LES ANTI PCSK9 : MECANISMES ET INDICATIONS

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PCSK9 - GENETICS AND BIOLOGY

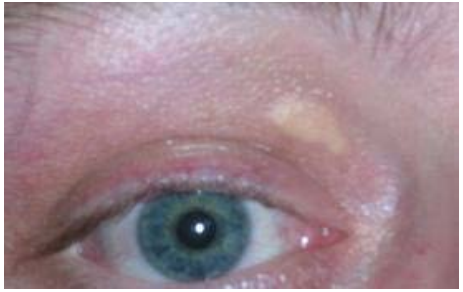
Plasma Total Cholesterol > 8mM (3g/L)

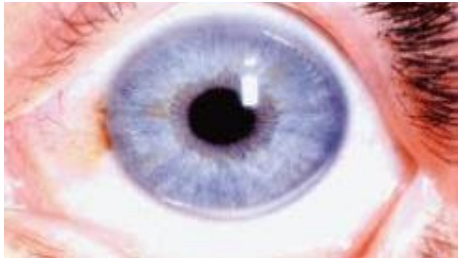
Tendon Xanthomas

Corneal Arcus

Xanthelasma

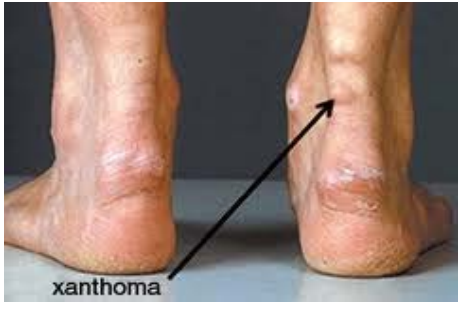
Coronary Syndromes (Family)





LDL Receptor 90%

ApoB100 (LBD) 5%



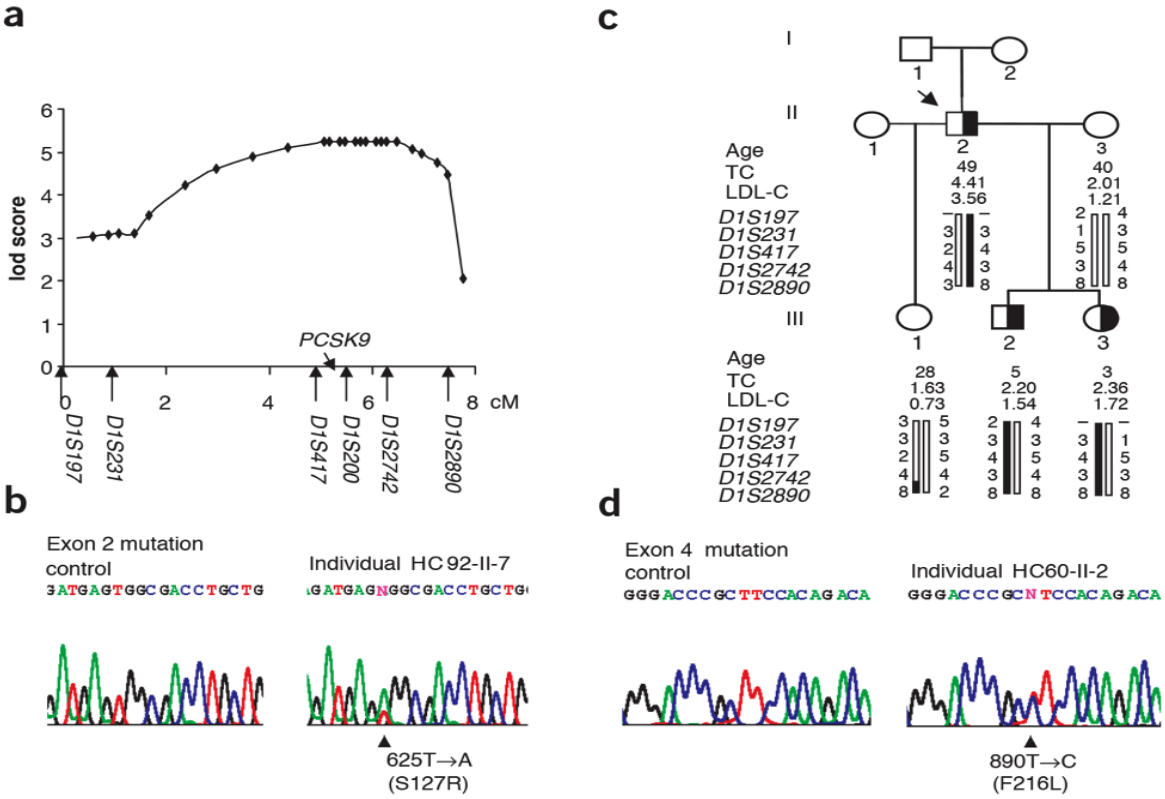
Genest J, Libby P. Lipoprotein disorders and cardiovascular disease. In: Bonow RO, Mann DL, Zipes DP, Libby P, eds. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine* . 9th ed. Philadelphia, PA:Saunders Elsevier; 2011:chap 47.
Semenkovich, CF. Disorders of lipid metabolism. In: Goldman L, Schafer AI, eds. *Cecil Medicine* . 24th ed. Philadelphia, PA: Saunders Elsevier; 2011:chap 213

