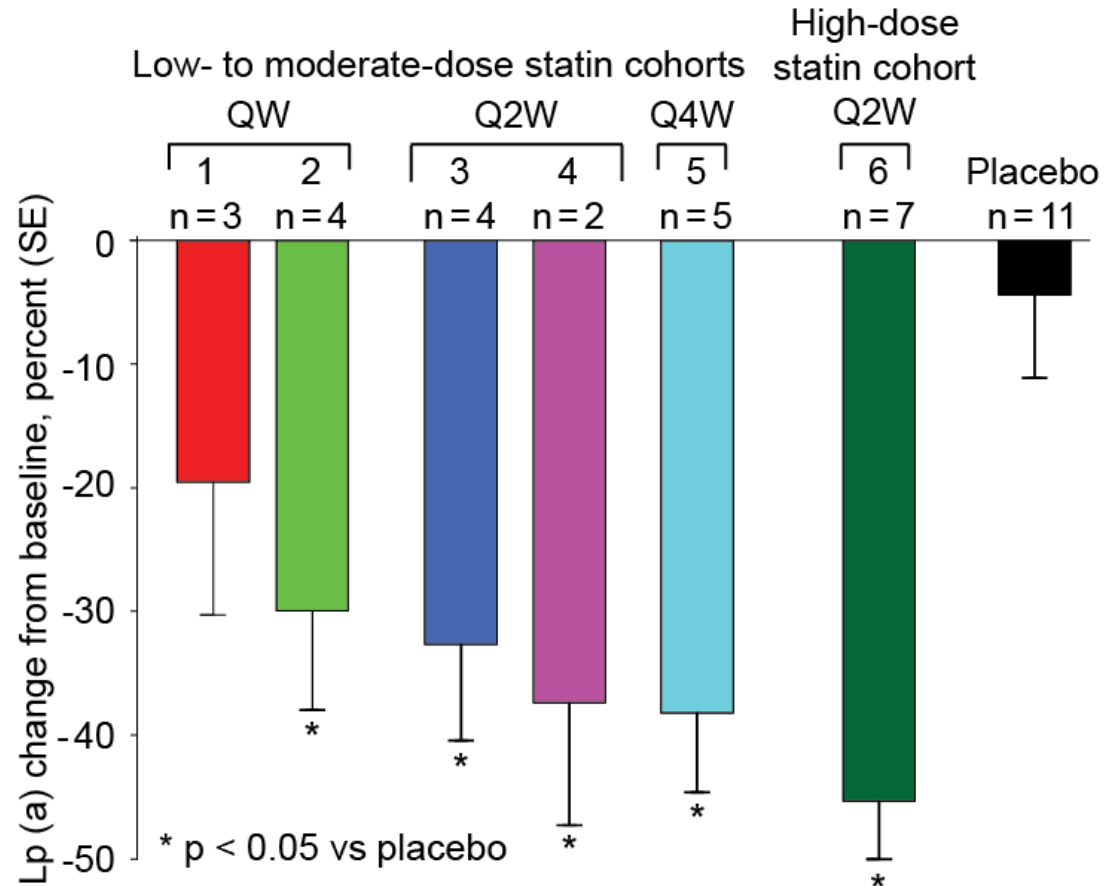
AMG 145 намалява Lp(a) до 43% vs плацебо

Средна редукция на Lp (a) в края на дозирания интервал:

▶ До 43% vs плацебо (p < 0.001)

