Moderna Terapia anti-dislipidemica

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Varese

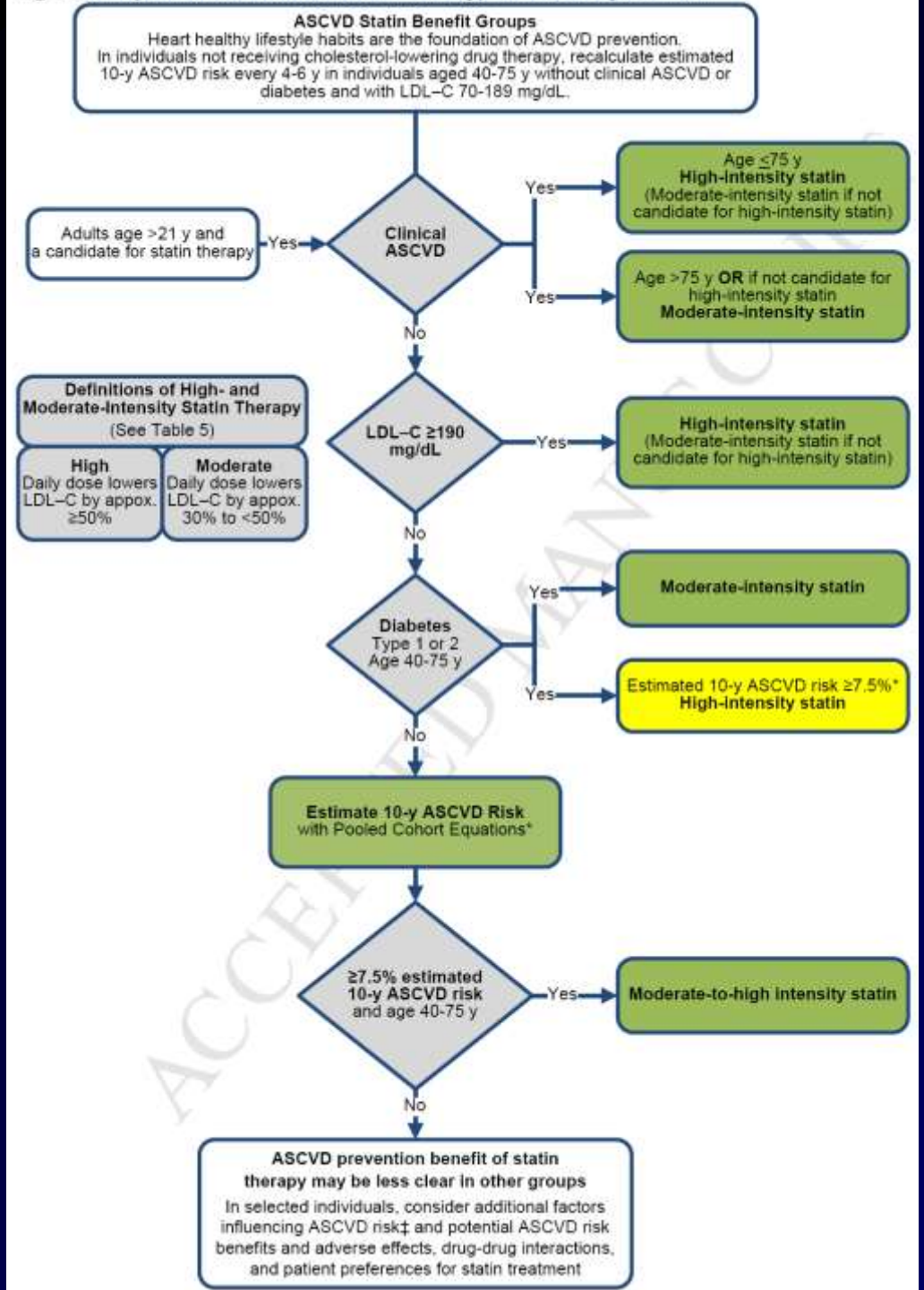
Cardiovascular Health Definition

LIFE'S SIMPLE 7	POOR	INTERMEDIATE	IDEAL
Smoking Status Adults >20 years of age Children (12–19)	Current Smoker Tried prior 30 days	Former ≤ 12 mos	Never /quit ≥ 12 mos
Physical Activity Adults > 20 years of age Children 12-19 years of age	None None	1-149 min/wk mod or 1-74 min/wk vig or 1-149 min/wk mod + vig >0 and <60 min of mod or vig every day	150+ min/wk mod or 75+ min/wk vig or 150+ min/wk mod + vig 60+ min of mod or vig every day
Healthy Diet Adults >20 years of age Children 5-19 years of age	0-1 components 0-1 components	2-3 components 2-3 components	4-5 components 4-5 components
Healthy Weight Adults > 20 years of age Children 2-19 years of age	≥30 kg/m^2 >95th percentile	25-29.9 kg/m2 85th-95th percentile	<25 kg/m^2 <85th percentile
Blood Glucose Adults >20 years of age Children 12-19 years of age	126 mg/dL or more 126 mg/dL or more	100-125 mg/dL or treated to goal 100-125 mg/dL	Less than 100 mg/dL Less than 100 mg/dL
Cholesterol Adults >20 years of age Children 6-19 years of age	≥240 mg/dL ≥200 mg/dL	200-239 mg/dL or treated to goal 170-199 mg/dL	<170 mg/dL
Blood Pressure Adults >20 years of age Children 8-19 years of age	SBP ≥140 or DBP ≥90 mm Hg >95th percentile	SBP120-139 or DBP 80-89 mm Hg or treated to goal 90th-95th percentile or SBP ≥120 or DBP ≥80 mm Hg	<120/<80 mm Hg <90th percentile

By 2020, to improve the cardiovascular health of all Americans by 20%, while reducing deaths from cardiovascular disease and stroke by 20%.

Guiding Concepts in Prevention

- Geoffrey Rose, 1981
  - "High-risk" vs. "population" strategies for prevention of disease
  - Current guidelines focus mostly on "high-risk" strategies, where relative risk is high
  - Shifting the population distribution of a risk factor can have dramatic impact on disease
- Thomas Strasser, 1978
  - "Primordial prevention"
  - Prevention of the development of *risk factors,* not just disease
    - Once risk factors develop, risk for disease is high and difficult to reduce substantially



CLASS I	CLASS IIa
Benefit >>> Risk	*Benefit >> Risk*
Procedure/Treatment **SHOULD** be performed/ administered	*Additional studies with focused objectives needed*
	IT IS REASONABLE to perform procedure/administer treatment

High-intensity statin: ≥50%

Moderate-intensity: 30-50%

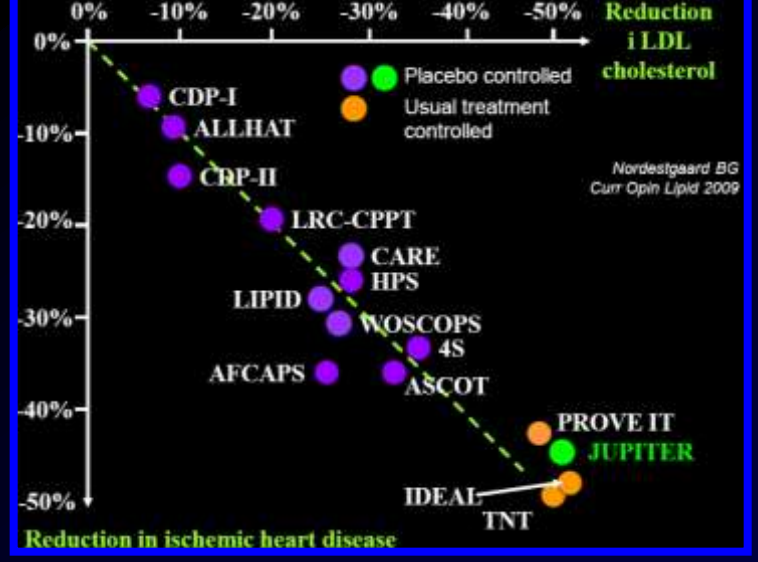
"Low-intensity": no !!

Stone NJ, et al.
2013 ACC/AHA Blood Cholesterol Guideline

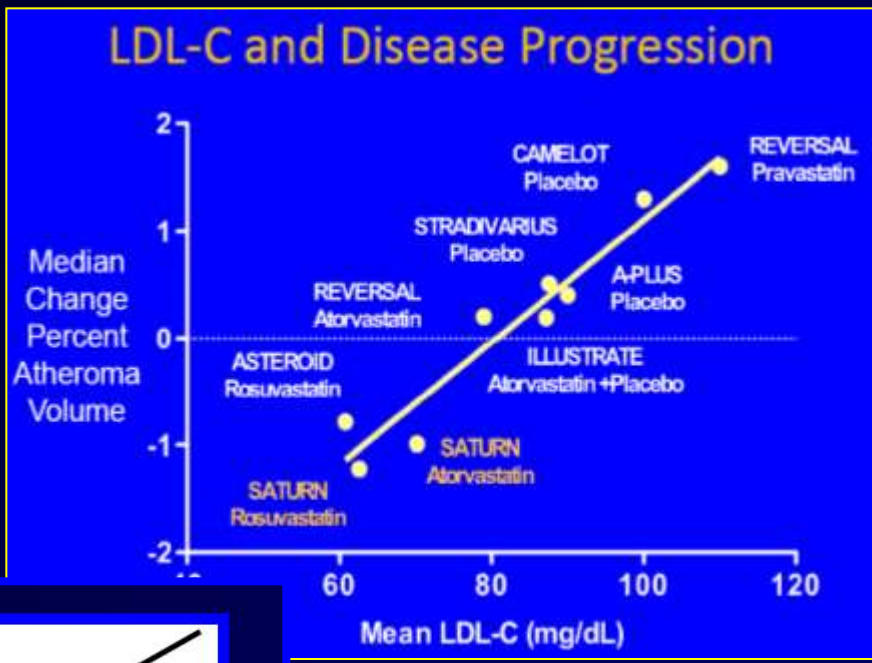
2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