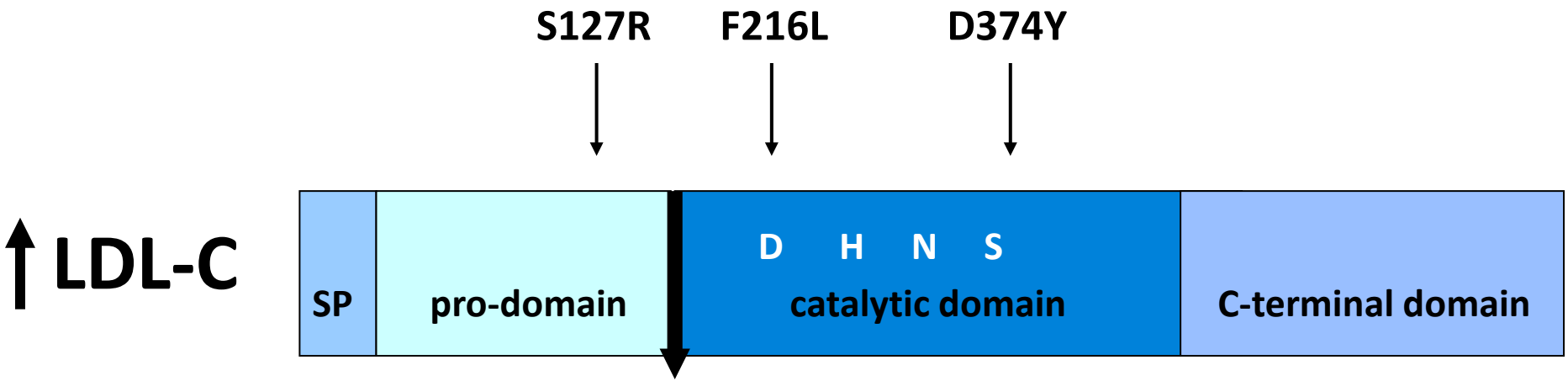
BRIEF COMMUNICATIONS

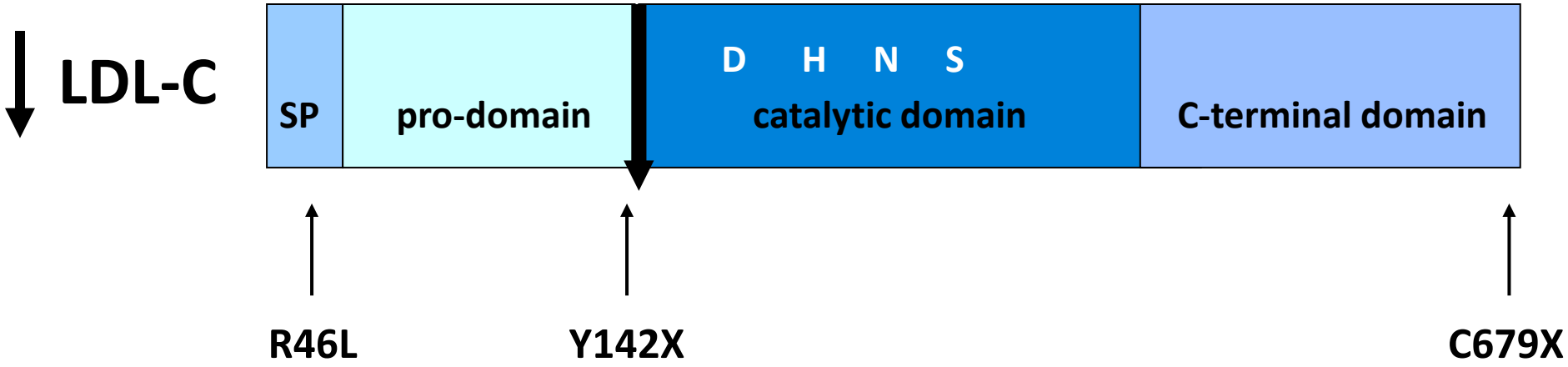
Mutations in *PCSK9* cause autosomal dominant hypercholesterolemia

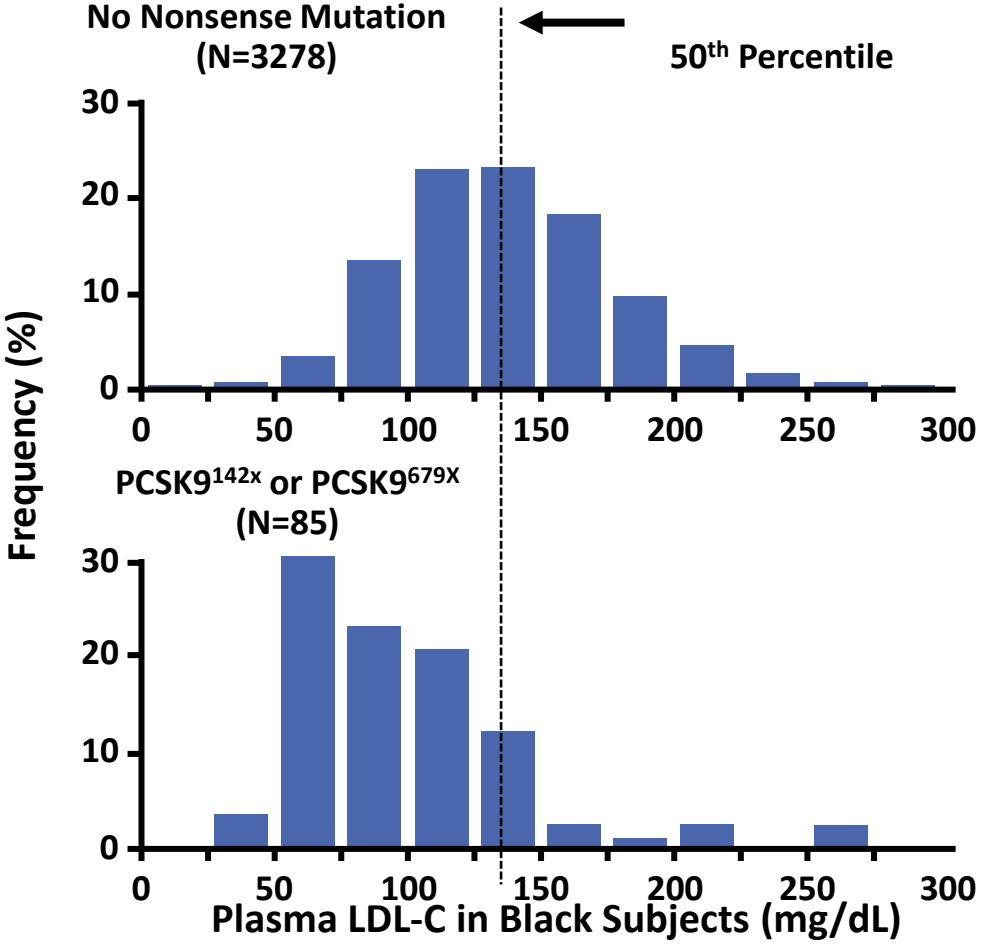
Marianne Abifadel[1,2], Mathilde Varret[1], Jean-Pierre Rabès[1,3], Delphine Allard[1], Khadija Ouguerram[4], Martine Devillers[1], Corinne Cruaud[5], Suzanne Benjannet[6], Louise Wickham[6], Danièle Erlich[1], Aurélie Derré[1], Ludovic Villéger[1], Michel Farnier[7], Isabel Beucler[8], Eric Bruckert[9], Jean Chambaz[10], Bernard Chanu[11], Jean-Michel Lecerf[12], Gerald Luc[12], Philippe Moulin[13], Jean Weissenbach[5], Annick Prat[6], Michel Krempf[4], Claudine Junien[1,3], Nabil G Seidah[6] & Catherine Boileau[1,3]

Autosomal dominant hypercholesterolemia (ADH; OMIM144400), a risk factor for coronary heart disease, is characterized by an increase in low-density lipoprotein cholesterol levels that is associated with mutations in the genes *LDLR* (encoding low-density lipoprotein receptor) or *APOB* (encoding apolipoprotein B). We mapped a third locus associated with ADH, *HCHOLA3* at 1p32, and now report two mutations in the gene *PCSK9* (encoding proprotein convertase subtilisin/kexin type 9) that cause ADH. *PCSK9* encodes NARC-1 (neural apoptosis regulated convertase), a newly identified human subtilase that is highly expressed in the liver and contributes to cholesterol homeostasis.