▶ До 45% от изходните

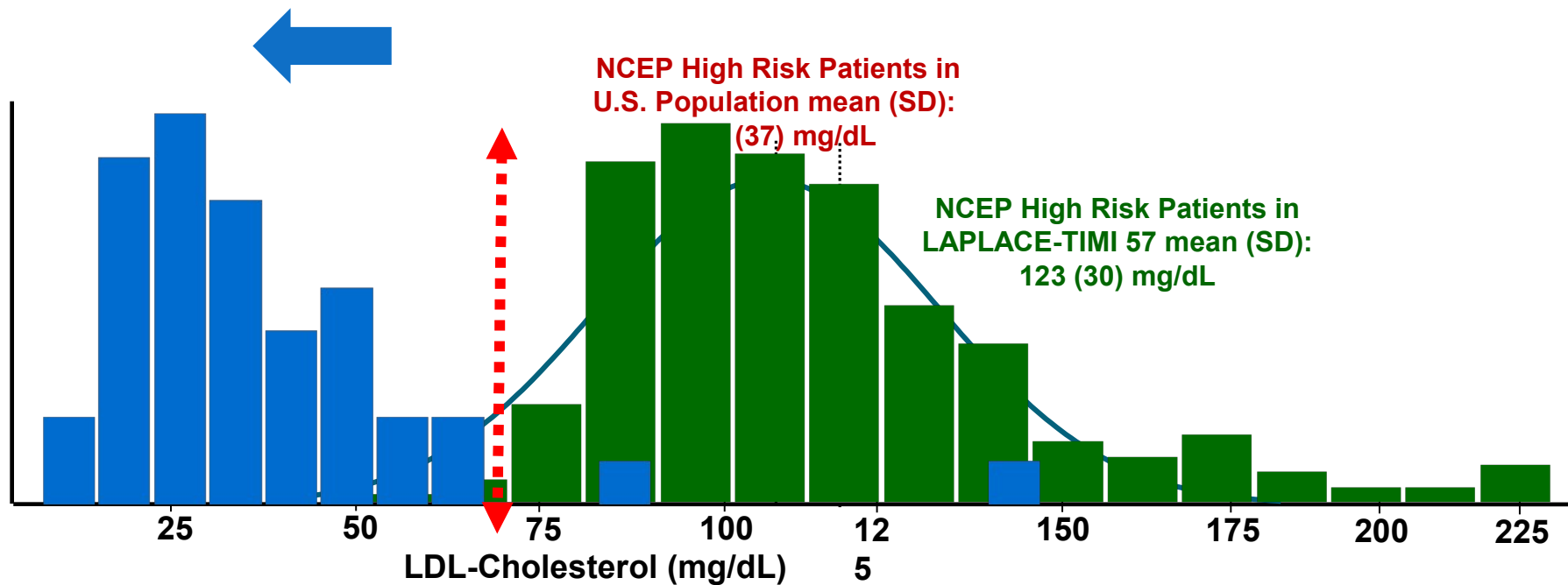
Lp(a) measured using an immunoturbidimetric assay by PPD, Global Central Lab, Highland Heights, KY, USA)



