I nuovi farmaci ipolipidemizzanti: gli inibitori della proteina PCSK9

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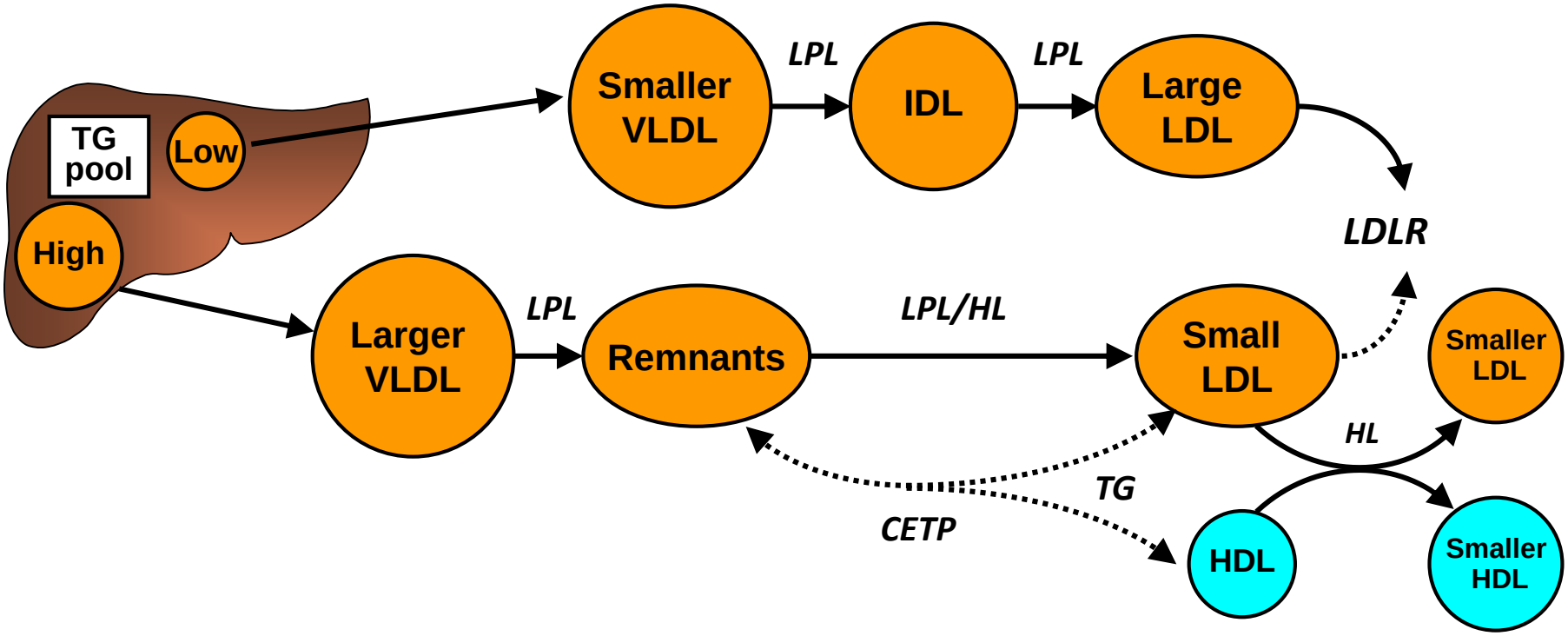
Disclosure from Prof Davide Lauro

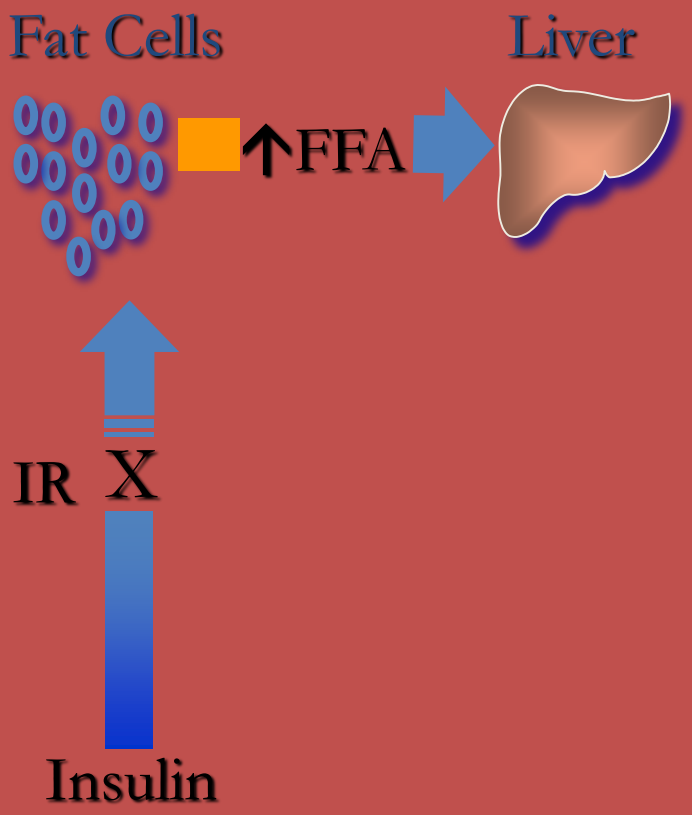
- BI/Lilly
- Takeda
- MSD
- Sanofi
- Novonordisk

Pathophysiology of Dyslipidemia in Type 2 Diabetes

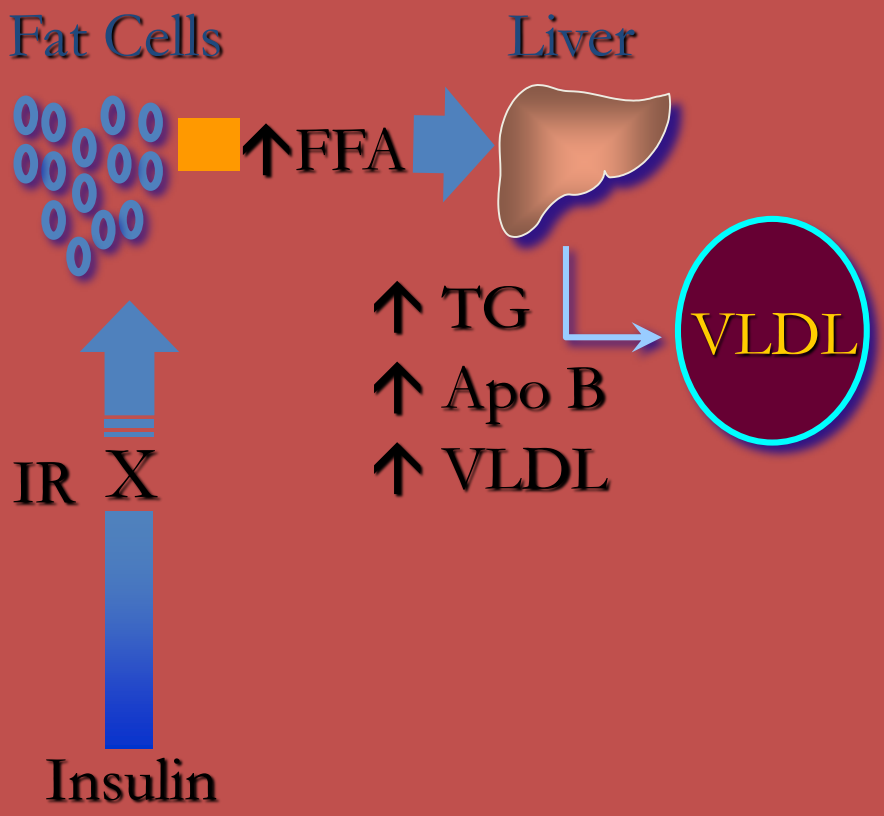


Krauss RM. *Diabetes Care*. 2004;27:1496-1504.

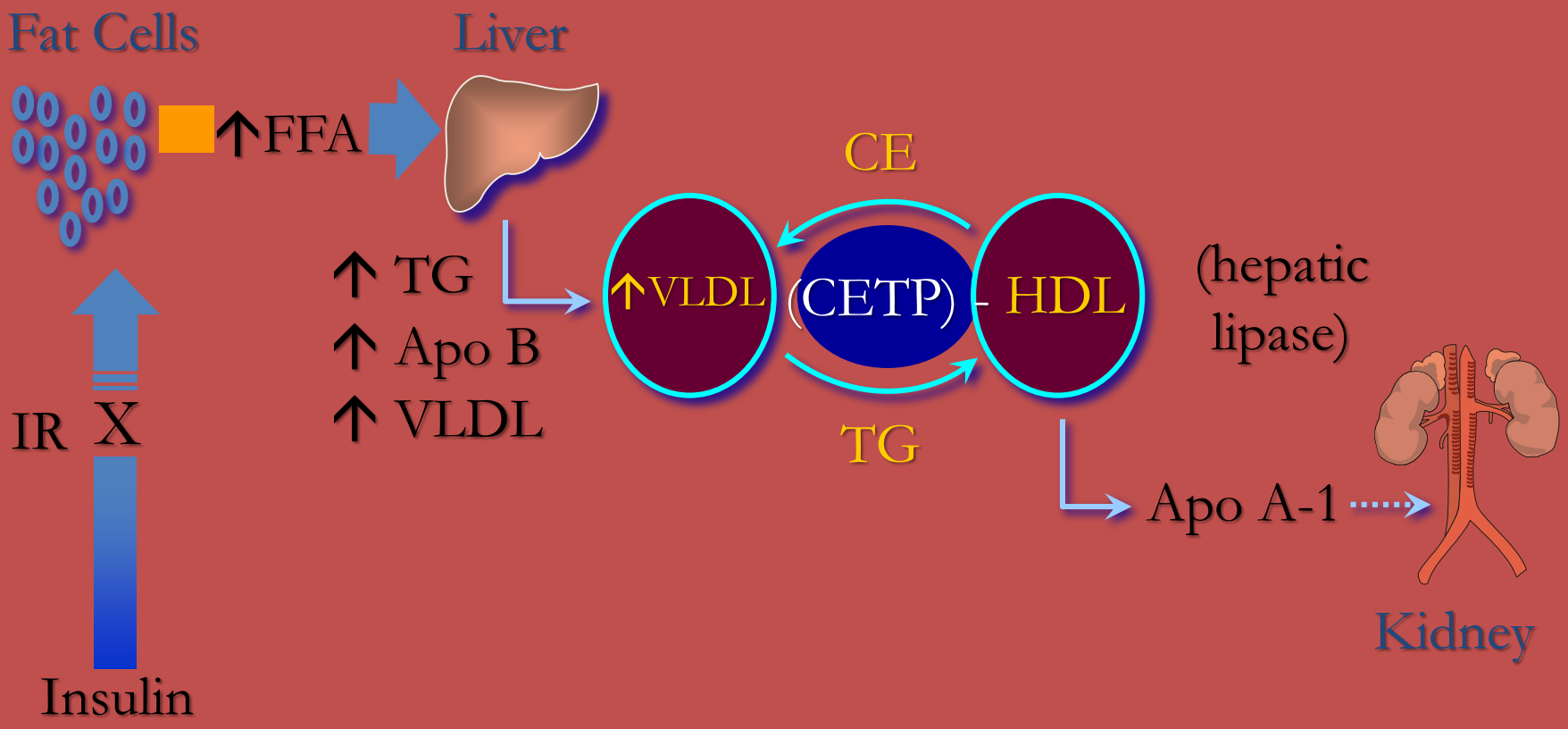
Mechanisms of DM Dyslipidemia



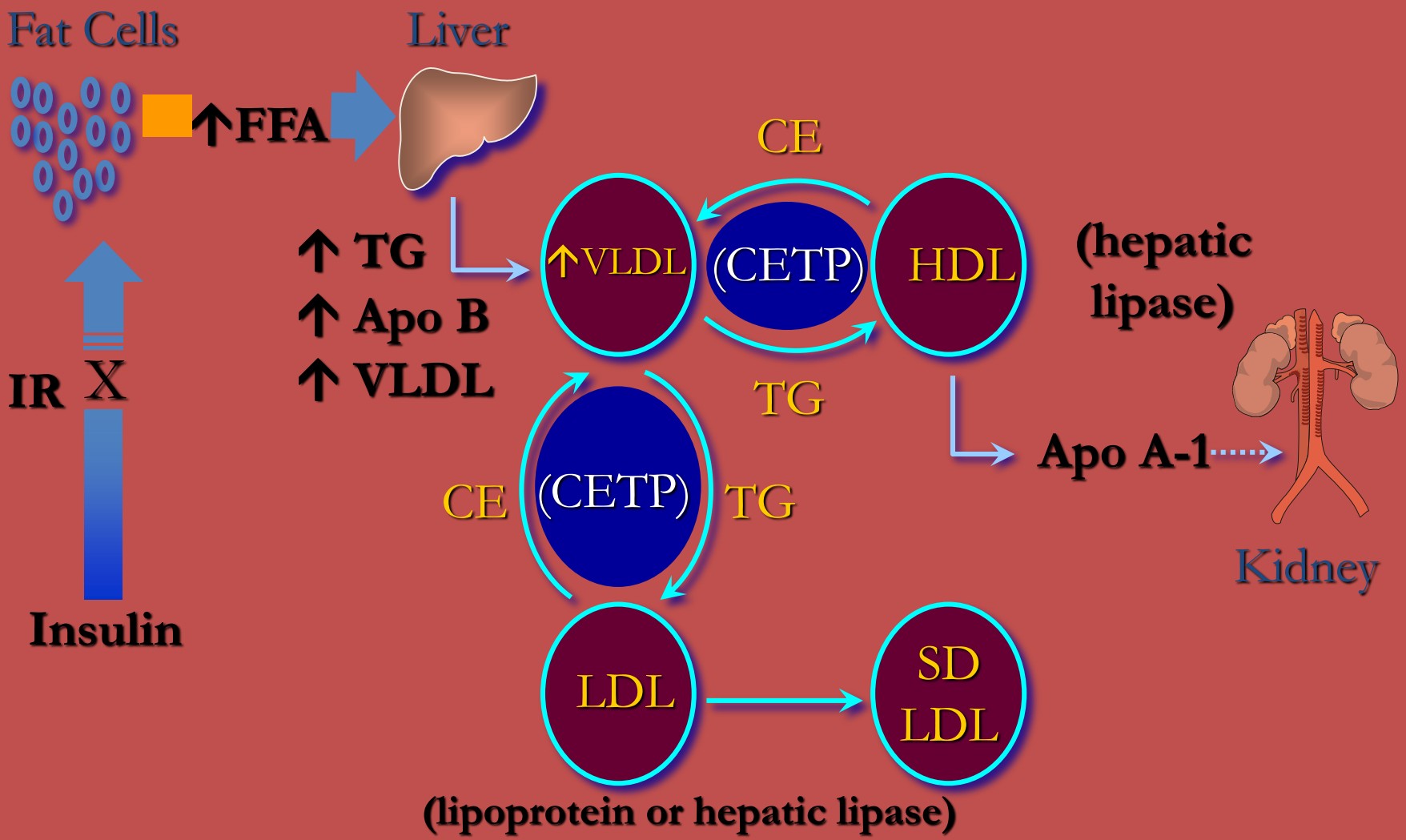
Mechanisms of DM Dyslipidemia



Mechanisms of DM Dyslipidemia



Mechanisms of DM Dyslipidemia

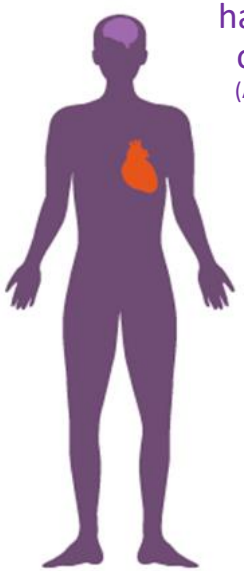


Diabetes: area of high unmet need

In studies of middle-aged people with diabetes living in high- and middle-income countries:

Up to **41%** had a history of **CVD**

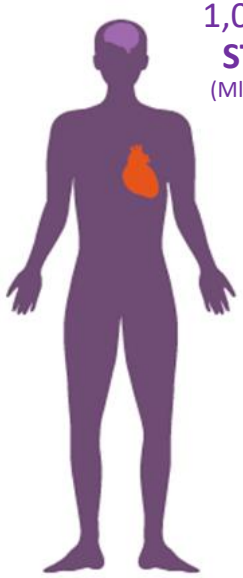
includes stroke, coronary artery disease and peripheral artery disease
(van Hateren, 2009)



Up to **10%** had a history of **STROKE**
(Alwakeel, 2008)

Up to **14%** had a history of **HEART ATTACK**
(Alwakeel, 2008)

Up to **27** per 1,000 died from **CVD** each year
(Miot, 2012)



Up to **9** per 1,000 died **STROKE**
(Mlacak, 1999)

Up to **7** per 1,000 died from **CORONARY HEART DISEASE** each year
(Bidel, 2006)

Mean age of study population: 50 to 69 years

Major Atherosclerotic Cardiovascular Disease Risk Factors

Major risk factors	Additional risk factors	Nontraditional risk factors
Advancing age	Obesity, abdominal obesity	⇧ Lipoprotein (a)
⇧ Total serum cholesterol level	Family history of hyperlipidemia	⇧ Clotting factors
⇧ Non–HDL-C	⇧ Small, dense LDL-C	⇧ Inflammation markers
⇧ LDL-C	⇧ Apo B	(hsCRP; Lp-PLA_2)
Low HDL-C	⇧ LDL particle concentration	⇧ Homocysteine levels
Diabetes mellitus	Fasting/postprandial	Apo E4 isoform
Hypertension	hypertriglyceridemia	⇧ Uric acid
Stage 3 or 4 chronic kidney disease	PCOS	⇧ TG-rich remnants
Cigarette smoking	Dyslipidemic triad	
Family history of ASCVD		

Abbreviations: apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; hsCRP, highly sensitive C-reactive protein; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; Lp-PLA2, lipoprotein-associated phospholipase; PCOS, polycystic ovary syndrome.

AACE POSWC. *Endocr Pract*. 2005;11:126-134; ADA. Diabetes Care. 2017;40(Suppl 1):S1-S135; Brunzell JD, et al. *Diabetes Care*. 2008;31:811-822; Cromwell WC, et al. *J Clin Lipidol*. 2007;1:583-592; Einhorn D, et al. *Endocr Pract*. 2003;9:237-252; Grundy SM, et al. *Circulation.* 1998;97:1876-1887; Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice*. 2017;23(4):479-497.; Kastelein JJ, et al. *Circulation.* 2008;117:3002-3009; NCEP. NIH Publication No. 02-5215. September 2002; Neaton JD, et al. *Arch Intern Med*. 1992;152:1490-1500; NHLBI. NIH Publication No. 04-5230. August 2004; Stamler J, el al. *JAMA*. 1986;256:2823-2828; Weiner DE, et al. *J Am Soc Nephrol.* 2004;15(5):1307-1315; Yusuf S, et al. *Lancet.* 2004;364(9438):937-952.