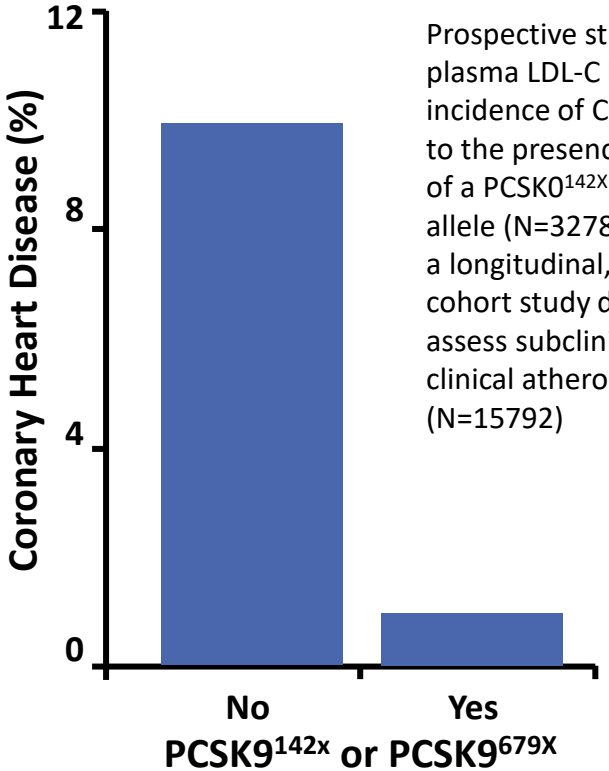



S127R
F216L
D374Y
LDL-C
SP
pro-domain
D H N S
catalytic domain
C-terminal domain


LDL-C
SP
pro-domain
D H N S
catalytic domain
C-terminal domain
R46L
Y142X
C679X



88% reduction in the risk of CHD

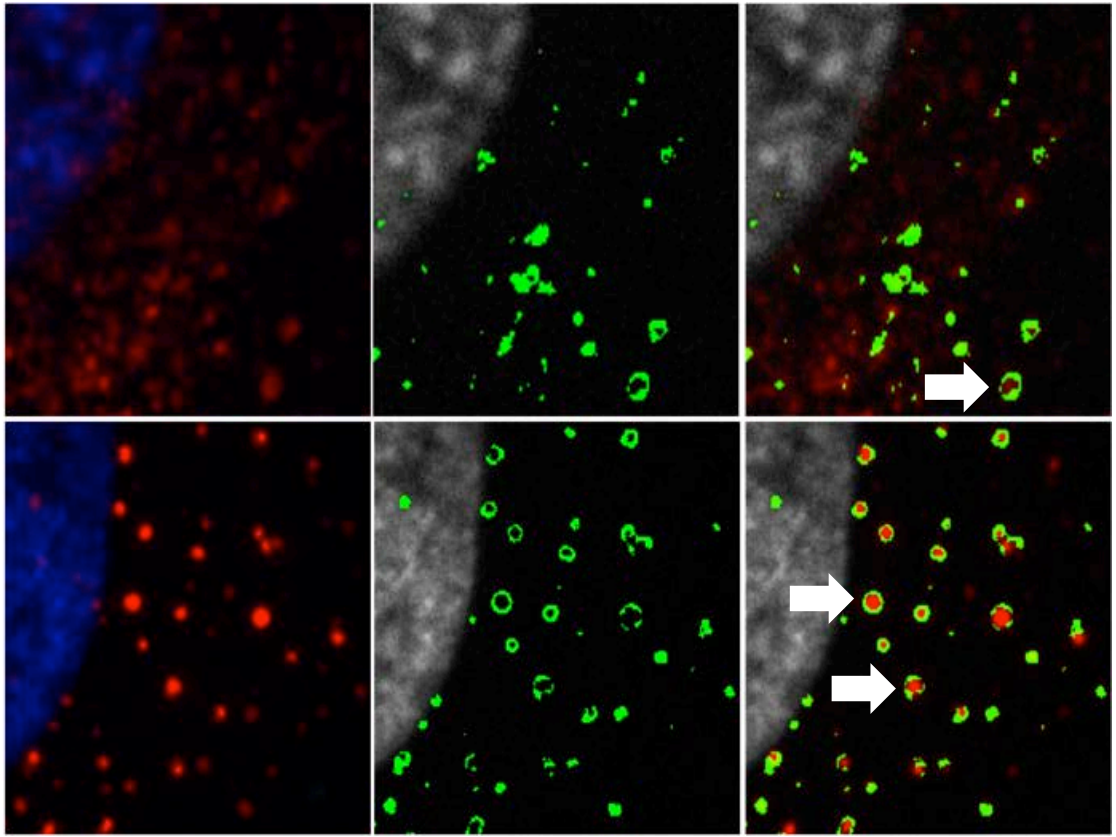


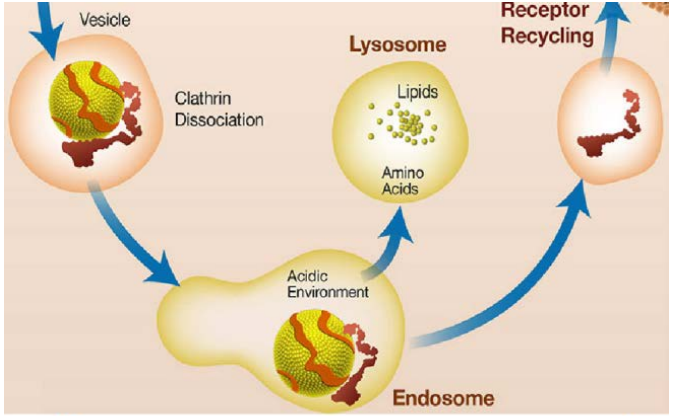
Prospective study of plasma LDL-C levels and incidence of CHD according to the presence or absence of a PCSK0^{142X} or PCSK9^{679X} allele (N=3278) taken from a longitudinal, biracial cohort study designed to assess subclinical and clinical atherosclerosis (N=15792)

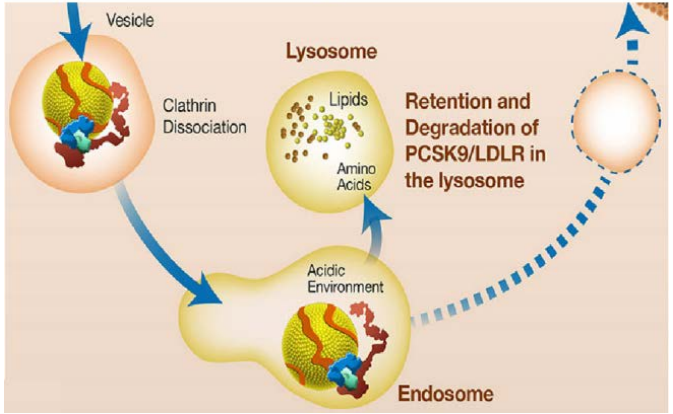
Cohen J, et al. N Engl J Med 2006;354:1264–1272

LDLR | Endosome | Merge

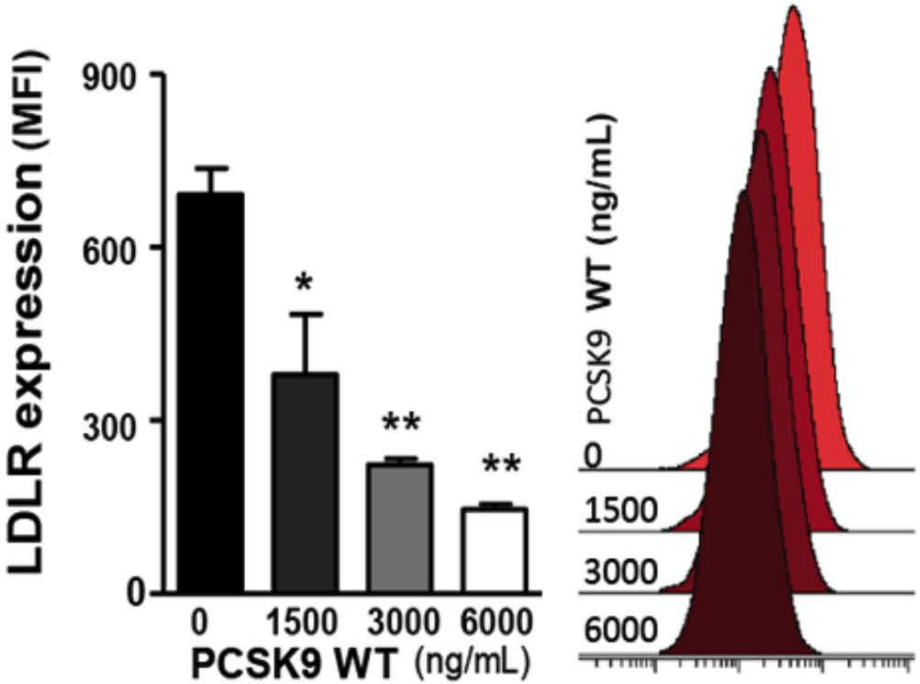
+ PCSK9



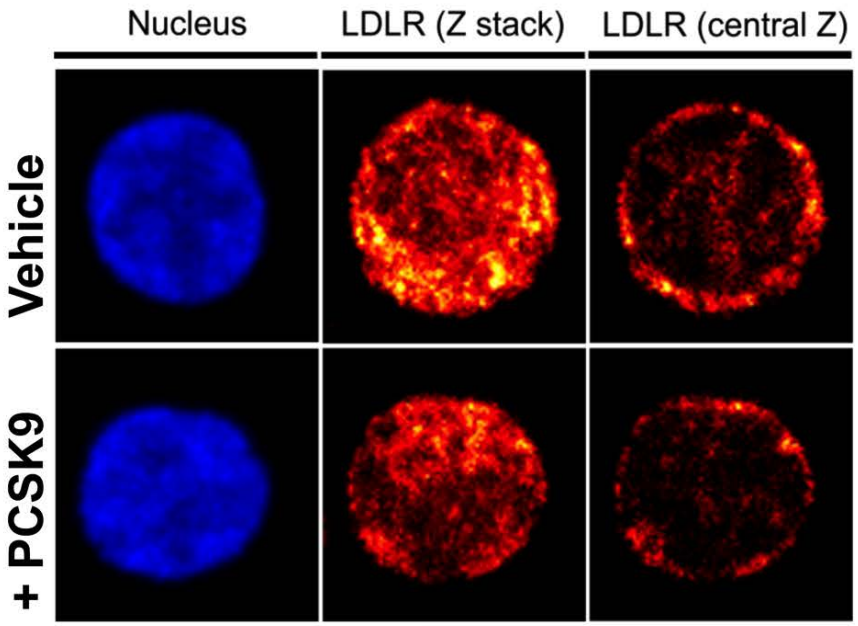




LDLR Cell Surface expression (Flow Cytometry)