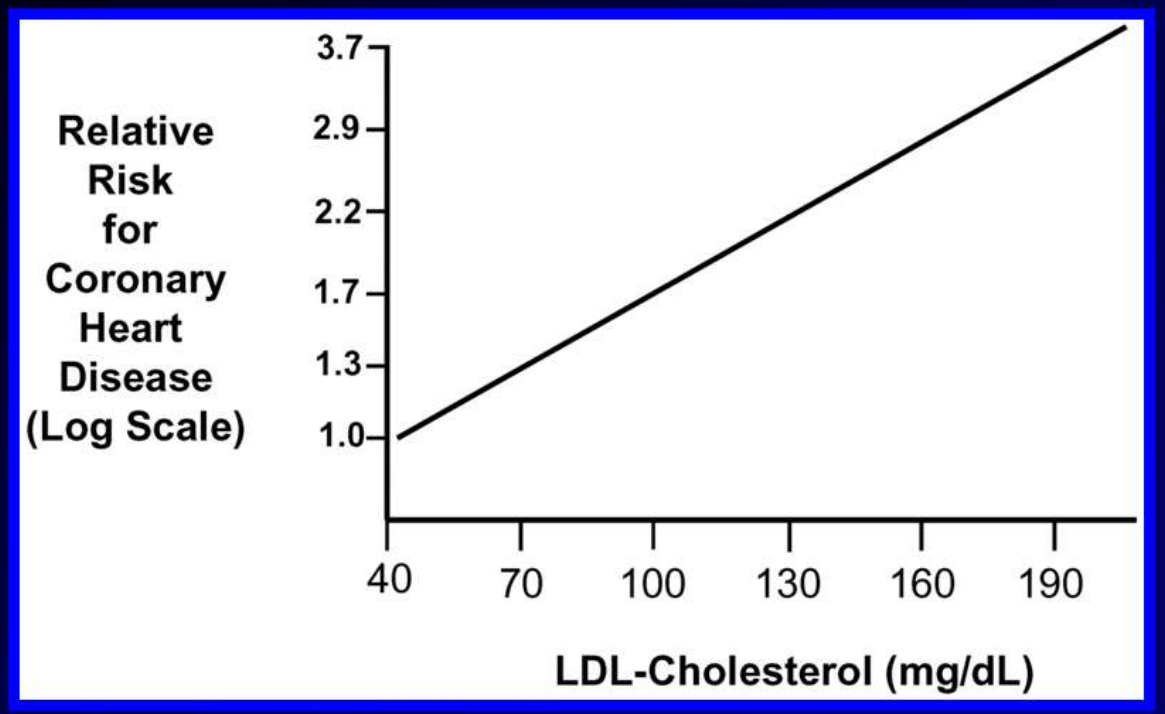
A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, American Pharmacists Association, American Society for Preventive Cardiology, Association of Black Cardiologists, Preventive Cardiovascular Nurses Association, and WomenHeart: The National Coalition for Women with Heart Disease



LDL





Grundy 2004

Statin intensity

Statin Therapy	Daily Dose		
	High-Intensity†	Moderate-Intensity‡	Low-Intensity§
Atorvastatin	40‖–80 mg	10 *(20)* mg	–
Rosuvastatin	20 *(40)* mg	*(5)* 10 mg	–
Simvastatin	–	20–40 mg¶	*10 mg*
Pravastatin	–	40 *(80)* mg	10–20 mg
Lovastatin	–	40 mg	20 mg
Fluvastatin	–	*80 mg (Fluvastatin XL)*	*20–40 mg*
Fluvastatin	–	40 mg**	–
Pitavastatin	–	*2–4 mg*	*1 mg*

* Individual responses to statin therapy varied in randomized, controlled trials and vary in clinical practice. A less-than-average response may have a biological basis. Statins and dosages in bold reduced major cardiovascular events in randomized, controlled trials. Statins and doses in italics were approved by the U.S. Food and Drug Administration (FDA) but were not tested in randomized, controlled trials.
† Daily dose decreases low-density lipoprotein cholesterol (LDL-C) levels by an average of ≥50%.
‡ Daily dose decreases LDL-C levels by an average of 30% to <50%.
§ Daily dose decreases LDL-C levels by an average of <30%.
‖ Evidence from 1 randomized, controlled trial only; down-titration if patient is unable to tolerate atorvastatin, 80 mg.
¶ Although simvastatin, 80 mg, was evaluated in randomized, controlled trials, the FDA recommends against initiation of or titration to 80 mg of simvastatin because of increased risk for myopathy and rhabdomyolysis.
** Twice daily.

Ann Intern Med. 2014;160:339-343.

Annals of Internal Medicine | CLINICAL GUIDELINE

Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Disease Risk in Adults: Synopsis of the 2013 American College of Cardiology/American Heart Association Cholesterol Guideline

Neil J. Stone, MD; Jennifer G. Robinson, MD, MPH; Alice H. Lichtenstein, ScD; David C. Goff Jr., MD, PhD; Donald M. Lloyd-Jones, MD, ScM; Sidney C. Smith Jr., MD; Conrad Blum, MD; and J. Sanford Schwartz, MD, for the 2013 ACC/AHA Cholesterol Guideline Panel*

Genetic Variants and Statin Resistance

Table 1 Possible genetic factors causing a reduced lipid-lowering response to statins.

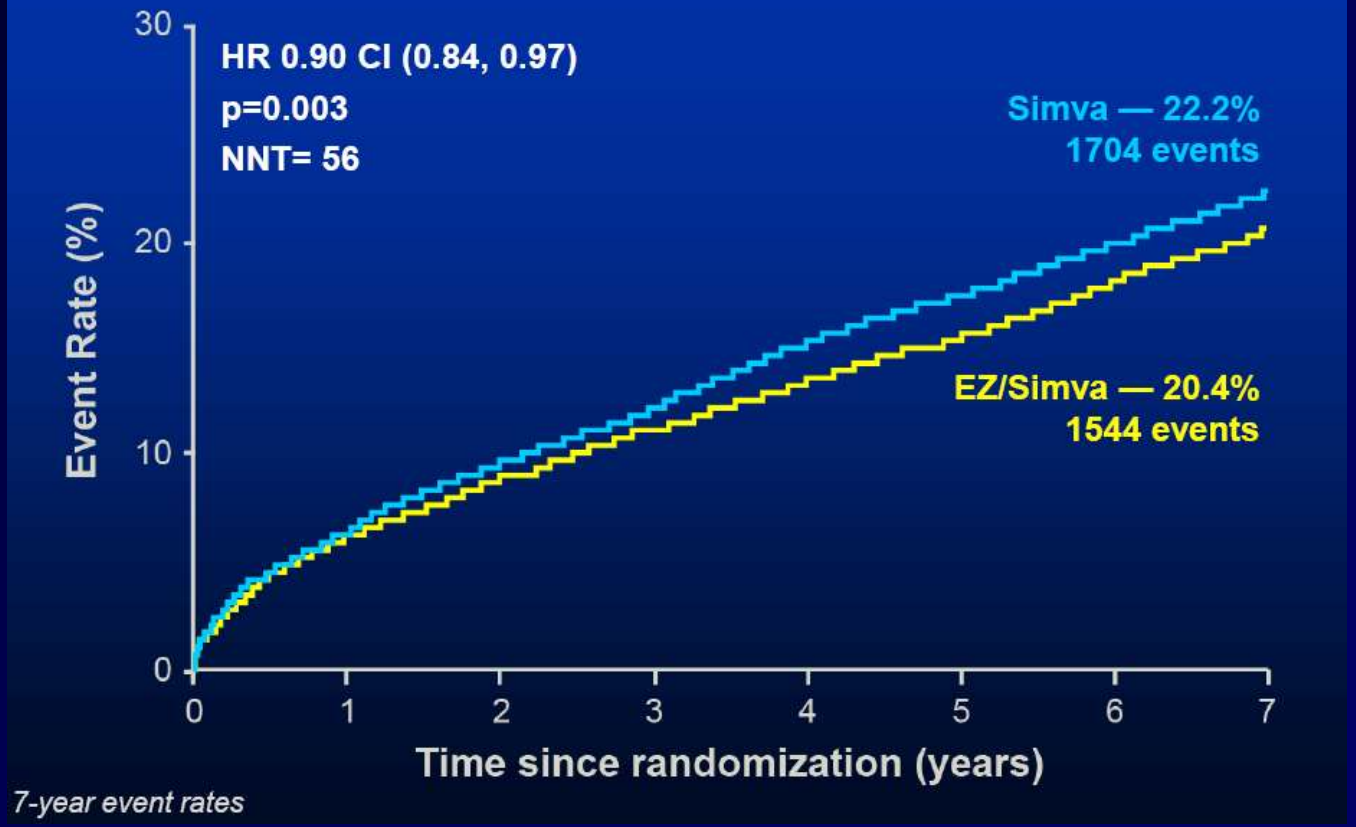
Gene	Mutation or polymorphism	Reference
MRP1	c.3435T	[17]
MRP2	c.1446G	[18]
ABCB1	2677T	[19]
OATP2B1	c.3886 and c.521C	[24]
NPC1L1	non-2/2 haplotype	[26]
HMG-CoA-R	heterozygous for SNP12, SNP2a	[10]
CYP7A1	A 204C	[29]
PCSK9	Gain-of-function	[35]
LDL-R	Ava II and Pvu II	[36]
ApoE	E_2	[32]
CETP	rs1532624	[42]
RHOA	H3B haplotype, rs 11716445	[25]
TNF-α	C-857T	[43]
LPA	rs 10455872	[32]

