Cholesterol, arterial inflammation and destabilization of atherosclerotic plaque: new indications and new weapons

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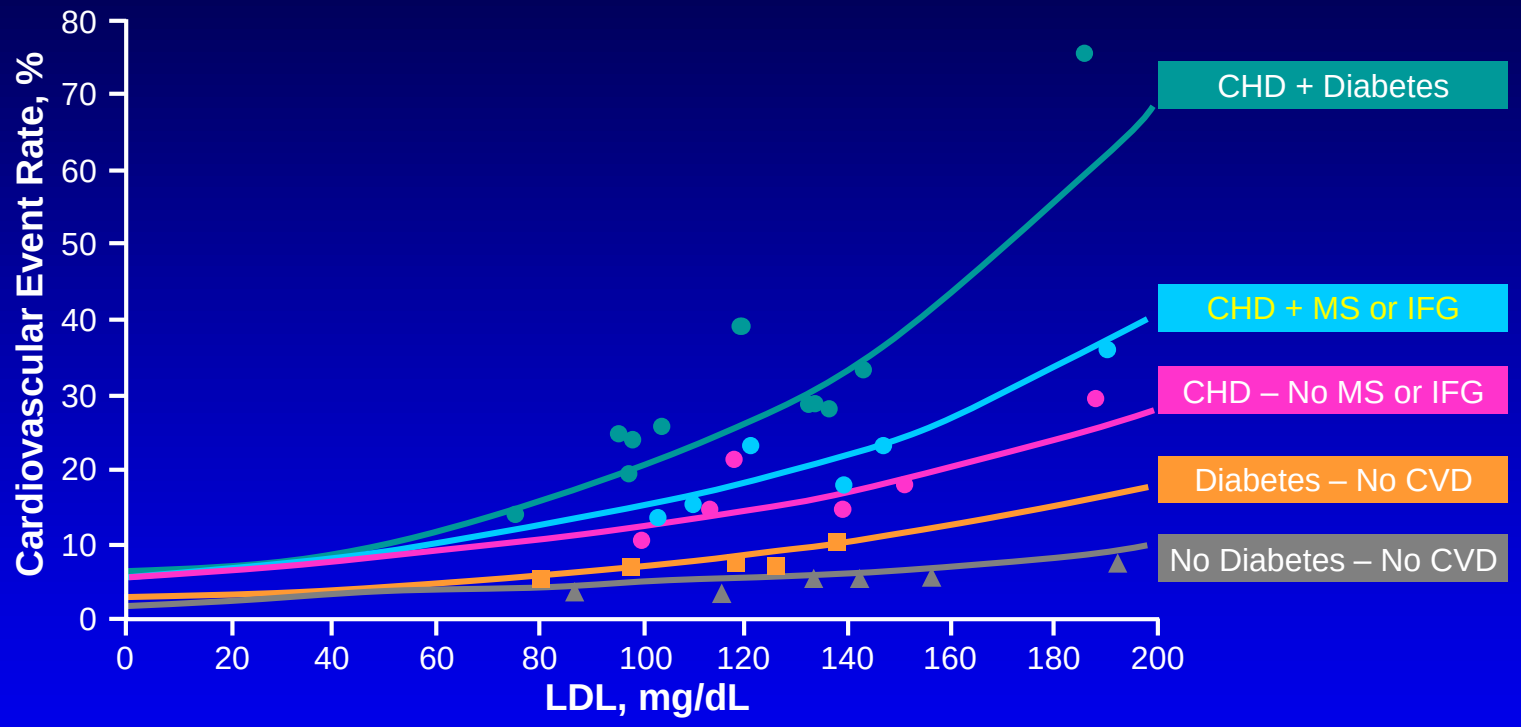
University of Milan, Italy

The LDL principle

- Epidemiology
- Pathophysiology
- Genetics
- Pharmacology

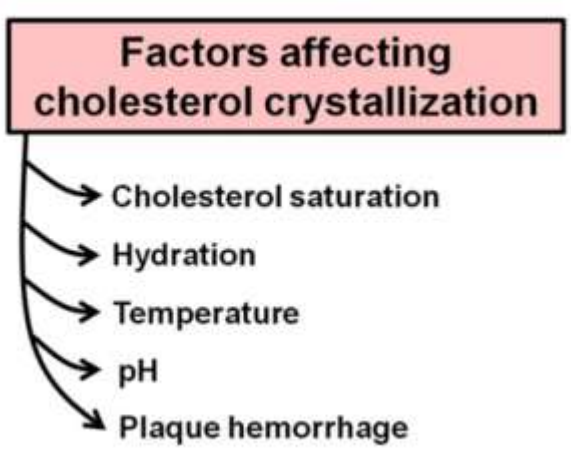
Risk Pattern for Subsequent CV Events Over a Range of LDL-C Values[1]

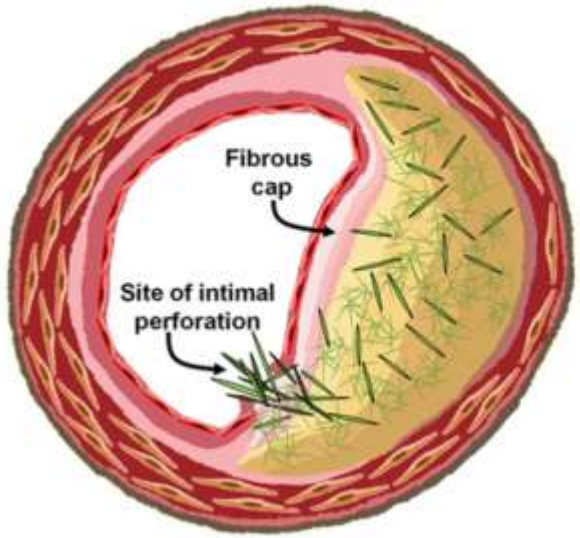


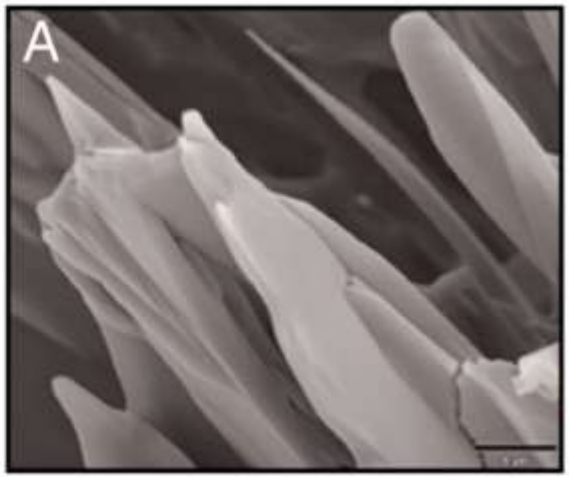
CV = cardiovascular; CHD = coronary heart disease; MS = metabolic syndrome; IFG = impaired fasting glucose; CVD = CV disease.

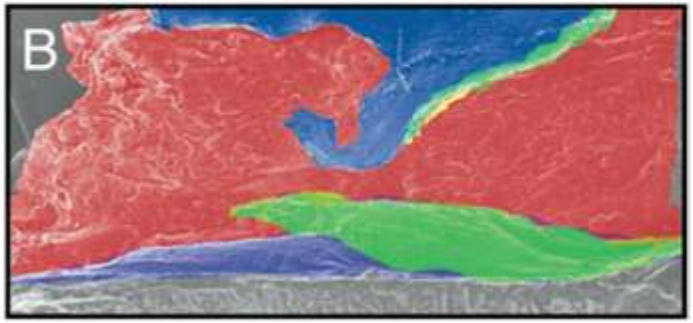
1. Robinson JG et al. *Am J Cardiol.* 2006;98:1405–1408.

Effects of cholesterol crystals on plaque integrity in coronary arteries of patients who died of ACS



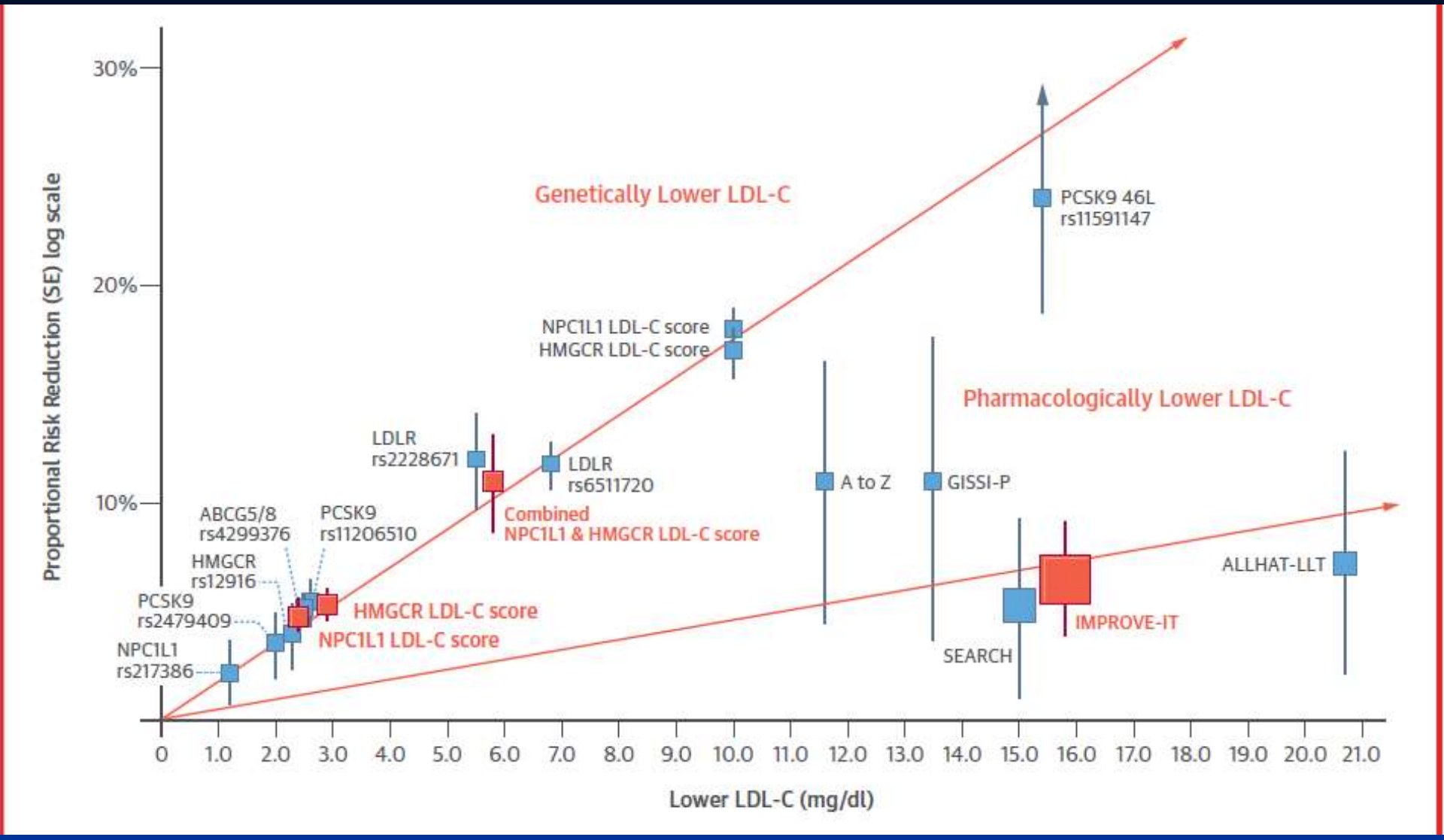






Crea F and Liuzzo G J Am Coll Cardiol 2013;61:1–11

Linear Association Between Genetically and Pharmacologically Mediated Lower LDL and Risk of Coronary Heart Disease



Ference BA et al. J Am Coll Cardiol 2015

- **Present**
- Future

European Heart Journal (2016) 37, 2999–3058
doi:10.1093/eurheartj/ehw272

2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

Developed with the special contribution of the European Assocciation for Cardiovascular Prevention & Rehabilitation (EACPR)