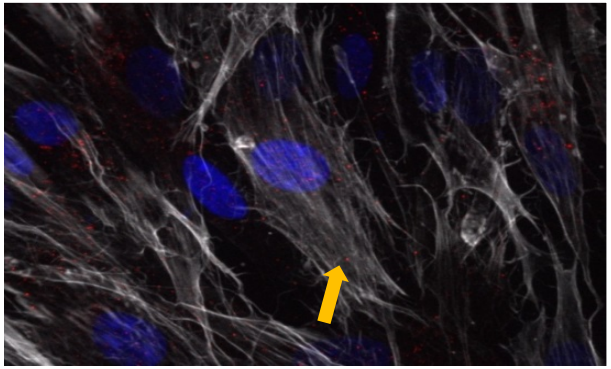


LDLR Cell Surface expression (Confocal Microscopy)

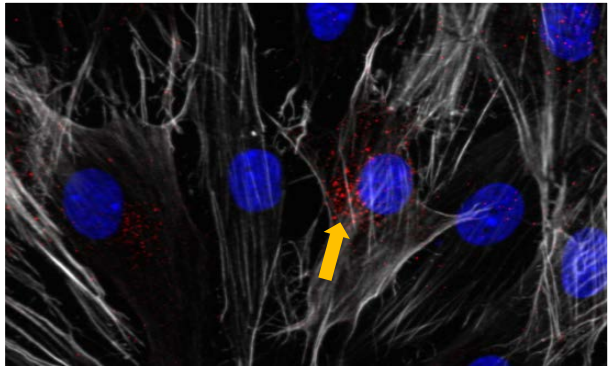


MFI = median fluorescence intensity
* p<0.05, ** p<0.01 vs. condition no PCSK9 (0)

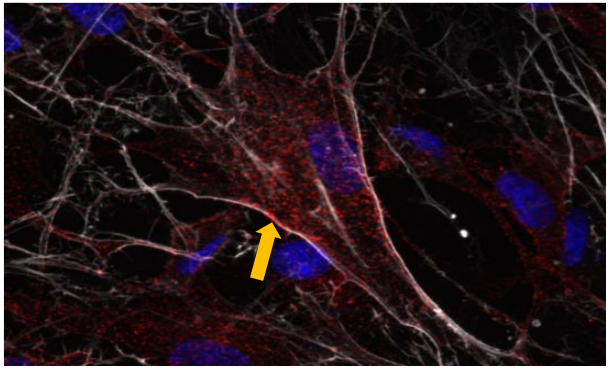
Lambert G, et al. J Am Coll Cardiol 2014;63:2365–2373



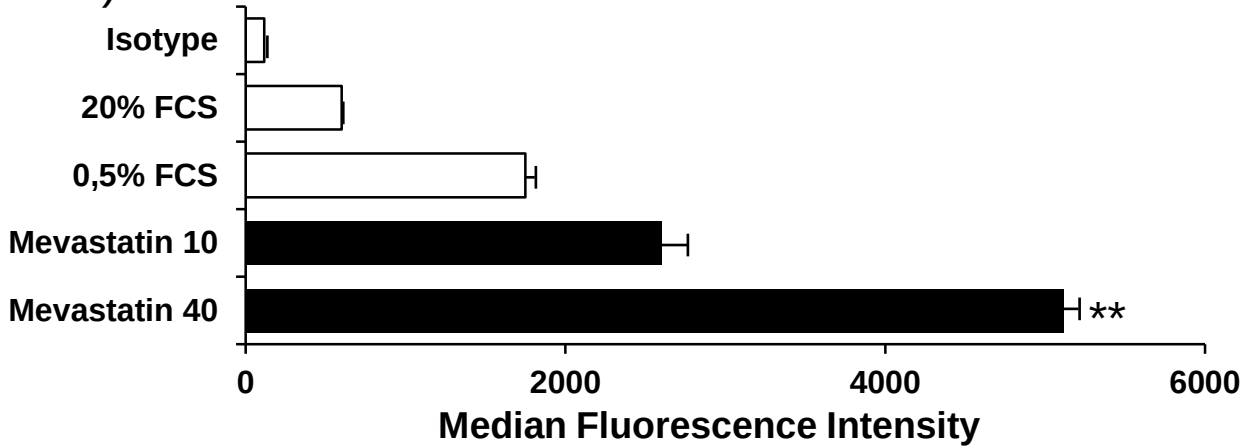
20% FCS
(fetal calf serum)