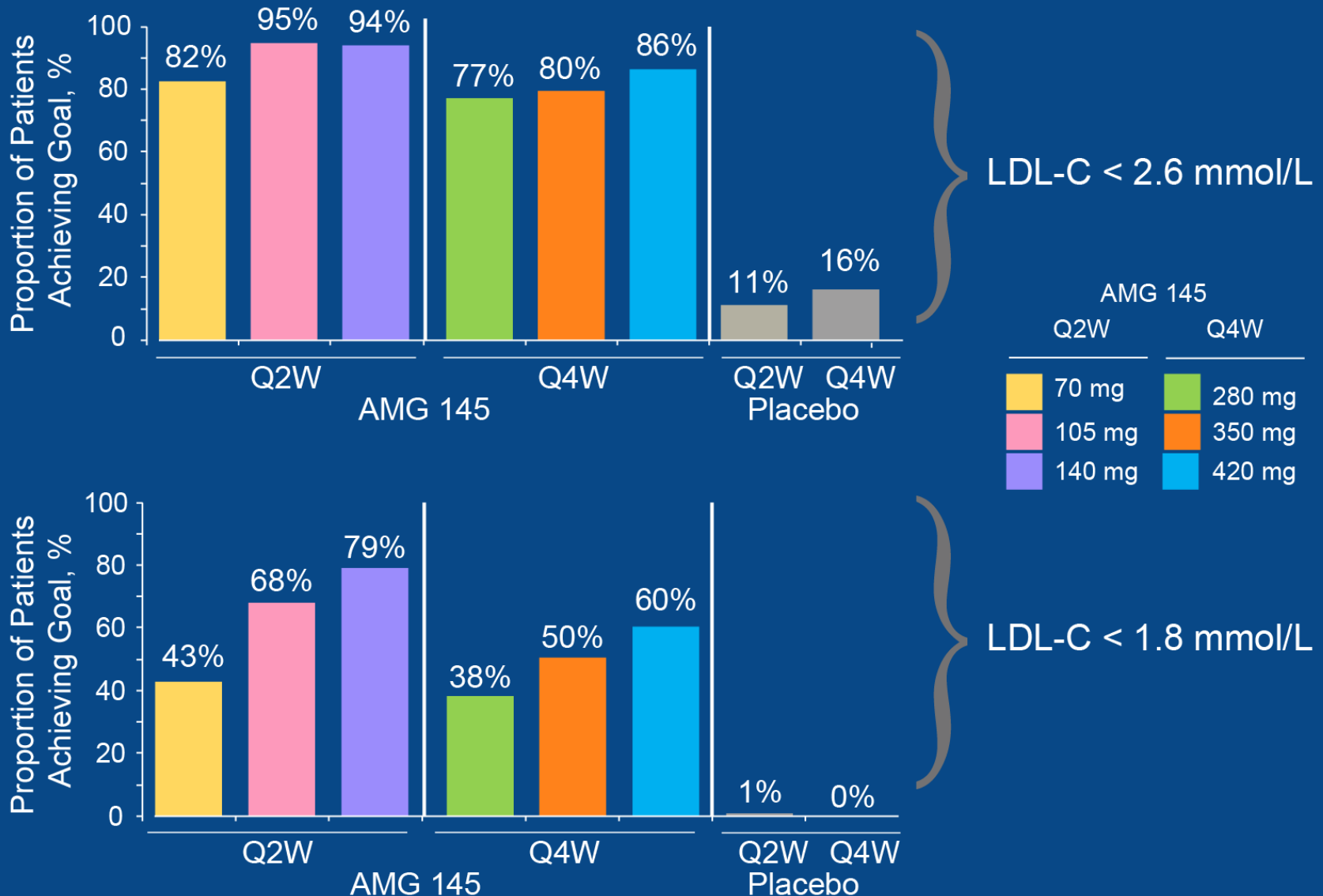
Outliers or subjects with baseline or screening values below the lower limit of quantitation were excluded from the analysis.