ASCVD Risk Categories

- **Low risk:**
  - No risk factors
- **Moderate risk**:
  - 2 or fewer risk factors and a calculated 10-year risk of less than 10%
- **High risk:**
  - An ASCVD equivalent including diabetes or stage 3 or 4 CKD with no other risk factors, or individuals with 2 or more risk factors and a 10-year risk of 10%-20%
- **Very high risk**:
  - Established or recent hospitalization for ACS; coronary, carotid or peripheral vascular disease; diabetes or stage 3 or 4 CKD with 1 or more risk factors; a calculated 10-year risk greater than 20%; or HeFH
- **Extreme risk:**
  - Progressive ASCVD, including unstable angina that persists after achieving an LDL-C less than 70 mg/dL, or established clinical ASCVD with diabetes, stage 3 or 4 CKD, and/or HeFH, or in those with a history of premature ASCVD (<55 years of age for males or <65 years of age for females)
  - This category was added in this CPG based on clinical trial evidence and supported by meta-analyses that further lowering of LDL-C produces better outcomes in individuals with ACS. IMPROVE-IT demonstrated lower rates of cardiovascular events in those with ACS when LDL-C levels were lowered to 53 mg/dL combining ezetimibe with statins.

Abbreviations: ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CPG, clinical practice guideline; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial.

AACE/ACE CPG. 2017;epub ahead of print; Cannon, CP, et al. *N Engl J Med.* 2015;372(25):2387-239; Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice*. 2017;23(4):479-497.

ASCVD Risk Categories and LDL-C Treatment Goals

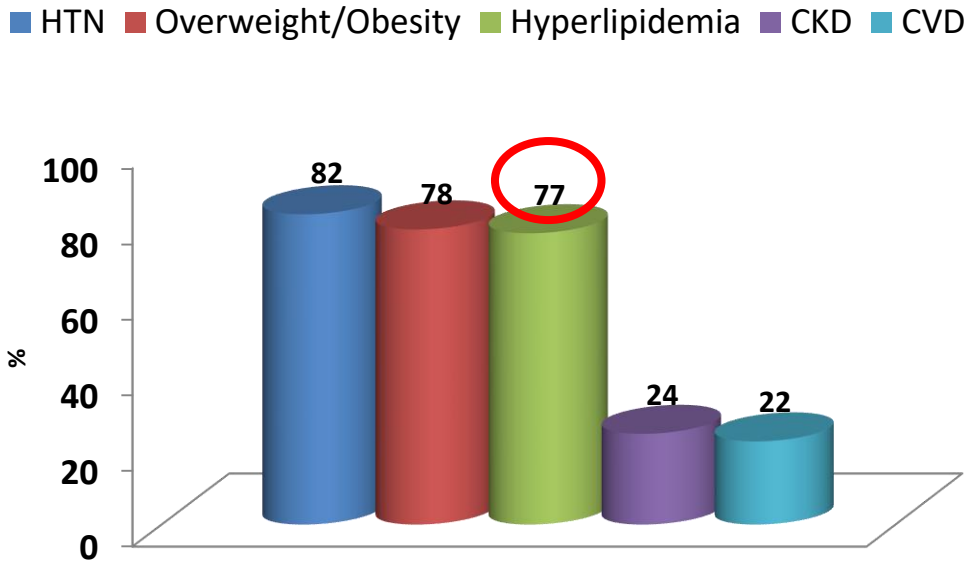
Risk category	Risk factors/10-year risk	Treatment goals		
		LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Apo B (mg/dL)
Extreme risk	– Progressive ASCVD including unstable angina in individuals after achieving an LDL-C <70 mg/dL – Established clinical cardiovascular disease in individuals with DM, stage 3 or 4 CKD, or HeFH – History of premature ASCVD (<55 male, <65 female)	<55	<80	<70
Very high risk	– Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20% – DM or stage 3 or 4 CKD with 1 or more risk factor(s) – HeFH	<70	<100	<80
High risk	– ≥2 risk factors and 10-year risk 10%-20% – DM or stage 3 or 4 CKD with no other risk factors	<100	<130	<90
Moderate risk	≤2 risk factors and 10-year risk <10%	<100	<130	<90
Low risk	0 risk factors	<130	<160	NR

Abbreviations: ACS, acute coronary syndrome; apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DM, diabetes mellitus; HeFH, heterozygous familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NR, not recommended.

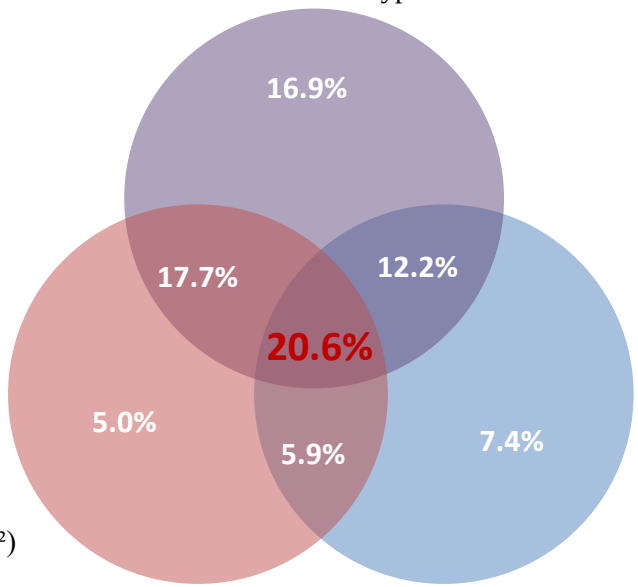
Barter PJ, et al. *J Intern Med*. 2006;259:247-258; Boekholdt SM, et al. *J Am Coll Cardiol*. 2014;64(5):485-494; Brunzell JD, et al. *Diabetes Care*. 2008;31:811-822; Cannon CP, et al. *N Engl J Med.* 2015;372(25):2387-2397; Grundy SM, et al. *Circulation.* 2004;110:227-239; Heart Protection Study Collaborative Group. *Lancet*. 2002;360:7-22; Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice*. 2017;23(4):479-497; Lloyd-Jones DM, et al. *Am J Cardiol*. 2004;94:20-24; McClelland RL, et al. *J Am Coll Cardiol*. 2015;66(15):1643-1653; NHLBI. NIH Publication No. 02-5215. 2002; Ridker PM, *J Am Coll Cardiol*. 2005;45:1644-1648; Ridker PM, et al. *JAMA*. 2007;297(6):611-619; Sever PS, et al. *Lancet*. 2003;361:1149-1158; Shepherd J, et al. *Lancet*. 2002;360:1623-1630; Smith SC Jr, et al. *Circulation*. 2006;113:2363-2372; Stevens RJ, et al. *Clin Sci*. 2001;101(6):671-679; Stone NJ. *Am J Med*. 1996;101:4A40S-48S; Weiner DE, et al. *J Am Soc Nephrol.* 2004;15(5):1307-1315.

DM associated with multiple comorbidities, that are also CV risk factors

Comorbidities and modifiable CV risk factors in DM



K. Iglay et al 2016 ; Current Medical Research and Opinion, 32:7, 1243-1252



Hypertension
(BP ≥ 140/90 mm Hg or taking antihypertensive medication)

Obesity
(BMI ≥ 30 kg/m²)

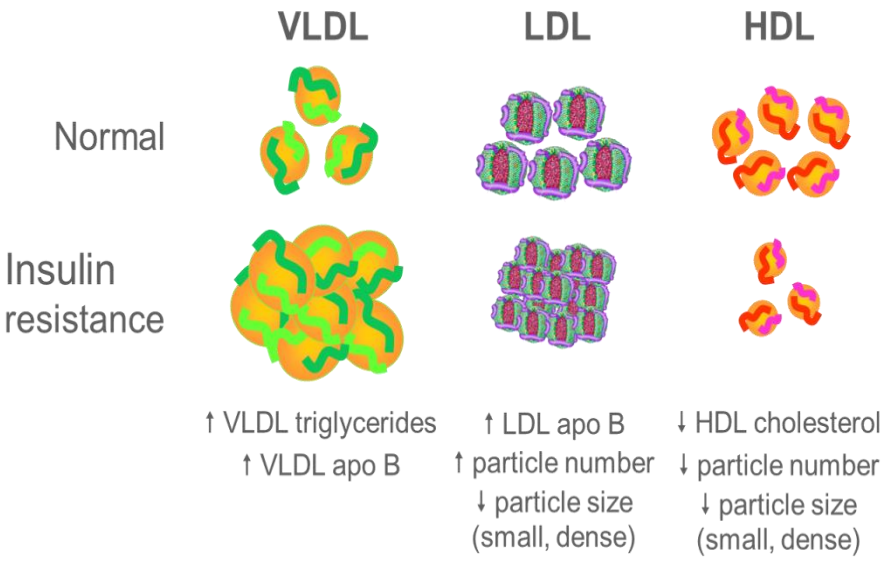
Hyperlipidemia
(LDL-C ≥ 100 mg/dL, TC ≥ 200 mg/dL, or TG ≥ 150 mg/dL)

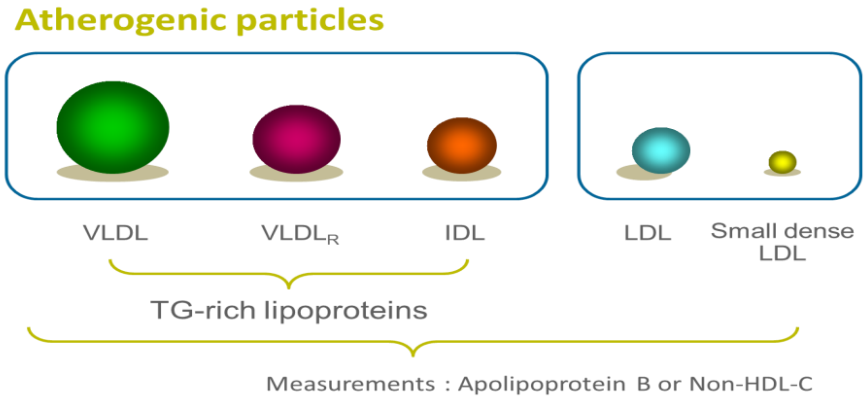
Main modifiable CV risk factors in DM (Grundy et al, 1999): Dyslipidemia, hypertension, hyperglycemia, obesity, smoking, albuminuria

HTN: hypertension ; CKD : chronic kidney disease, CVD: cardiovascular disease

Suh DC, et al. J Diabetes Complications. 2010;24:382-391.

DM: Unique lipid profile "atherogenic diabetic dyslipidemia" with Insulin resistance playing a Key Role





MAIN FEATURES

Quantitative

Variable increase in LDL, ↘ HDL-C, ↗ Triglycerides (TGs), ↗ VLDL, Chylomicron ↗

Postprandial ↗ TRL

Catabolism: ↘ LDL, VLDL, chylomicron, ↗ HDL

Qualitative changes

Small, dense LDL and HDL particles, ↗ larger VLDL1 particles

Kinetic changes

Production: ↗ Chylomicron, VLDL

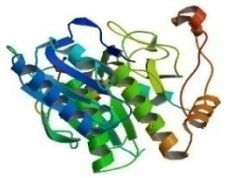
Catabolism: ↘ LDL, Chylomicron, VLDL, ↗

Non-HDL-C: stronger predictor of CVD than LDL-C DM (accounts for all atherogenic lipoproteins)

Watts G. Diapedia 2014. Available at: http://www.diapedia.org/61040851150/rev/5 Last accessed September 2016;

Verges B. Diabetologia 2015;58:886–9

WHAT IS PCSK9 ?



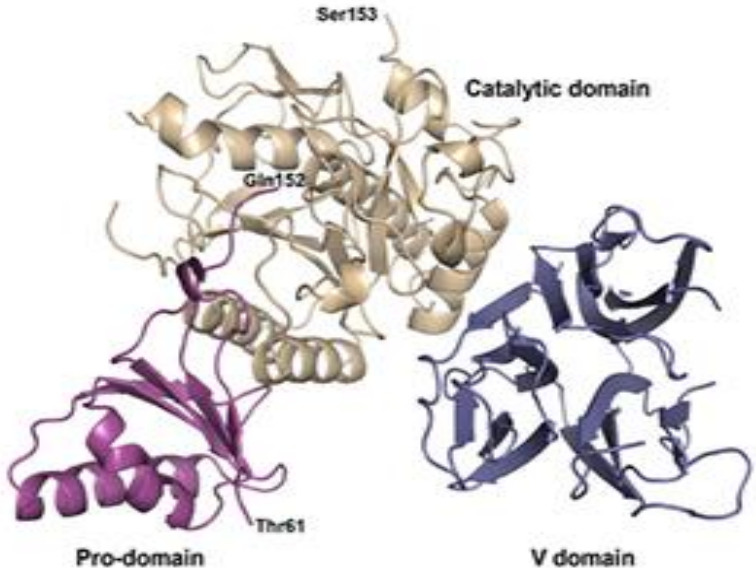
PCSK9 = Proprotein convertase subtilisin/kexin type 9

Human PCSK9 gene : located on chromosome 1p32.3, expressed in several organs (liver, kidney, intestine)

Structure :

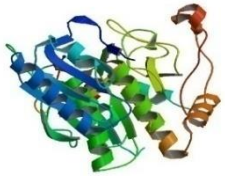
- **692 amino-acid – 73kDa**
- **3 domains :**
  - **Signal sequence (aa 1-30)**
  - **Prodomain (aa 31-152)**
  - **Mature PCSK9 : catalytic domain (aa 153-425) and C-terminal domain (aa 426-692)**

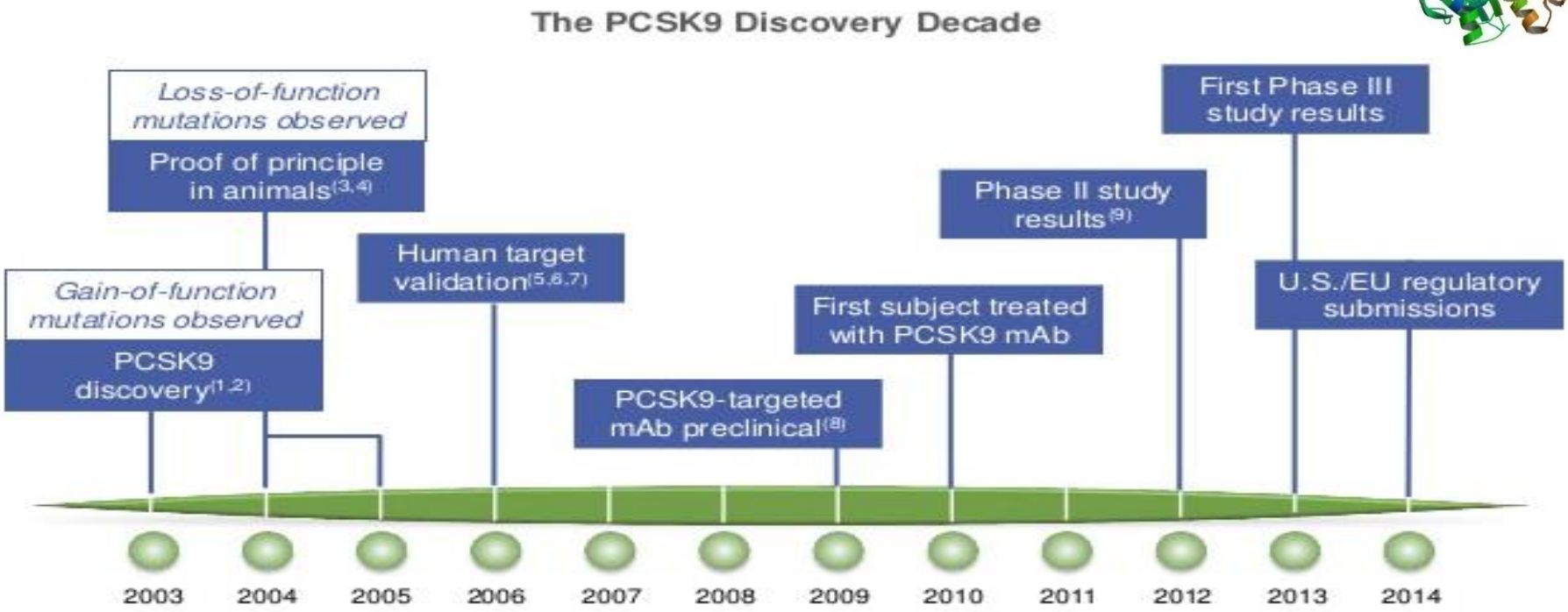
⇒Cleavage of the prodomain is required for the maturation and secretion of PCSK9



Mayne J, Dewpura T, Raymond A, et al. Novel loss-of-function PCSK9 variant is associated with low plasma LDL cholesterol in a French-Canadian family and with impaired processing and secretion in cell culture. Clin Chem 2011;57:1415—23