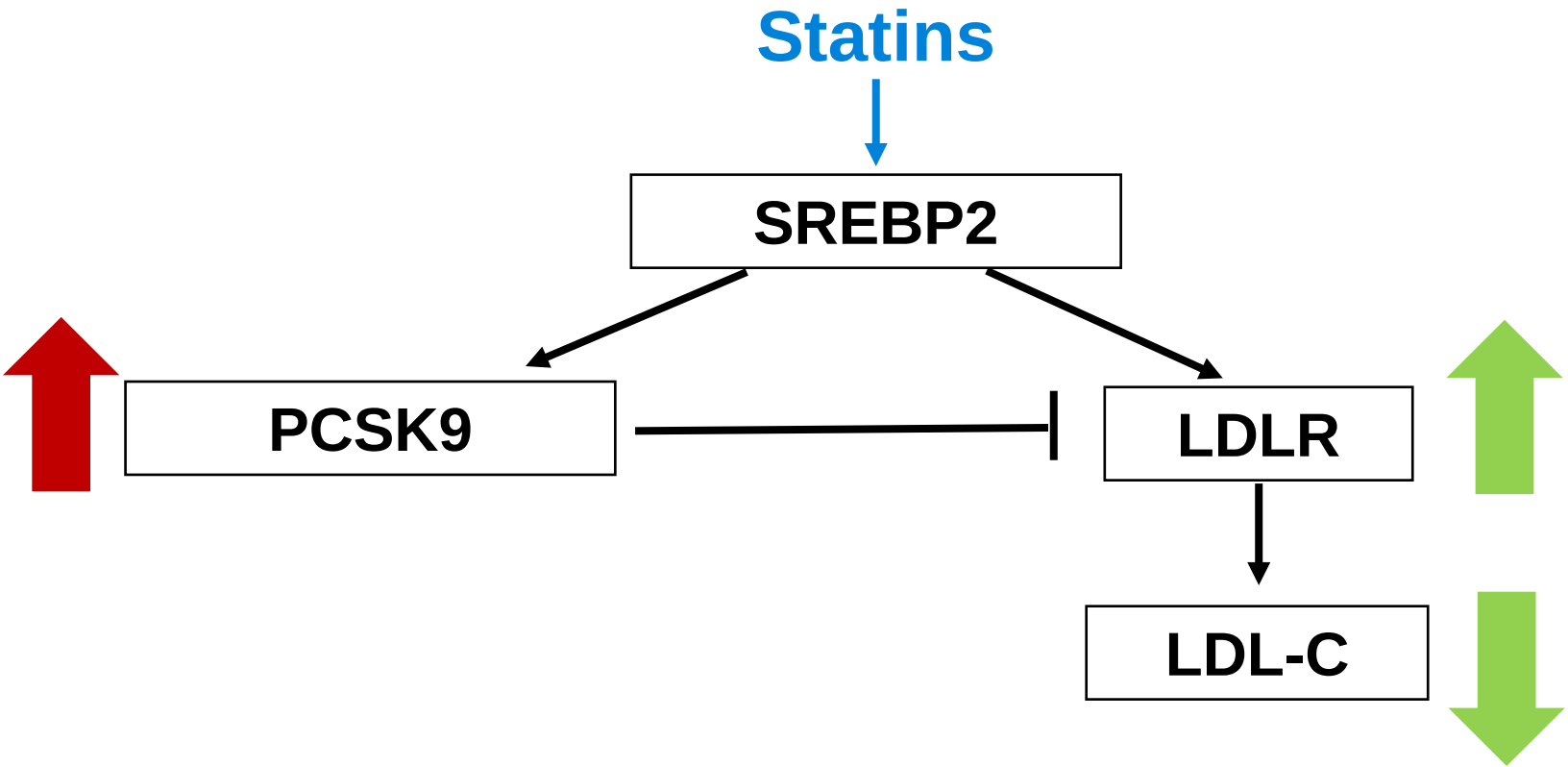


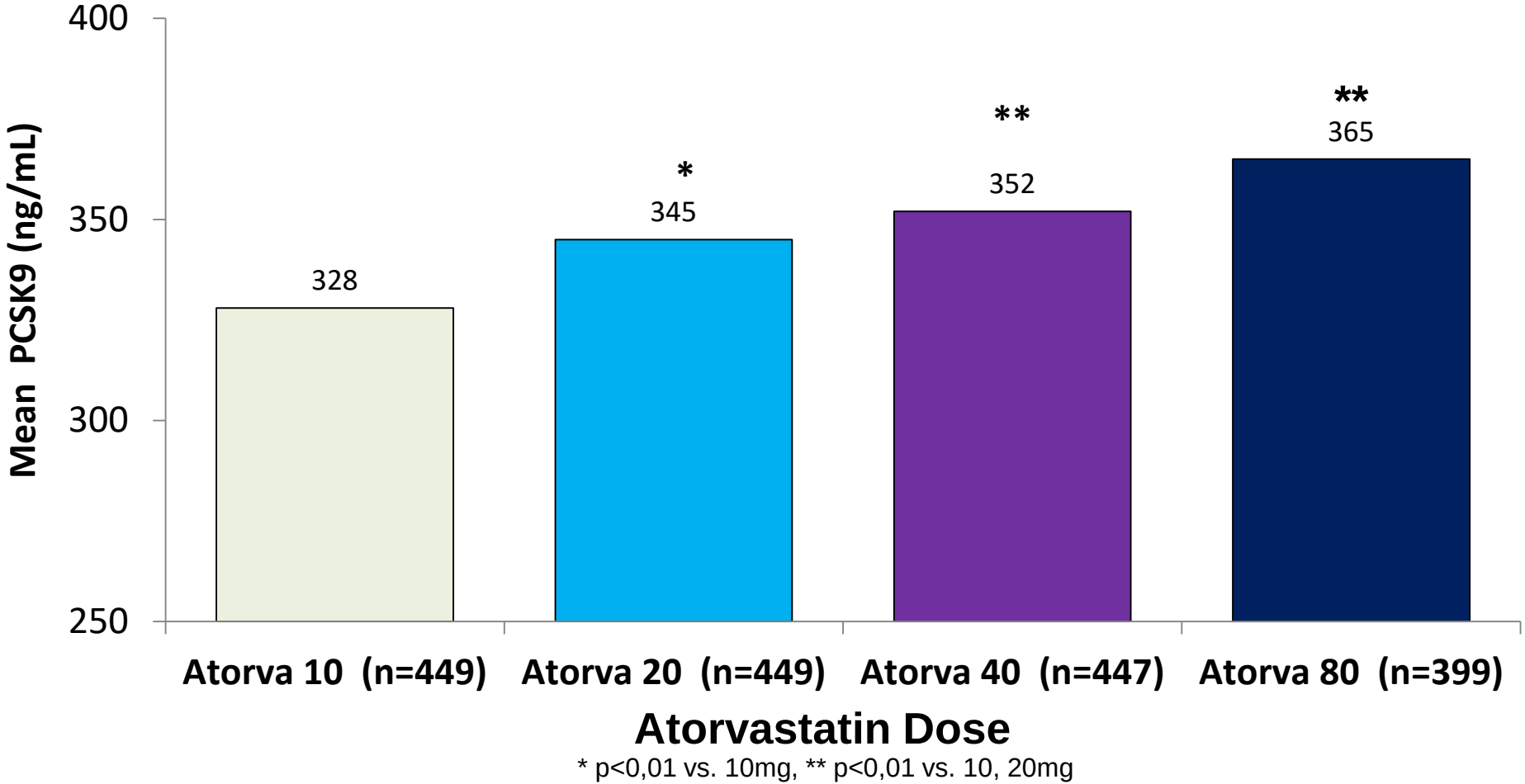
0,5% FCS

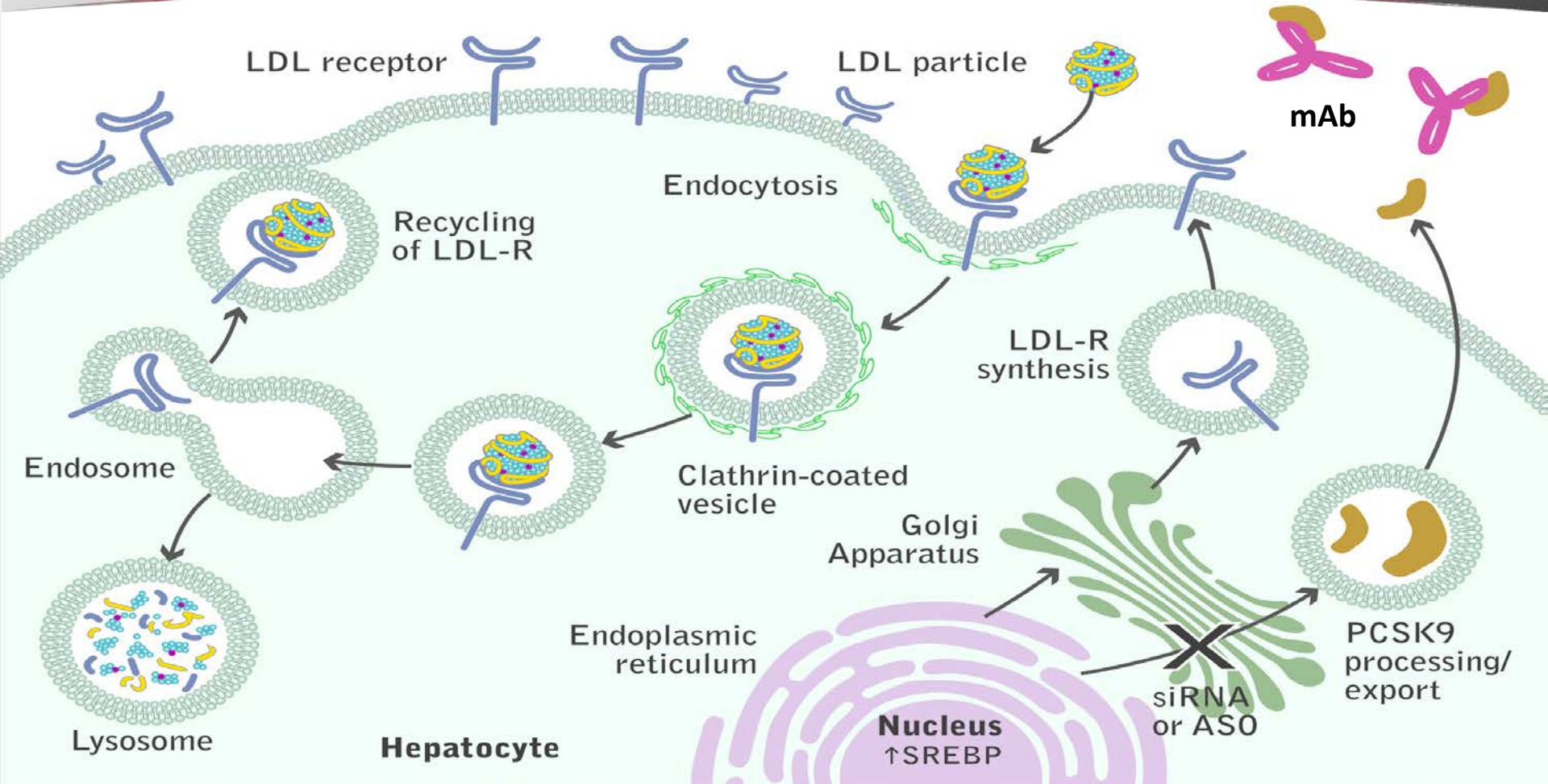


0,5% FCS + Mevastatin

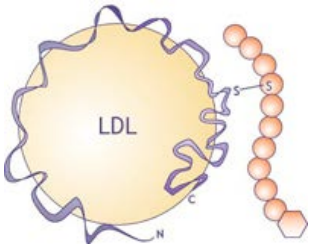



Statins
SREBP2
PCSK9
LDLR
LDL-C

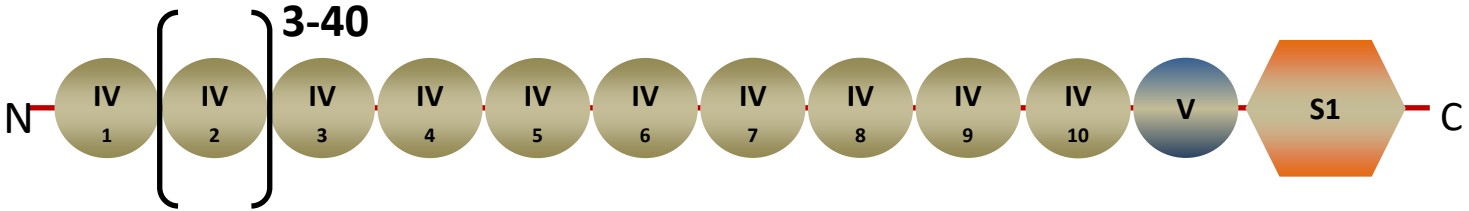

400
350
300
250
Mean PCSK9 (ng/mL)
328
*
345
**
352
**
365
Atorva 10 (n=449)
Atorva 20 (n=449)
Atorva 40 (n=447)
Atorva 80 (n=399)
Atorvastatin Dose
* p<0,01 vs. 10mg, ** p<0,01 vs. 10, 20mg


LDL receptor
LDL particle
mAb
Endocytosis
Recycling of LDL-R
LDL-R synthesis
Endosome
Clathrin-coated vesicle
Golgi Apparatus
Endoplasmic reticulum
PCSK9 processing/ export
siRNA or ASO
Nucleus ↑SREBP
Lysosome
Hepatocyte

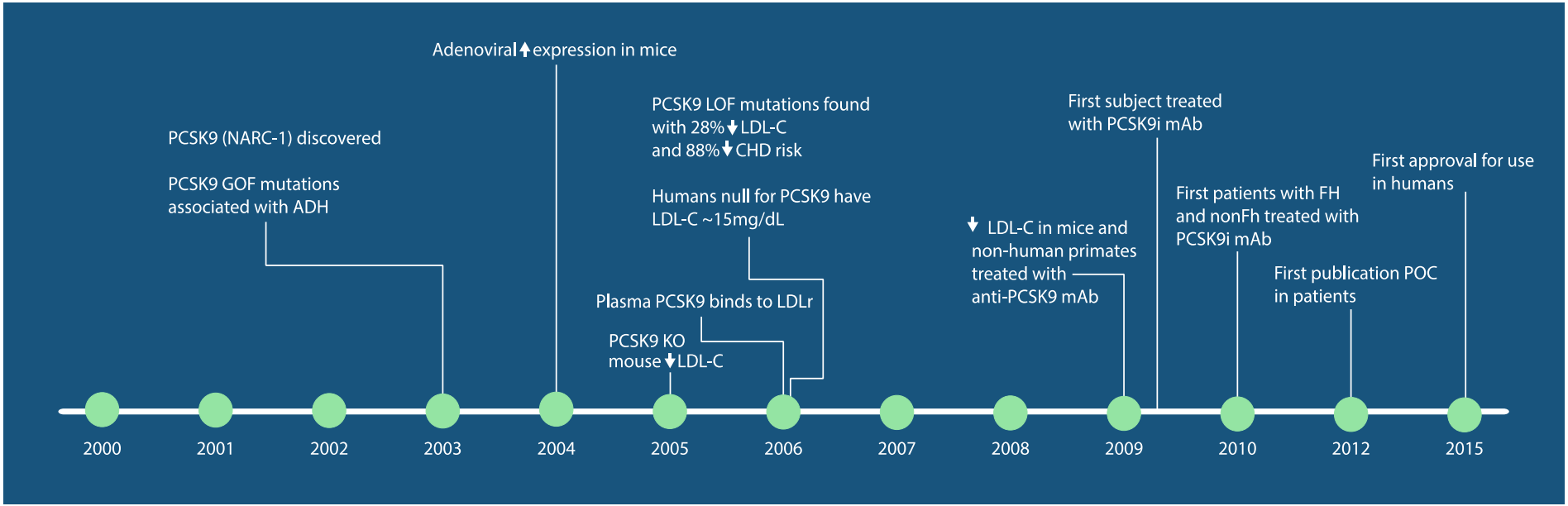
	Statins	Pcsk9 mAbs
PCSK9 ⊣ LDLR	⇧	⇧
LDL-C	⇩	⇩
Lp(a)	=	⇩



Apo(a)



PCSK9i: Rapid Progress From Discovery to Clinic



PCSK9 inhibitors in PHASE III trials

Alirocumab ODYSSEY Phase 3 Lipid Lowering Studies*

Heterozygous FH patients

FH1 (n=486):
Het FH LDL-C ≥70 (+CVD)/ ≥100 mg/dL (-CVD)
Ali vs. placebo (on background max tolerated statin +/- LLT)

FH2 (n=249):
Het FH LDL-C ≥70 (+CVD)/ ≥100 mg/dL (-CVD)
Ali vs. placebo (on background max tolerated statin +/- LLT)