Authors/Task Force Members: Alberico L. Catapano* (Chairperson) (Italy), Ian Graham* (Chairperson) (Ireland), Guy De Backer (Belgium), Olov Wiklund (Sweden), M. John Chapman (France), Heinz Drexel (Austria), Arno W. Hoes (The Netherlands), Catriona S. Jennings (UK), Ulf Landmesser (Germany), Terje R. Pedersen (Norway), Željko Reiner (Croatia), Gabriele Riccardi (Italy), Marja-Riita Taskinen (Finland), Lale Tokgozoglu (Turkey), W. M. Monique Verschuren (The Netherlands), Charalambos Vlachopoulos (Greece), David A. Wood (UK), Jose Luis Zamorano (Spain)

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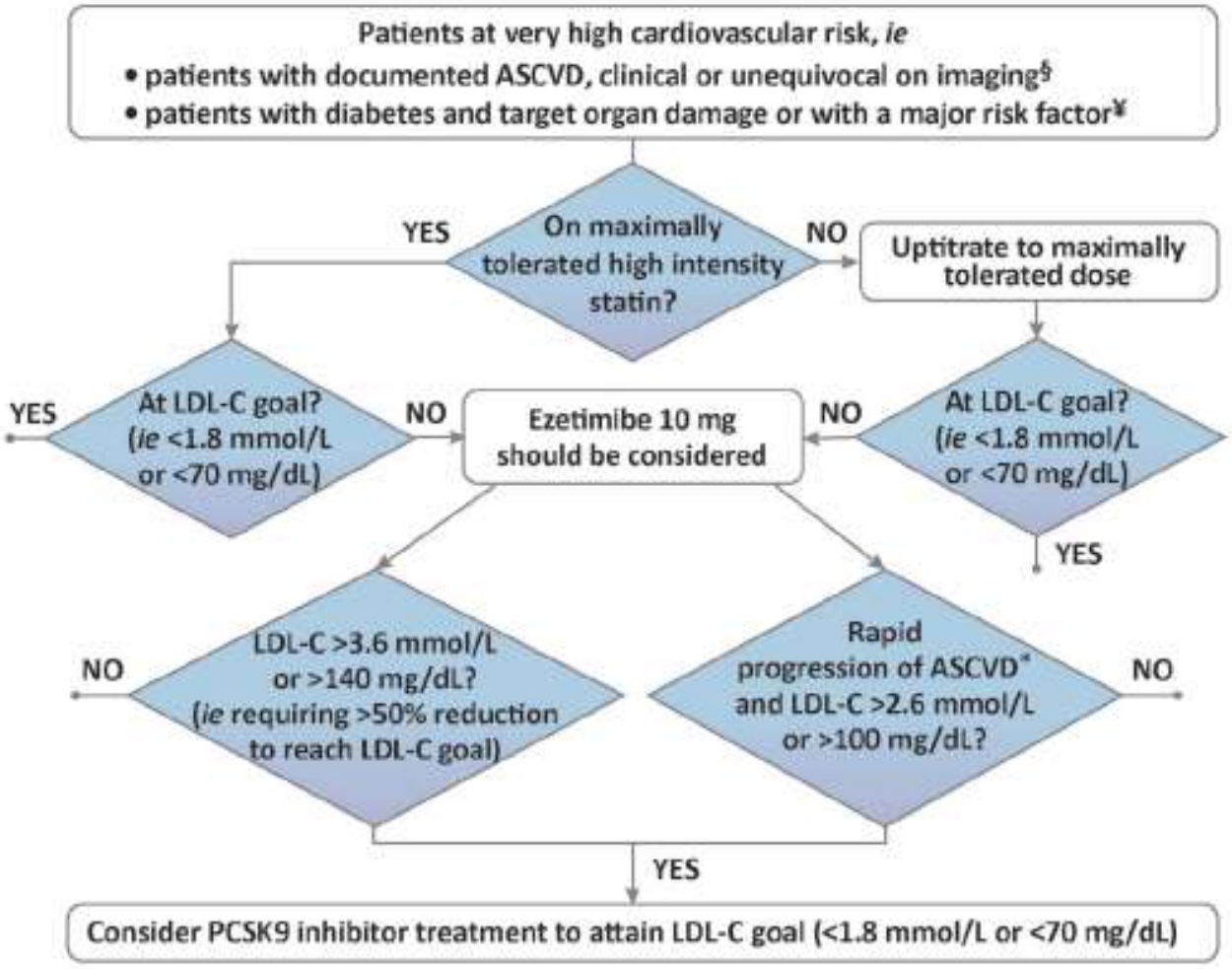
ESC European Society of Cardiology European Heart Journal (2017) 38, 2245–2255 doi:10.1093/eurheartj/ehw480

European Society of Cardiology/European Atherosclerosis Society Task Force consensus statement on proprotein convertase subtilisin/kexin type 9 inhibitors: practical guidance for use in patients at very high cardiovascular risk

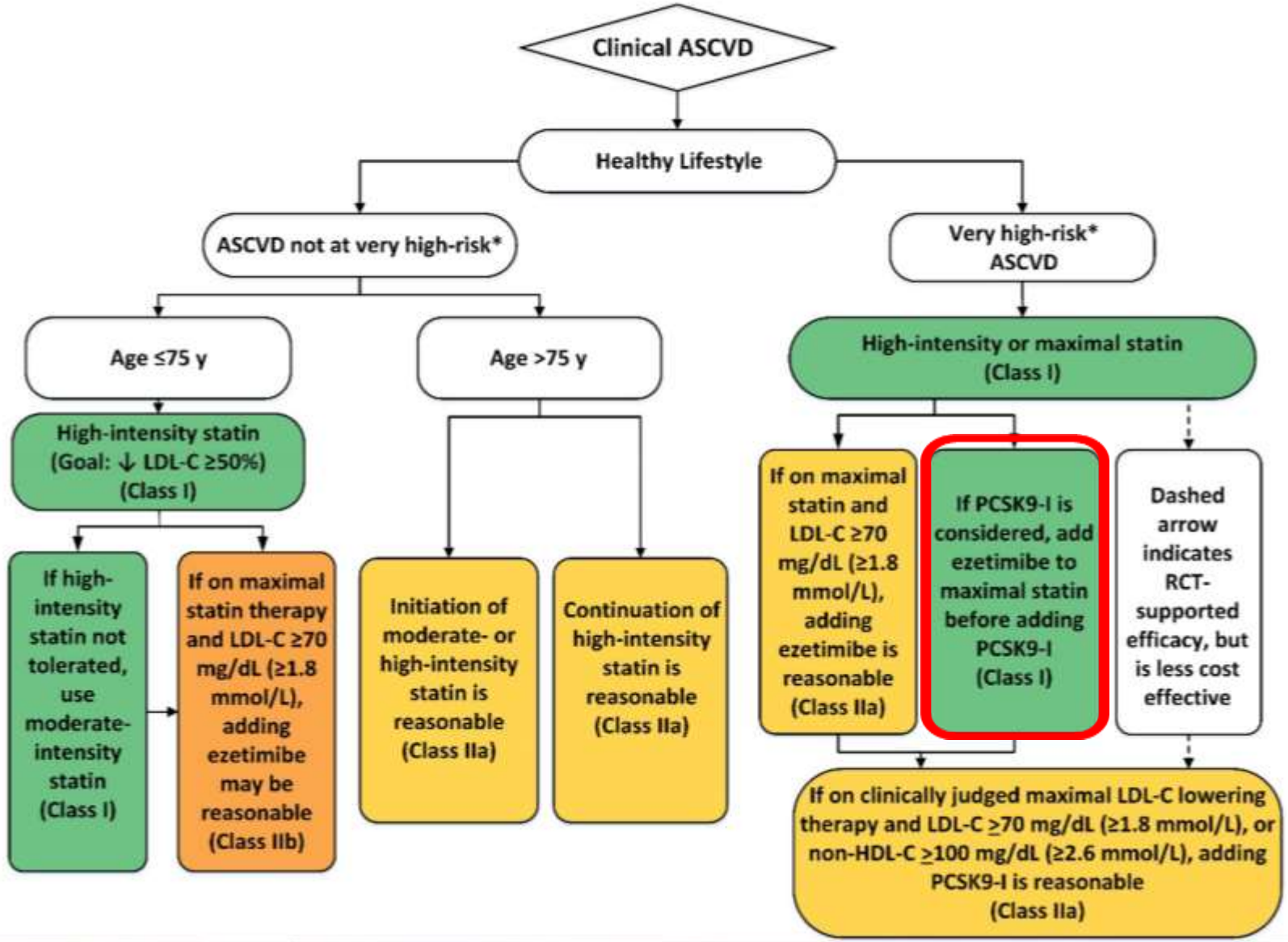


Grundy SM, et al.
2018 Cholesterol Clinical Practice Guidelines

2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol

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

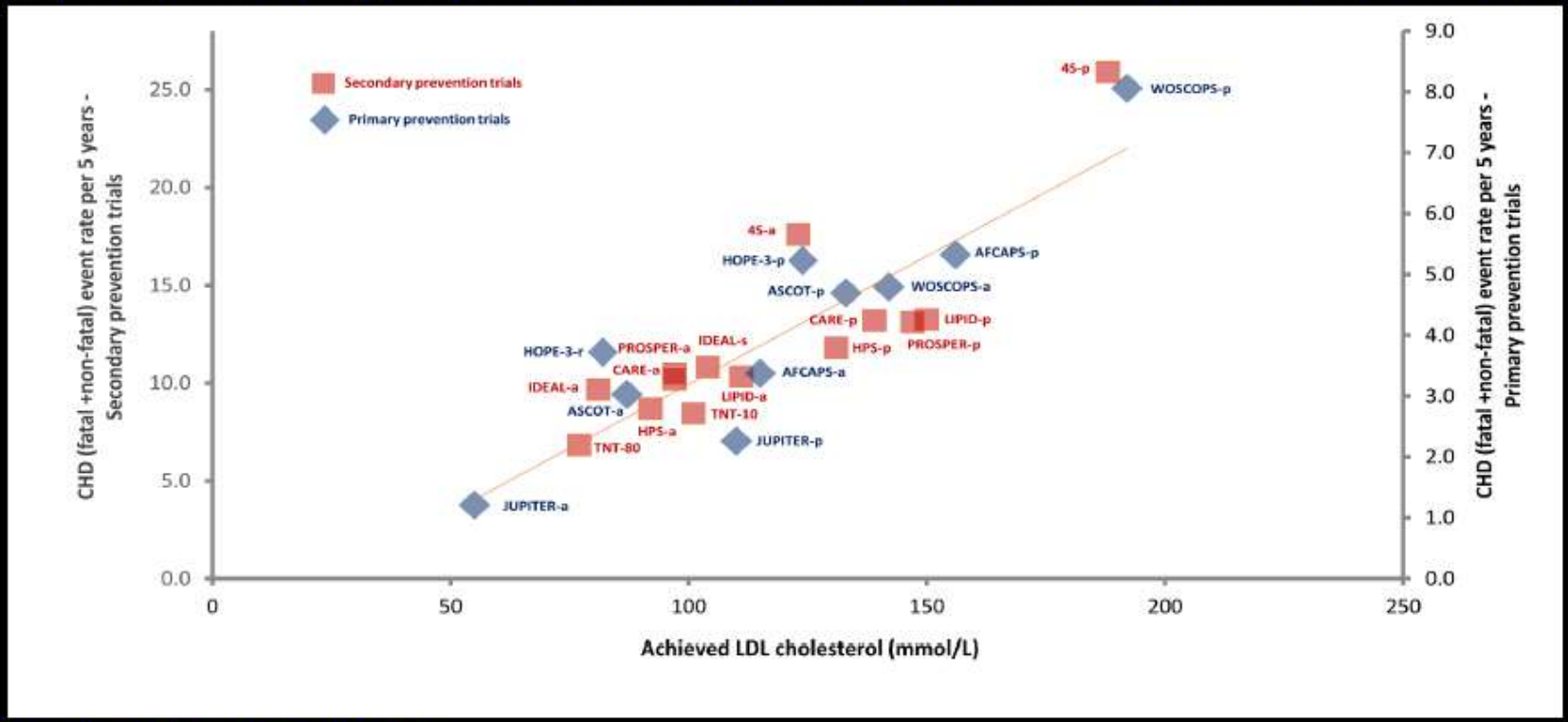
Figure 1. Secondary Prevention in Patients With Clinical ASCVD



J Am Coll Cardiol. 2018 Nov 8.