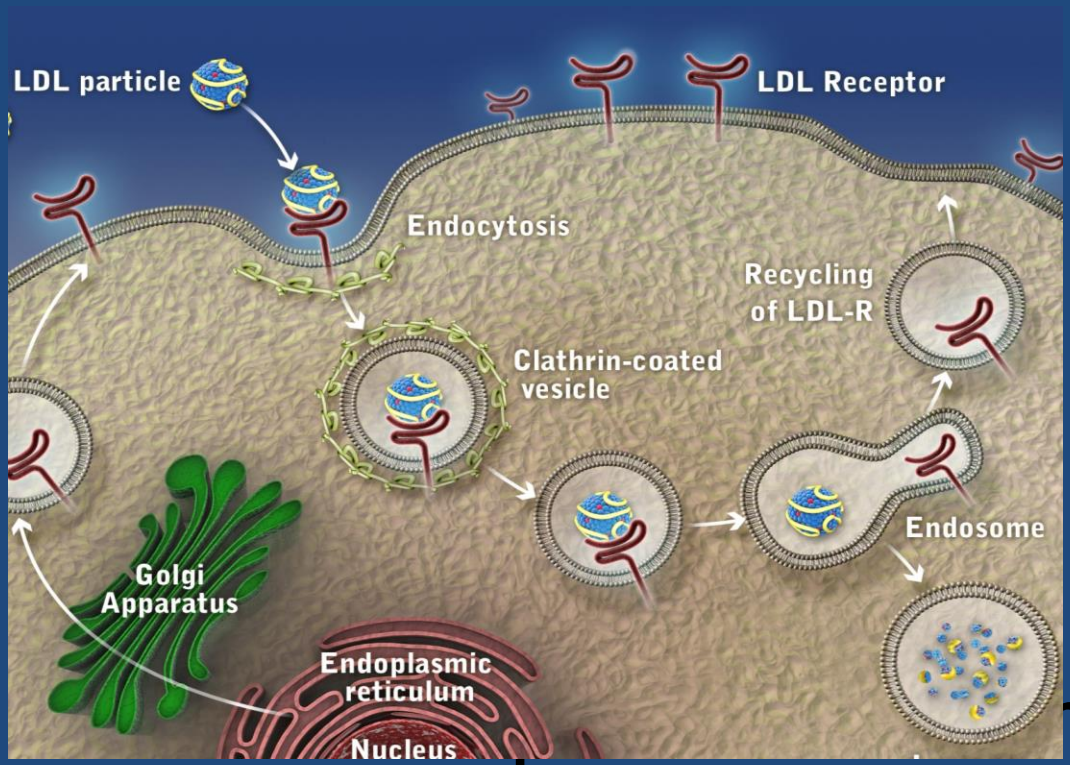
PCSK9 : KEY EVENTS



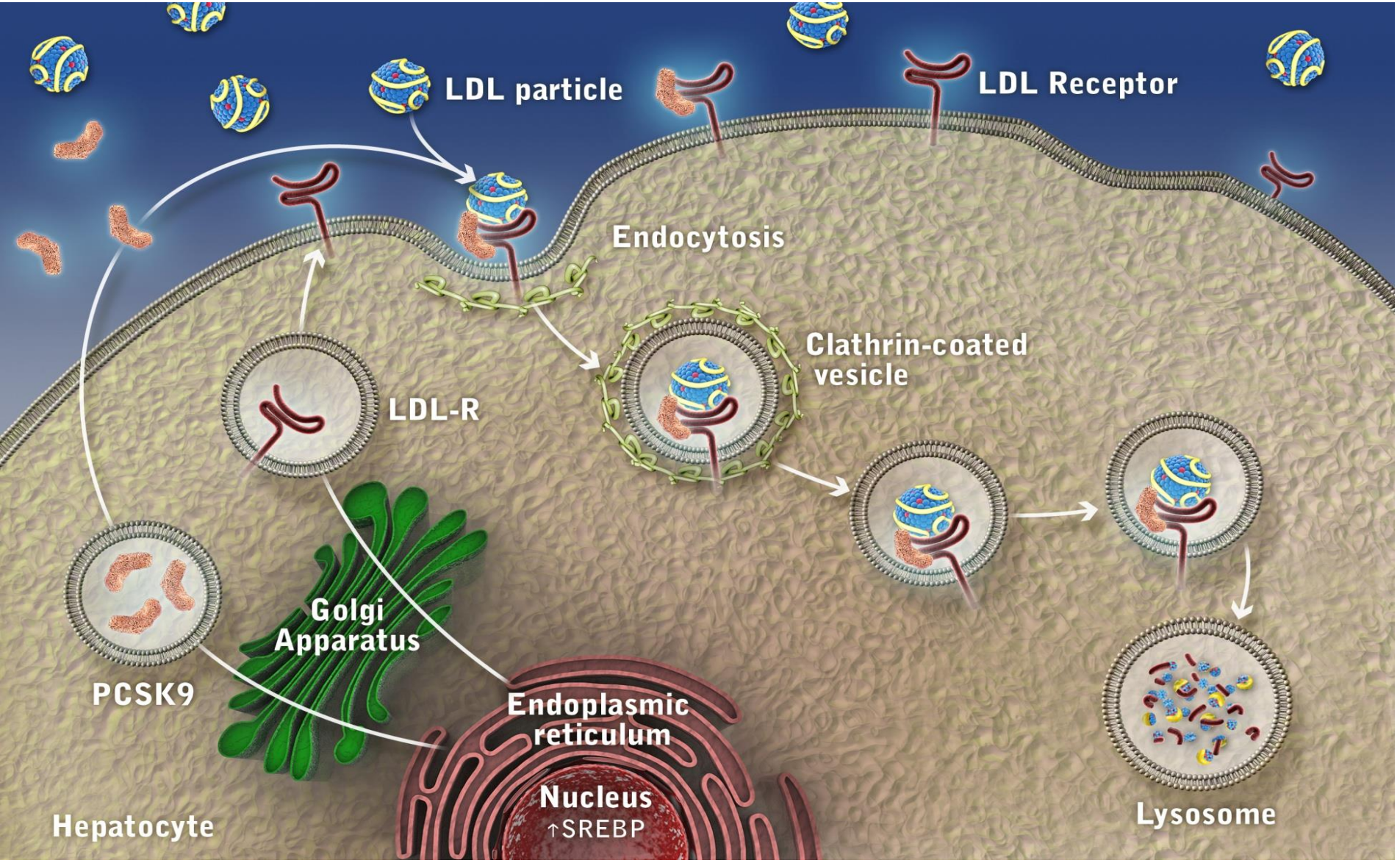


(1) Seidah NG. Proc Natl Acad Sci USA 003;100:928-33
(2) Abifadel M. Nat Genet 2003;34:154-6
(3) Maxwell KN. Proc Natl Acad Sci USA 2004;101:7100-5
(4) Rashid S. Proc Natl Acad Sci USA 2005;102:5374-79
(5) Cohen JC. N Engl J Med 2006;354:1264-72
(6) Zhao Z. Am J Hum Genet 2006;79:514-23
(7) Hooper AJ. Atherosclerosis 2007;193:445-8
(8) Chan JC. Proc Natl Acad Sci USA 2009;106:9820-5
(9) Lambert G et al. J Lipid Res 2012; 53(12): 2515-24

1985 Goldstein & Brown

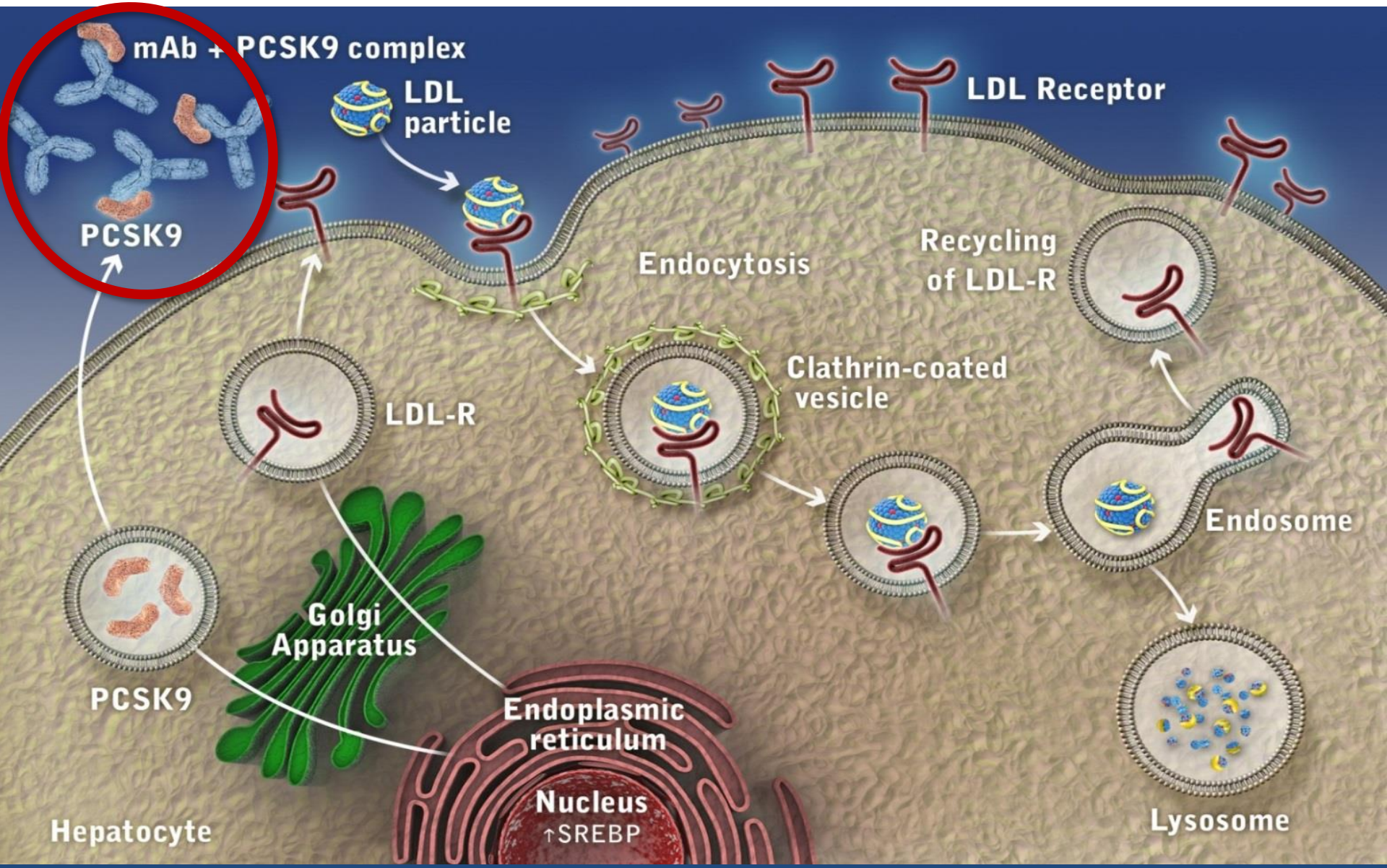


Role of PCSK9 in the Regulation of LDL Receptor Expression

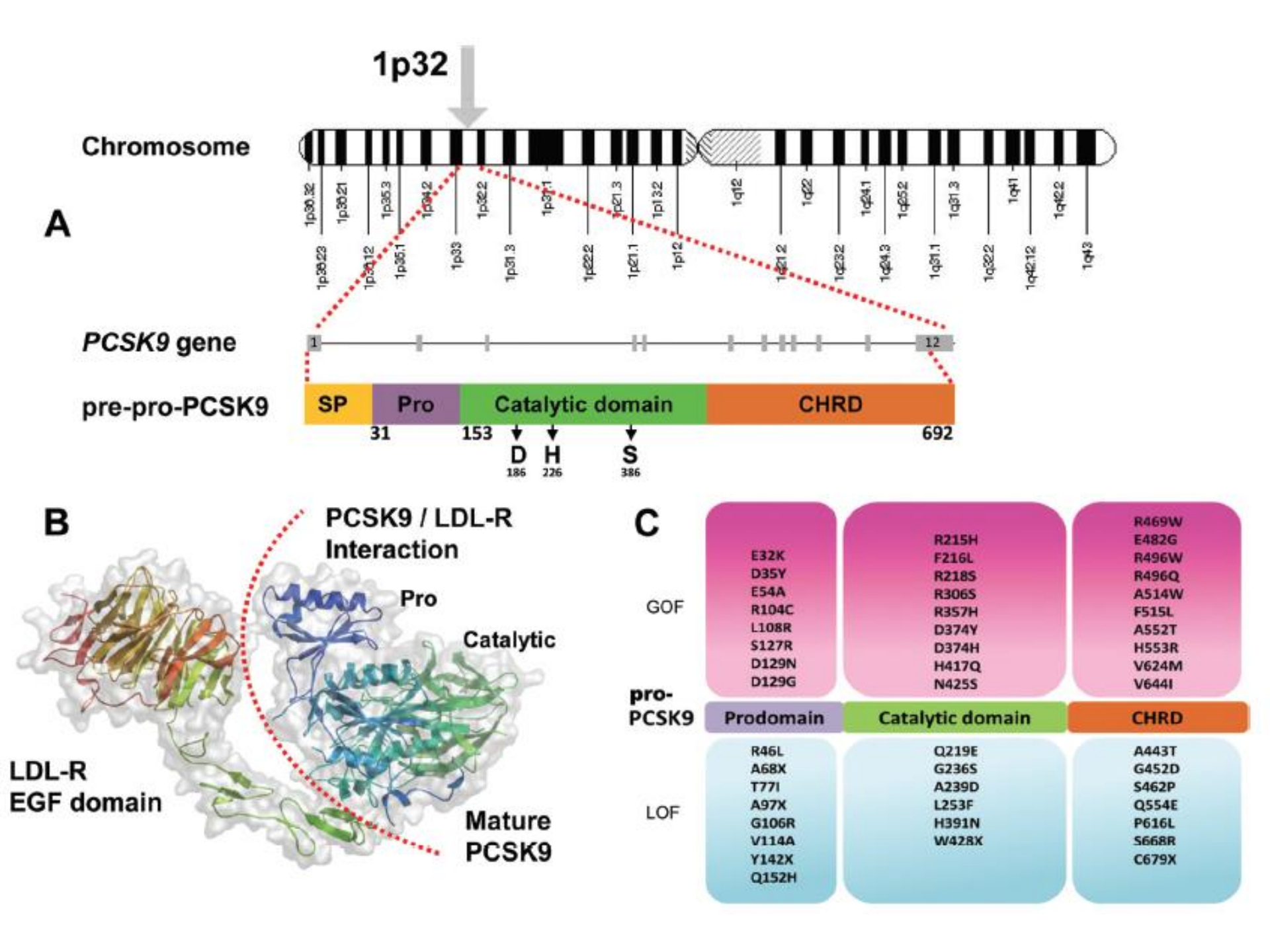


Adapted from Catapano & Papadopoulos Atherosclerosis 2013;228:18–28

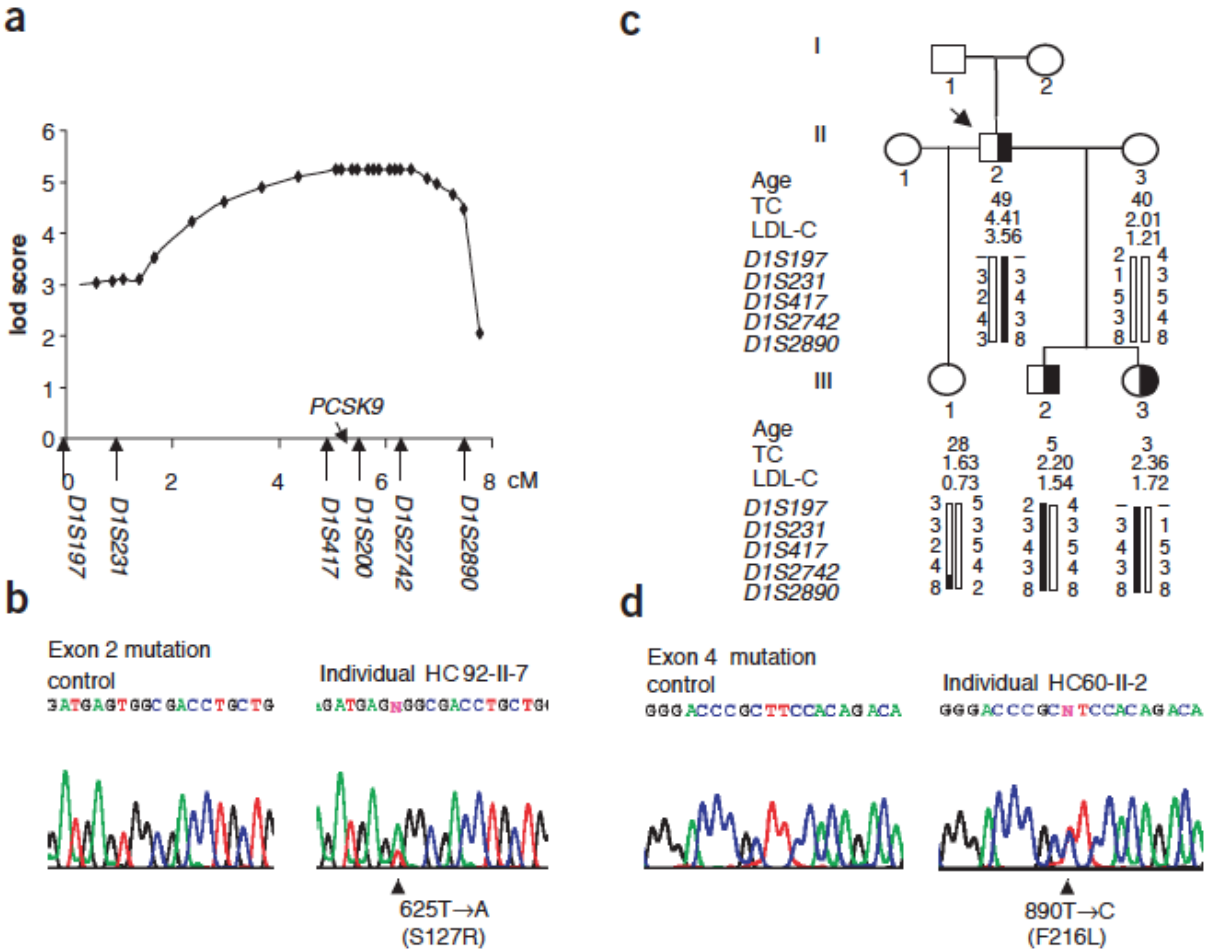
Impact of a PCSK9 Monoclonal Antibody on LDL Receptor Expression



Adapted from Catapano & Papadopoulos Atherosclerosis 2013;228:18–28

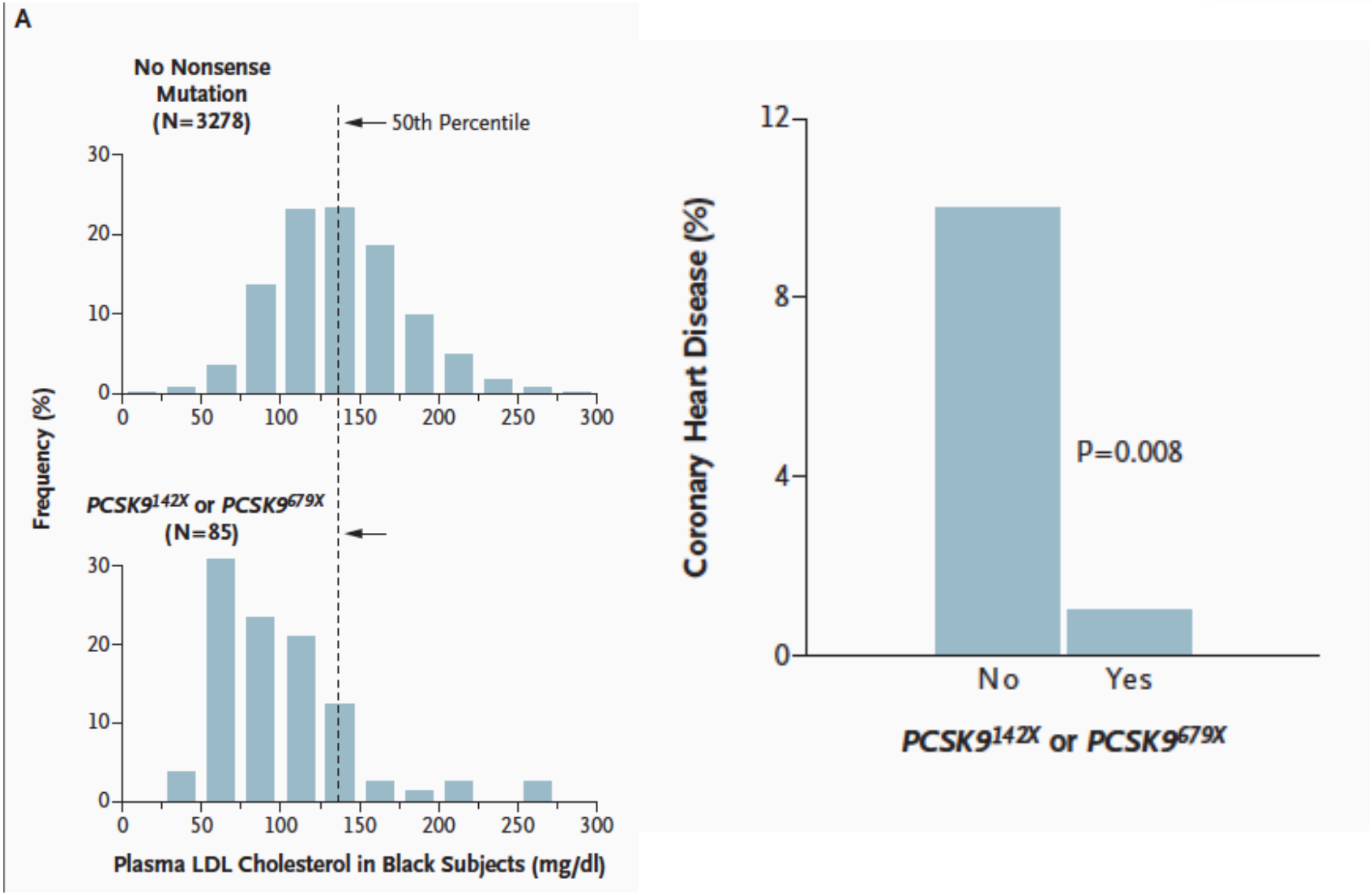

A
1p32
Chromosome
PCSK9 gene
pre-pro-PCSK9
SP
Pro
Catalytic domain
CHRD
31
153
692
D
186
H
226
S
386
B
PCSK9 / LDL-R
Interaction
Pro
Catalytic
LDL-R
EGF domain
Mature
PCSK9
C
GOF
E32K
D35Y
E54A
R104C
L108R
S127R
D129N
D129G
R215H
F216L
R218S
R306S
R357H
D374Y
D374H
H417Q
N425S
R469W
E482G
R496W
R496Q
A514W
F515L
A552T
H553R
V624M
V644I
pro-
PCSK9
Prodomain
Catalytic domain
CHRD
LOF
R46L
A68X
T77I
A97X
G106R
V114A
Y142X
Q152H
Q219E
G236S
A239D
L253F
H391N
W428X
A443T
G452D
S462P
Q554E
P616L
S668R
C679X