SE: standard error; QW: once weekly; Q2W: every 2 weeks; Q4W: every 4 weeks

AMG 145 дава възможност високорисковите пациенти да достигнат LDL-C целеви нива



Процент пациенти достигащи LDL-C таргет



PROFICIO Pooled Safety Analysis: 4 Phase 2 Trials

AMG 145 Was Well Tolerated Across Patient Populations

Treatment (number of patients)		AMG 145 (n = 981)	Placebo (n = 333)
Adverse events (AEs), n (%)		57%	49%
Most common AEs, n (%)	Nasopharyngitis	8%	8%
	Upper respiratory tract infection	4%	3%
	Myalgias	3%	1%
	Headache	3%	3%
	Back pain	3%	2%
Treatment-related AEs, n (%)		12%	10%
Serious AEs, n (%)		2.0%	1.2%
AEs of interest, n (%)	Injection-site reactions	4%	3%
	Muscle-related AEs	6%	4%
	Creatine kinase >5x ULN	1%	1%
	ALT or AST > 3x ULN	0.4%	0.6%

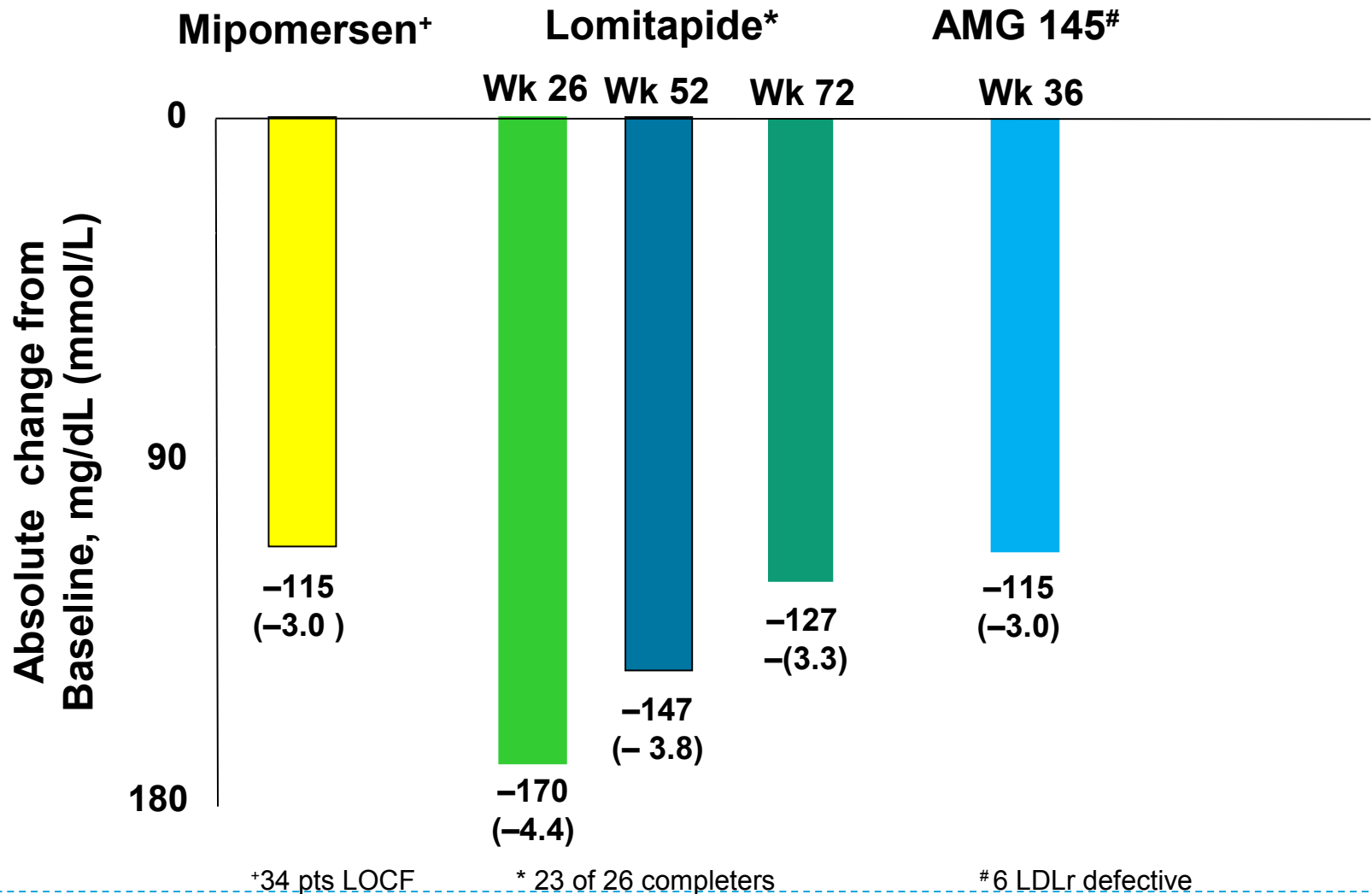
SAE rates were similar with no treatment-related SAEs in either group and no relation of AEs to dose/frequency was observed with AMG 145

Effect of AMG 145, a PCSK9 Monoclonal Antibody, in Homozygous Familial Hypercholesterolemia*

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Scott M. Wasserman, M.D., Feng Xu, M.S., Rob Scott, M.D.,
Frederick J. Raal, M.B., BCh, Ph.D.



Сравнение на абсолютната редукция на (mg/dL) LDL-C при пациенти с HoFH, Apo B Antisense¹, MTP inhibitor² and PCSK9 Inhibitor³



¹Raal et al *Lancet* 2010 375: 998–1006 ²Cuchel et al *Lancet* 2013 381:40-46

³Stein EA et al. *Circulation* 2013; in press

Декември 2013г.

Amgen today announced that the Phase 3 MENDEL-2 trial with evolocumab **met its co-primary endpoints: the percent reduction from baseline in LDL-C at week 12 and the mean percent reduction from baseline in LDL-C at weeks 10 and 12.** The mean percent reductions in LDL-C, or "bad" cholesterol, compared to placebo and ezetimibe were consistent with **results observed in the MENDEL Phase 2 study**

Amgen today announced that the Phase 3 DESCARTES study evaluating the long-term 52-week safety and efficacy of evolocumab for the treatment of high cholesterol **met its primary endpoint of percent reduction from baseline in LDL-C at week 52.** The mean percent reduction in LDL-C, or "bad" cholesterol, was consistent with the results observed in **the 52-week analysis of the Phase 2 OSLER study.**





THANK

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Спасибо

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Merci

Multumesc

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Добре дош

Deküü

Takk

Спасибо

Дзякуй

Дарам

udvoz