Randomized Controlled Trials

Absolute yearly event rate on LDL-lowering treatment was strongly and linearly associated with the absolute achieved LDL-C level



European Heart Journal. doi:10.1093/eurheartj/ehx144.

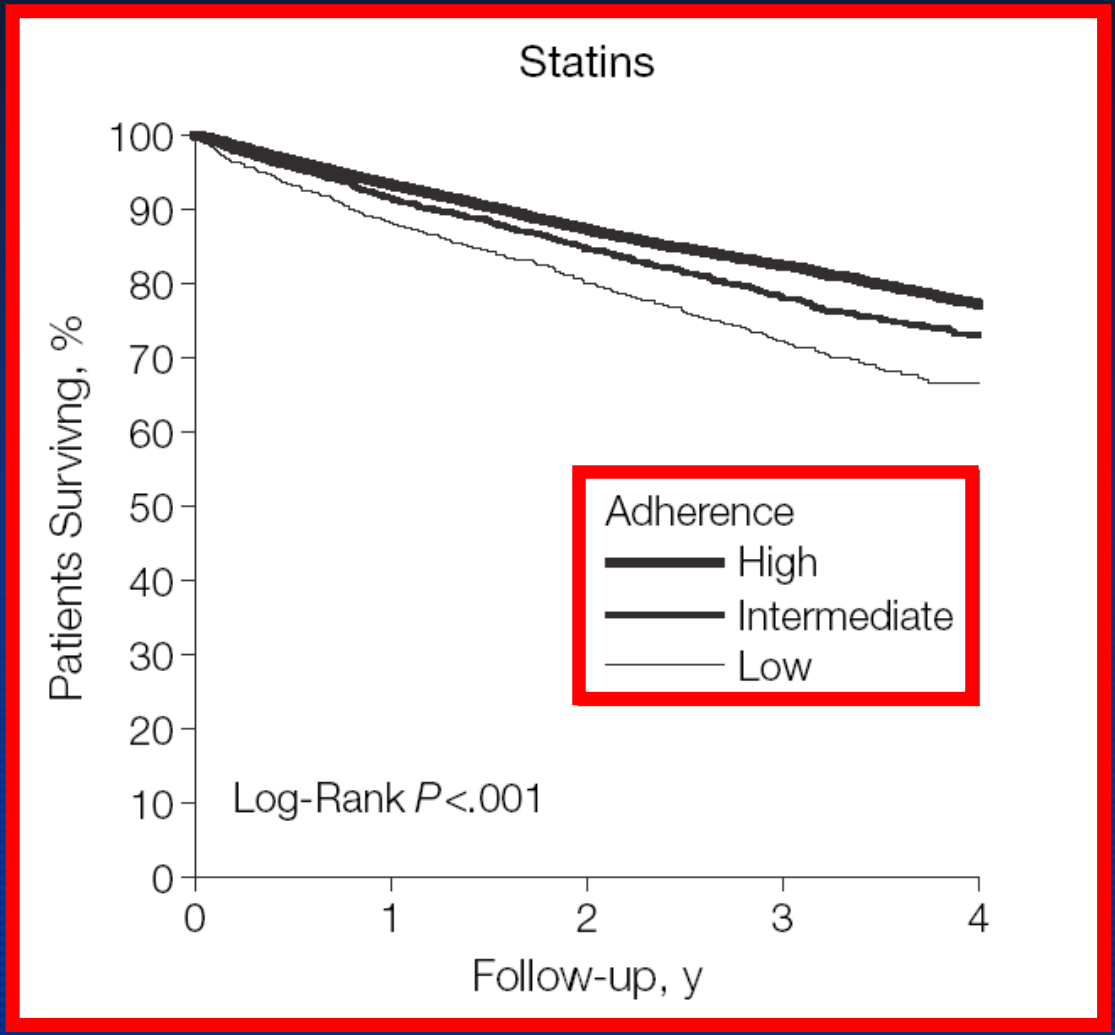
Therapeutic control of LDL cholesterol

LDL-C < 1.8 mmol/L in patients using lipid-lowering drugs

	EUROASPIRE IV	EUROASPIRE V	Change
Belgium	13%	33%	+20%
Bosnia and Herzegovina	16%	21%	+5%
Bulgaria	8%	19%	+10%
Croatia	22%	31%	+9%
Czech Republic	23%	39%	+15%
Finland	33%	50%	+17%
Germany	12%	25%	+13%
Greece	14%	25%	+12%
Latvia	30%	32%	+2%
Lithuania	5%	9%	+4%
Netherlands	21%	36%	+15%
Poland	23%	41%	+18%
Romania	21%	32%	+11%
Russian Federation	16%	29%	+13%
Serbia	12%	19%	+7%
Slovenia	34%	41%	+8%
Spain	41%	57%	+17%
Sweden	20%	41%	+21%
Turkey	10%	19%	+9%
Ukraine	15%	20%	+5%
United Kingdom	31%	42%	+11%
OVERALL	20.1%	30.6%	+10.5%

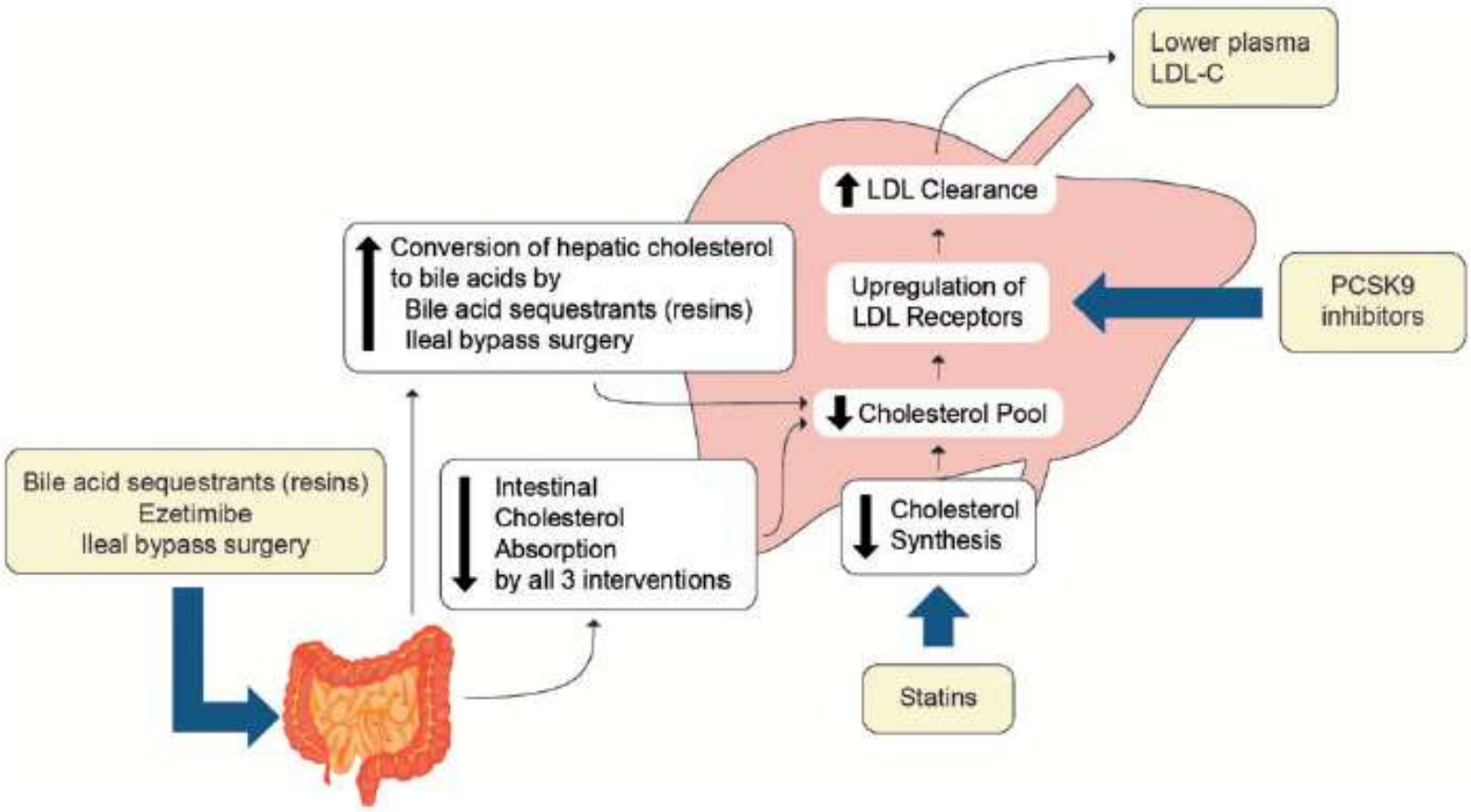
P<0.0001

Estimates of Time to Death for Statin Users According to Adherence Level



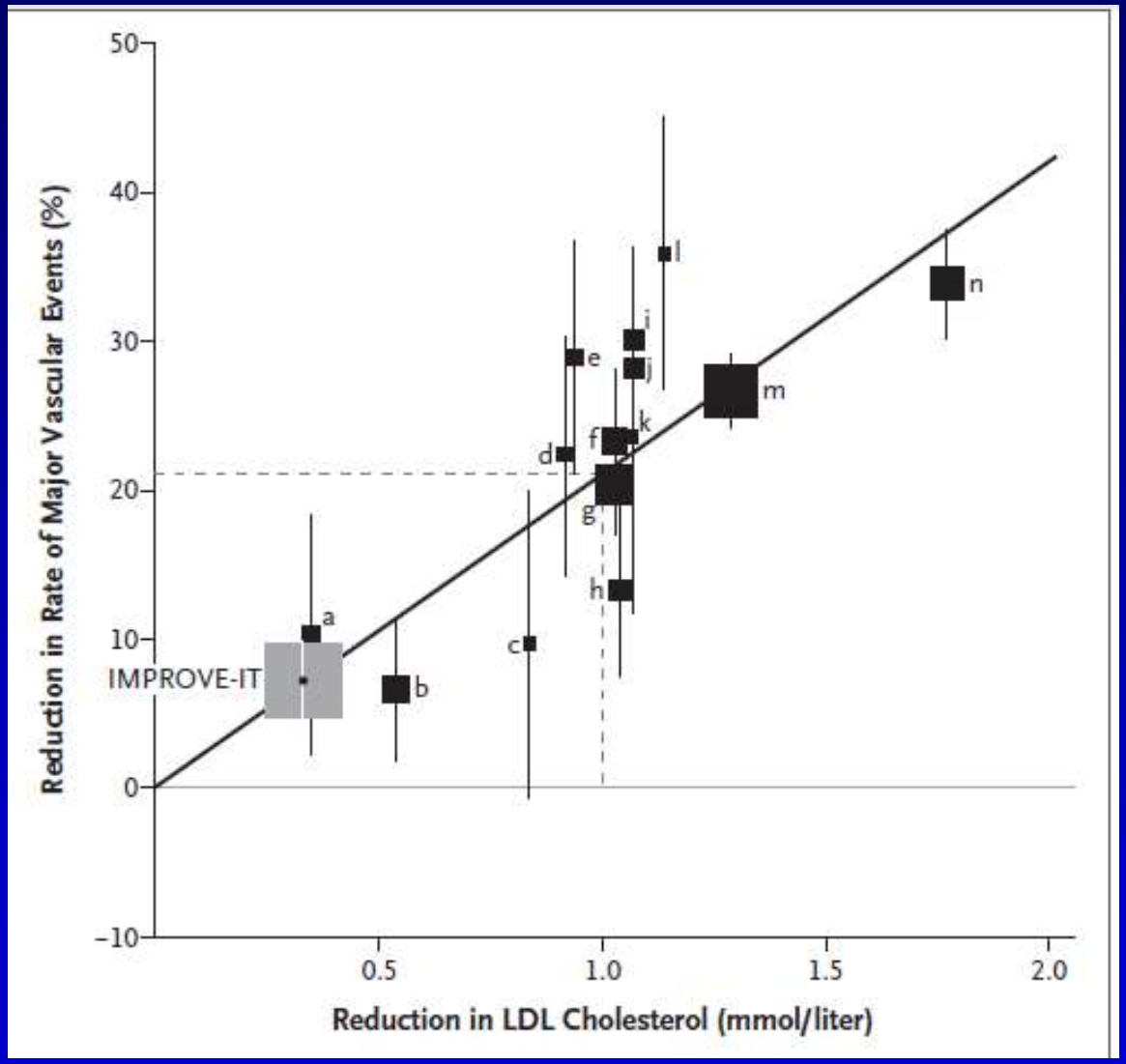
Rasmussen JN et al. JAMA. 2007;297:177-186