IMProved Reduction of Outcomes: Vytorin Efficacy International Trial

A Multicenter, Double-Blind, Randomized Study to Establish the Clinical Benefit and Safety of Vytorin (Ezetimibe/Simvastatin Tablet) vs Simvastatin Monotherapy in High-Risk Subjects Presenting With Acute Coronary Syndrome

CV Death, Non-fatal MI, or Non-fatal Stroke

IMPROVE-IT



7-year event rates

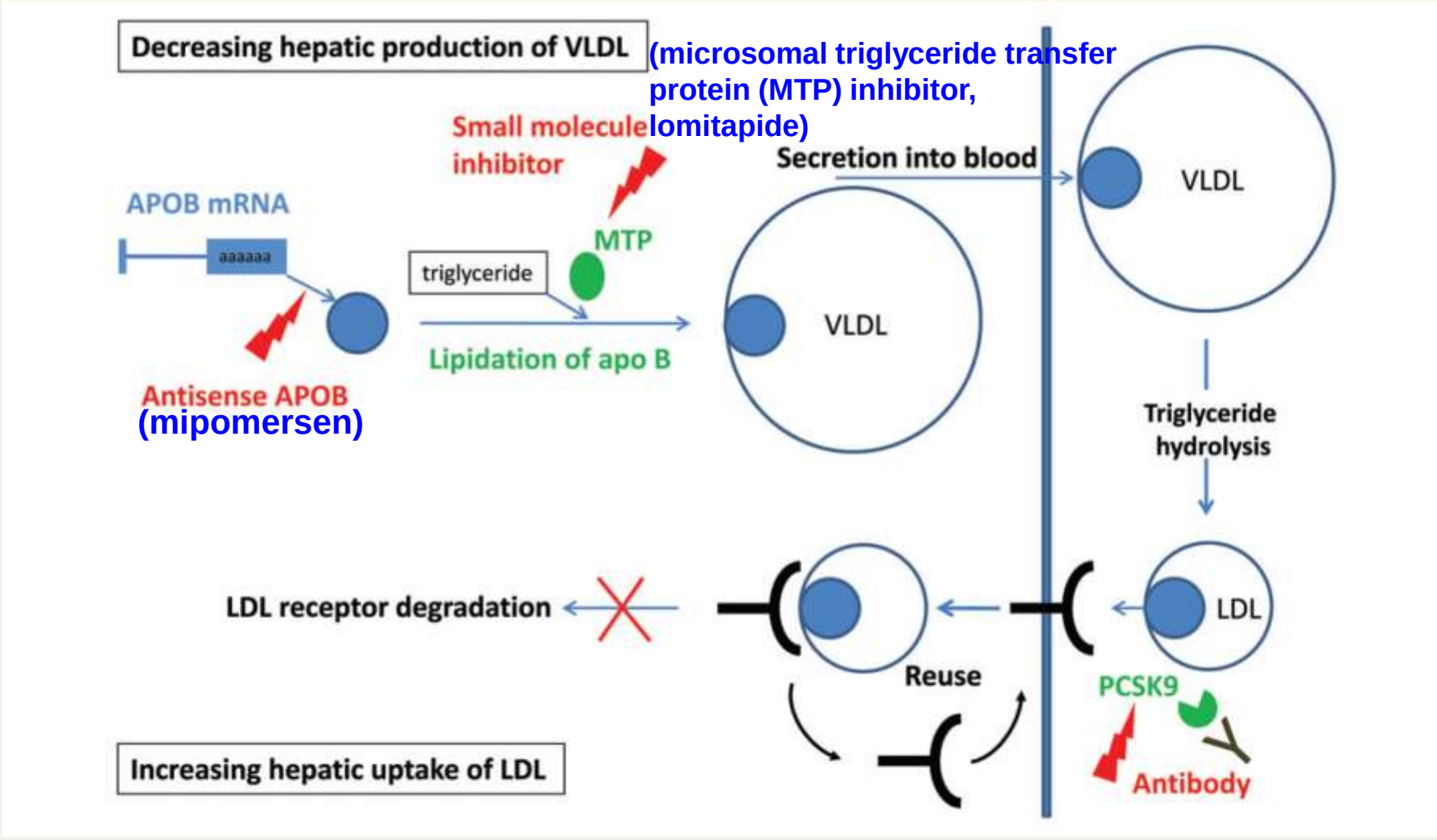
Even Lower is Even Better
(achieved mean LDL-C 53 vs. 70 mg/dL at 1 year)

REVIEW

Clinical update

Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society

Eur Heart J 2014



Curr Opin Lipidol 2014, 25:000–000

Inhibition of ApoCIII: the next PCSK9?

Sophie J.B. Moens, Julian C. van Capelleveen, and Erik S.G. Stroes

Purpose of review
Recent large Mendelian randomization studies associate loss-of-function mutations in apolipoprotein CIII (*APOCIII*) with low levels of triglycerides and decreased incidence of cardiovascular disease. With ample in-vitro and in-vivo evidence for a role of apoCIII in lipoprotein lipase-mediated triglyceride clearance and remnant removal, it is, thus, an attractive target for the treatment of hypertriglyceridemia and the prevention of cardiovascular disease. This review evaluates the current position of apoCIII in clinical practice and provides a glimpse into the future in terms of treatment options.

Recent findings
Two large Mendelian randomization studies have sho
APOCIII to be linked to favorable lipid profiles and lo
generation antisense oligonucleotide, which selectively
apoCIII and triglyceride levels in rodents, nonhuman p

Summary
The central role of apoCIII in hypertriglyceridemia and
recent findings and promising intervention data that sh
lower apoCIII and triglyceride levels. Currently, planne
to long-term efficacy and safety of this novel therapy.

Keywords
antisense therapy, apolipoprotein CIII, cardiovascular

INTRODUCTION

On 18 June 2014, two publications were available online, associating loss-of-function mutations in apolipoprotein CIII (*APOCIII*) with low levels of triglycerides and decreased cardiovascular disease (CVD) [1▪,2▪]. The connection was swiftly made with proprotein convertase subtilisin/kexin type 9 (PCSK9), emphasizing the importance of naturally occurring loss-of-function mutations in the development of novel therapeutic agents.

The unprecedented and rapid translation from the identification of PCSK9 in 2003 [3], with the first use of a monoclonal antibody in monkeys [4], to the currently ongoing phase 3 clinical outcome trials with almost 40 000 persons included [5], has paved the way for other therapeutics to swiftly proceed from bench to bedside. Although not as novel as PCSK9, apoCIII may be one of those targets profiting from the rapid development of new techniques, such as silencing RNA and novel human antibody technology.

TRIGLYCERIDE LEVELS AND CARDIOVASCULAR DISEASE

Even though hypertriglyceridemia, defined as fasting plasma triglycerides above 200 mg/dl (or >2.2 mmol/l)

KEY POINTS

- The rapid translation from bench to bedside in the case of PCSK9 inhibitors is exemplary for the importance of knowledge gained from loss-of-function mutations.
- The long-recognized connection between apoCIII, serum triglycerides and CVD was recently substantiated with two large Mendelian randomization studies, showing that loss-of-function mutations in apoCIII are associated with lower serum triglycerides and a lower CVD incidence.
- An ASO that selectively inhibits apoCIII was shown to lower serum apoCIII and triglycerides in mice, nonhuman primates and healthy volunteers, and showed comparable results in phase 2 trials.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Loss-of-Function Mutations in *APOC3*, Triglycerides, and Coronary Disease

The TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute*

ABSTRACT

BACKGROUND

Plasma triglyceride levels are heritable and are correlated with the risk of coronary heart disease. Sequencing of the protein-coding regions of the human genome (the exome) has the potential to identify rare mutations that have a large effect on phenotype.

METHODS

We sequenced the protein-coding regions of 18,666 genes in each of 3734 participants of European or African ancestry in the Exome Sequencing Project. We conducted tests to determine whether rare mutations in coding sequence, individually or in aggregate within a gene, were associated with plasma triglyceride levels. For mutations associated with triglyceride levels, we subsequently evaluated their association with the risk of coronary heart disease in 110,970 persons.

RESULTS

An aggregate of rare mutations in the gene encoding apolipoprotein C3 (*APOC3*) was associated with lower plasma triglyceride levels. Among the four mutations that drove this result, three were loss-of-function mutations: a nonsense mutation (R19X) and two splice-site mutations (IVS2+1G→A and IVS3+1G→T). The fourth was a missense mutation (A43T). Approximately 1 in 150 persons in the study was a heterozygous carrier of at least one of these four mutations. Triglyceride levels in the carriers were 39% lower than levels in noncarriers ($P<1\times10^{-20}$), and circulating levels of APOC3 in carriers were 46% lower than levels in noncarriers ($P=8\times10^{-10}$). The risk of coronary heart disease among 498 carriers of any rare *APOC3* mutation was 40% lower than the risk among 110,472 noncarriers (odds ratio, 0.60; 95% confidence interval, 0.47 to 0.75; $P=4\times10^{-6}$).

CONCLUSIONS

Rare mutations that disrupt *APOC3* function were associated with lower levels of plasma triglycerides and APOC3. Carriers of these mutations were found to have a reduced risk of coronary heart disease. (Funded by the National Heart, Lung, and Blood Institute and others.)

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*The authors and members of the Triglycerides and High-Density Lipoprotein (TG and HDL) Working Group and their affiliations are listed in the Appendix. Ms. Jacy Crosby and Drs. Gina Peloso, Paul L. Auer, Alex P. Reiner, Eric Boerwinkle, and Sekar Kathiresan contributed equally to this article and assume responsibility for its content and integrity.

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DOI: 10.1056/NEJMoa1307095

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Loss-of-Function Mutations in *APOC3* and Risk of Ischemic Vascular Disease

Anders Berg Jørgensen, M.D., Ph.D., Ruth Frikke-Schmidt, M.D., D.M.Sc., Børge G. Nordestgaard, M.D., D.M.Sc., and Anne Tybjærg-Hansen, M.D., D.M.Sc.