HIGH FH (n=107):
Het FH LDL-C ≥160 mg/dL
Ali vs. placebo (on background max tolerated statin +/- LLT)

ESCAPE (n=63):
Het FH undergoing apheresis
Ali vs. placebo

'High CV risk' population

COMBO I (n=316):
CHD or CHD RE
Ali vs. placebo (on background max tolerated statin +/- LLT)

COMBO II (n=720):
CHD or CHD RE
Ali vs. eze (on background max tolerated statin)

LONG TERM (n=2,341):
Het FH, CHD or CHD RE
LDL-C ≥70 mg/dL
Ali vs. placebo (on background max tolerated statin +/- LLT)

Statin intolerance or monotherapy

ALTERNATIVE (n=314):
Statin intolerant at mod/high CV risk
LDL-C ≥70 mg or ≥100 mg/dL
Ali vs. eze vs. ATV

MONO (n=103):
LDL-C 100-190 mg/dL
SCORE ≥1% and <5%; no LLT
Ali vs. eze

CHOICE II (n=233):
LDL-C ≥70 mg or ≥100 mg/dL
Mod/high CV risk
Ali 75 Q2W or ali 150 Q4W or placebo (+/- non-statin LLT)

Statin-specific combinations

CHOICE I (n=804):
Mod/high CV risk
Ali 75 Q2W or ali 300 Q4W or placebo (+/- background statin)

OPTIONS I (n=355):
CHD or CHD RE
LDL-C ≥70 or ≥100 mg/dL on background mod ATV randomized to ali, eze, double ATV or RSV switch

OPTIONS II (n=305):
CHD or CHD RE
LDL-C ≥70 or ≥100 mg/dL on background mod RSV randomized to ali, eze, double RSV