All therapies that act predominantly to lower LDL up-regulate LDL receptors and thus increase LDL clearance



Ference B et al European Heart Journal (2017) 0, 1–14

Plot of the IMPROVE-IT Trial Data and Statin Trials for Change LDL-C vs Clinical Benefit



Cannon CP et al. N Engl J Med 2015;372:2387-2397

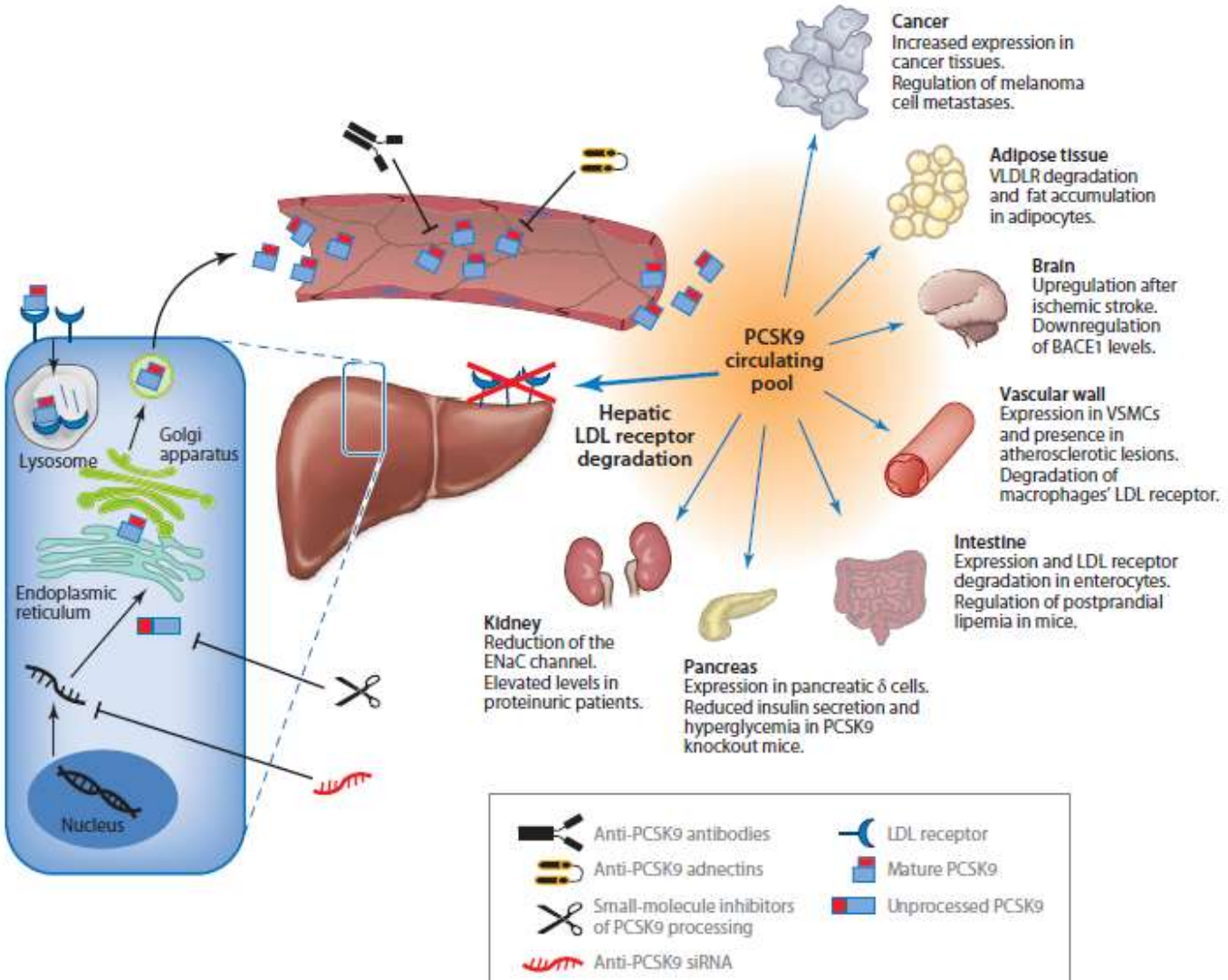
Why PCSK9 as a new target?

Why a monoclonal antibody?

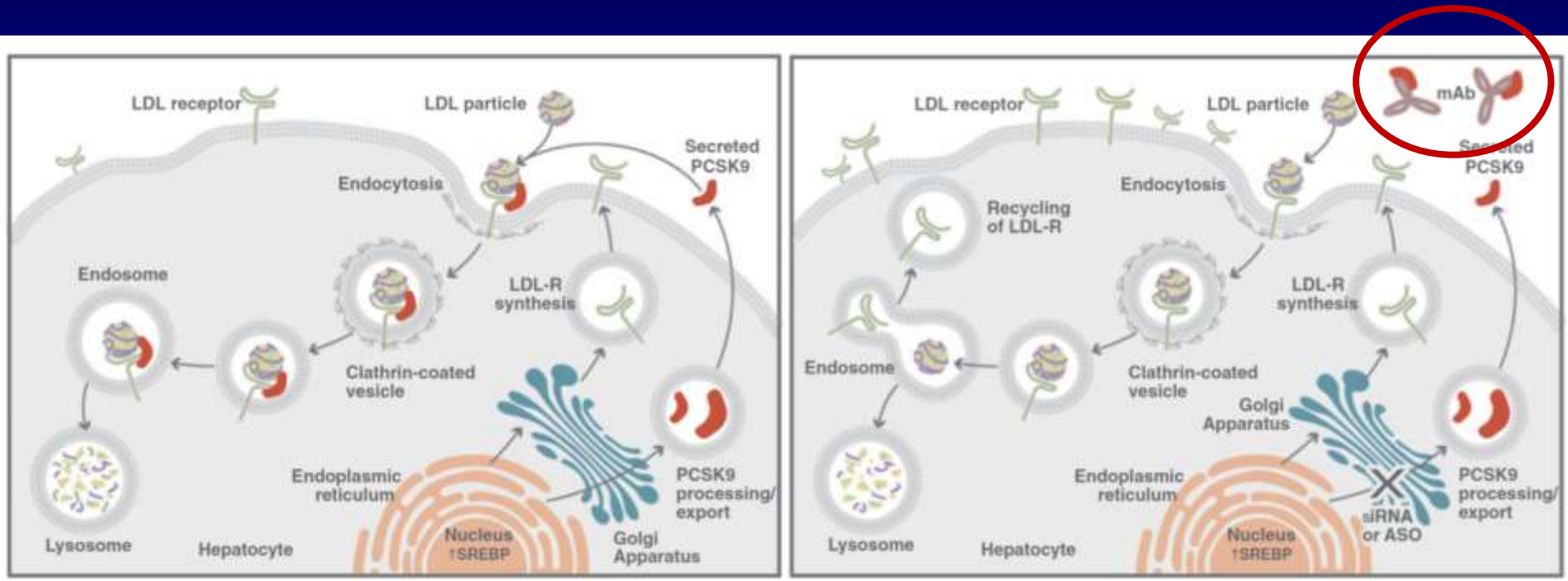
Proprotein convertase subtilisin/kexin 9 (PCSK9)