Mutations in PCSK9 cause autosomal dominant hypercholesterolemia



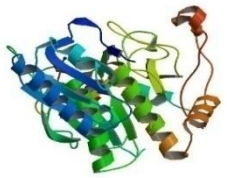
Abifadel M et al. VOLUME 34 | NUMBER 2 | JUNE 2003 NATURE GENETICS

Sequence Variations in PCSK9, Low LDL, and Protection against Coronary Heart Disease



Cohen JC et al. New Engl Journal of Med 354;12 www.nejm.org march 23, 2006

PCSK9 : FUNCTIONS

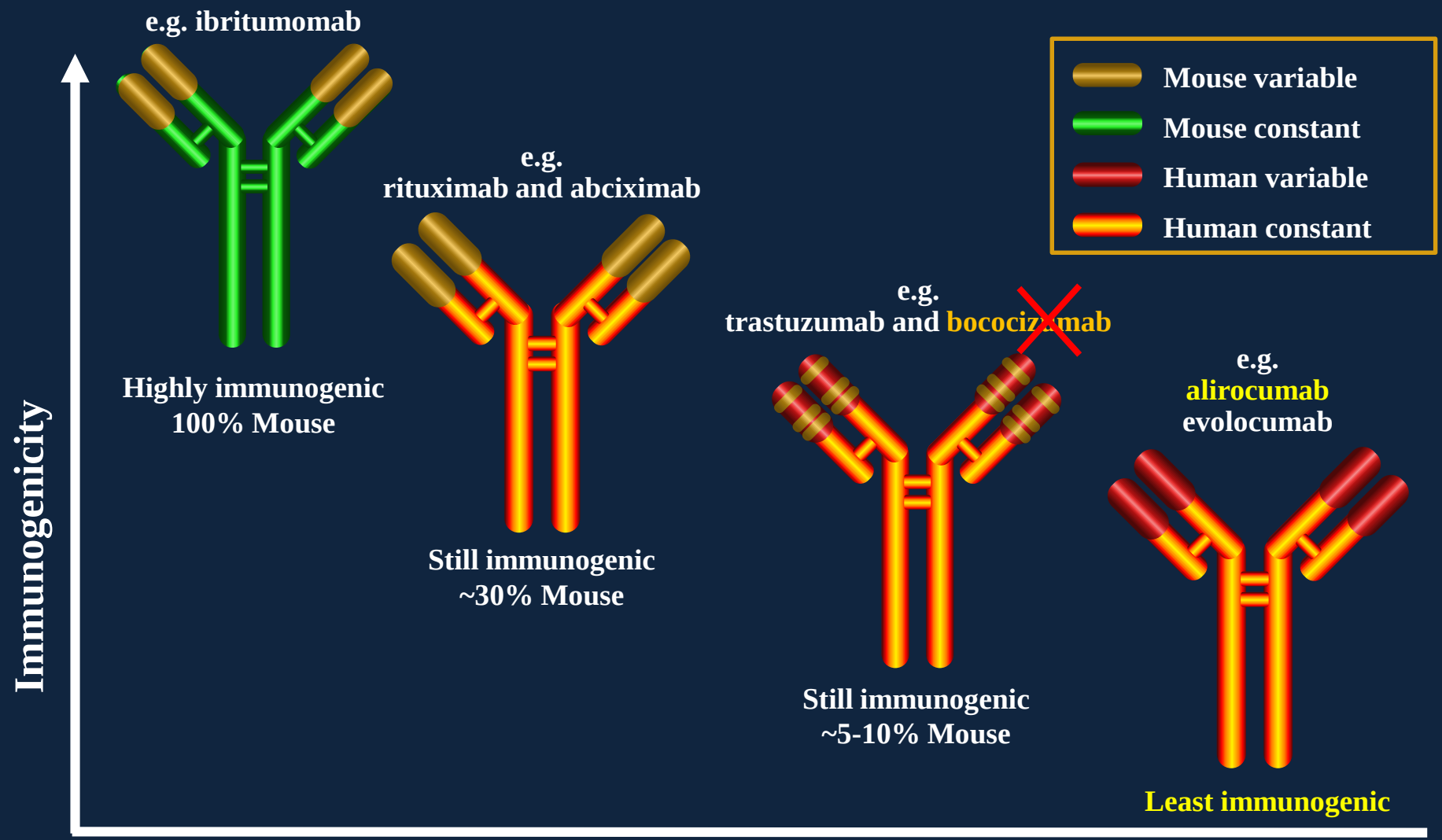


Key player in the LDL-C regulation

- ↑ PCSK9 → ↓ LDLR protein → ↑ LDL-C
- ~~PCSK9~~ → ↑ LDLR protein → ↓ LDL-C

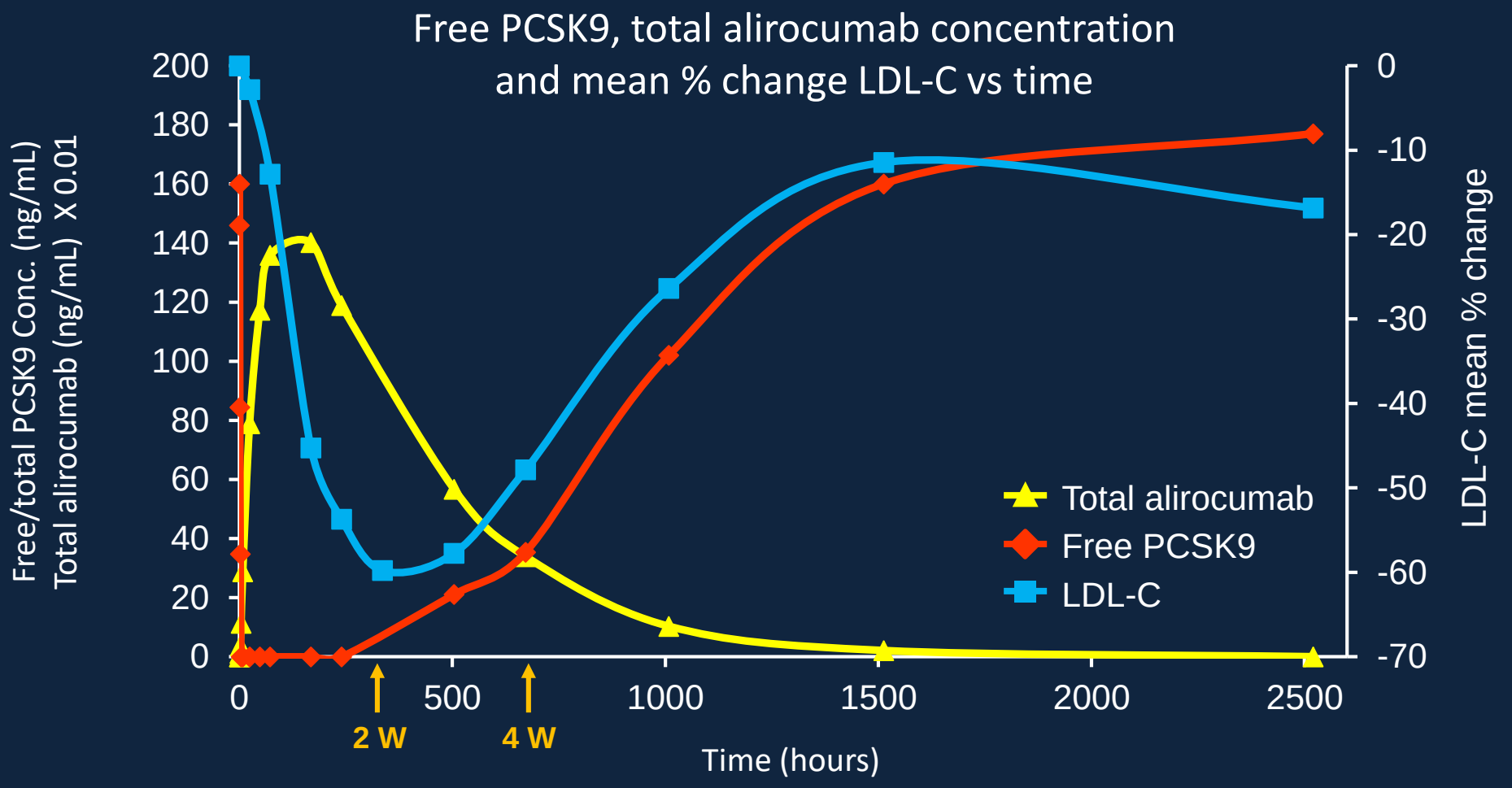
PCSK9: From discovery to therapeutic Applications – Michel Farnier - Archives of Cardiovascular Disease (2014) 107, 58—66

Monoclonal Antibody Evolution



1. Foltz I *et al*. *Circulation* 2013;127(22):2222-30;
2. Nelson AL *et al*. *Nature Reviews Drug Discovery* 2010;9(10):767-74.

Alirocumab: Dynamic Relationship Between mAb Levels, PCSK9 and LDL-C



Stein EA *et al. New Engl J Med* 2012;366:1108–18.

Overview of ODYSSEY Phase III Program

22 global trials, including more than 29,000 patients across more than 3,000 study centers

HeFH population	HC in high CV risk population	Additional populations/studies
Add-on to max tolerated statin (± other LMT)	Add-on to max tolerated statin (±other LMT)	
	ODYSSEY OUTCOMES (EFC11570) N=18,600 **Event-driven, 2 year minimum follow-up** **Enrollment Completed Nov 2015 [Ongoing]**	
ODYSSEY OLE (LTS13463) N=1000 18 months **[Ongoing]**	**ODYSSEY COMBO I** (EFC11568) N=316 12 months ✓	**ODYSSEY MONO** (EFC11716) N=103 6 months ✓
ODYSSEY FH I (EFC12492) N=486 18 months ✓	**ODYSSEY COMBO II** (EFC11569) N=720 24 months ✓	**ODYSSEY ALTERNATIVE** (CL1119) N=314 6 months (+OLE) ✓
ODYSSEY FH II (CL1112) N=249 18 months ✓	**ODYSSEY EAST** (EFC13389) N=600 6 months ✓	**ODYSSEY OPTIONS I** (CL1110) N=355 6 months ✓
ODYSSEY HIGH FH (EFC12732) N=107 18 months ✓	**ODYSSEY KT** (EFC14074) N=199 6 months ✓	**ODYSSEY OPTIONS II** (CL1118) N=305 6 months ✓
ODYSSEY LONG TERM (LTS11717) N=2,341 18 months ✓		**ODYSSEY CHOICE I** (CL1308) 300 mg Q4w dosing 12 months ✓
ODYSSEY JAPAN (EFC 13672) N=216 12 months ✓		**ODYSSEY CHOICE II** (EFC13786) N=233 150 mg Q4W dosing, 6 months (+OLE) ✓
ODYSSEY APPRISE (LPS14245) N=1300 3 – 30 months **[Ongoing]**		**ODYSSEY NIPPON** (EFC14305) N=159 3 months (+OLE) ✓
ODYSSEY ESCAPE (R727-CL-1216) N=63 4 months ✓	**ODYSSEY DM – Insulin** (LTS14354) N=500 6 months ✓	
	ODYSSEY DM – Dyslipidemia (LTS14355) 6 months ✓	

Core Registrational Studies

✓ Primary endpoint met; data presented or published

Effect of Statins and other lipid-modifying therapies on PCSK9

- **Statins Increase LDLR expression and density on cell surface**
- **PCSK9 levels increase as a feedback response to statin treatment rising by 10-15%**
- **Fenofibrate and ezetimibe may also significantly increase PCSK9 levels**

European Heart Journal Advance Access published July 26, 2016

European Heart Journal
doi:10.1093/eurheartj/ehw292

CLINICAL RESEARCH
Lipids

No effect of PCSK9 inhibitor alirocumab on the incidence of diabetes in a pooled analysis from 10 ODYSSEY Phase 3 studies

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ODYSSEY diabetes program: overview

ODYSSEY DM-INSULIN[1]

- Alirocumab versus Placebo
- Participants: Insulin-treated with T1DM or T2DM
  - High CV risk + LDL-C above goal despite max tolerated statin ±other LLT
- Primary endpoints: % change from baseline in calculated LDL-C at Week 24, and safety over 32 weeks

ODYSSEY DM-DYSLIPIDEMIA[2]

- Alirocumab versus Usual Care
- Participants: T2DM + mixed dyslipidemia
  - High CV risk + non-HDL-C not controlled despite max tolerated statin
- Primary endpoint: % change from baseline in non-HDL-C at Week 24

ClinicalTrials.gov Identifier: DM-INSULIN (NCT02585778); DM-DYSLIPIDEMIA (NCT02642159).
CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; non-HDL-C, non-high-density lipoprotein cholesterol; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.
1. Cariou B et al. *Diabetes Metab*. 2017 [Epub ahead of print]; 2. Müller-Wieland D et al. *Cardiovasc Diabetol*. 2017;16:70.

ODYSSEY DM-INSULIN: study population

Key inclusion criteria

- Age ≥18 years
- T1DM or T2DM (≥1 year)
- A1C <10%
- Insulin use
- Stable max tolerated statin ± other LLT
- LDL-C ≥70 mg/dL (1.81 mmol/L)
- ASCVD* and/or at least one additional CV risk factor

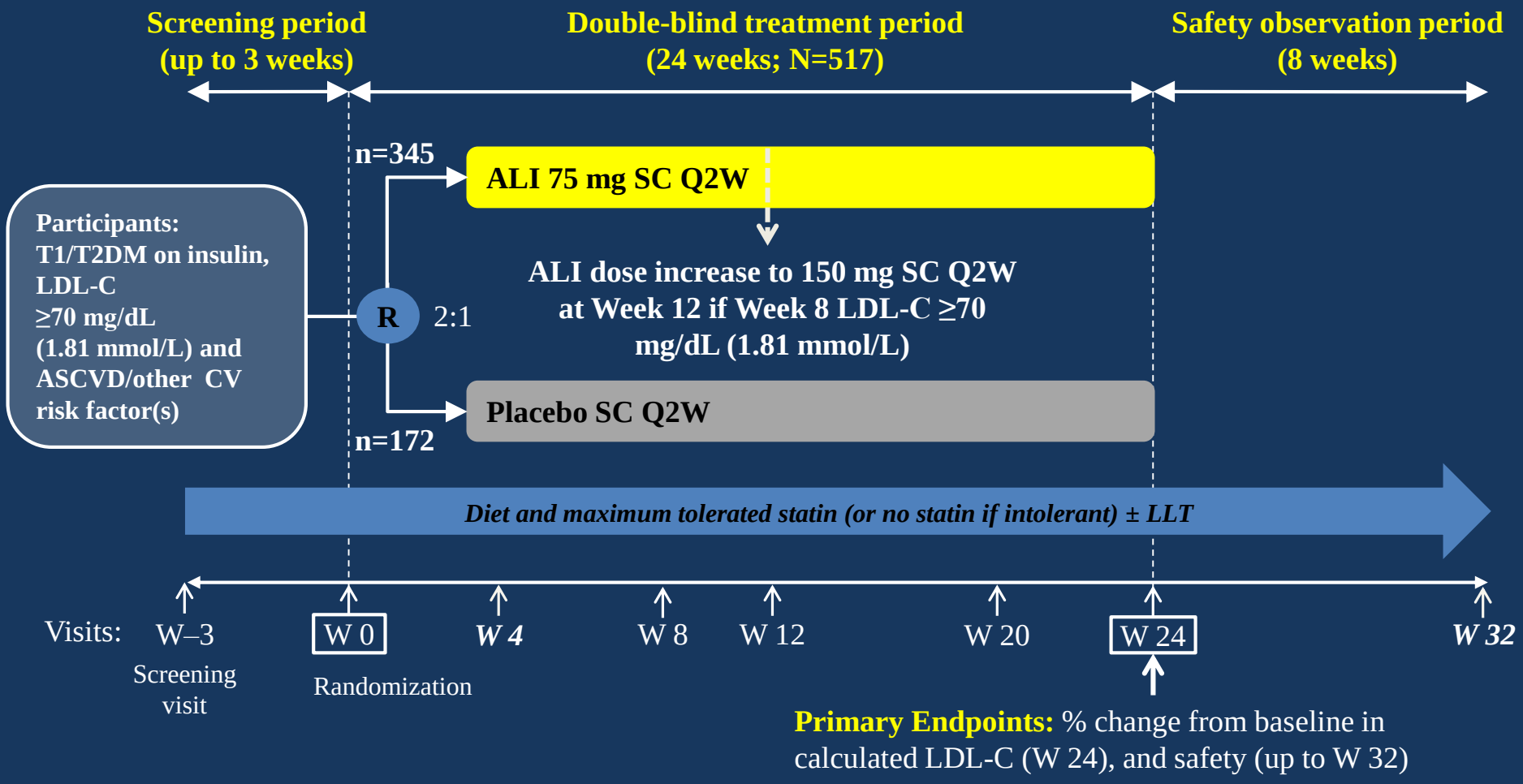
Key exclusion criteria

- eGFR <15 mL/min/1.73 m^2
- BMI >45 kg/m^2 or weight variation >5 kg within 2 months
- TGs >400 mg/dL (4.52 mmol/L)
- Insulin treatment duration <6 months or regimen/dose not stable within past 3 months
- Current or planned renal replacement therapy

- **Stable antihyperglycemic therapy throughout trial**

*ASCVD was defined as coronary heart disease, peripheral arterial disease, and/or ischemic stroke.
A1C, glycated hemoglobin; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; eGFR, estimated glomerular filtration rate; TG, triglyceride.
ClinicalTrials.gov Identifier: DM-INSULIN (NCT02585778). Cariou B et al. *Diabetes Metab*. 2017 [Epub ahead of print].