ABSTRACT

BACKGROUND

High plasma levels of nonfasting triglycerides are associated with an increased risk of ischemic cardiovascular disease. Whether lifelong low levels of nonfasting triglycerides owing to mutations in the gene encoding apolipoprotein C3 (*APOC3*) are associated with a reduced risk of ischemic cardiovascular disease in the general population is unknown.

METHODS

Using data from 75,725 participants in two general-population studies, we first tested whether low levels of nonfasting triglycerides were associated with reduced risks of ischemic vascular disease and ischemic heart disease. Second, we tested whether loss-of-function mutations in *APOC3*, which were associated with reduced levels of nonfasting triglycerides, were also associated with reduced risks of ischemic vascular disease and ischemic heart disease. During follow-up, ischemic vascular disease developed in 10,797 participants, and ischemic heart disease developed in 7557 of these 10,797 participants.

RESULTS

Participants with nonfasting triglyceride levels of less than 1.00 mmol per liter (90 mg per deciliter) had a significantly lower incidence of cardiovascular disease than those with levels of 4.00 mmol per liter (350 mg per deciliter) or more (hazard ratio for ischemic vascular disease, 0.43; 95% confidence interval [CI], 0.35 to 0.54; hazard ratio for ischemic heart disease, 0.40; 95% CI, 0.31 to 0.52). Heterozygosity for loss-of-function mutations in *APOC3*, as compared with no *APOC3* mutations, was associated with a mean reduction in nonfasting triglyceride levels of 44% ($P<0.001$). The cumulative incidences of ischemic vascular disease and ischemic heart disease were reduced in heterozygotes as compared with noncarriers of *APOC3* mutations ($P=0.009$ and $P=0.05$, respectively), with corresponding risk reductions of 41% (hazard ratio, 0.59; 95% CI, 0.41 to 0.86; $P=0.007$) and 36% (hazard ratio, 0.64; 95% CI, 0.41 to 0.99; $P=0.04$).

CONCLUSIONS

Loss-of-function mutations in *APOC3* were associated with low levels of triglycerides and a reduced risk of ischemic cardiovascular disease. (Funded by the European Union and others.)

From Copenhagen University Hospital and Faculty of Health and Medical Sciences, University of Copenhagen (A.B.J., R.F.-S., B.G.N., A.T.-H.), the Department of Clinical Biochemistry, Rigshospitalet (A.B.J., R.F.-S., A.T.-H.), the Department of Clinical Biochemistry (B.G.N.) and the Copenhagen General Population Study (R.F.-S., B.G.N., A.T.-H.), Herlev Hospital, and the Copenhagen City Heart Study, Frederiksberg Hospital (B.G.N., A.T.-H.) — all in Copenhagen. Address reprint requests to Dr. Tybjærg-Hansen at the Department of Clinical Biochemistry KB 3011, Section for Molecular Genetics, Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, DK-2100 Copenhagen Ø, Denmark, or at anne.tybjaerg.hansen@regionh.dk.

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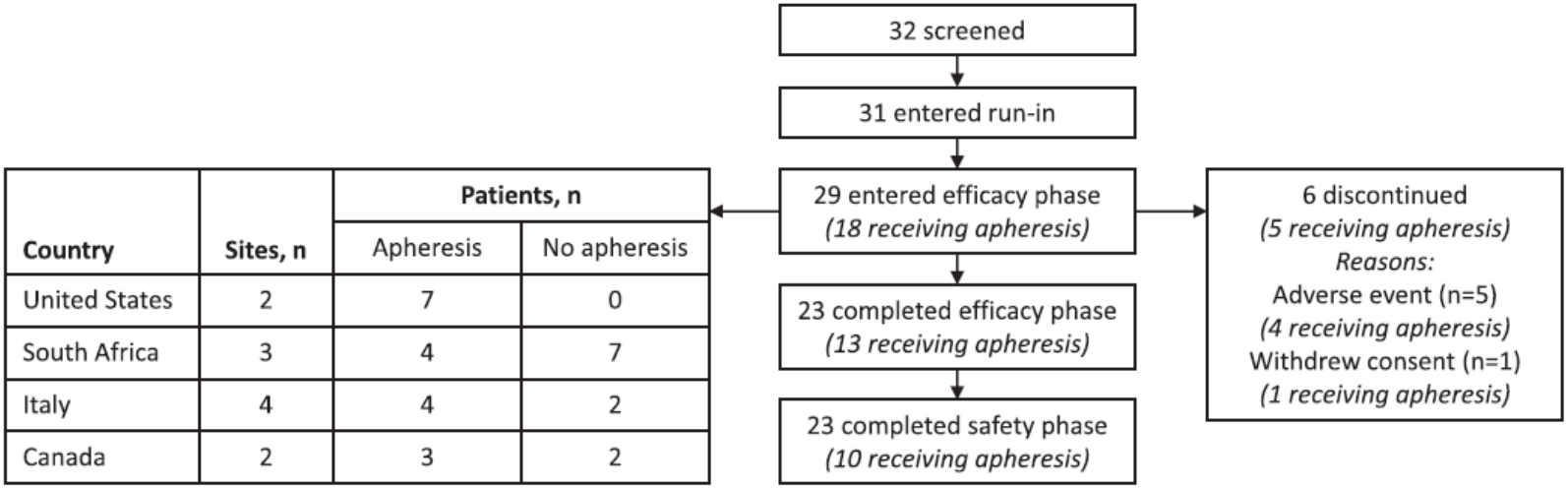
The lipid-lowering effects of lomitapide are unaffected by adjunctive apheresis in patients with homozygous familial hypercholesterolaemia – A post-hoc analysis of a Phase 3, single-arm, open-label trial

C. Stefanutti [a], D.J. Blom [b], M.R. Averna [c], E.A. Meagher [d], H. dT. Theron [e], A.D. Marais [b], R.A. Hegele [f], C.R. Sirtori [g], P.K. Shah [h], D. Gaudet [i], G.B. Vigna [j], B.S. Sachais [d], S. Di Giacomo [a], A.M.E. du Plessis [k], L.T. Bloedon [l], J. Balser [m], D.J. Rader [d], M. Cuchel [d,*], For the Phase 3 HoFH Lomitapide Study Investigators

Atherosclerosis 240 (2015) 408–414



Country	Sites, n	Patients, n	
		Apheresis	No apheresis
United States	2	7	0
South Africa	3	4	7
Italy	4	4	2
Canada	2	3	2

Fig. 1. Patient disposition.

Table 2
Percent change from baseline in lipid and lipoprotein levels at Week 26 in patients with and without apheresis treatment using Mixed Model Repeated Measures.[a]

Parameter	Overall (n = 29)		Apheresis (n = 18)		No apheresis (n = 11)		p-value[b]
	Baseline (range)	% Change	Baseline (range)	% Change	Baseline (range)	% Change	
TC, mmol/L	11.1 (4.9–18.7)	−46.3	10.7 (4.9–16.4)	−43.8	11.8 (6.3–18.7)	−49.8	0.575
LDL-C, mmol/L	8.7 (3.9–14.6)	−51.0	8.4 (3.9–12.9)	−48.0	9.2 (4.3–14.6)	−55.1	0.545
Non-HDL, mmol/L	10.0 (4.1–17.1)	−50.7	9.6 (4.1–15.4)	−48.3	10.7 (5.0–17.1)	−54.2	0.613
TG, mmol/L	2.7 (0.8–6.5)	−43.3	2.8 (0.8–6.5)	−45.2	2.5 (1.3–4.6)	−41.2	0.777
ApoB, g/L	2.6 (1.2–4.3)	−50.1	2.5 (1.2–3.6)	−47.9	2.8 (1.4–4.3)	−53.2	0.625
HDL-C, mmol/L	1.1 (0.7–1.8)	−11.3	1.1 (0.9–1.7)	−10.3	1.1 (0.7–1.8)	−12.4	0.760
ApoA-I, g/L	1.1 (0.6–1.9)	−10.6	1.2 (0.8–1.6)	−11.3	1.1 (0.6–1.9)	−9.2	0.730
Lp(a), μmol/L	2.8 (0.6–12.1)	−17.2	2.3 (0.7–4.7)	−12.8	3.5 (0.6–12.1)	−23.1	0.436

[a] Mixed model includes treatment with apheresis (yes/no), baseline lipid level, and categorical study week as fixed parameters and a study week-by-apheresis interaction.
[b] Apheresis *versus* no apheresis.