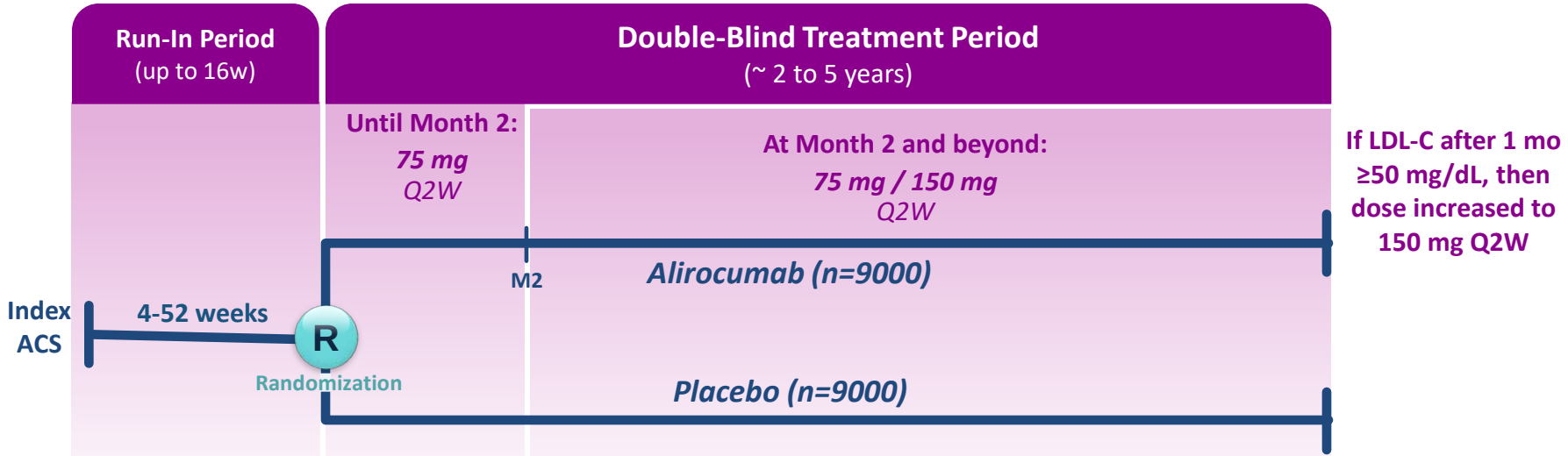
	Phase 3 Dosing and Titration
Start Dose	75 mg Q2W
Initial Titration	↑ to 150 mg Q2W if LDL ≥70 mg/dL

Patient population:

- ACS event 4 to 52 weeks prior to randomization
- Age >40 years
- LDL-C ≥70 mg/dL (1.81 mmol/L) despite optimal lipid treatment

Primary endpoint: Composite of

- CHD death
- Non-fatal MI
- Ischemic stroke
- Unstable angina requiring hospitalization



Background Lipid Treatment: *Atorvastatin 40/80 mg, or rosuvastatin 20/40 mg, or atorvastatin/rosuvastatin at maximal tolerated dose, with or without non-statin lipid treatments, throughout study* **Diet:** *NCEP-ATPIII Therapeutic Lifestyle Changes or equivalent throughout study*

Evolocumab PROFICIO Phase 3 Lipid Lowering Studies*

High LDL range (FH patients)

RUTHERFORD-2 (n=329):
Het FH LDL-C ≥100 mg/dL
Evo Q2W or Q4W vs. placebo (on background stable statin +/- LLT)

TESLA (n=49):
HoFH LDL-C ≥130 mg/dL
Evo Q4W vs. placebo (on background stable statin +/- LLT)

TAUSSIG (n=300):
Severe FH; LT safety
LDL-C ≥100 mg/dL (+) CHD RE; ≥130 mg/dL (-) CHD RE (on background LLT)
Evo Q2W or Q4W

Broad range +/-CHD

DESCARTES (n=901):
LDL-C ≥75 mg/dL (+/-CHD RE)
Evo Q4W vs. placebo (on background ATV 10, ATV 80, ATV 80 +eze 10, or diet only)

LAPLACE-2 (n=1896):
LDL-C ≥80 mg/dL
CV risk on mod/high intensity statin + evo Q2W/Q4W or eze or placebo

Statin intolerance or monotherapy

GAUSS-2 (n=307):
Statin intolerant
Evo Q2W or Q4W vs. eze

GAUSS-3 (n=519):
Statin intolerant
ATV rechallenge or evo Q4W vs. eze

MENDEL-2 (n=614):
LDL-C ≥100 mg/dL + FRS <10%
Evo Q2W or Q4W vs. eze vs. placebo

Safety

OSLER-2 (n>2928):
OLE of PIII parent studies
Evo Q2W or Q4W + standard therapy vs. standard therapy

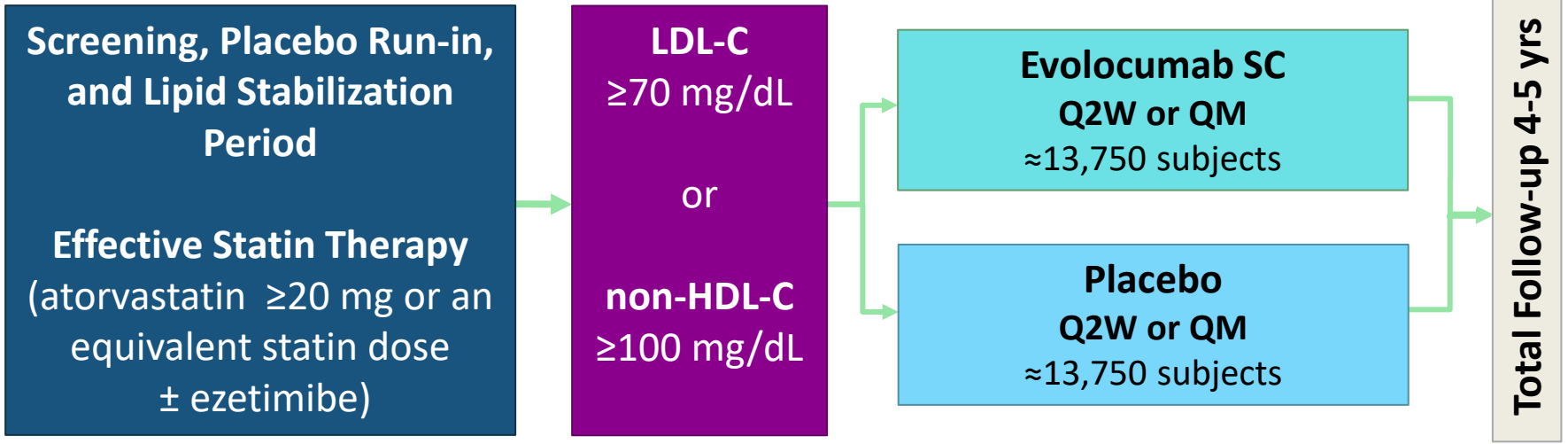
	Phase 3 Dosing and Titration
Start Dose	140 mg Q2W or 420 mg Q4W

Patient population:

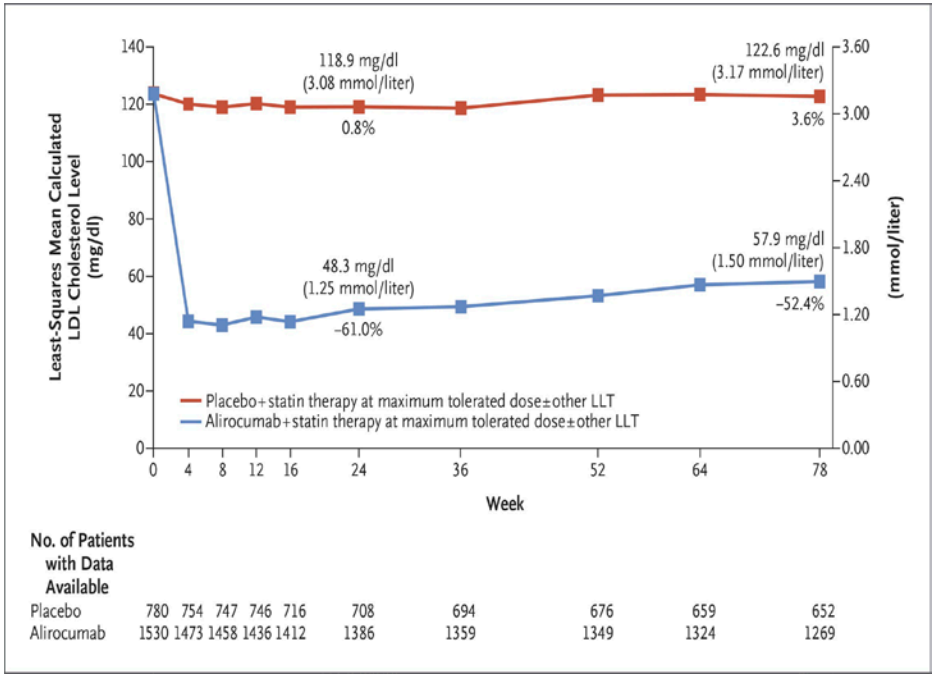
- 27,564 patients with CVD (prior MI, stroke, or PAD)
- Age 40 to 85 years
- ≥1 other high-risk feature