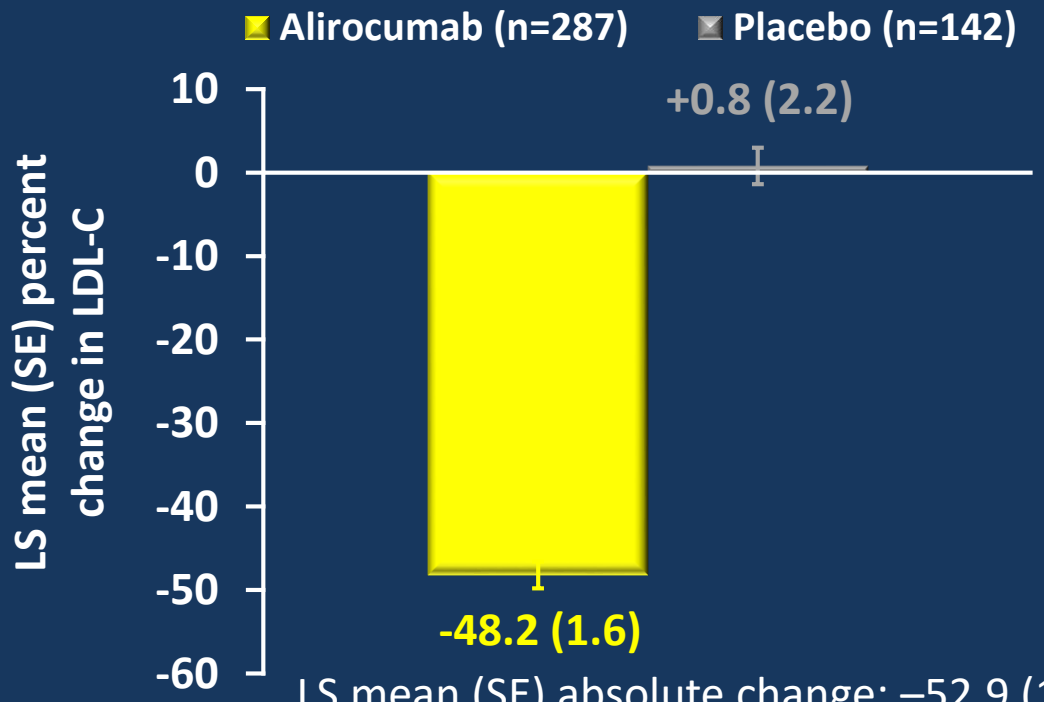
ODYSSEY DM-INSULIN: study design



Phone-call 'visits' at Weeks 4 and 32. N numbers indicate the final sample sizes.
ALI, alirocumab; Q2W, every 2 weeks; R, randomization; SC, subcutaneous; W, week.
Cariou B et al. *Diabetes Metab*. 2017 [Epub ahead of print].

ODYSSEY DM-INSULIN: Alirocumab significantly reduced LDL-C from baseline to Week 24 versus placebo (ITT)†

Primary efficacy endpoint: Percent change in calculated LDL-C from baseline to Week 24



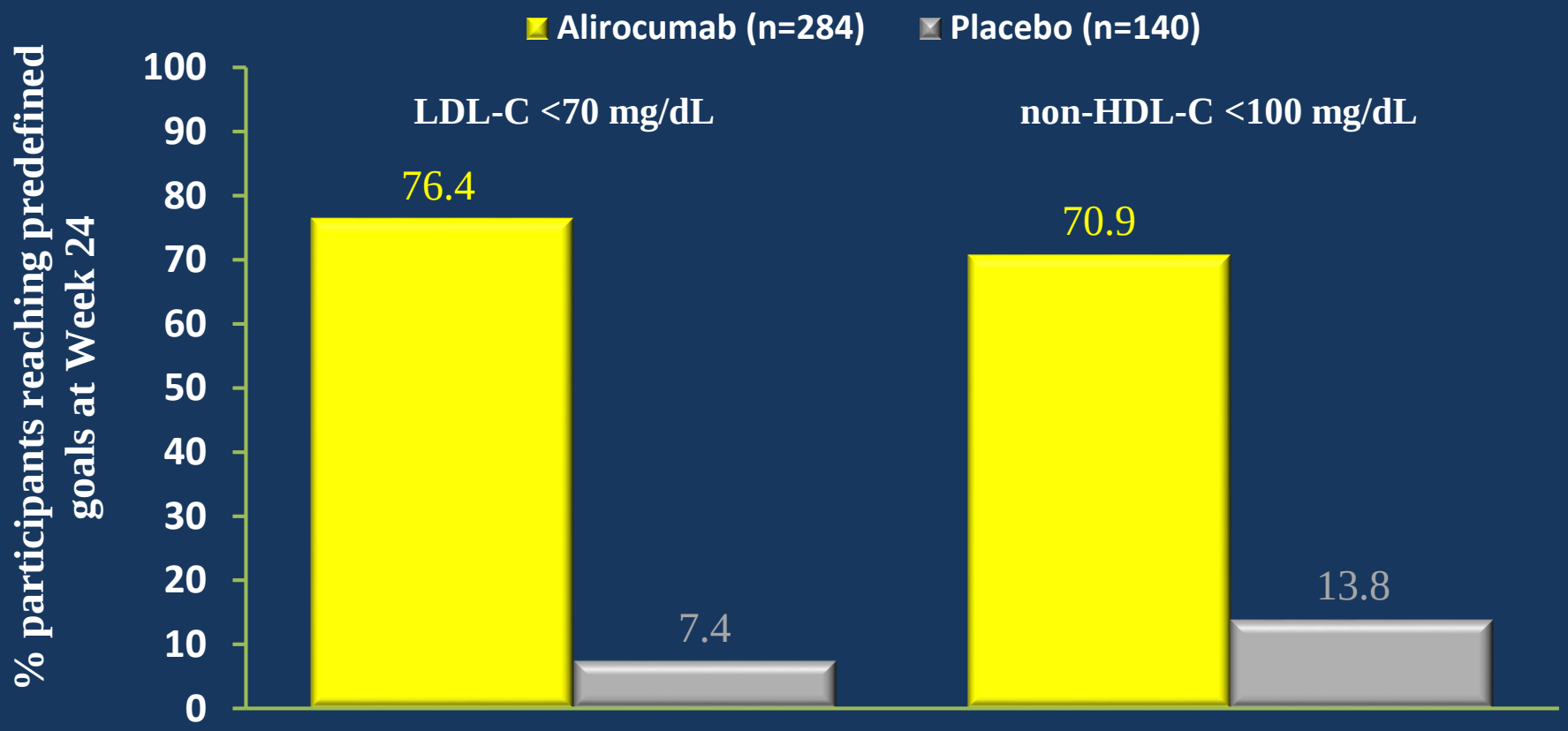
LS mean (SE) absolute change: –52.9 (1.9) mg/dL

LS mean difference (SE) versus placebo:
–49.0% (2.7)
***P*<0.0001**

Alirocumab dose at Week 12 (ITT), % (n)	
Dose increase to 150 mg Q2W	20.2% (58/287)
Maintained at 75 mg Q2W	79.8% (229/287)

†Mixed effect model with repeated measures analysis.
ITT, intention-to-treat; LS, least squares; Q2W, every two weeks; SE, standard error.

ODYSSEY DM-INSULIN: Goal attainment at Week 24 (on-treatment)†



Combined estimate for odds ratio [95% CI]	84.6 [36.5 to 196.1]	27.1 [14.2 to 51.5]
	P<0.0001	*P*<0.0001

†Multiple imputation followed by logistic regression.

ODYSSEY DM-DYSLIPIDEMIA: study population

Key inclusion criteria

- Age ≥18 years
- T2DM with mixed dyslipidemia
- Stable anti-hyperglycemic treatment (including insulin)
- Stable max tolerated statin without other LLT
- Non-HDL-C ≥100 mg/dL (2.59 mmol/L)
- TG ≥150 and <500 mg/dL (1.70–5.65 mmol/L)
- No weight variation >5 kg within 3 months
- ASCVD* and/or at least one additional CV risk factor

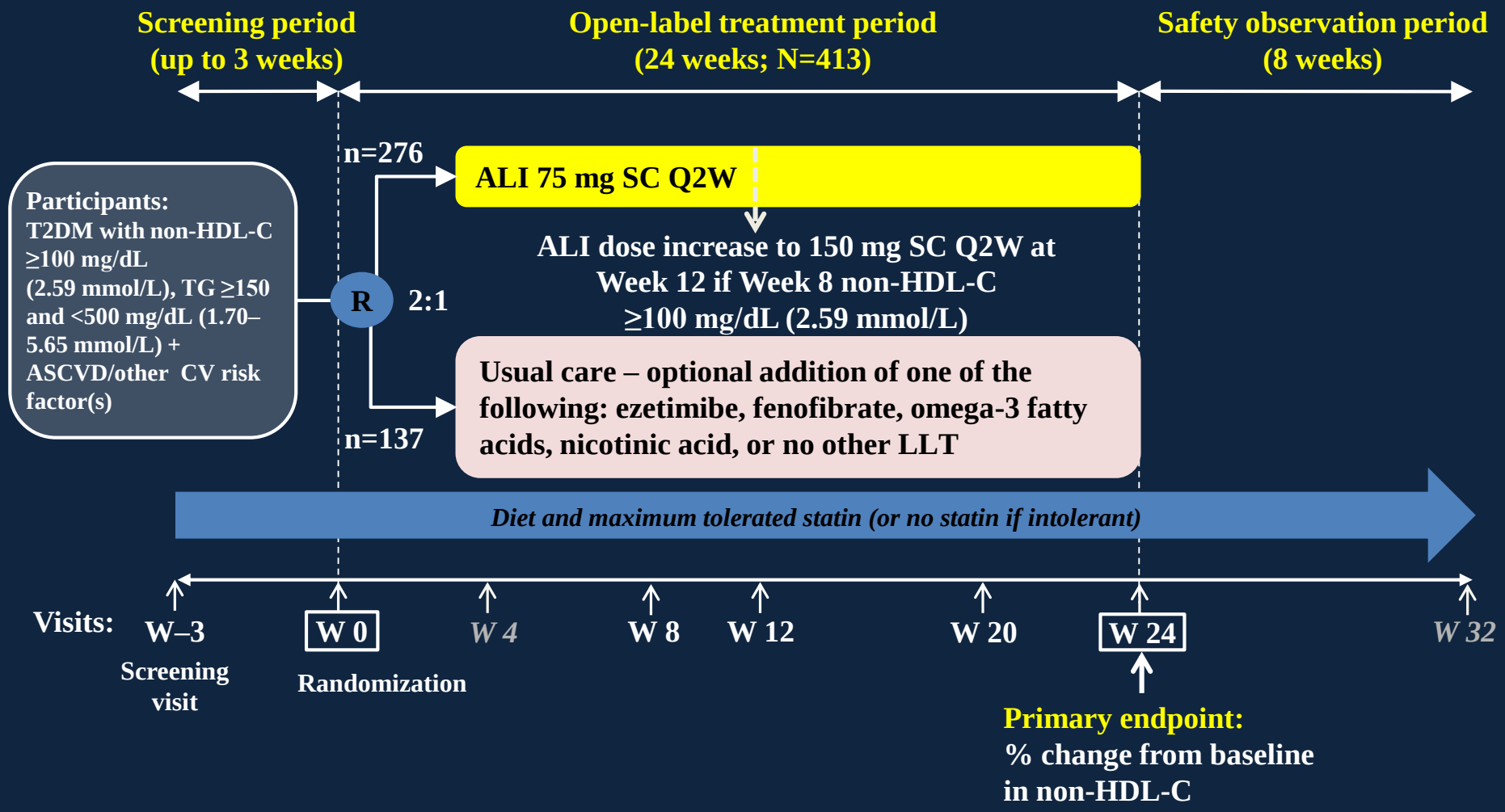
Key exclusion criteria

- A1C ≥9.0%
- Use of any LLT (other than statin) or over-the-counter product/ nutraceuticals known to impact lipids
- BMI >45 kg/m^2
- >2 standard alcoholic drinks/day

*ASCVD was defined as coronary heart disease, peripheral arterial disease, and/or ischemic stroke.

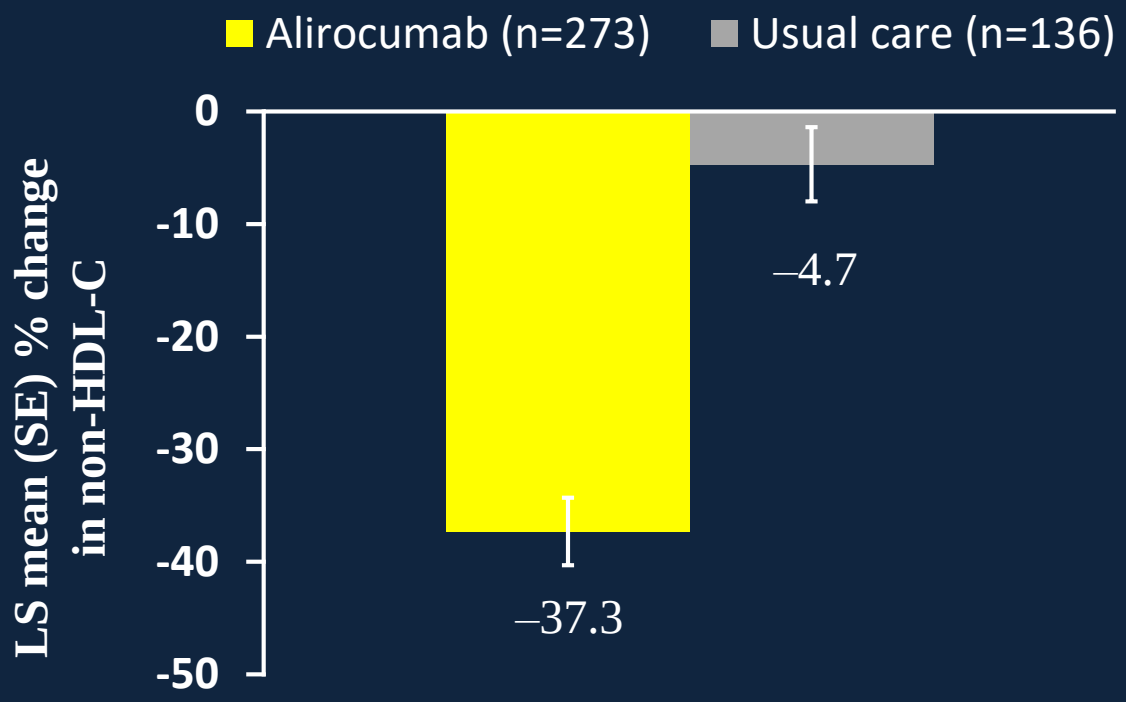
Müller-Wieland D et al. *Cardiovasc Diabetol*. 2017;16:70.

ODYSSEY DM-DYSLIPIDEMIA: study design



Randomization was stratified by the investigator's selection of usual care therapy prior to randomization. Usual care also includes the option to continue on max tolerated statin without the addition of another LLT at randomization. Phone-call 'visits' at Weeks 4 and 32. N numbers indicate the final sample sizes. Müller-Wieland D et al. *Cardiovasc Diabetol*. 2017;16:70.

ODYSSEY DM-DYSLIPIDEMIA : % change in non-HDL-C from baseline to Week 24 vs usual care (primary efficacy endpoint; ITT†)

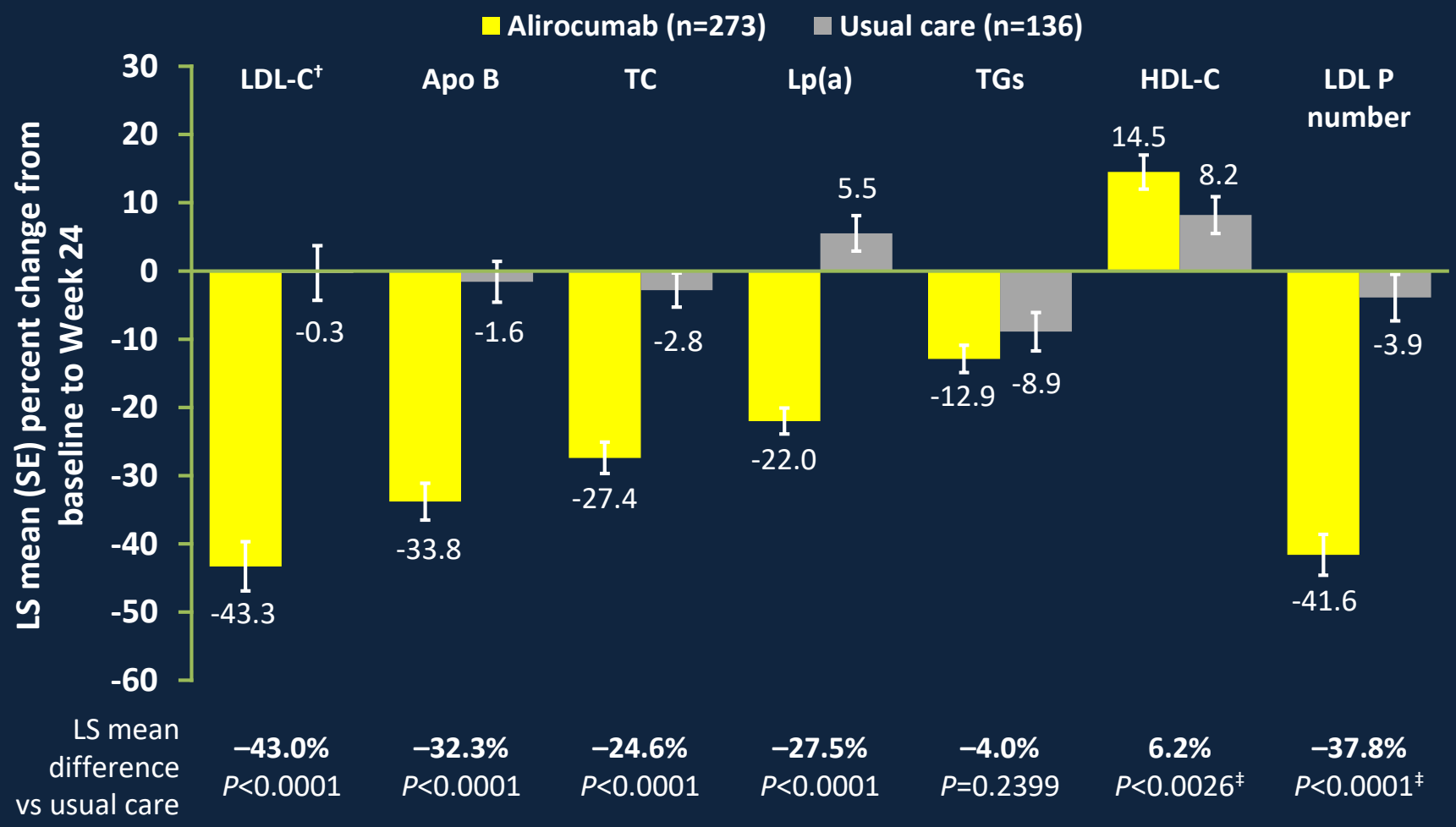


LS mean difference (SE) versus usual care: –32.5% (2.5) *P*<0.0001

Alirocumab dose at Week 12, % (n)	
Dose increase to 150 mg Q2W	36.4% (94/275)
Maintained at 75 mg Q2W	63.6% (182/275)

†Mixed effect model with repeated measures analysis.
ITT, intention-to-treat analysis.