The Crystal Structure of PCSK9: A Regulator of Plasma LDL-Cholesterol

2007

Derek E. Piper,[1] Simon Jackson,[2] Qiang Liu,[3] William G. Romanow,[1] Susan Shetterly,[2] Stephen T. Thibault,[1] Bei Shan,[2] and Nigel P.C. Walker[1,*]

crystal structure of human PCSK9 at 2.3 A°resolution

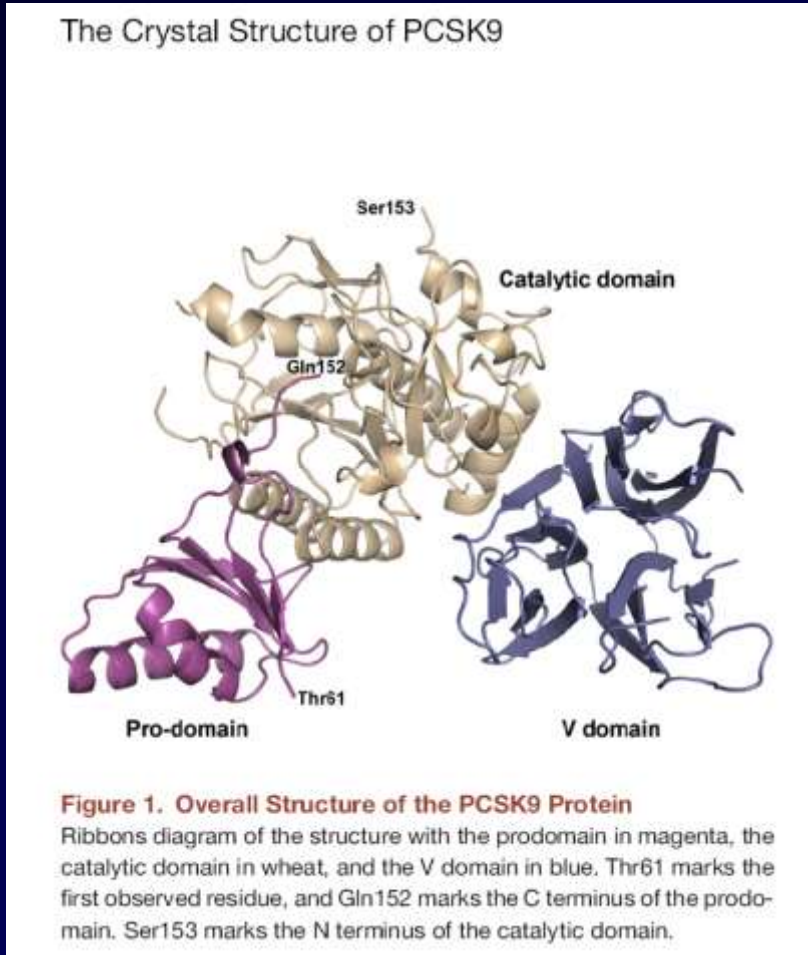


Figure 1. Overall Structure of the PCSK9 Protein
Ribbons diagram of the structure with the prodomain in magenta, the catalytic domain in wheat, and the V domain in blue. Thr61 marks the first observed residue, and Gln152 marks the C terminus of the prodomain. Ser153 marks the N terminus of the catalytic domain.

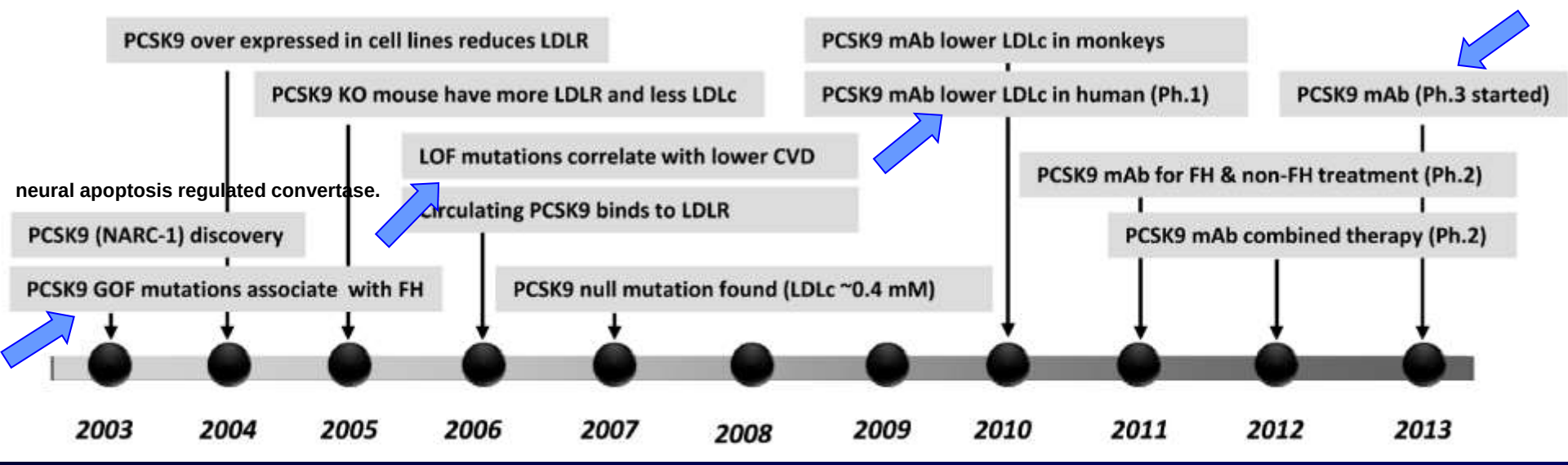
proprotein convertase subtilisin kexin 9 (PCSK9)

PCSK9

A Key Modulator of Cardiovascular Health

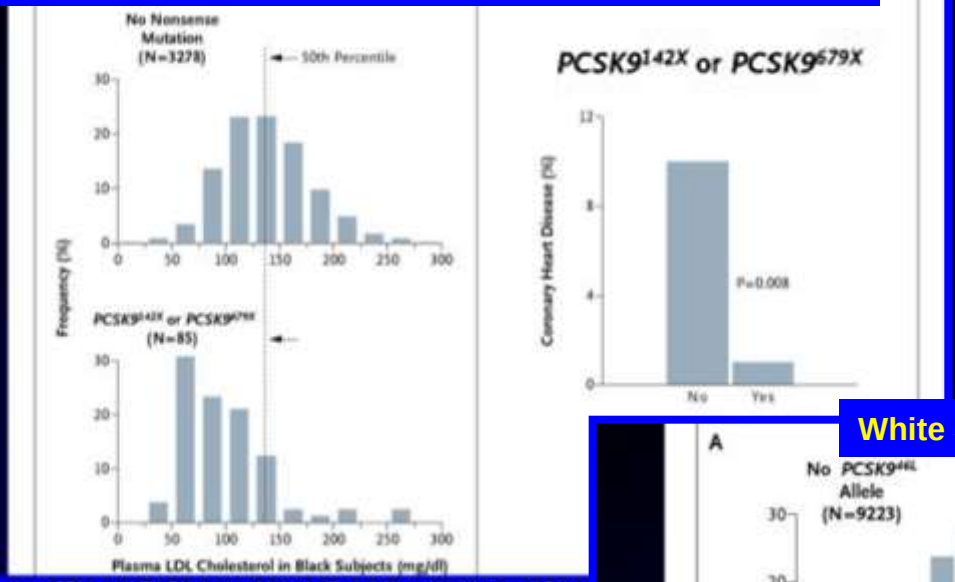
Nabil G. Seidah, Zuhier Awan, Michel Chrétien, Majambu Mbikay

Circ Res. 2014;



conversion of an inactive secretory precursor into active product(s) is catalyzed by a special group of proteases denoted as the proprotein convertases (PCs). From 1990 to 1999, 8 mammalian PCs were discovered and shown to be responsible for the tissue-specific processing of various secretory Precursors. The ninth and last member of the family, known as PC subtilisin kexin 9 (PCSK9), was reported in early 2003.

Black Subjects,
Presence or Absence of a *PCSK9142X* or *PCSK9679X* Allele.



Distribution of Plasma LDL Cholesterol Levels (Panel A) and Incidence of Coror
Subjects, According to the Presence or Absence of a *PCSK914*
In Panel A, the distribution of plasma LDL cholesterol levels at baseline among
PCSK9142X or *PCSK9679X* allele (top) is compared with the distribution of levels
of these two alleles (bottom). Panel B shows the percentage of participants from
coronary heart disease at baseline and in whom coronary heart disease develop
convert values for LDL cholesterol to millimoles per liter,

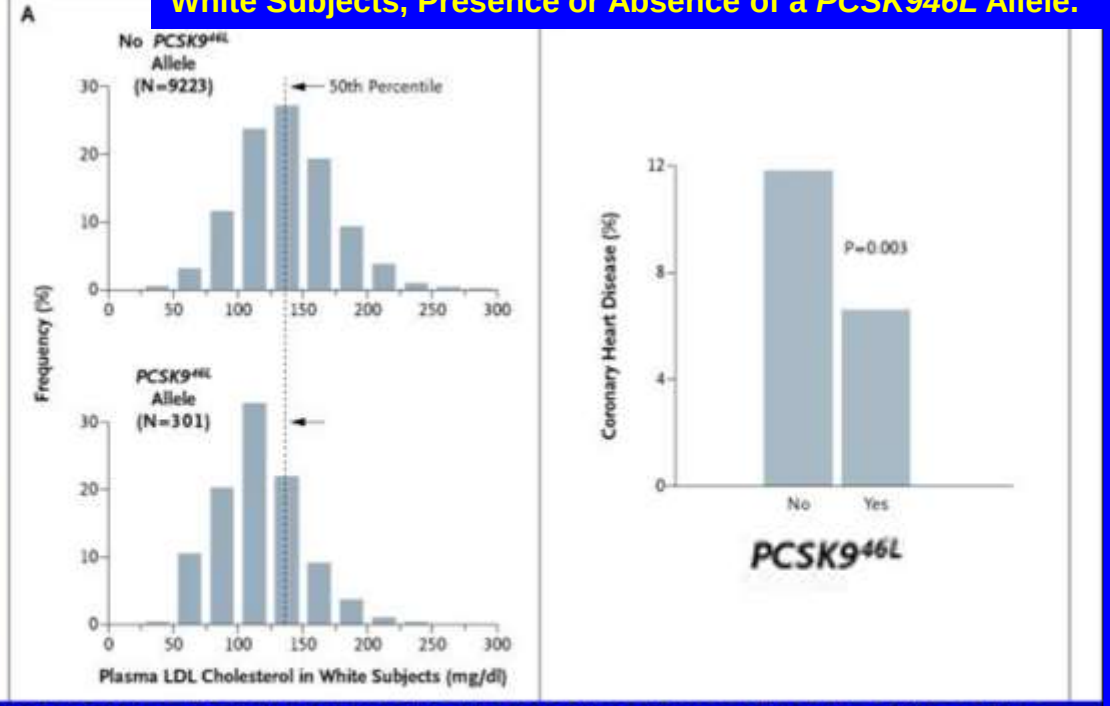
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

Jonathan C. Cohen, Ph.D., Eric Boerwinkle, Ph.D., Thomas H. Mosley, Jr., Ph.D., and Helen H. Hobbs, M.D.