- **Biochemistry / Physiology**
- Epidemiology
- Genetics
- Pharmacology

PCSK9: physiological role and pharmacological modulation

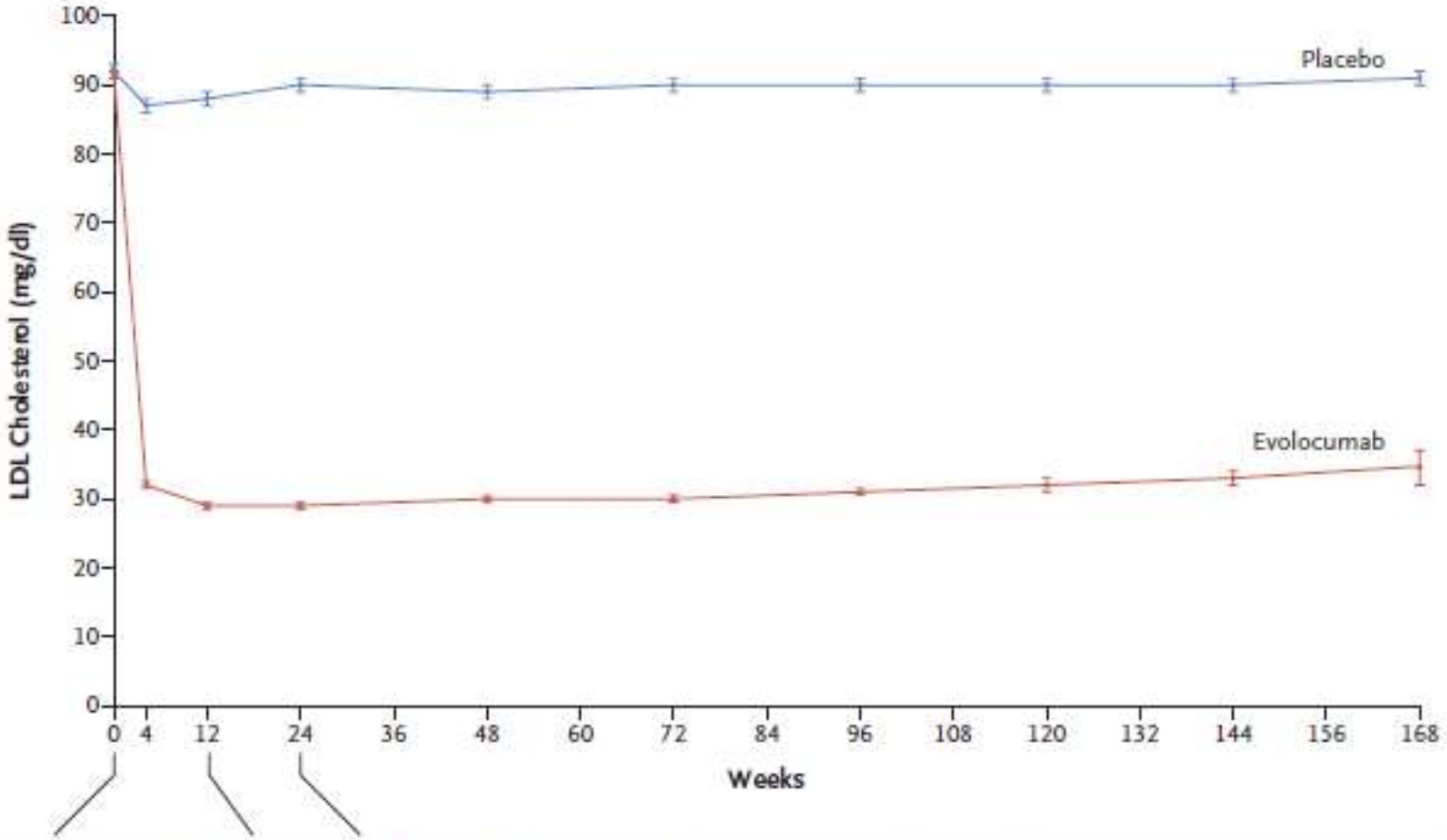


Interaction of PCSK9 and the LDL receptor



Stein EA and Swergold GD Curr Atheroscler Rep (2013) 15:310

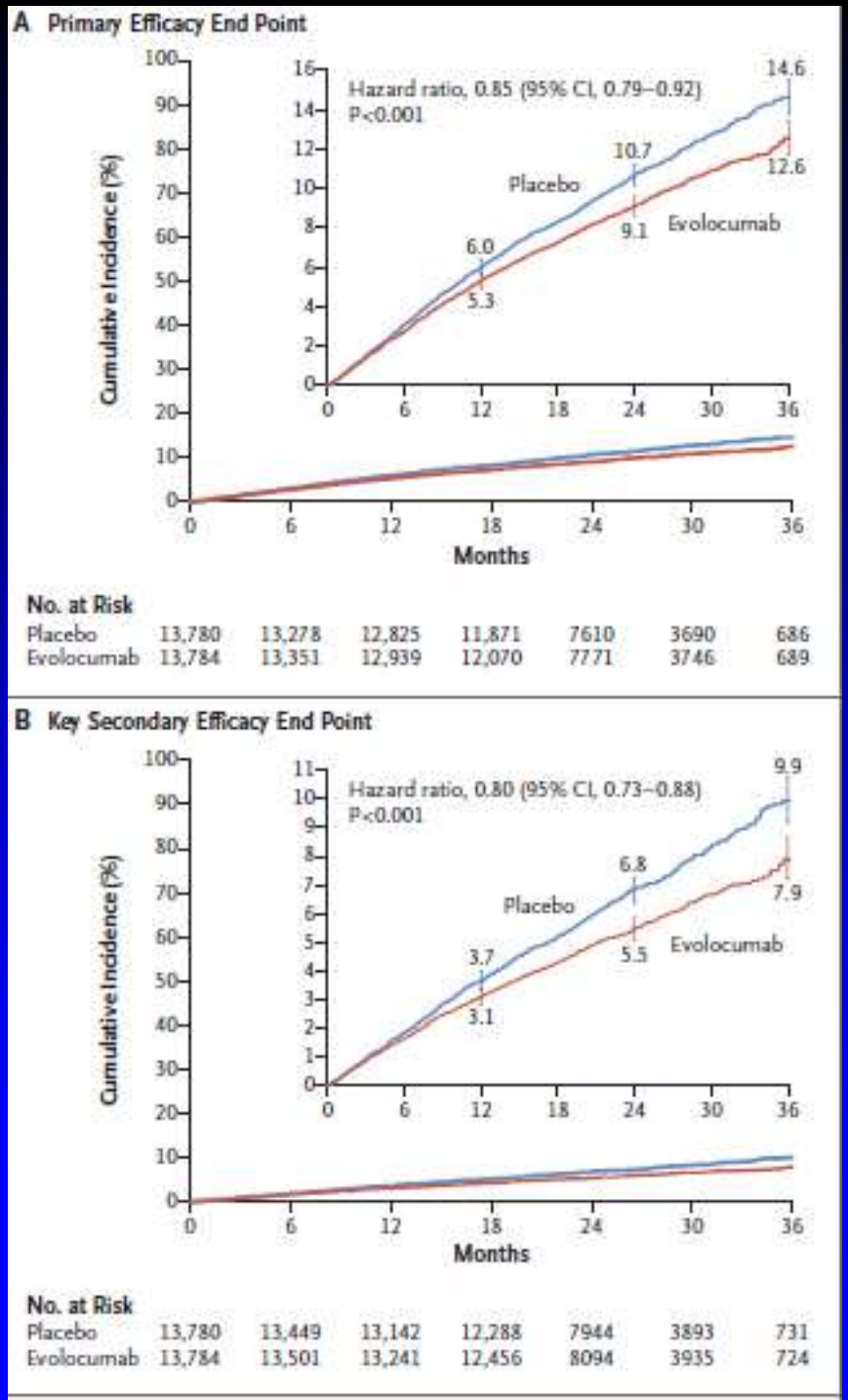
	FOURIER	ODYSSEY OUTCOMES
Population	Stable ASCVD	Recent ACS
Qualifying LDL-C, mg/dL	≥70	≥70
Primary endpoint	5-point MACE: CV death, MI, CVA, UA, coronary revasc.	4-point MACE: CHD death, MI, CVA, UA
Follow up	26 months	34 months
Age (median, years)	63	58
ACS <1 year	20%	100%
High-intensity statin	69%	89%
No statin	0.2%	2.5%



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

Figure 1. Low-Density Lipoprotein (LDL) Cholesterol Levels over Time.

Cumulative Incidence of Cardiovascular Events



Sabatine MS et al N Engl J Med. 2017 376(18):1713-1722

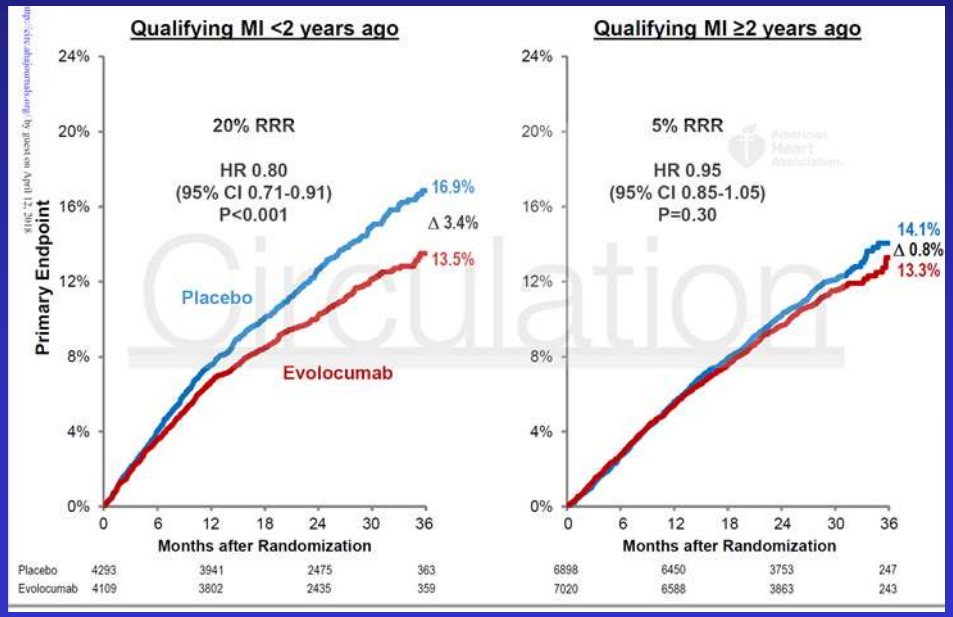
Circulation

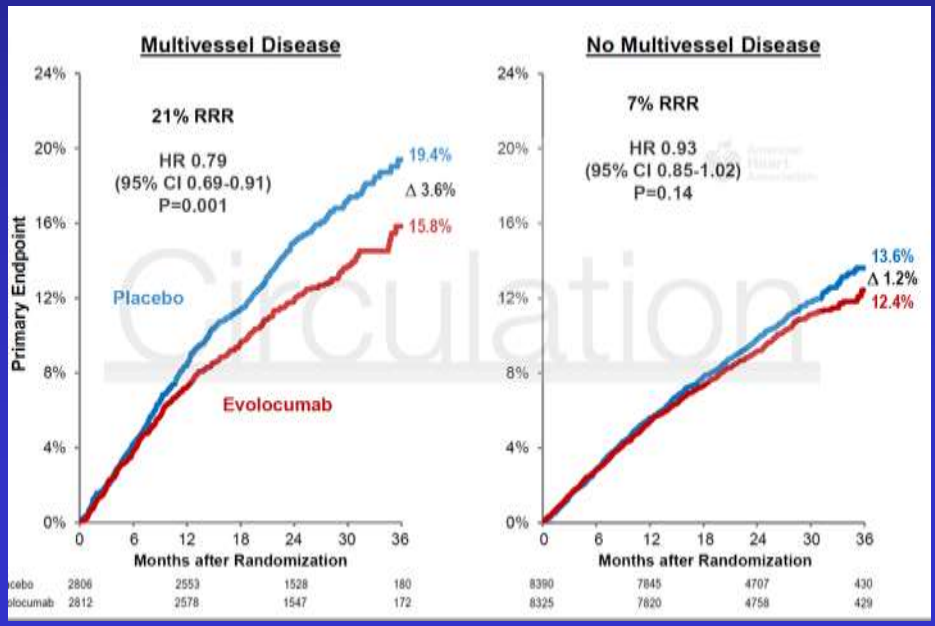
American Heart Association

Clinical Benefit of Evolocumab by Severity and Extent of Coronary Artery Disease: An Analysis from FOURIER

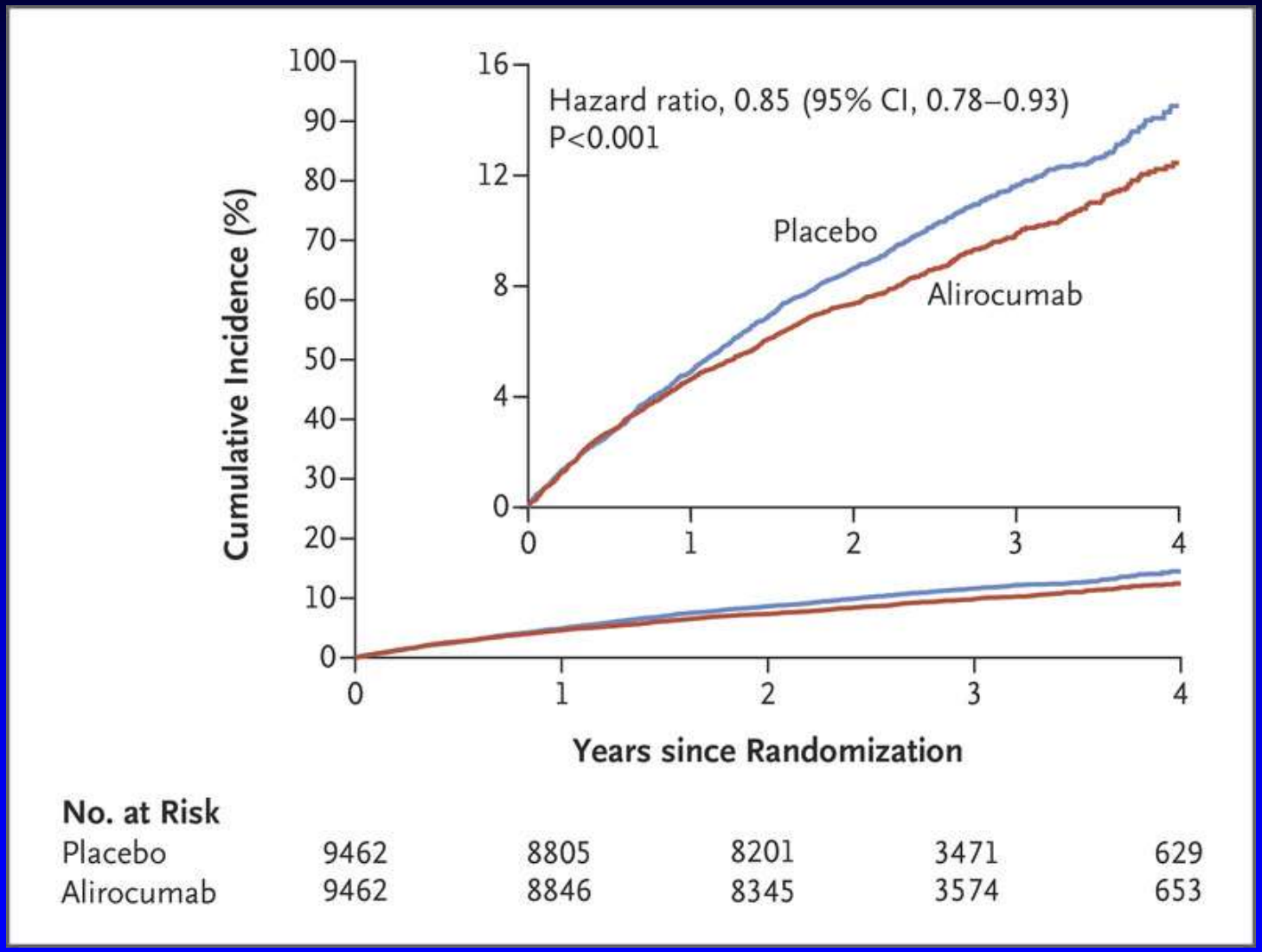
Marc S. Sabatine, Gaetano M. De Ferrari, Robert P. Giugliano, Kurt Huber, Basil S. Lewis, Jorge Ferreira, Julia F. Kuder, Sabina A. Murphy, Stephen D. Wiviott, Christopher E. Kurtz, Narimon Honarpour, Anthony C. Keech, Peter S. Sever and Terje R. Pedersen