ODYSSEY DM-DYSLIPIDEMIA: Selected secondary lipid parameters at Week 24 versus usual care (ITT†)

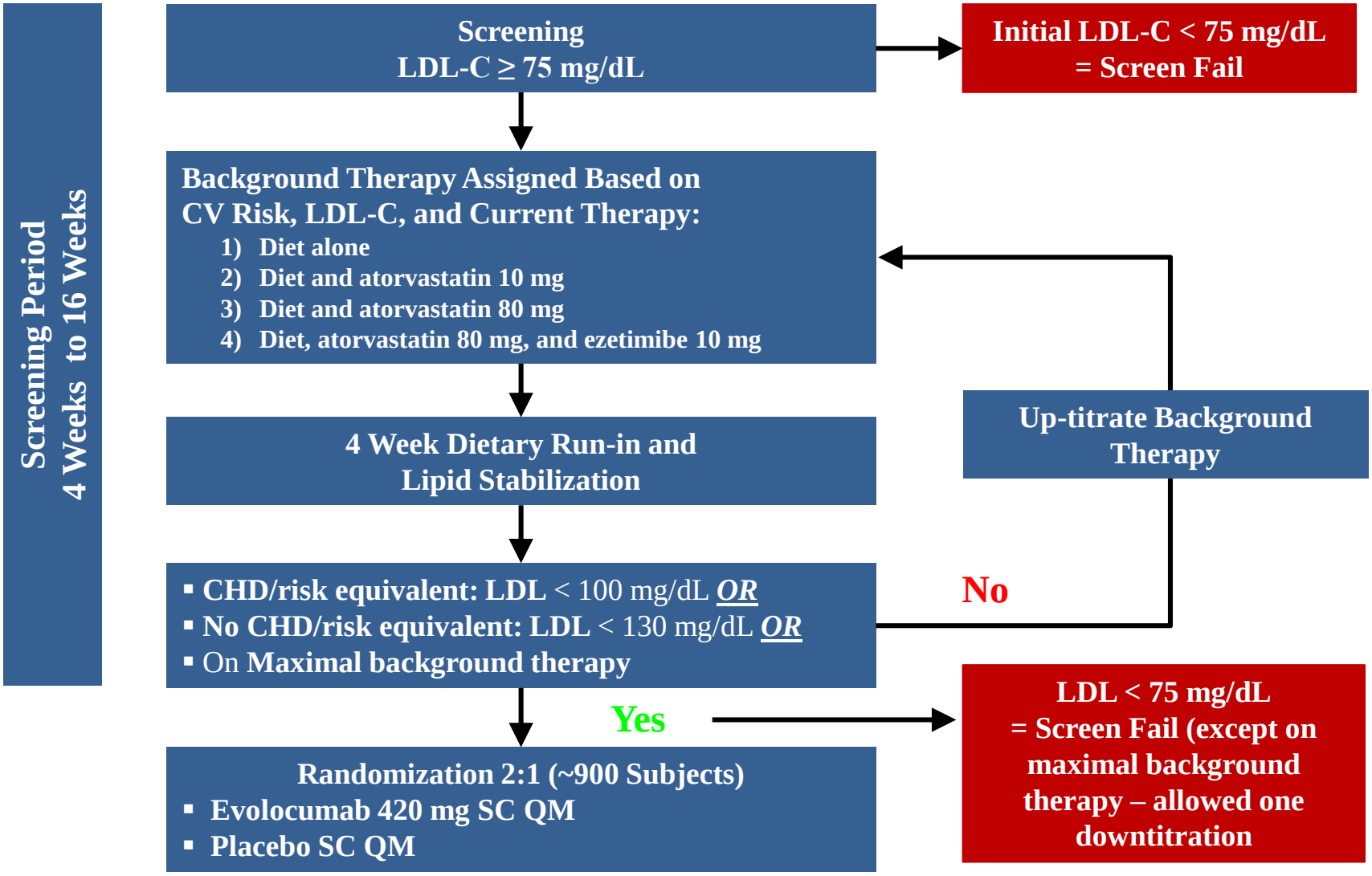


†Mixed effect model with repeated measures analysis.

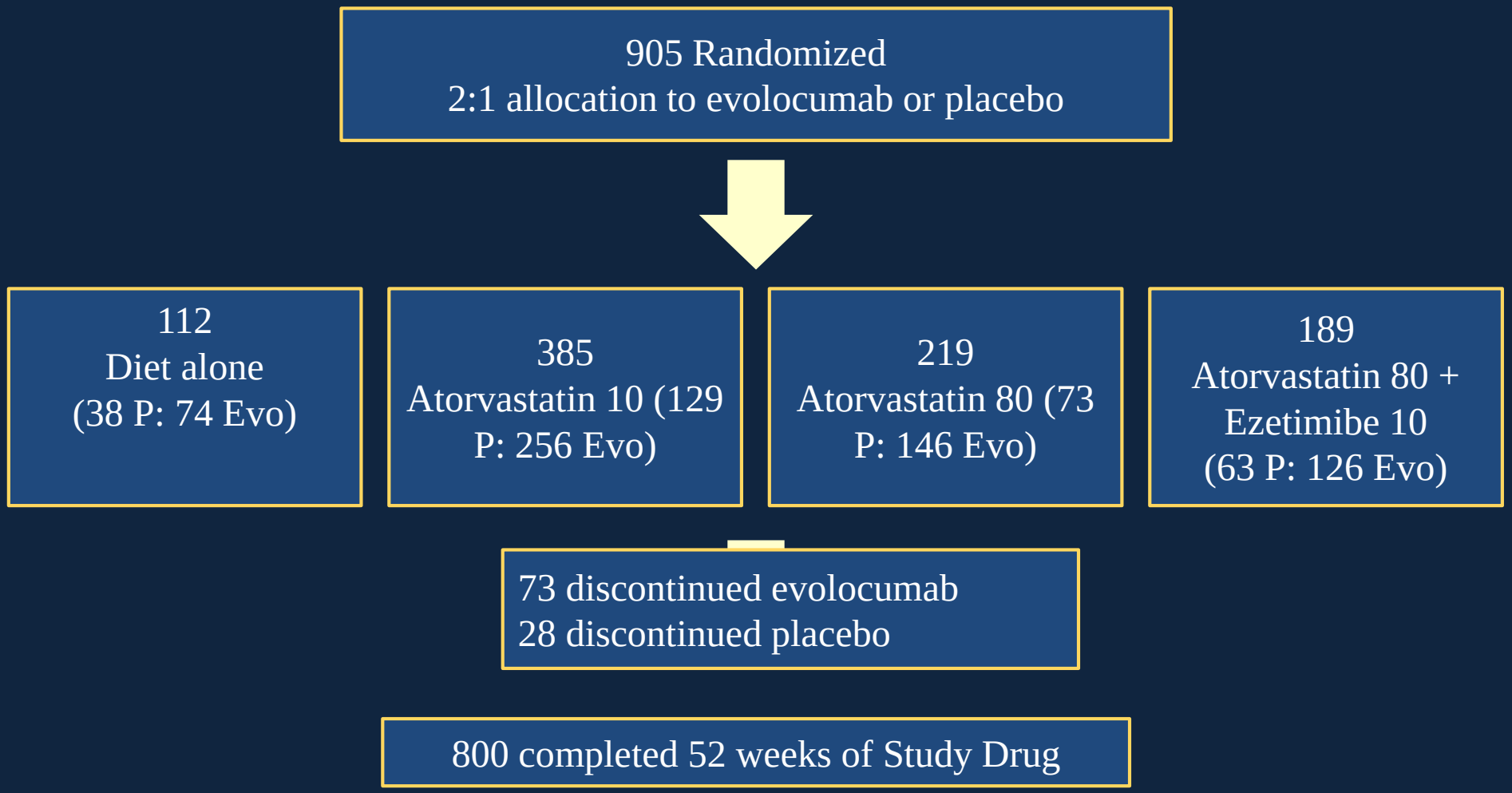
ITT, intention-to-treat analysis. †Measured; ‡Nominal *P*-values due to the non-significance for TG within the hierarchical testing procedure.

LDL P, low-density lipoprotein particle; TC, total cholesterol.

DESCARTES: Screening and Lipid Stabilization



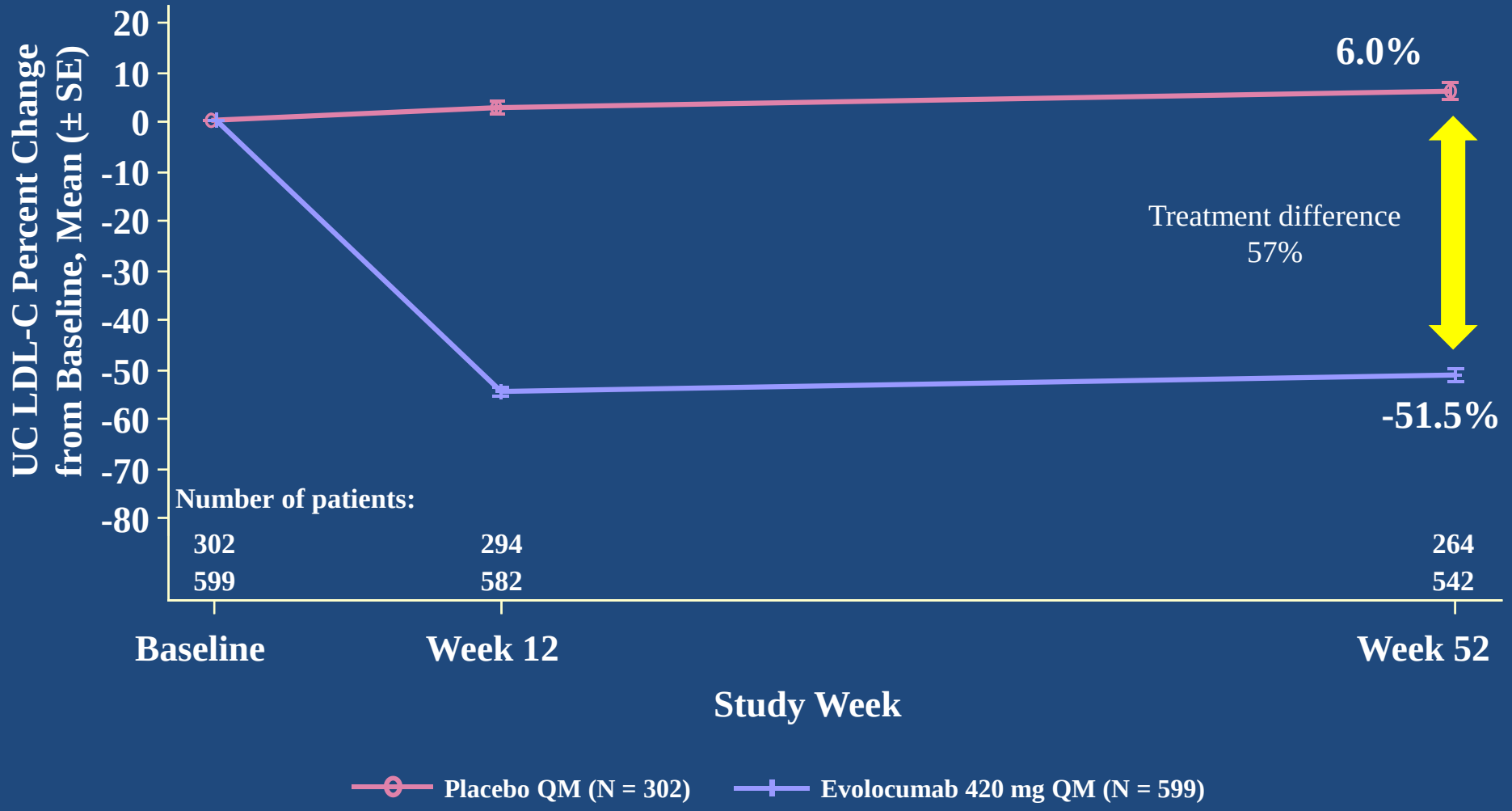
DESCARTES: Patient Disposition II



E = Ezetimibe, Evo = Evolocumab, P = Placebo

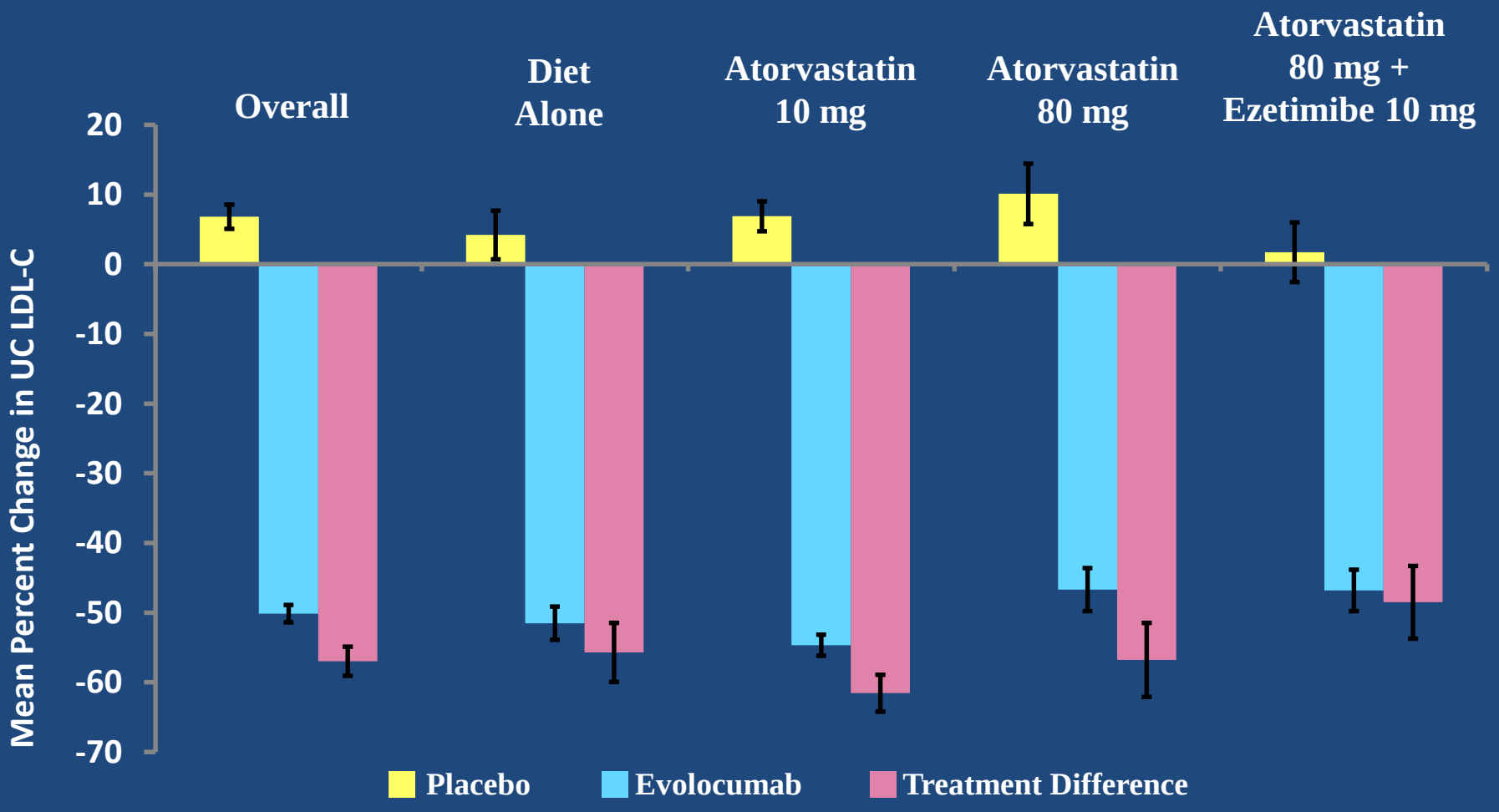
* Study Drug

DESCARTES: % Change in UC LDL-C From Baseline - *FAS*



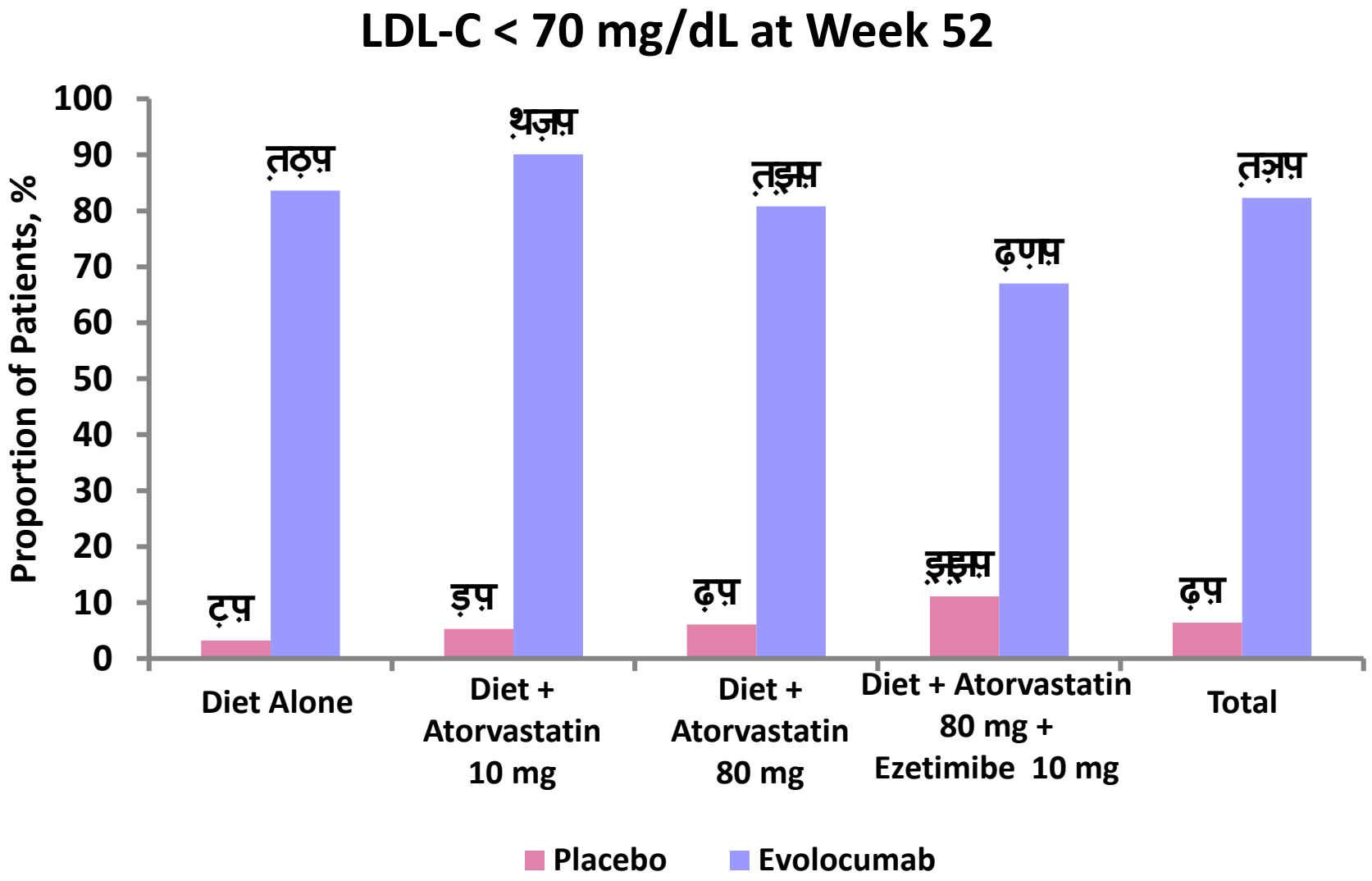
FAS = Full analysis set, UC = ultracentrifugation