Primary endpoint:

- CV death
- MI
- Hospitalization for unstable angina
- Stroke
- Coronary revascularization

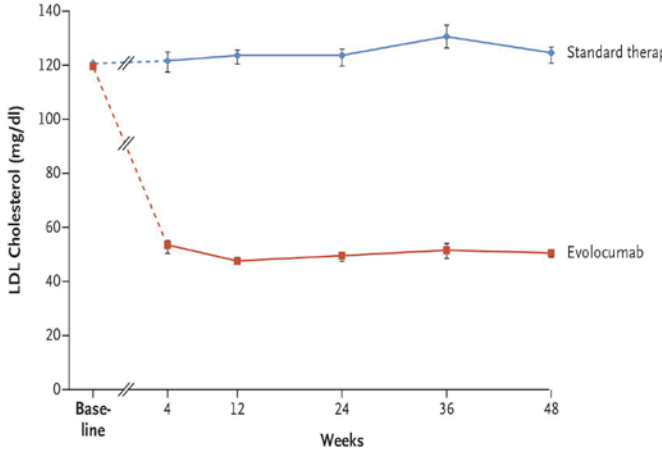


Alirocumab



No. of Patients with Data Available										
Placebo	780	754	747	746	716	708	694	676	659	652
Alirocumab	1530	1473	1458	1436	1412	1386	1359	1349	1324	1269

Evolocumab



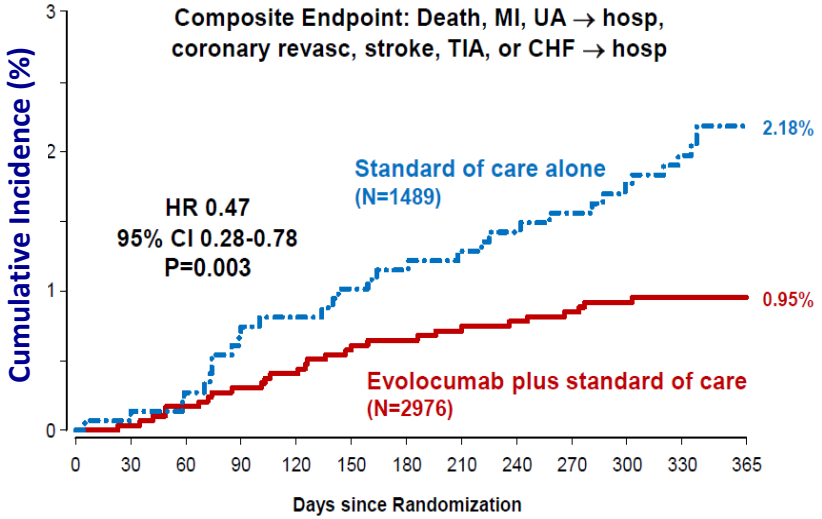
No. at Risk						
Standard therapy	1489	394	1388	1376	402	1219
Evolocumab	2976	864	2871	2828	841	2508
Absolute reduction (mg/dl)		60.4	73.4	70.4	72.7	70.5
Percentage reduction		45.3	60.9	58.8	54.0	58.4
P value		<0.001	<0.001	<0.001	<0.001	<0.001

Robinson JG et al. N Engl J Med 2015;372:1489-1499
Sabatine MS et al. N Engl J Med 2015;372:1500-1509

Sabatine MS, et al. *N Engl J Med*. 2015;372(16):1500-9.

OSLER 1/2

Cumulative Incidence of CV Events

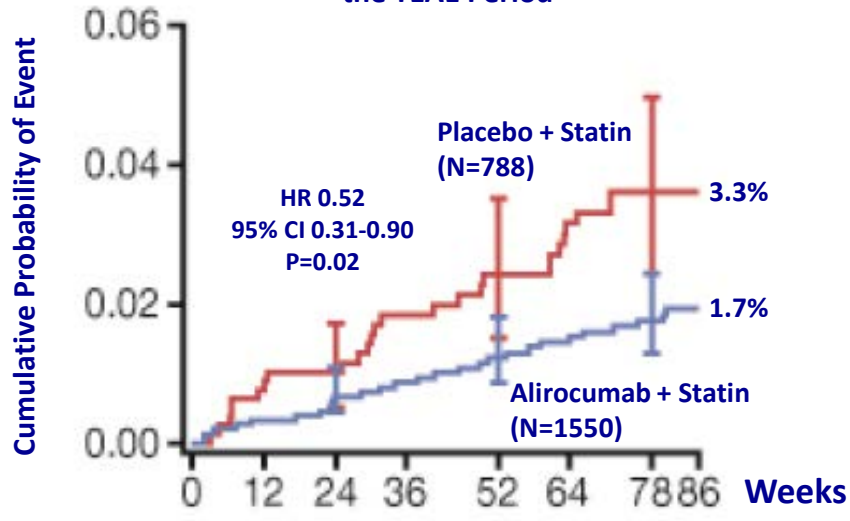


- CV outcomes declined by 53% over 1 year
  - Prespecified exploratory outcome with relatively few events
  - CV events were reported in 29 of 2976 patients in the evolocumab group and 31 of 1489 patients in the standard-therapy group

Robinson J et al. *N Engl J Med*. 2015;372(16):1489-99.

ODYSSEY LONG TERM

Time to First Positively Adjudicated CV Event During the TEAE Period



- In a post hoc analysis, the rate of death from CHD, nonfatal MI, ischemic stroke, or unstable angina requiring hospitalization was 3.3% in the placebo group (26 of 788 patients) and 1.7% in the intervention group (27 of 1550 patients)

	SPIRE-1	SPIRE-2
Key Inclusion Criteria	LDL-C ≥70 to <100 mg/dL (1.81-2.6 mmol/L)	LDL-C ≥100 mg/dL (2.6 mmol/L)
	High-risk primary prevention (Diabetes, CKD, PVD, Het FH) High-risk secondary prevention On highly effective statin* (unless statin intolerant)	
Key Exclusion Criteria	Planned coronary revascularization NYHA Class IV CHF or LVEF <25% eGFR <30 mL/min/1.73 m^2 Prior hemorrhagic stroke	
Treatment	Bococizumab 150 mg Q2 weeks SQ vs Placebo	
Primary Endpoint	Composite endpoint of CV death / non-fatal MI / non-fatal stroke / hospitalization for unstable angina needing urgent revascularization	

- PCSK9 est un inhibiteur naturel circulant du récepteur aux LDL. Il envoie le récepteur dans le lysosome ou il est dégradé, empêchant ainsi son recyclage.

- PCSK9 et le LDLR sont tous deux régulés par les niveaux intra-cellulaires en cholestérol et donc par les statines.

- L'inhibition de PCSK9 est une nouvelle approche thérapeutique permettant d'abaisser les niveaux de LDL de 60% par rapport aux niveaux déjà atteints avec des doses maximales de statines +/- ézétimibe.

- PCSK9 réduit aussi très significativement (-30%) les niveaux circulants de lipoprotéine (a) athérogène sur laquelle les statines n'ont aucun effet.

- Les indications concernent les patients FH ainsi que les patients à très haut risque CV pour lesquels les doses maximales de statines +/- ezétimibe n'abaissent pas le LDL-C suffisamment. Les patients intolérants aux statines pourraient bénéficier de ces thérapies.