Circulation. published online April 6, 2018;





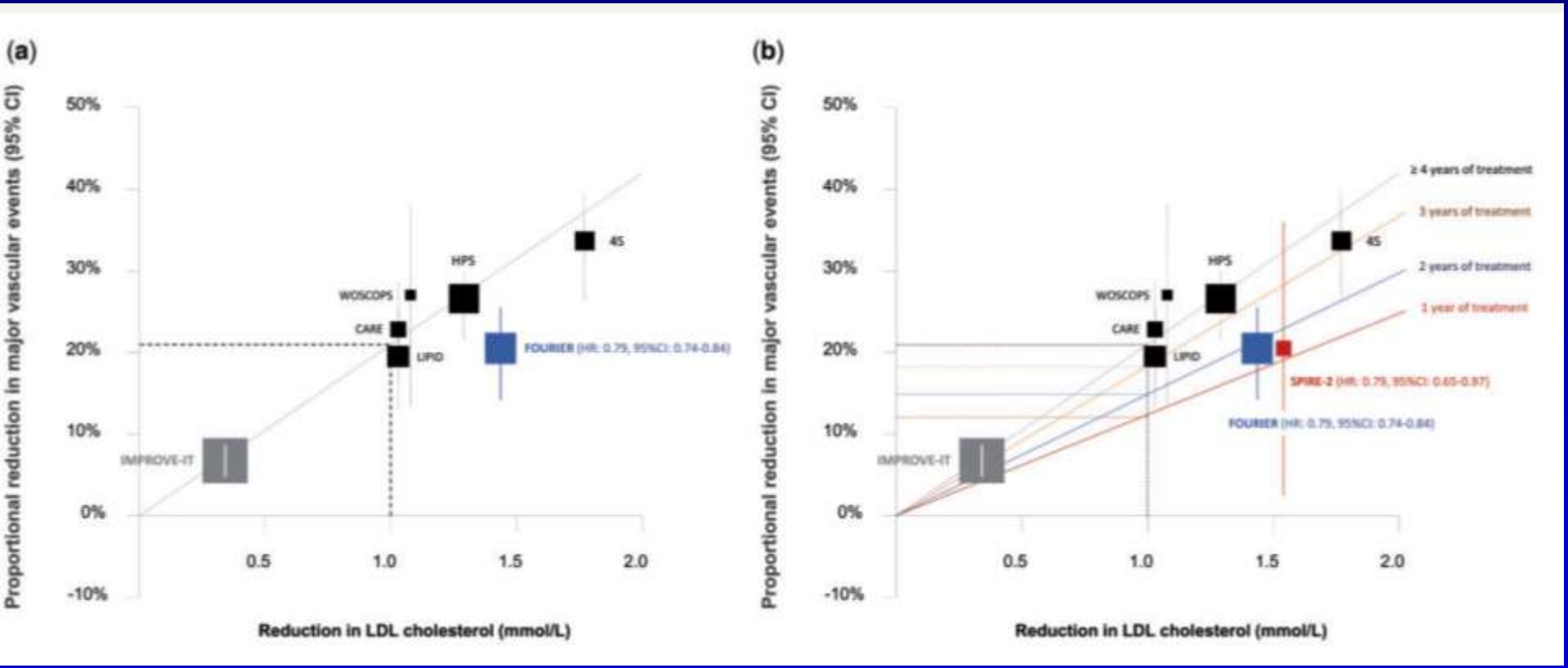
Cumulative Incidence of the Composite Primary End Point



No. at Risk					
Placebo	9462	8805	8201	3471	629
Alirocumab	9462	8846	8345	3574	653

Schwartz GG et al N Engl J Med. 2018 Nov 7

Effect of statins and PCSK9 inihibitors on the risk of CVD for various durations of total treatment



Ference BA et al Eur Heart J. 2018 Jul 14;39(27):2540-2545

Combined lipid-lowering therapy

Drug class	LDL-C Decrease (%)	Non-HDL-C Decrease (%)	HDL-C Increase (%)	TG Decrease (%)
Statin	+++	+++	+	++
Ezetimibe	++	++	+	+
Feno	+	+	++	++++
PCSK9 inhibotor	++++	++++	+	+

- Present
- **Future**

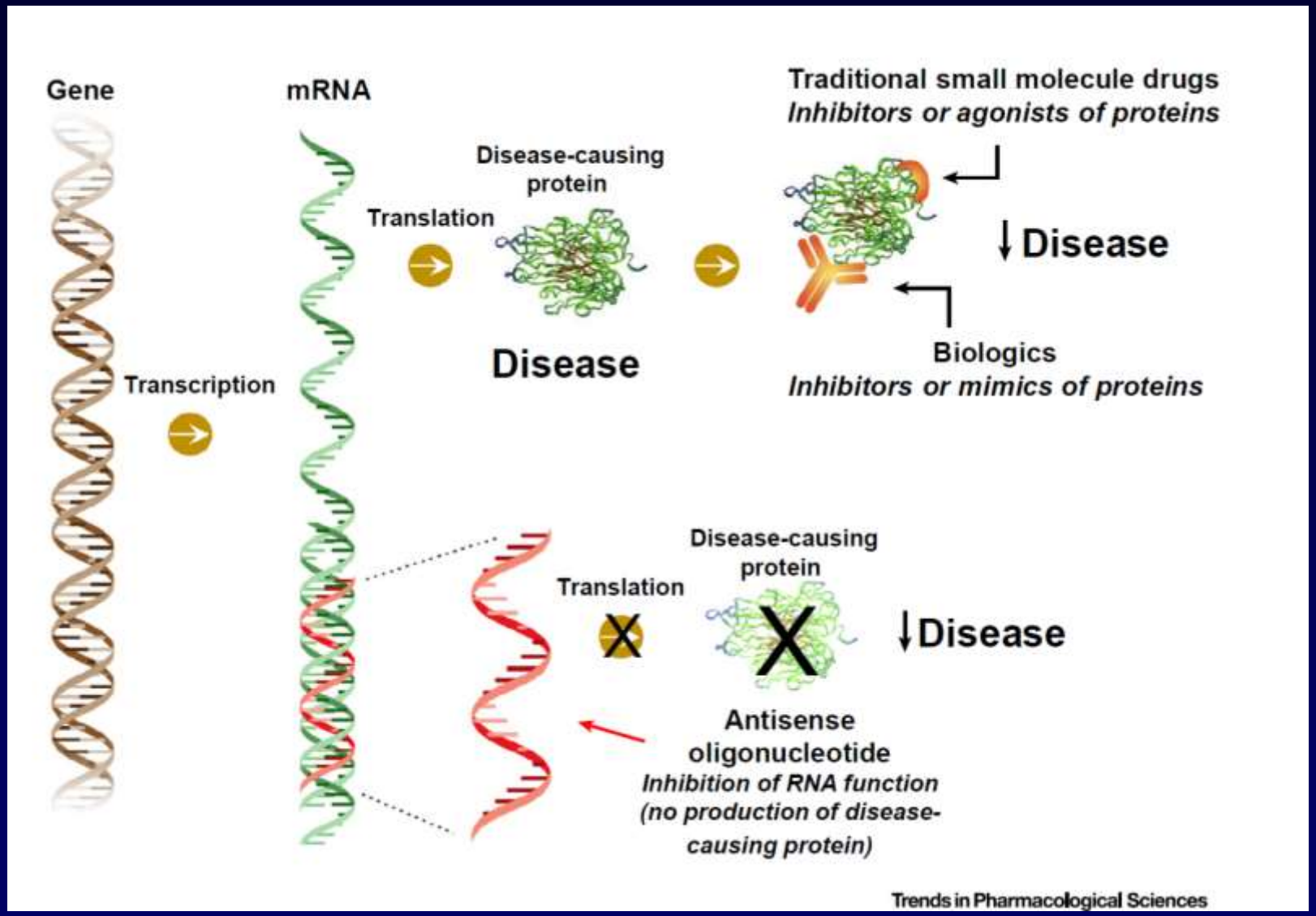
Table 1. Novel therapies for lipid disorders

Addressed pathway	Therapy	Lipid disorder to be addressed
PCSK9	Antibodies	LDL-hypercholesterolemia
	Antisense oligo nucleotides (inclisiran)	
	Genome editing	
	Vaccination	
CETP	Inhibition (anacetrapib)	LDL-hypercholesterolemia
ANGPTL3	Antibody (evinacumab)	Homozygous FH, severe hypertriglyceridemia, combined dyslipidemia
	Antisense oligo nucleotides	
PPARα	New fibrates (pemafibrate)	hypertriglyceridemia
Acetyl-Coenzyme A carboxylase	Inhibitor (gemcabene)	hypercholesterolemia, homozygous FH, severe hypertriglyceridemia
Adenosine triphosphate citrate lyase	Inhibitor (ETC-1002, Bempedoic acid)	hypercholesterolemia
Diacylglycerol Acyltransferase	Inhibitor (pradigastat)	Severe hypertriglyceridemia
	Antisense oligo nucleotides	
ApoA1	Reconstituted lipoprotein (CSL112)	Independent of lipid disorders (low HDL-cholesterol);
ApoC-III	Antisense oligonucleotides (volanesorsen)	hypertriglyceridemia
Apoprotein(a)	Antisense oligonucleotides (IONIS-APO(a)Rx)	Elevated lipoprotein(a)

ANGPTL3, angiopoetin-like protein 3; apo, apolipoprotein; CETP, cholesterol ester transfer protein; FH, familial hypercholesterolemia; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PCSK9, proprotein convertase subtilisin kexin type 9; PPAR, peroxisome proliferator-activated receptor.