DESCARTES: % Change in UC LDL-C from Baseline at Week 52

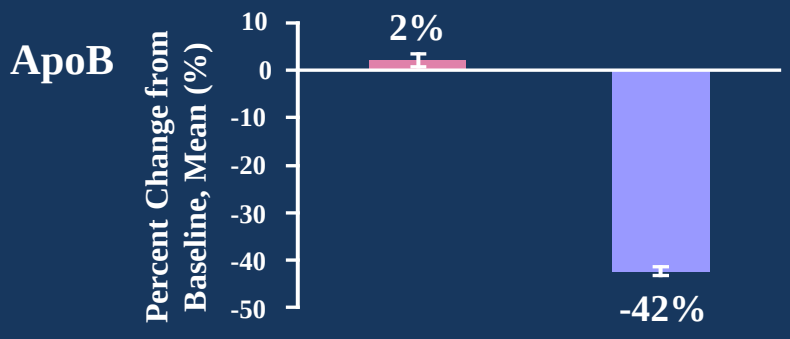


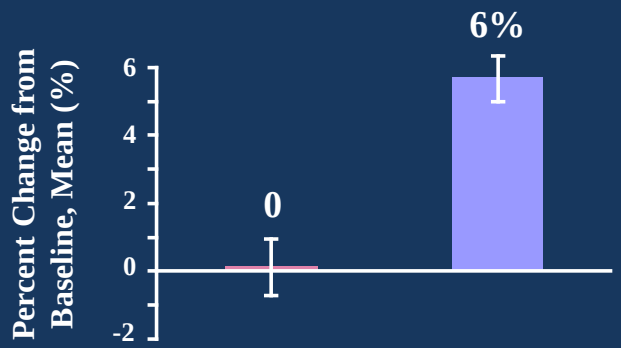
Error bars represent standard error for treatment difference
Treatment difference are least squares mean derived from a repeated measures model

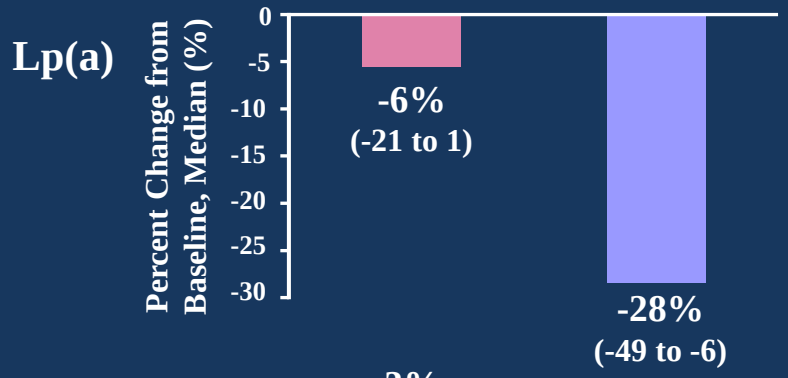
DESCARTES: UC LDL-C Goal Achievement

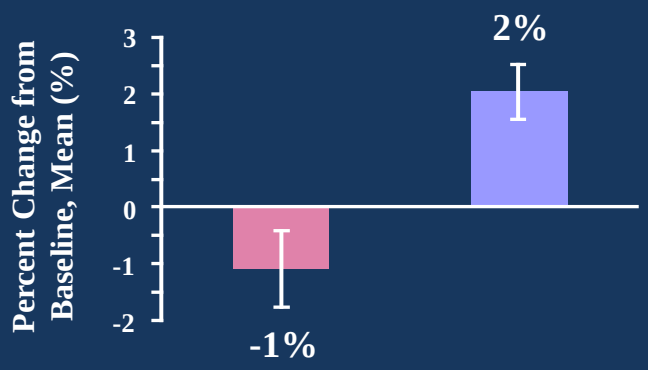


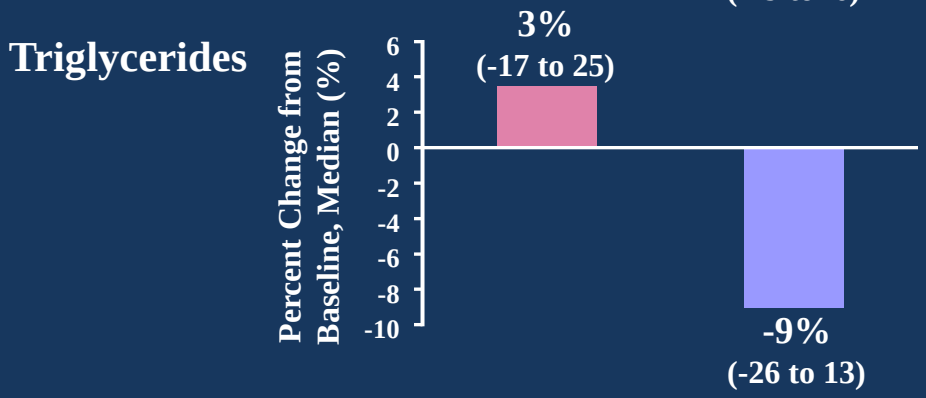
DESCARTES: Other Lipids at Week 52











Placebo QM

Evolocumab 420 mg QM

Error bars represent standard error
Data in parentheses represent Q1 to Q3

- **OUTCOMES With PCSK9i Inhibitor treatment**

FOURIER Trial: Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects with Elevated Risk

- This randomized, double-blind, placebo-controlled trial investigated the effects of adding evolocumab to high-intensity statin therapy compared with high-intensity statins alone.
- Study results included data for over 27,500 individuals with clinically evident atherosclerotic disease and baseline LDL-C levels ≥70 mg/dL and non-HDL-C levels ≥100 mg/dL; mean patient follow-up was 2.2 years.
- All study participants were receiving statin therapy with or without ezetimibe, and the evolocumab and placebo groups had the same baseline LDL-C (92 mg/dL).

Abbreviations:; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.

Sabatine MS, et al. *NEJM.* 2017; epub ahead of print.

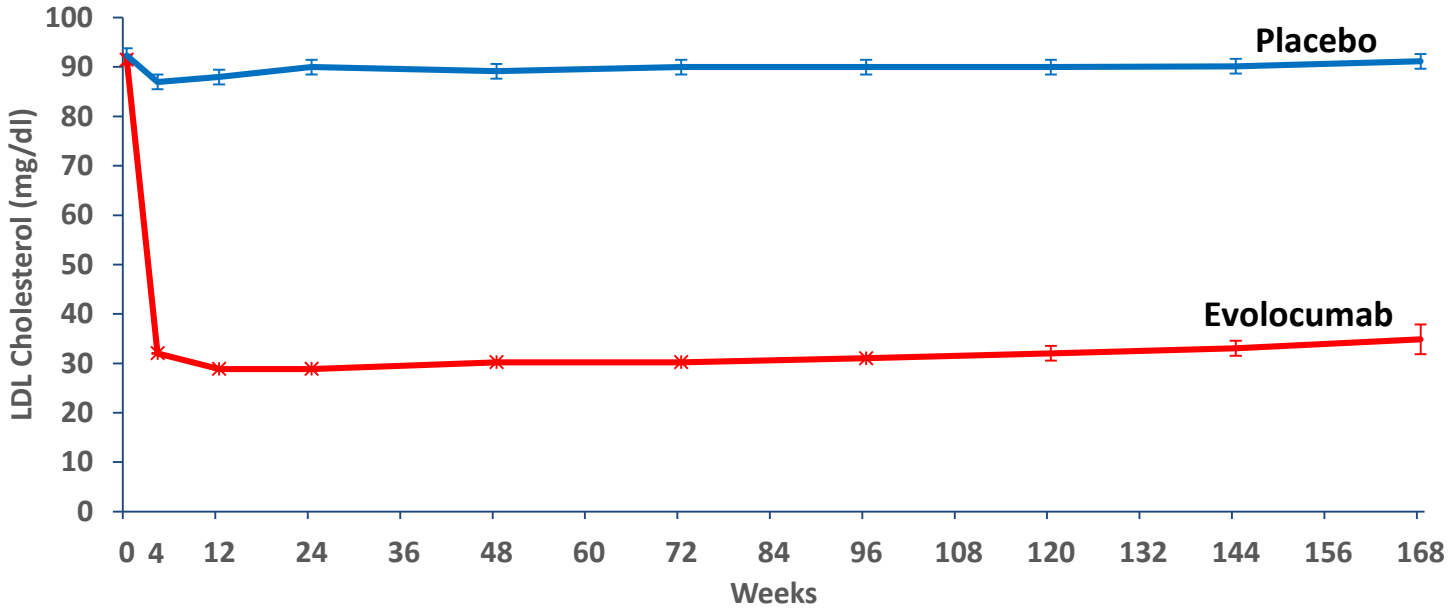
FOURIER Primary and Secondary Endpoints

- At 26 months, extremely tight lipid control with evolocumab led to a 15% decrease in risk for the primary composite endpoint and 20% decrease in risk for a secondary composite endpoint
  - The primary endpoint included MI, cardiovascular death, stroke, coronary revascularization, or hospitalization for unstable angina
  - The secondary endpoint included cardiovascular death, MI, or stroke
- Beyond the second year of follow-up, the risk reduction increased to 20% for the primary endpoint and to 25% for the secondary endpoint
- For singular endpoints at 26 months, very tight lipid control reduced the risk of MI by 27%, stroke by 21%, and coronary revascularization by 22%

Abbreviations: FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk trial; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.

Sabatine MS, et al. *NEJM*. 2017; epub ahead of print.

FOURIER Evolocumab Study
LDL-C Levels Over time



No. at Risk

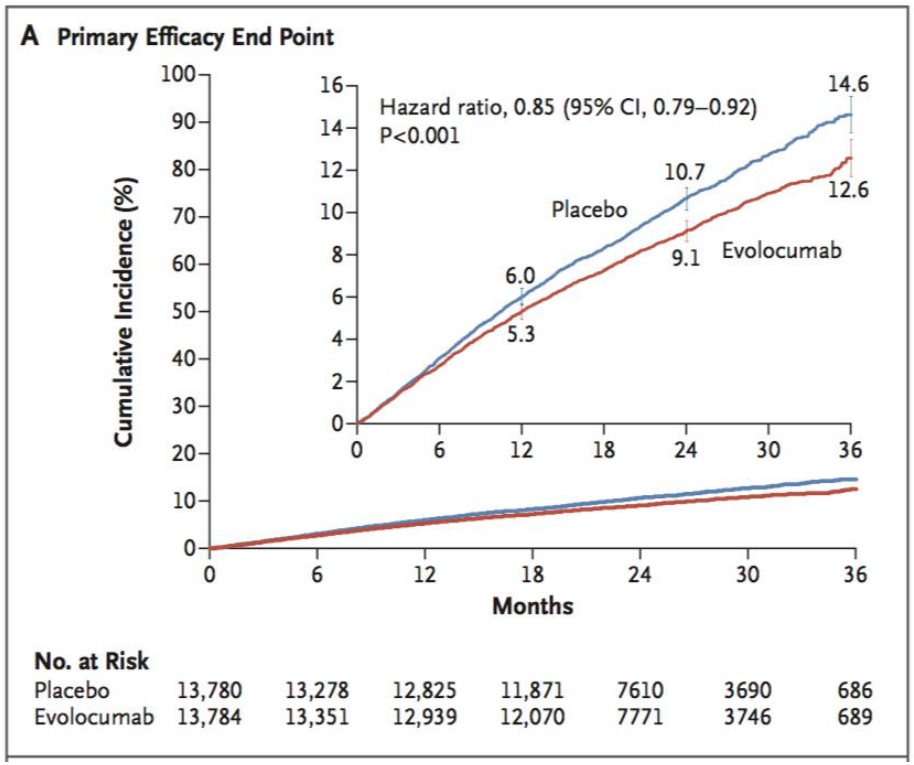
Placebo	13,779	13,251	13,151	12,954	12,596	12,311	10,812	6926	3352	790
Evolocumab	13,784	13,288	13,144	12,964	12,645	12,359	10,902	6958	3323	768

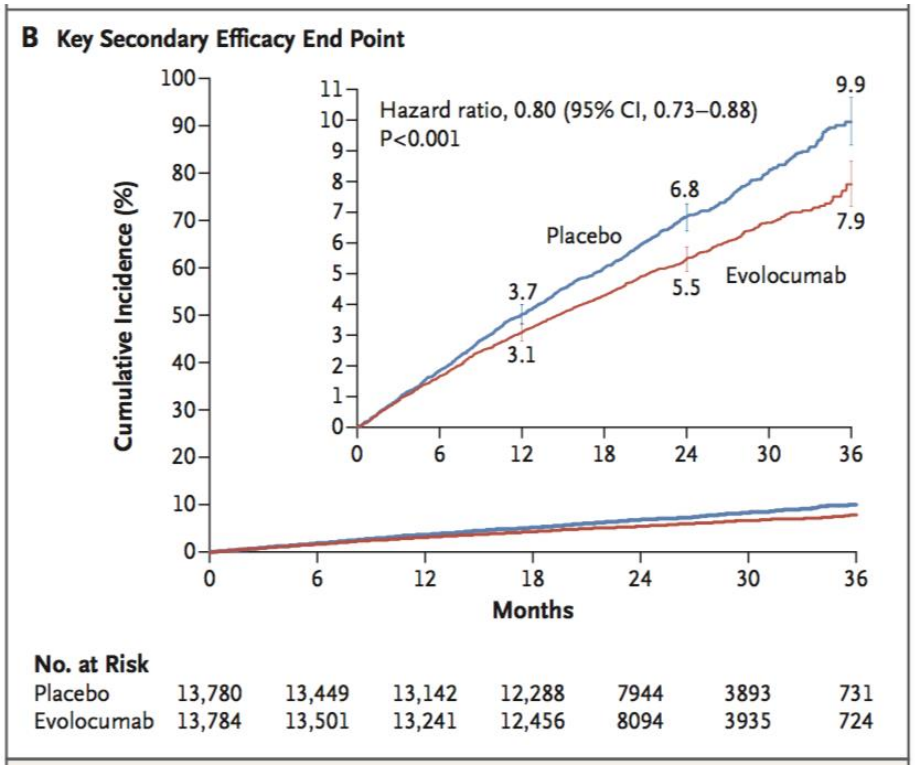
Absolute difference (mg/dL)	54	58	57	56	55	54	52	53	50
Percentage difference	57	61	61	59	58	57	55	56	54
P-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Abbreviations: FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk trial; LDL-C, low-density lipoprotein cholesterol.

Sabatine MS, et al. *NEJM*. 2017; epub ahead of print.

FOURIER Evolocumab Study Endpoints





Cumulative event rates for the primary efficacy endpoint (Composite of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization)

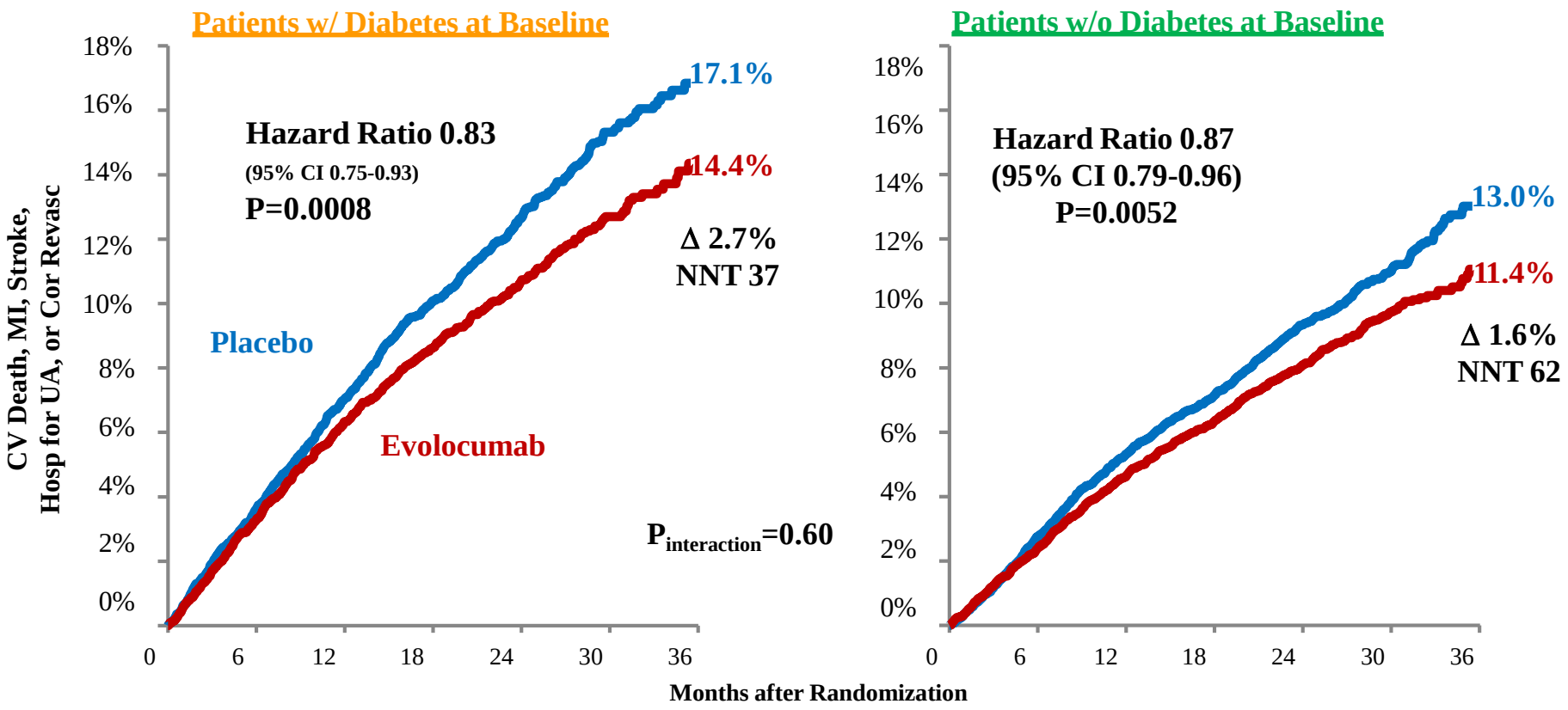
Cumulative rates for the key secondary efficacy endpoint (Composite of cardiovascular death, MI, or stroke)

Abbreviations: FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk trial; MI, myocardial infarction.