White Subjects, Presence or Absence of a *PCSK946L* Allele.



Distribution of Plasma LDL Cholesterol Levels (Panel A) and Incidence of Coronary Events (Panel B) among White Subjects, According to the Presence or Absence of a *PCSK946L* Allele.
In Panel A, the distribution of plasma LDL cholesterol levels at baseline among 9223 white subjects who did not have a *PCSK946L* allele (top) is compared with the distribution of levels among the 301 white subjects who were either heterozygous or homozygous for this allele (bottom). Panel B shows the percentage of participants from these two groups who had no evidence of coronary heart disease at baseline and in whom coronary heart disease developed during the 15-year follow-up period. To convert values for LDL cholesterol to millimoles per liter, multiply by 0.02586.

Cohen NEJM 2006

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doi:10.1016/j.jacc.2010.02.044

Lipids and Risk

PCSK9 R46L, Low-Density Lipoprotein Cholesterol Levels, and Risk of Ischemic Heart Disease

3 Independent Studies and Meta-Analyses

Marianne Benn, MD, PhD,*†§ Børge G. Nordestgaard, MD, DMSc,†‡§‖ Peer Grande, MD, DMSc,†
Peter Schnohr, MD, DMSc,‖ Anne Tybjærg-Hansen, MD, DMSc*§‖
Copenhagen, Denmark

JACC 2010

Conclusions

The *PCSK9* 46L allele was associated with reductions in LDL-C of 11% to 16% in all age groups from 20 to 80+ years in the general population. The 30% reduction in risk of IHD observed in our 3 studies combined was larger than predicted by the reduction in LDL-C alone. This could be because genotype is a better predictor of lifelong exposure to LDL-C than LDL-C measured in adult life.

Copenhagen City Heart Study CCHS (prospective)
Copenhagen General Population Study CGPS (crosssectional)
Copenhagen Ischemic Heart Disease Study CIHDS (case-control)

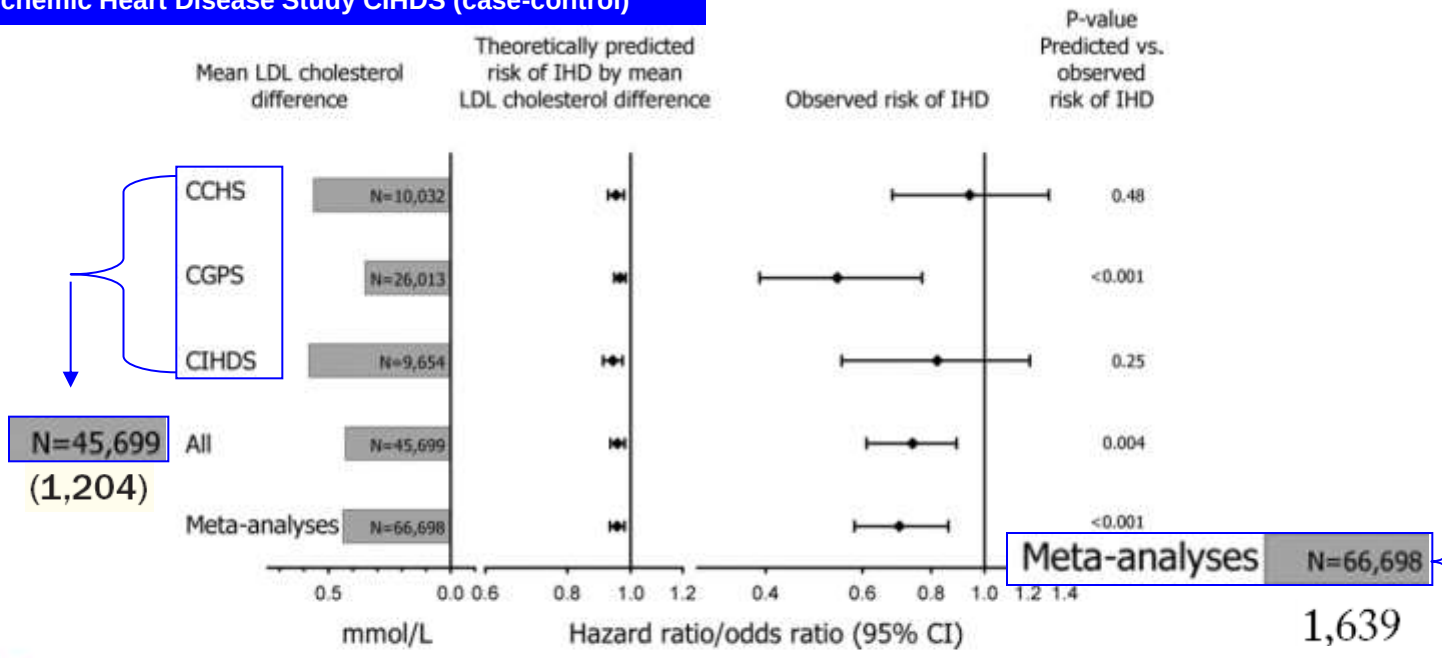
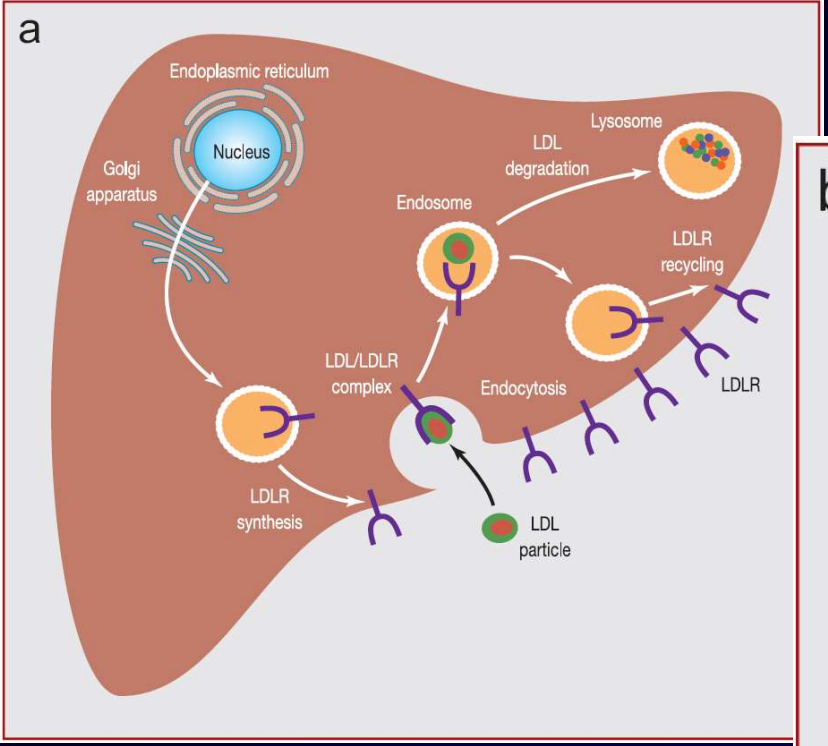
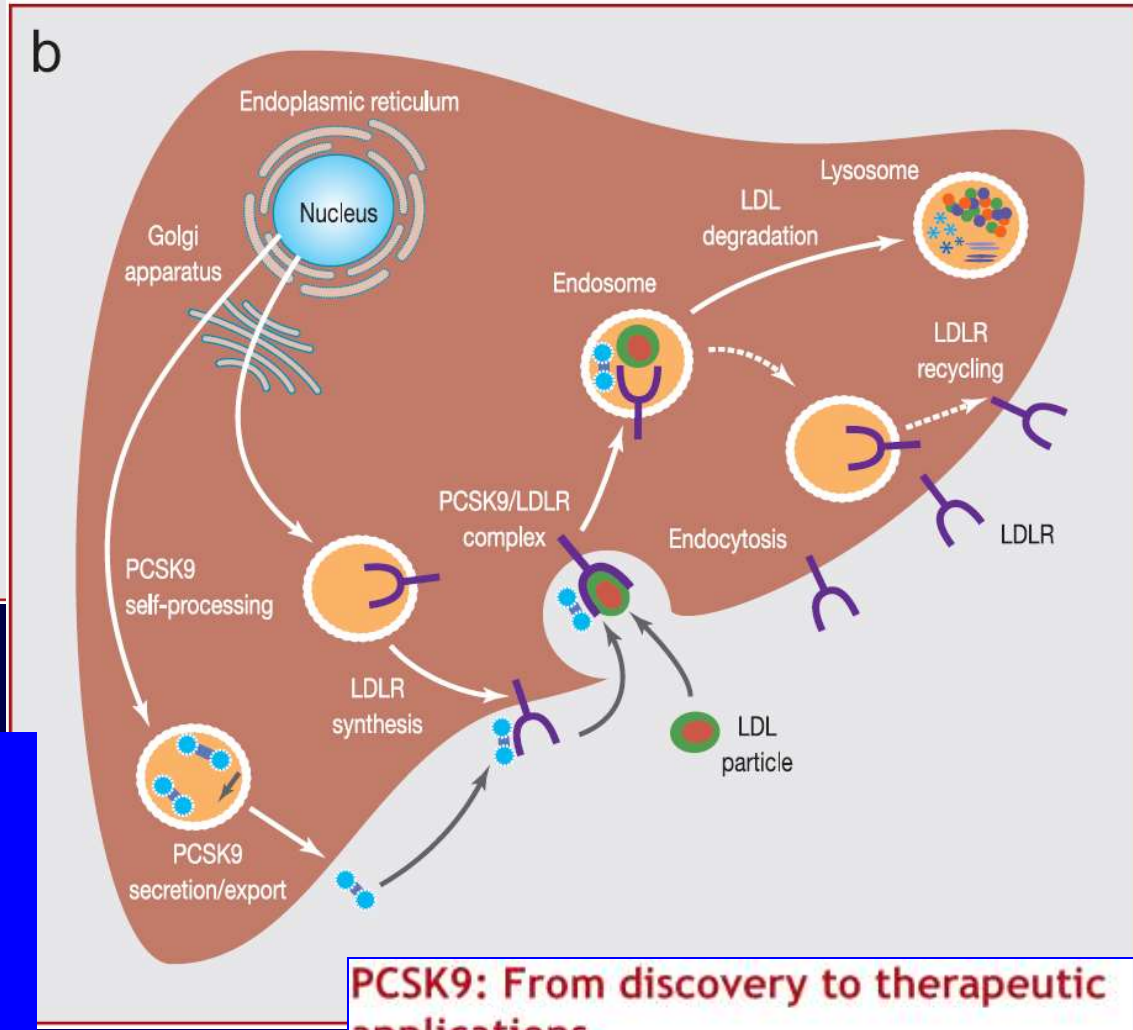