Parhofer KG Curr Opin Lipidol 2017, 28:452–457

Therapeutic Approaches for Managing Dyslipidemia



Sathiyakumar V et al Trends Pharmacol Sci. 2018 Aug;39(8):733-747

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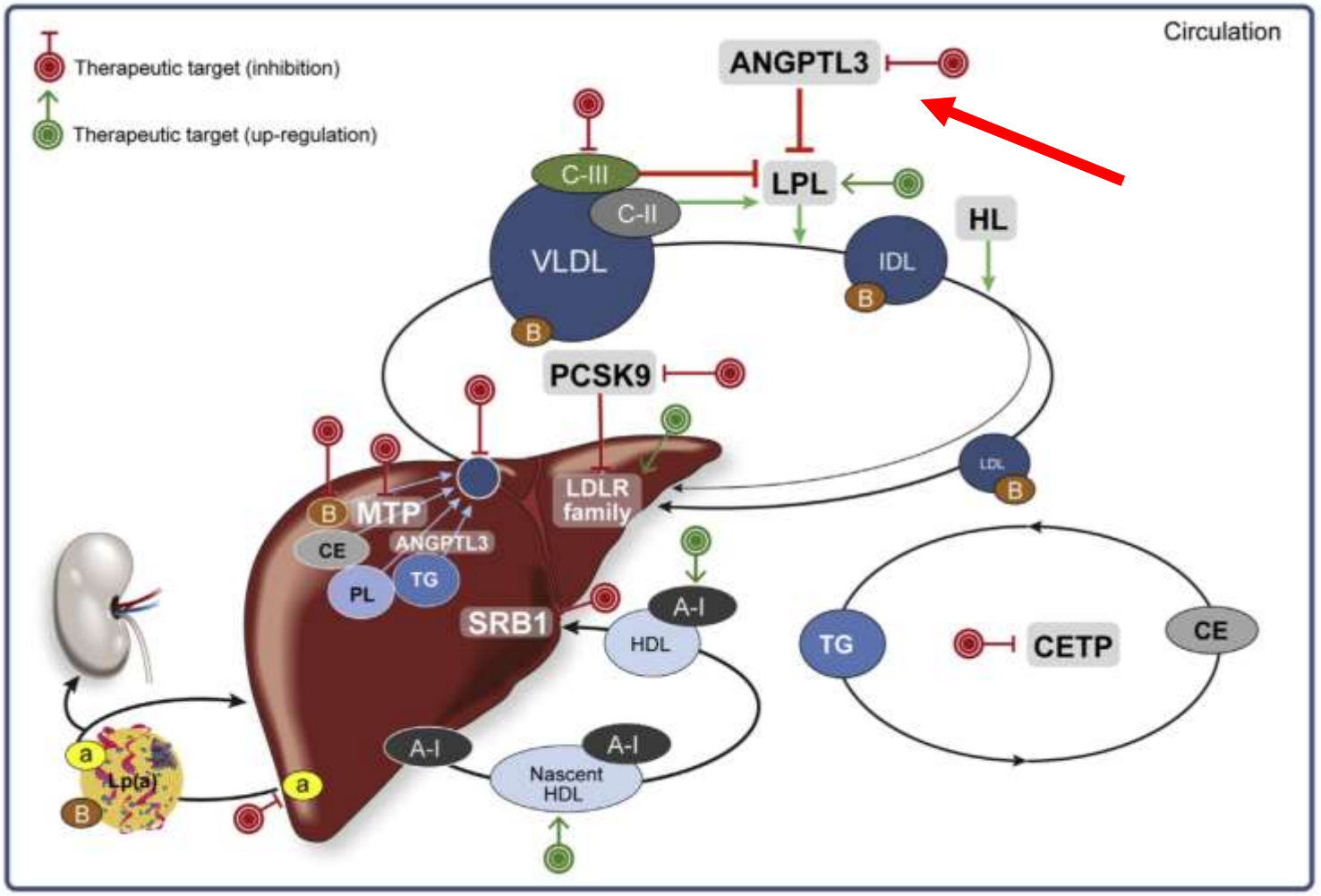
PPARα	New fibrates (pemafibrate)	hypertriglyceridemia
Acetyl-Coenzyme A carboxylase	Inhibitor (gemcabene)	hypercholesterolemia, homozygous FH, severe hypertriglyceridemia
Adenosine triphosphate citrate lyase	Inhibitor (ETC-1002, Bempedoic acid)	hypercholesterolemia
Diacylglycerol Acyltransferase	Inhibitor (pradigastat)	Severe hypertriglyceridemia
	Antisense oligo nucleotides	
ApoA1	Reconstituted lipoprotein (CSL112)	Independent of lipid disorders (low HDL-cholesterol);
ApoC-III	Antisense oligonucleotides (volanesorsen)	hypertriglyceridemia
Apoprotein(a)	Antisense oligonucleotides (IONIS-APO(a)Rx)	Elevated lipoprotein(a)

ANGPTL3, angiopoetin-like protein 3; apo, apolipoprotein; CETP, cholesterol ester transfer protein; FH, familial hypercholesterolemia; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PCSK9, proprotein convertase subtilisin kexin type 9; PPAR, peroxisome proliferator-activated receptor.

Parhofer KG Curr Opin Lipidol 2017, 28:452–457

Overview of lipoprotein metabolism and emerging targets for lipid-lowering therapies



Gaudet D et al Canadian Journal of Cardiology 33 (2017) 872e882

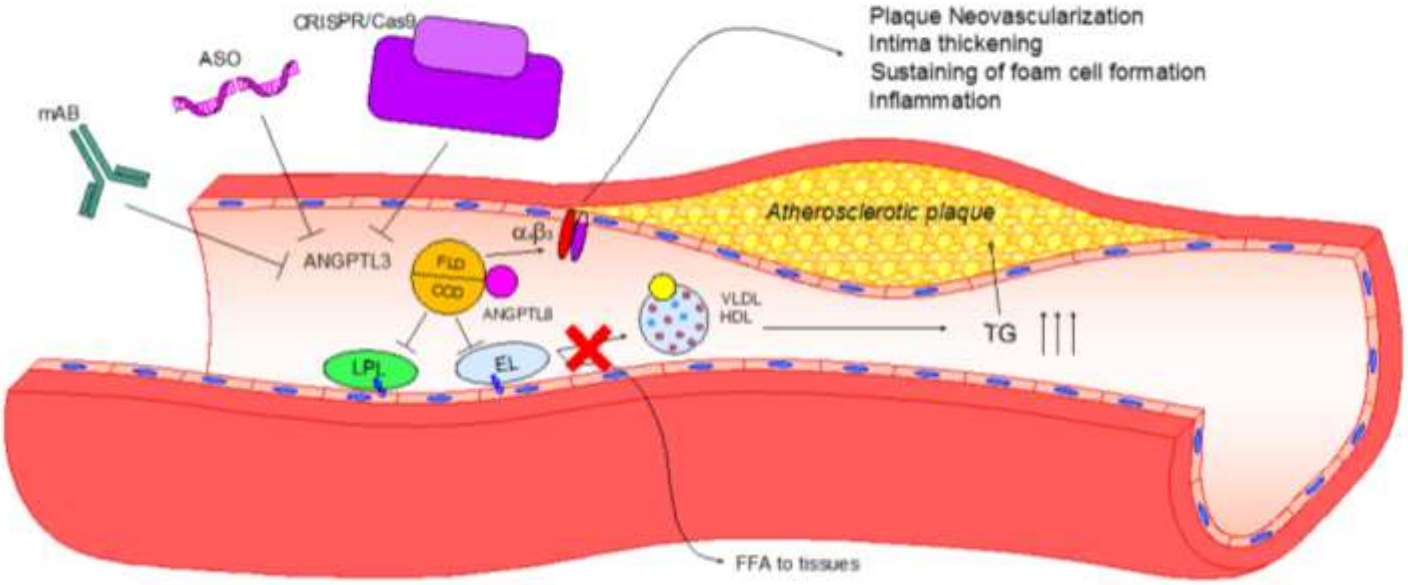


Figure 2. Lipid and non-lipid direct effects of ANGPTL3 and its pharmacological inhibition. Upon activation by ANGPTL8, ANGPTL3 binds to LPL and EL through its coiled-coil domain (CCD), inhibiting their ability to release free fatty acids and phospholipids from VLDL and HDL-C, respectively. Consequently, TG plasma levels increase, eliciting hypertriglyceridemia and atherosclerotic plaque development. Atherosclerotic plaque progression can be enhanced after the activation of the integrin $\alpha_V\beta_3$ by the fibrinogen-like domain (FLD) of ANGPTL3, leading to plaque neovascularization, intima thickening, foam cell formation and inflammation. To date, three different pharmacological inhibitors have been tested: Monoclonal antibody (evinacumab), antisense oligonucleotide (ASO) and CRISPR/Cas9 editing. All of these effectively reduce ANGPTL3 activity, and thus hypertriglyceridemia and atherosclerotic lesion size in rodent models.

Lupo MG and Ferri N

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 20, 2017 VOL. 377 NO. 3

Genetic and Pharmacologic Inactivation of ANGPTL3 and Cardiovascular Disease

F.E. Dewey, V. Gusarova, R.L. Dunbar, C. O'Dushlaine, C. Schurmann, O. Gottesman, S. McCarthy, C.V. Van Hout, S. Bruse, H.M. Dansky, J.B. Leader, M.F. Murray, M.D. Ritchie, H.L. Kirchner, L. Habegger, A. Lopez, J. Penn, A. Zhao, W. Shao, N. Stahl, A.J. Murphy, S. Hamon, A. Bouzelmat, R. Zhang, B. Shumel, R. Pordy, D. Gipe, G.A. Herman, W.H.H. Sheu, I-T. Lee, K.-W. Liang, X. Guo, J.I. Rotter, Y.-D.I. Chen,* W.E. Kraus, S.H. Shah, S. Damrauer, A. Small, D.J. Rader, A.B. Wulff, B.G. Nordestgaard, A. Tybjærg-Hansen, A.M. van den Hoek, H.M.G. Princen, D.H. Ledbetter, D.J. Carey,* J.D. Overton, J.G. Reid, W.J. Sasiela, P. Banerjee, A.R. Shuldiner, I.B. Borecki, T.M. Teslovich, G.D. Yancopoulos, S.J. Mellis, J. Gromada, and A. Baras

Table 1. Associations between *ANGPTL3* Predicted Loss-of-Function Variants and Lipid Levels in DiscovEHR Study Participants.*

Trait	Noncarriers		Carriers of *ANGPTL3* Loss-of-Function Variants		P Value†
	No. of Participants	Median Level (IQR)	No. of Participants	Median Level (IQR)	
		mg/dl		*mg/dl*	
Triglycerides	45,015	130 (94–179)	191	94 (75–125)	2.5×10^{-21}
HDL cholesterol	45,036	49 (40–59)	190	46 (38–56)	0.02
LDL cholesterol	44,629	121 (100–146)	190	112 (90–136)	2.8×10^{-5}
Total cholesterol	44,877	204 (179–232)	191	179 (160–203)	1.7×10^{-17}