Sabatine MS, et al. *NEJM*. 2017; epub ahead of print.

Evolocumab in Diabetes, and Risk of Development of Diabetes: An Analysis from the FOURIER Trial

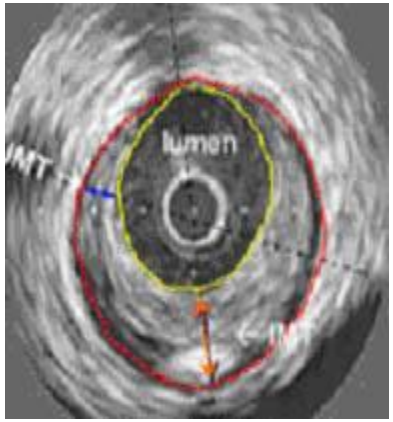
MS Sabatine, LA Leiter, SD Wiviott, RP Giugliano, P Deedwania, GM De Ferrari, SA Murphy, JF Kuder, AC Keech, PS Sever, and TR Pedersen, for the FOURIER Steering Committee & Investigators

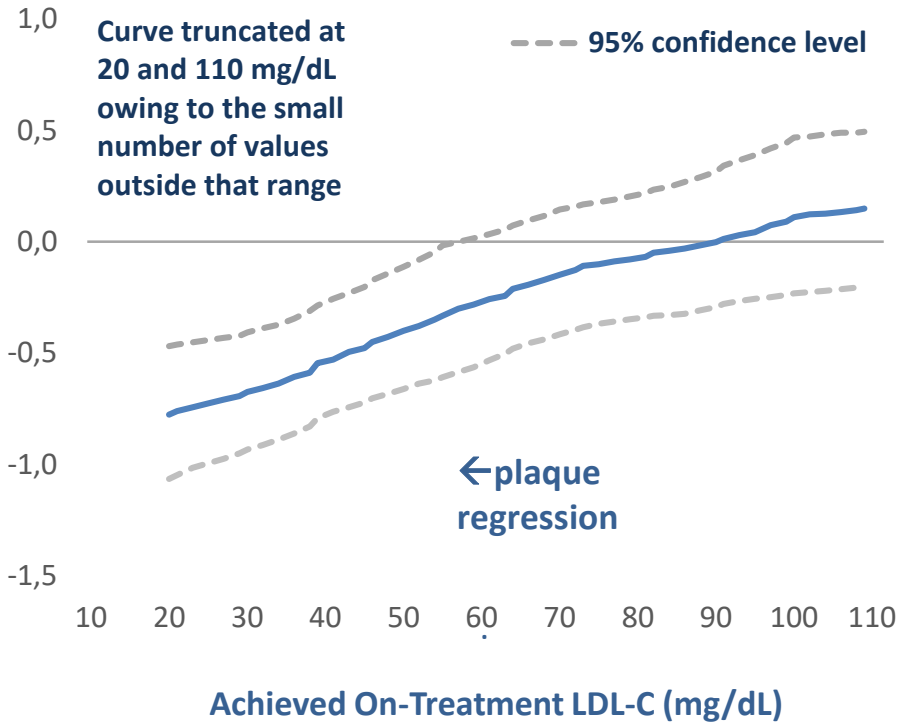


***Primary endpoint*: Composite cardiovascular death, myocardial infarction, stroke, hospital admission for unstable angina or coronary revascularization**

GLAGOV: Mean On-Treatment LDL-C vs. Change in Percent Atheroma Volume

The GLAGOV multicenter, double-blind, placebo-controlled, randomized clinical trial (enrollment 5/2013 to 1/2015) conducted at 197 academic and community hospitals in 6 continents, enrolling 968 patients (mean age 59.8 years, 27.8% female) with CAD





Patients with angiographic CAD were randomized to receive monthly evolocumab (420 mg) (n=484) or placebo (n=484) SQ for 76 weeks, in addition to statins

Locally weighted polynomial regression (LOESS) plot demonstrates a linear continuous relationship between achieved LDL-C level and PAV progression/ regression for levels of LDL-C ranging from 110 mg/dL to as low as 20 mg/dL

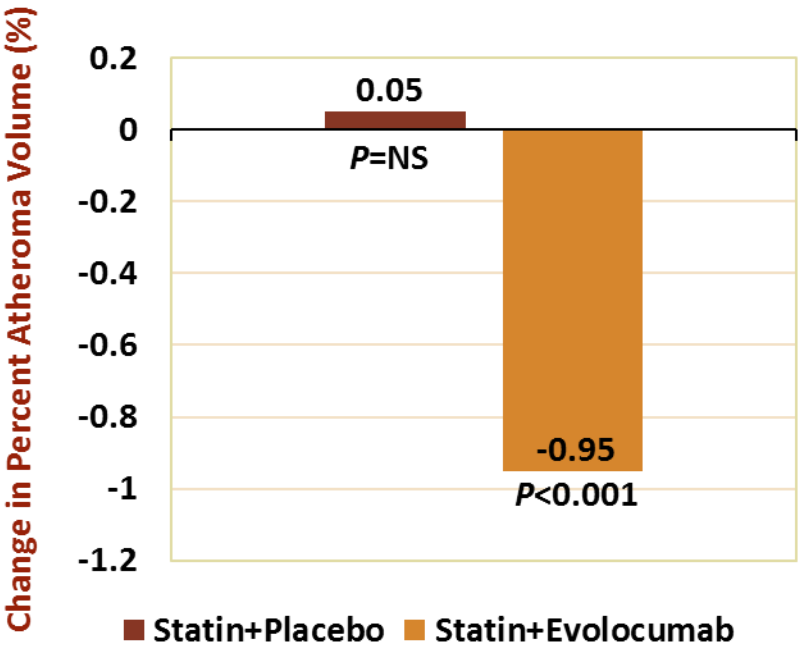
Abbreviations: CAD, coronary artery disease; GLAGOV, Global Assessment of Plaque Regression With a PCSK9 Antibody ;LDL-C, low-density lipoprotein cholesterol; SQ, subcutaneous.

Nicholls SJ. *JAMA*. 2016;316(22):2373-2384.

GLAGOV: Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound

Trial design: Patients with CAD and elevated LDL-C on statin therapy were randomized to SQ evolocumab (n=484) vs SQ placebo (n=486).

Primary Endpoint: Percent Atheroma Volume



Results

- Nominal change in percent atheroma volume at 78 weeks: -0.95% in the evolocumab group vs. 0.05% in the placebo group (*P*<0.001 for between-group comparison)
- Patients with plaque regression: 64.3% with evolocumab vs. 47.3% with placebo (*P*<0.001)
- Major adverse cardiac events: 12.2% with evolocumab vs. 15.3% with placebo

Conclusions

- Among patients with angiographic evidence of CAD on chronic statin therapy, the PCSK9 inhibitor evolocumab resulted in a greater change in percent atheroma volume and a greater proportion of patients with plaque regression

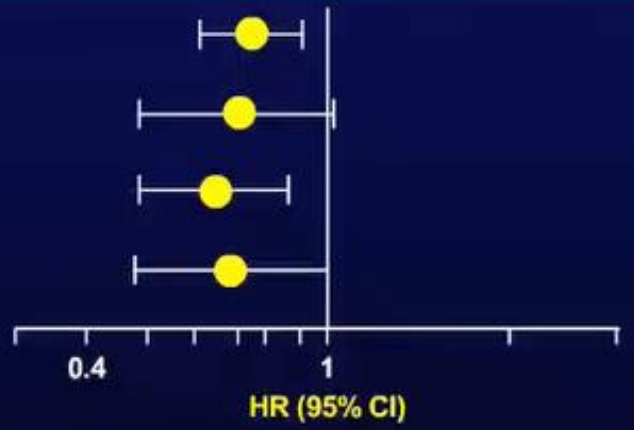
Abbreviations: CAD, coronary artery disease; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; SQ, subcutaneous.

Nicholls SJ, et al. *JAMA.* 2016;316:2373-2384.

Effect of Alirocumab in Addition to a Statin On CV Risk in High-Risk ASCVD

- Pooled analysis of 10 phase 3 ODYSSEY trials
  - Patients with high-risk ASCVD, 91.1%-92.9% had CHD
  - Most patients on a background of maximally tolerated statin treated with alirocumab or control (placebo or ezetimibe)
- Lower achieved levels of LDL-C on alirocumab correlated with a lower MACE risk

Population	N	HR (95% CI) per 39 mg/dL lower LDL-C
Overall ASCVD	3503	0.75 (0.62 to 0.90)
Polyvascular disease	943	0.71 (0.49 to 1.01)
ASCVD + DM	980	0.65 (0.49 to 0.86)
ASCVD + eGFR <60	660	0.69 (0.48 to 1.00)



ASCVD=atherosclerotic cardiovascular disease; CHD=coronary heart disease; CI=confidence interval; CV=cardiovascular; DM=diabetes mellitus; eGFR=estimated glomerular filtration rate; HR=hazard ratio; LDL-C=low-density lipoprotein-cholesterol; MACE=major adverse cardiovascular events.

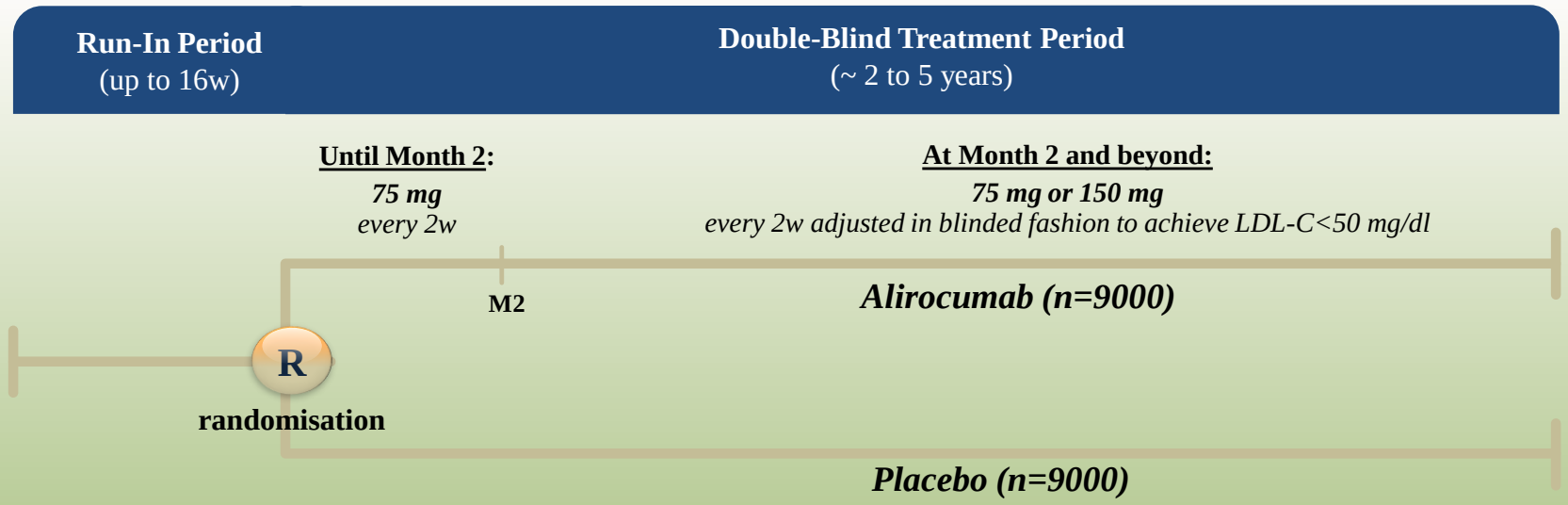
Ray KK et al. ACC 66th Annual Scientific Session, 2017. Poster.

ODYSSEY Outcomes Study

A study specifically designed to evaluate the long-term clinical benefit of alirocumab initiation post Acute Coronary Syndrome

- **Patient population:**
  - **Recent ACS (4-52 wks before randomisation*)**
  - **At least one of the following: LDL-C ≥70 mg/dL (1.81 mmol/L), non-HDL-C ≥100 mg/dL (2.59 mmol/L), or apo B ≥80 mg/dL despite optimal statin treatment**

- **Primary endpoint (1° EP):** Composite of
  - **CHD death**
  - Non-fatal MI
  - Ischaemic stroke
  - Unstable angina requiring hospitalisation



Background Lipid Treatment: *Atorvastatin 40/80mg, rosuvastatin 20/40 mg, or maximal tolerated dose of one of these statins, with non-statin lipid treatments allowed*

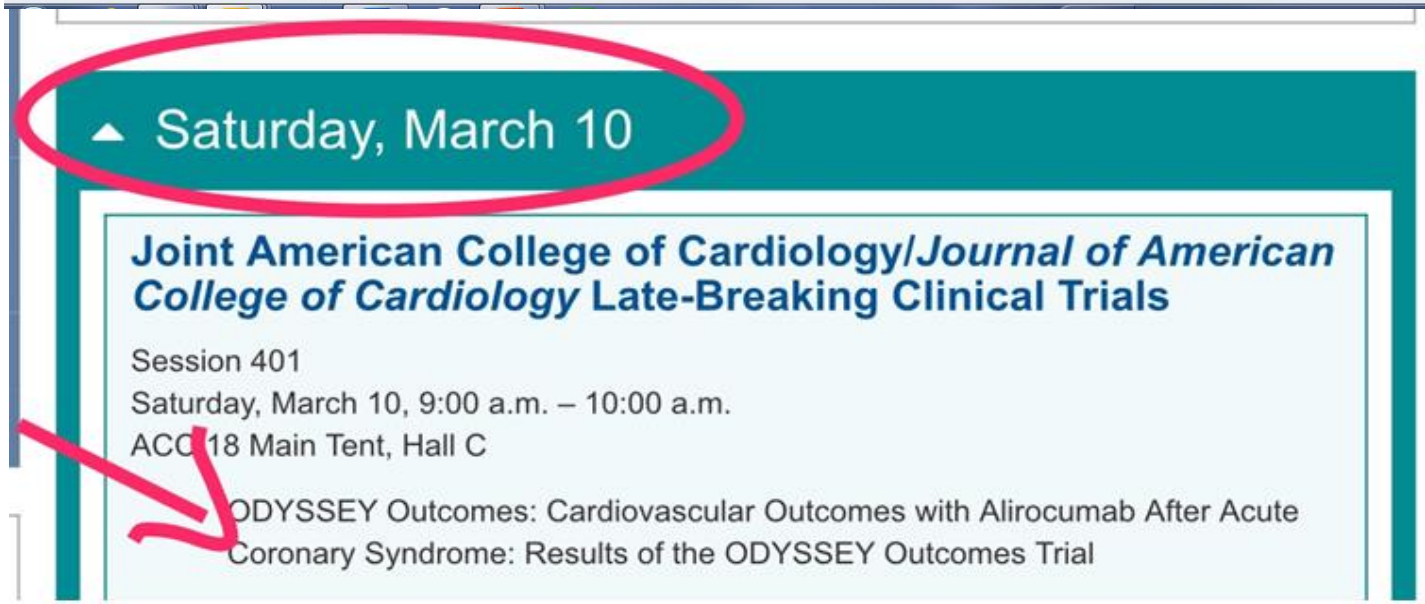
ODYSSEY

Baseline Odyssey Outcomes N=18.535

Population	Patient with a coronary **Event within a year (ACS)**
Baseline Demographics	**Diabetes: 24%** Recurrent MI: 20% Prior CAD 20% Prior stroke 3% Prior PAD 4%
Statin Background	**Maximally tollerated** **High-intensity: 89%** Moderate- intensity 8%:
Dosing Regimen	**Treat-to target** 75Q2W ->150Q2W if ldl-c > 50mg/dL
Follow-up	**2-to-5 years**

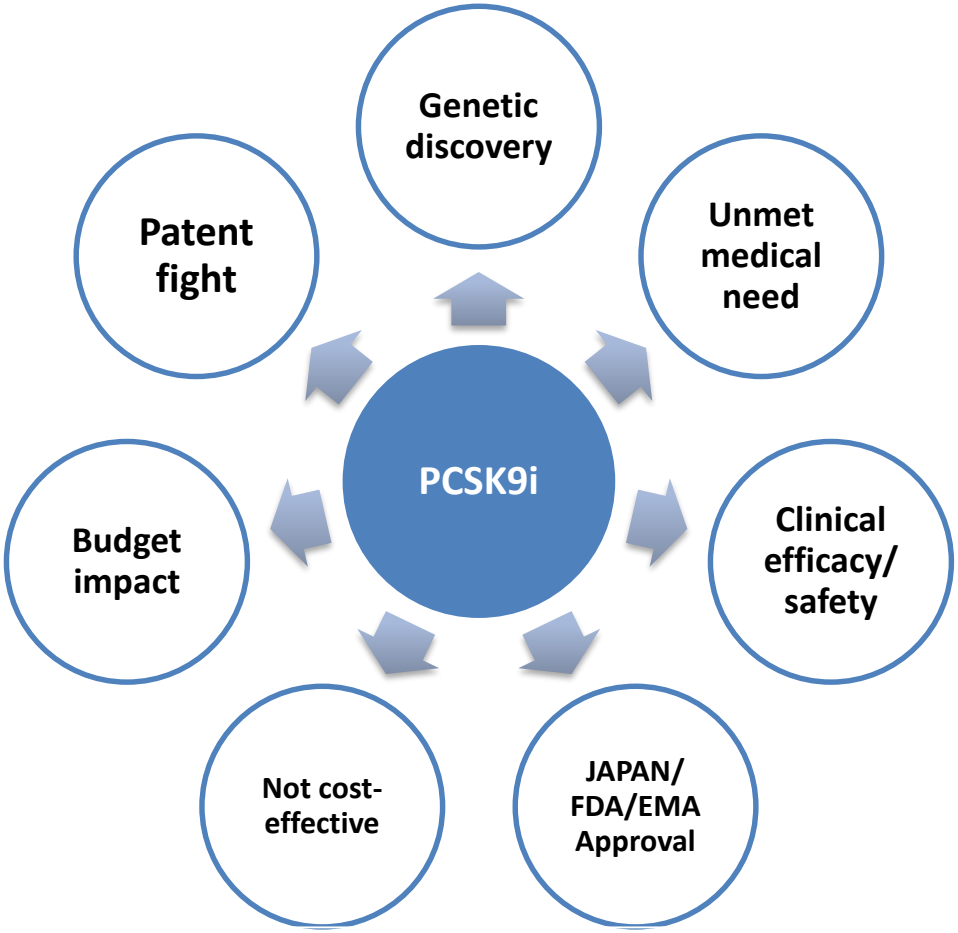
ODYSSEY

ODYSSEY Outcomes data in ACC 2018



ODYSSEY

CONCLUSION


PCSK9i
Genetic discovery
Unmet medical need
Clinical efficacy/ safety
JAPAN/ FDA/EMA Approval
Not cost-effective
Budget impact
Patent fight