Figure 4 LDL Cholesterol, Predicted and Observed Risks for IHD

Differences in mean LDL cholesterol levels in *PCSK9* 46L allele carriers (RL heterozygotes plus LL homozygotes) versus noncarriers (RR homozygotes) **(left panel)**, the corresponding theoretically predicted risks **(middle panel)**, and the observed risks for ischemic heart disease (IHD) **(right panel)**. Shown for the following studies **(top to bottom)**: CCHS, n = 10,032; CGPS, n = 26,032; CIHDS, n = 9,654; the 3 studies combined; and in meta-analysis (n = 66,698). The theoretically predicted hazard ratios/ORs (age- and sex-adjusted) for IHD corresponding to the observed mean reduction in LDL cholesterol levels in 46L allele carriers versus noncarriers is based on the risk reduction for IHD observed for a similar LDL reduction in the CCHS study as a whole. Abbreviations as in Figures 2 and 3.





PCSK9

1)Via intracellulare
nascent PCSK9 can bind to the LDLR and direct it from the trans-Golgi to lysosomes for degradation

2)Via extracellulare
secreted PCSK9 binds at the cell surface to the first epidermal growth factor-like repeat (EGF-A) of LDLR

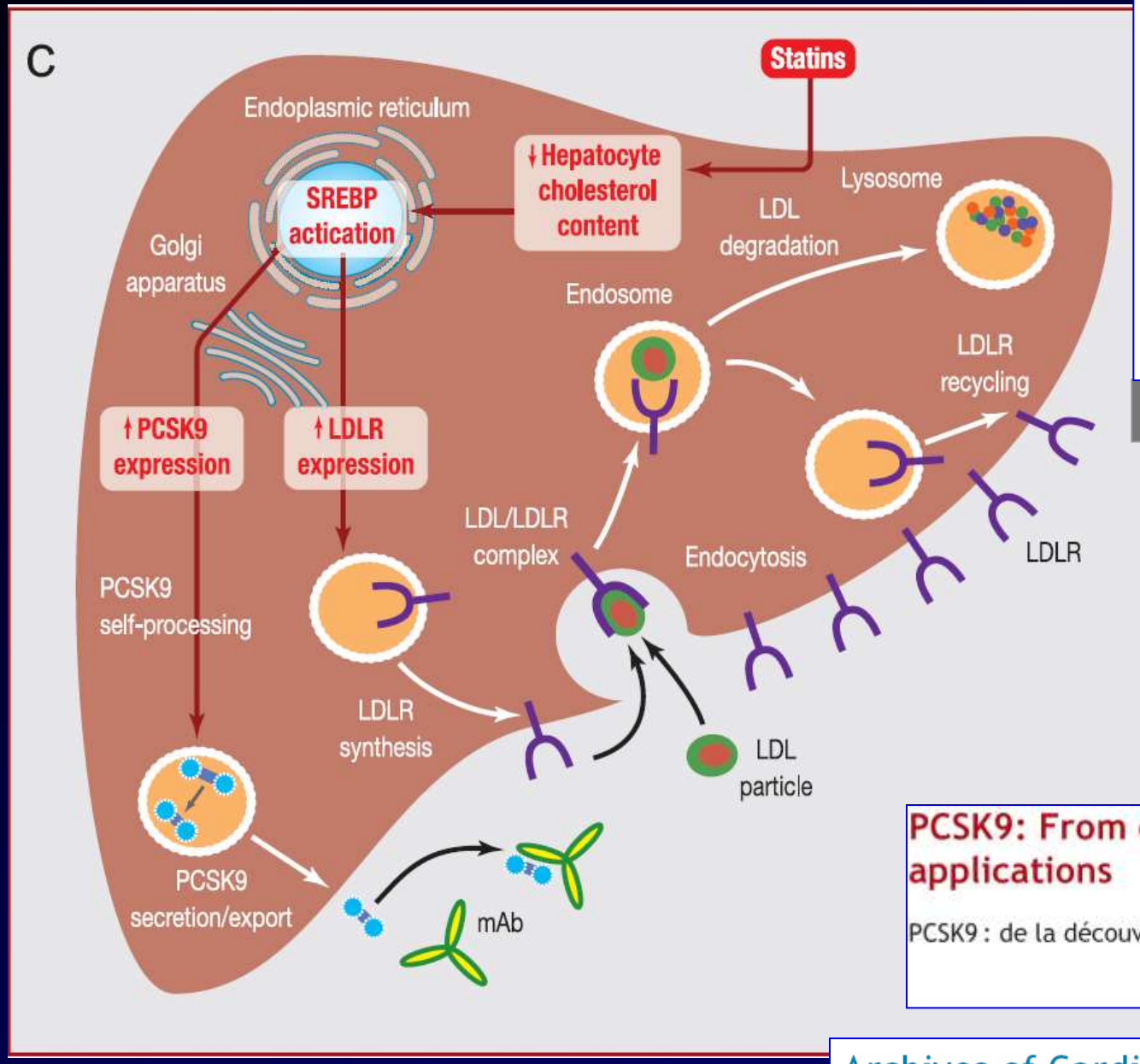
PCSK9: From discovery to therapeutic applications

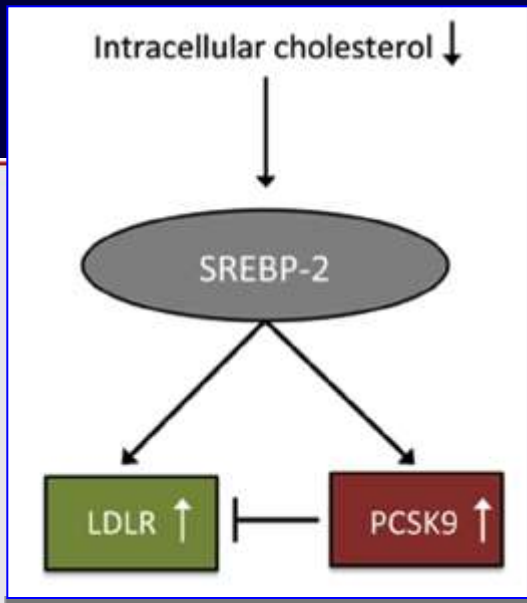
PCSK9 : de la découverte aux applications thérapeutiques

Michel Farnier

Archives of Cardiovascular Disease (2014)

Low intracellular cholesterol levels in response to statin treatment activate the sterol regulatory element-binding protein-2 (SREBP-2), resulting in coexpression of LDLR and PCSK9.





cholesterol homeostasis

Urban JACC 2013

PCSK9: From discovery to therapeutic applications

PCSK9 : de la découverte aux applications thérapeutiques

Michel Farnier

Archives of Cardiovascular Disease (2014)

Targeting the Proprotein Convertase Subtilisin/Kexin Type 9 for the Treatment of Dyslipidemia and Atherosclerosis

JACC 2013

Daniel Urban, MD, Janine Pöss, MD, Michael Böhm, MD, Ulrich Laufs, MD

Table 1 LDL-Independent Effects of PCSK9

LDL-Independent Effect	Molecular Mechanism	Ref. #
Inflammation	In mice, lipopolysaccharide-induced inflammation is associated with enhanced expression of PCSK9.	33
	siRNA-mediated knockdown of PCSK9 in human macrophages attenuates oxLDL-induced IκB-α degradation and Nf-κB nuclear translocation.	34
	PCSK9 gain-of-function mutation D374Y reduces expression of stress response genes and specific inflammatory pathways in HepG2 cells.	38
Endothelial apoptosis	Knockdown of PCSK9 by siRNA reduces oxLDL-induced endothelial apoptosis by altering the Bcl-2/Bax ratio and by inhibiting the activation of both caspase-9 and -3.	39
Blood pressure regulation	Transfection of epithelial cells with PCSK9 reduces expression of cell surface ENaC.	41
Glucose metabolism	In mice, gene inactivation of PCSK9 reduces insulin levels, resulting in glucose intolerance, which is associated with malformation, apoptosis, and inflammation of pancreatic islets.	43
Adipogenesis	PCSK9 limits murine adipogenesis via regulation of adipose VLDLR levels.	45

Bax = Bcl-2-associated X protein; Bcl-2 = B-cell lymphoma 2; ENaC = Epithelial (NA^+) channel; IκB-α = inhibitor of nuclear factor kappaB alpha; LDLR = low-density lipoprotein receptor; Nf-κB = nuclear factor kappaB; oxLDL = oxidized LDL; PCSK9 = proprotein convertase subtilisin/kexin type 9; siRNA = small interfering RNA; VLDLR = very low-density lipoprotein receptor.

PCSK9

A Key Modulator of Cardiovascular Health

Nabil G. Seidah, Zuhier Awan, Michel Chrétien, Majambu Mbikay

Circ Res. 2014;

Attenzioni teoriche di sicurezza: fegato, metab insulina, ts adiposo

LDLR and CD81, 2 HCV entry receptors are dose dependently downregulated by PCSK9, resulting in the reduction of the cellular infectivity of HCV in mice. Because PCSK9 seems to target a number of LDLR family members for degradation, some of which act as entry receptors for infectious viruses, it is **recommended that those individuals harboring a viral infection be carefully monitored for viral titers or excluded from anti–PCSK9-based therapy.**

Critical importance of PCSK9 in liver regeneration**, patients undergoing liver resection should not take anti-PCSK9 medication.**

Lack of PCSK9 increases the surface expression of the VLDLR that facilitates triglycerides hydrolysis and FFA uptake in the visceral adipocytes (visceral fat accumulates - but no liver steatosis and no IR reported in 1 woman completely lacking PCSK9); **anti-PCSK9 therapy in patients must be monitored for the possible occurrence of insulin resistance and glucose intolerance**

Anti PCSK9 th

compound	company	Pre-clinical	Phase I	Pha
Evolocumab-mAb-AMG145	Amgen			
Alirocumab - mAb-REG727/SAR236553	SA / Regeneron			
Bococizumab - mAb-RN316(PF-04950615)	Pfizer-Rinat			
mAb - LGT209	Novartis			
mAb - RG7652	Roche / Genentech			
Adnectin Ad BMS962476	BMS / Adnexus			
siRNA ALN-PCS	Alnylam			
Small chemical inhibitors	Shifa Biomedical Corp.			

Molecular Medicine

Permanent Alteration of PCSK9 With In Vivo CRISPR-Cas9 Genome Editing

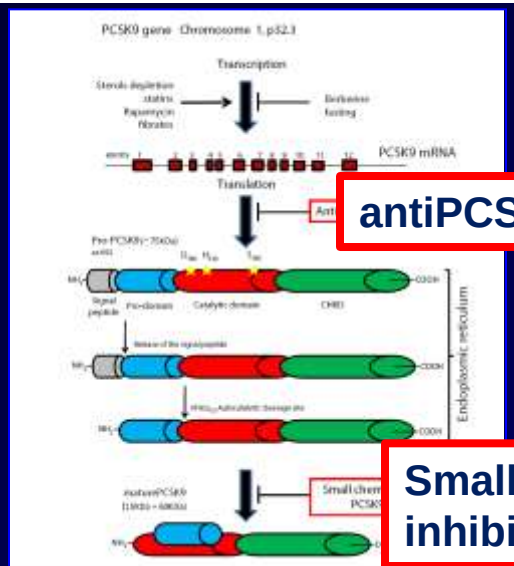
Qiurong Ding, Alanna Strong, Kevin M. Patel, Sze-Ling Ng, Bridget S. Gosis, Stephanie N. Regan, Chad A. Cowan, Daniel J. Rader, Kiran Musunuru

Rationale: **Individuals with naturally occurring loss-of-function proprotein convertase subtilisin/kexin type 9 (*PCSK9*) mutations experience reduced low-density lipoprotein cholesterol levels and protection against cardiovascular disease.**

Objective: **The goal of this study was to assess whether genome editing using a clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated system can efficiently introduce loss-of-function mutations into the endogenous *PCSK9* gene in vivo.**

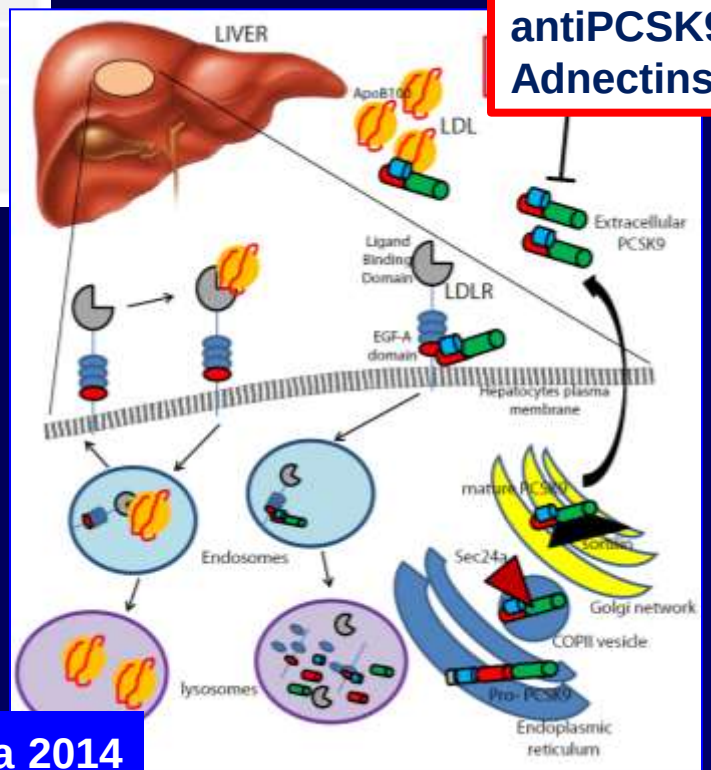
Methods and Results: **We used adenovirus to express CRISPR-associated 9 and a CRISPR guide RNA targeting *Pcsk9* in mouse liver, where the gene is specifically expressed. We found that <3 to 4 days of administration of the virus, the mutagenesis rate of *Pcsk9* in the liver was as high as >50%. This resulted in decreased plasma PCSK9 levels, increased hepatic low-density lipoprotein receptor levels, and decreased plasma cholesterol levels (by 35–40%). No off-target mutagenesis was detected in 10 selected sites.**

Conclusions: **Genome editing with the CRISPR–CRISPR-associated 9 system disrupts the *Pcsk9* gene in vivo with high efficiency and reduces blood cholesterol levels in mice. This approach may have therapeutic potential for the prevention of cardiovascular disease in humans. (*Circ Res*. 2014;115:488-492.)**



antiPCSK9 siRNAs

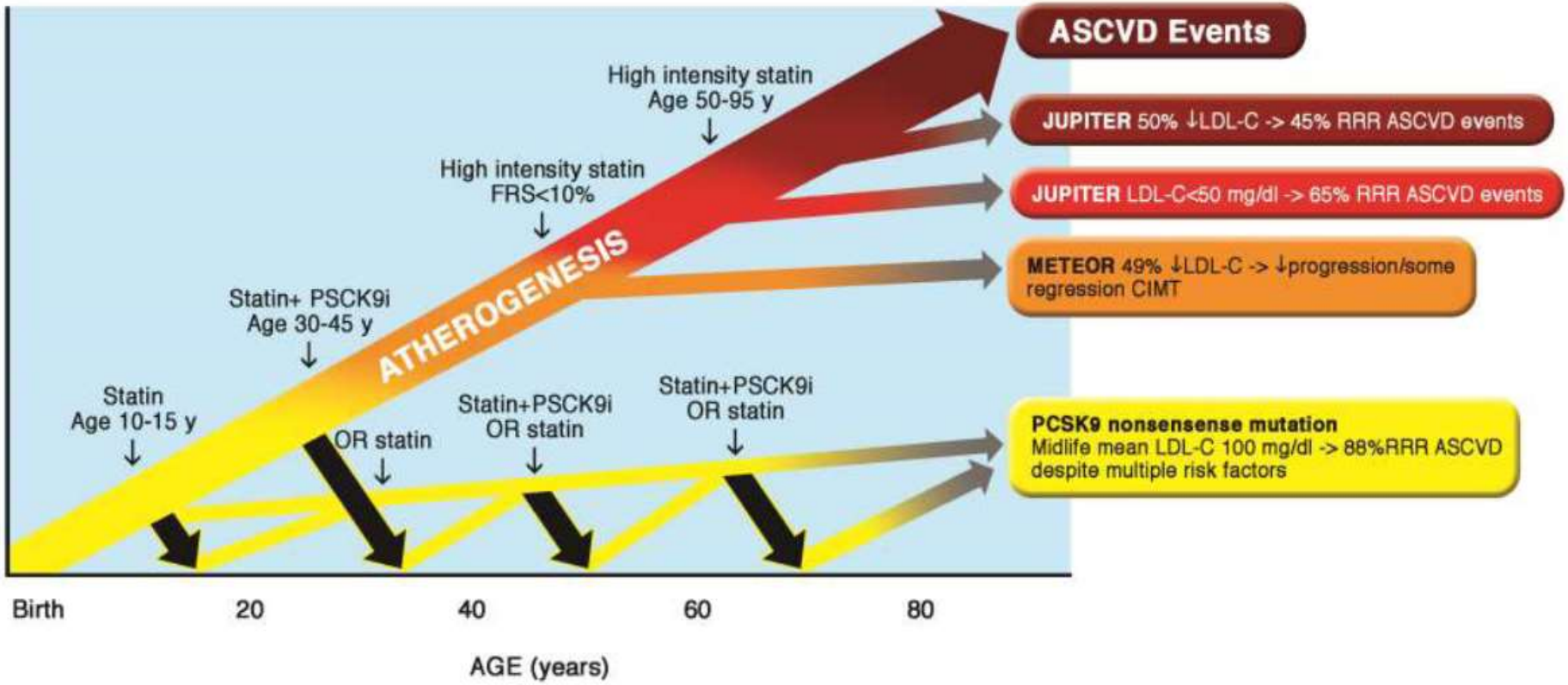
Small chemical inhibitors



antiPCSK9 mAb Adnectins

Norata 2014

New paradigm: Resetting the (vascular aging) clock early



Robinson JG, Gidding SS. Curing Atherosclerosis Should Be the Next Major Cardiovascular Prevention Goal. *JACC.* 2014;63(25, Part A):2779-2785

grazie per l’attenzione