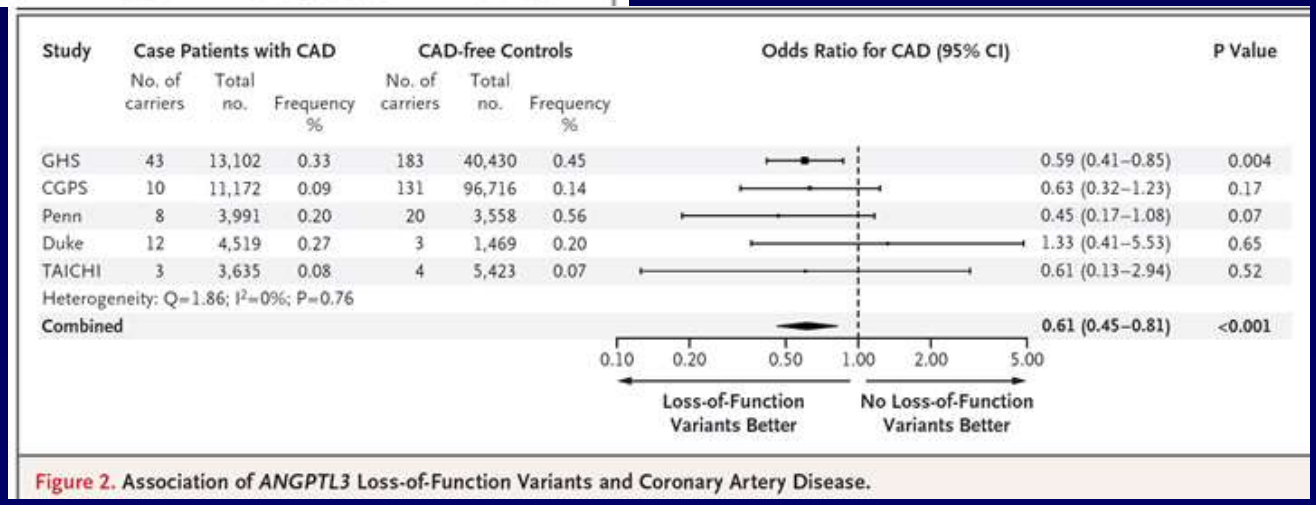
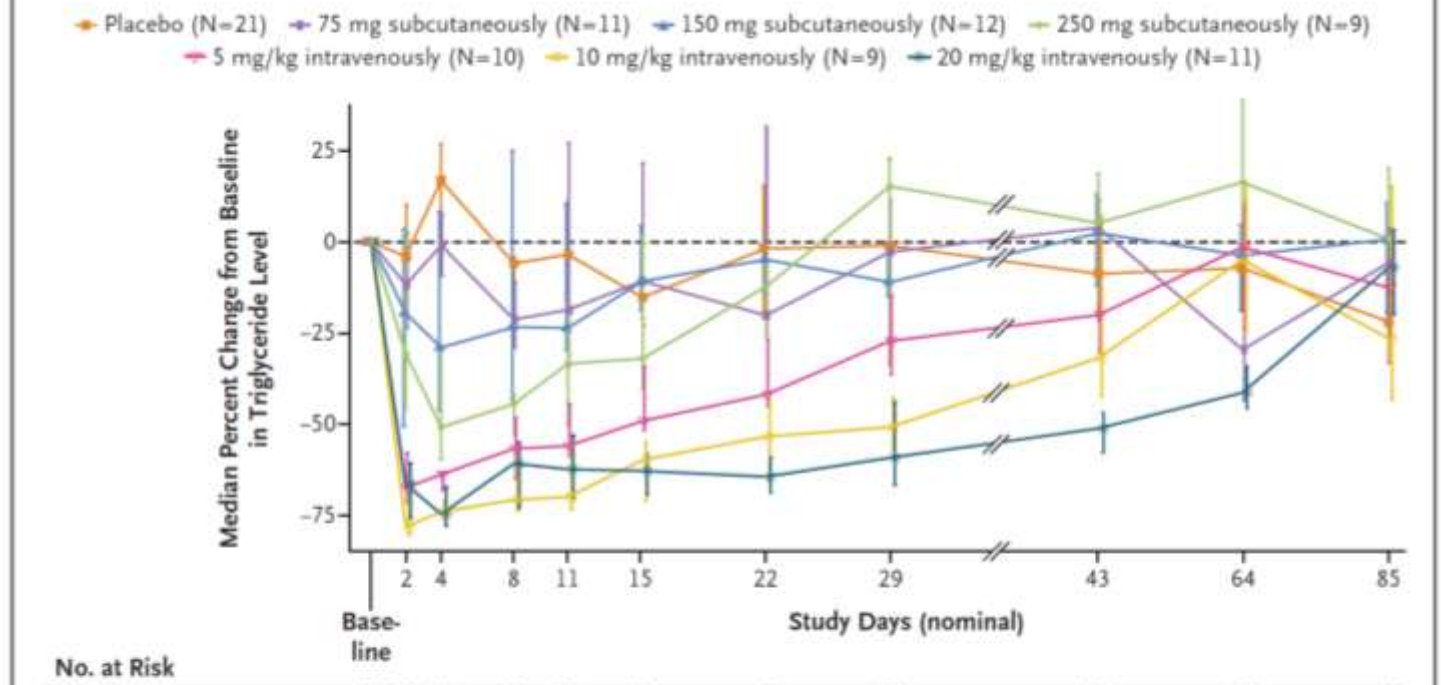


Figure 2. Association of *ANGPTL3* Loss-of-Function Variants and Coronary Artery Disease.

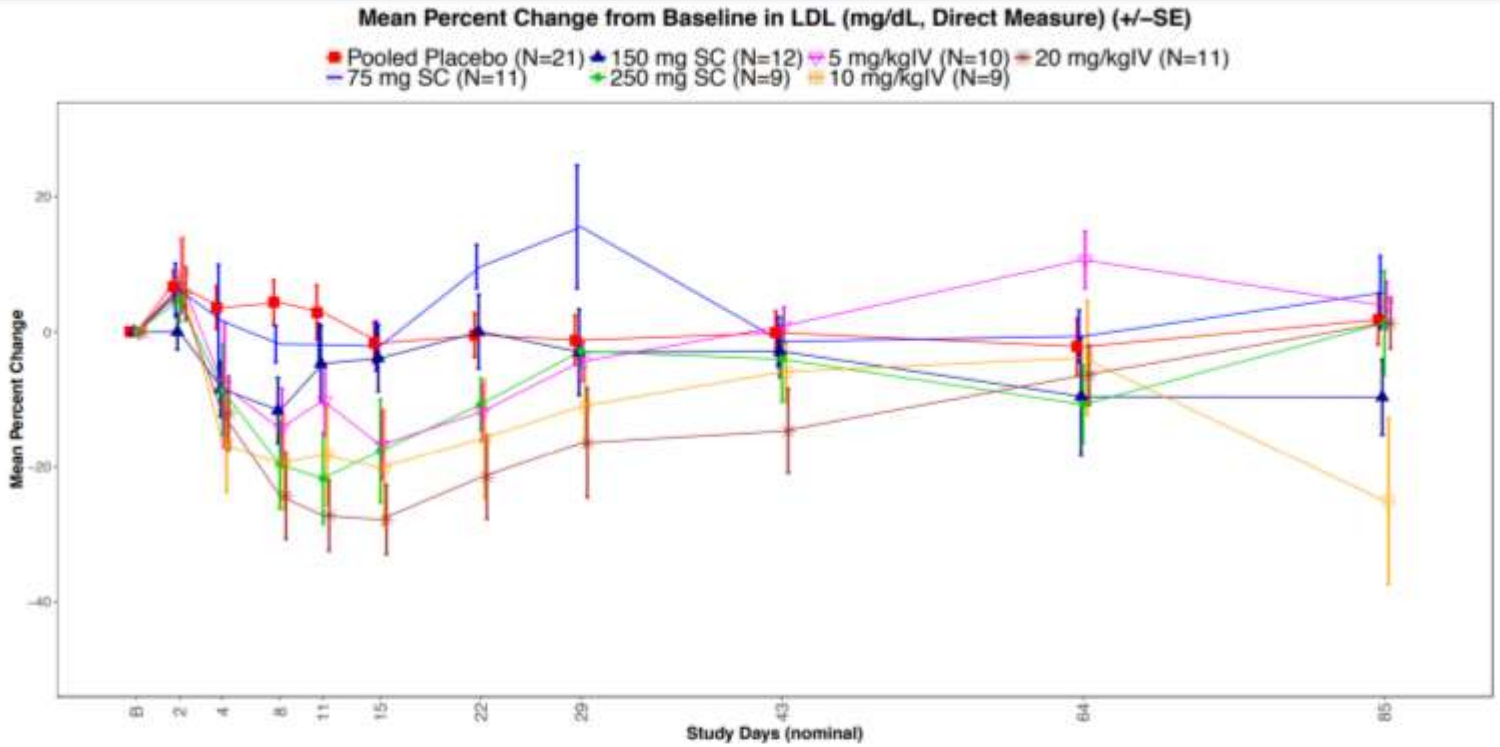
Effects of Inhibition of ANGPTL3 with a Monoclonal Antibody on Triglyceride Levels in Human Volunteers



No. at Risk											
Placebo	21	21	21	21	20	18	19	19	19	18	19
75 mg subcutaneously	11	11	11	9	10	10	9	8	8	9	9
150 mg subcutaneously	12	12	12	12	12	12	11	11	10	8	8
250 mg subcutaneously	9	9	9	7	7	7	7	7	7	7	6
5 mg/kg intravenously	9	10	10	10	10	9	10	10	10	9	9
10 mg/kg intravenously	9	9	9	9	8	9	8	8	8	7	6
20 mg/kg intravenously	11	11	11	11	11	11	11	10	10	10	10

Figure 4. Effects of Inhibition of ANGPTL3 with a Monoclonal Antibody on Triglyceride Levels in Human Volunteers.

N Engl J Med. 2017 Jul 20;377(3):211-221

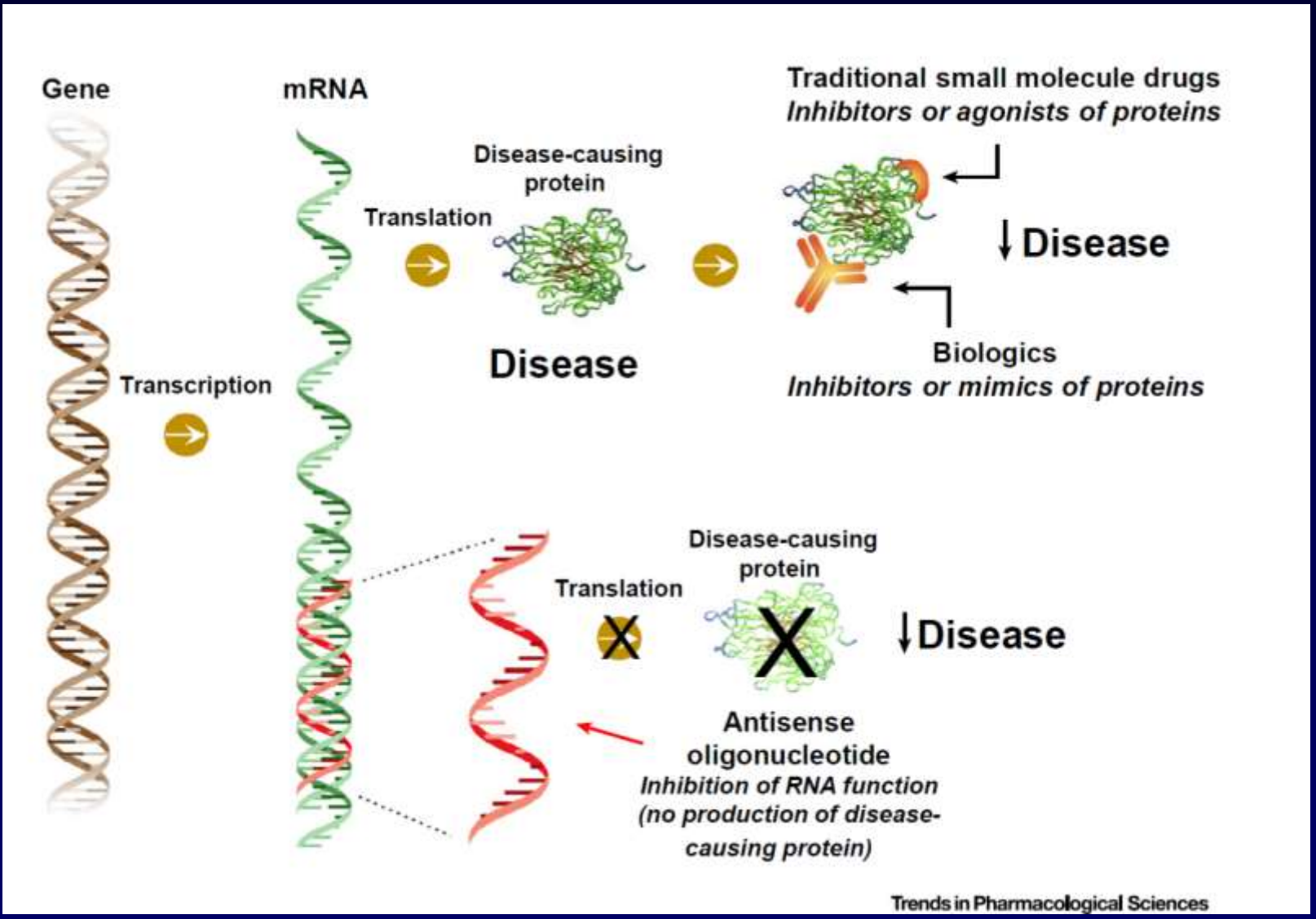


Placebo	21	21	21	21	20	18	19	19	19	18	19
75 mg SC	11	11	11	9	10	10	9	8	8	9	9
150 mg SC	12	12	12	12	12	12	11	11	10	8	8
250 mg SC	9	9	9	7	7	7	7	7	7	7	6
5 mg/kgIV	9	10	10	10	10	9	10	10	10	9	9
10 mg/kgIV	9	9	9	9	8	9	8	8	8	7	8
20 mg/kgIV	11	11	11	11	11	11	11	10	10	10	10

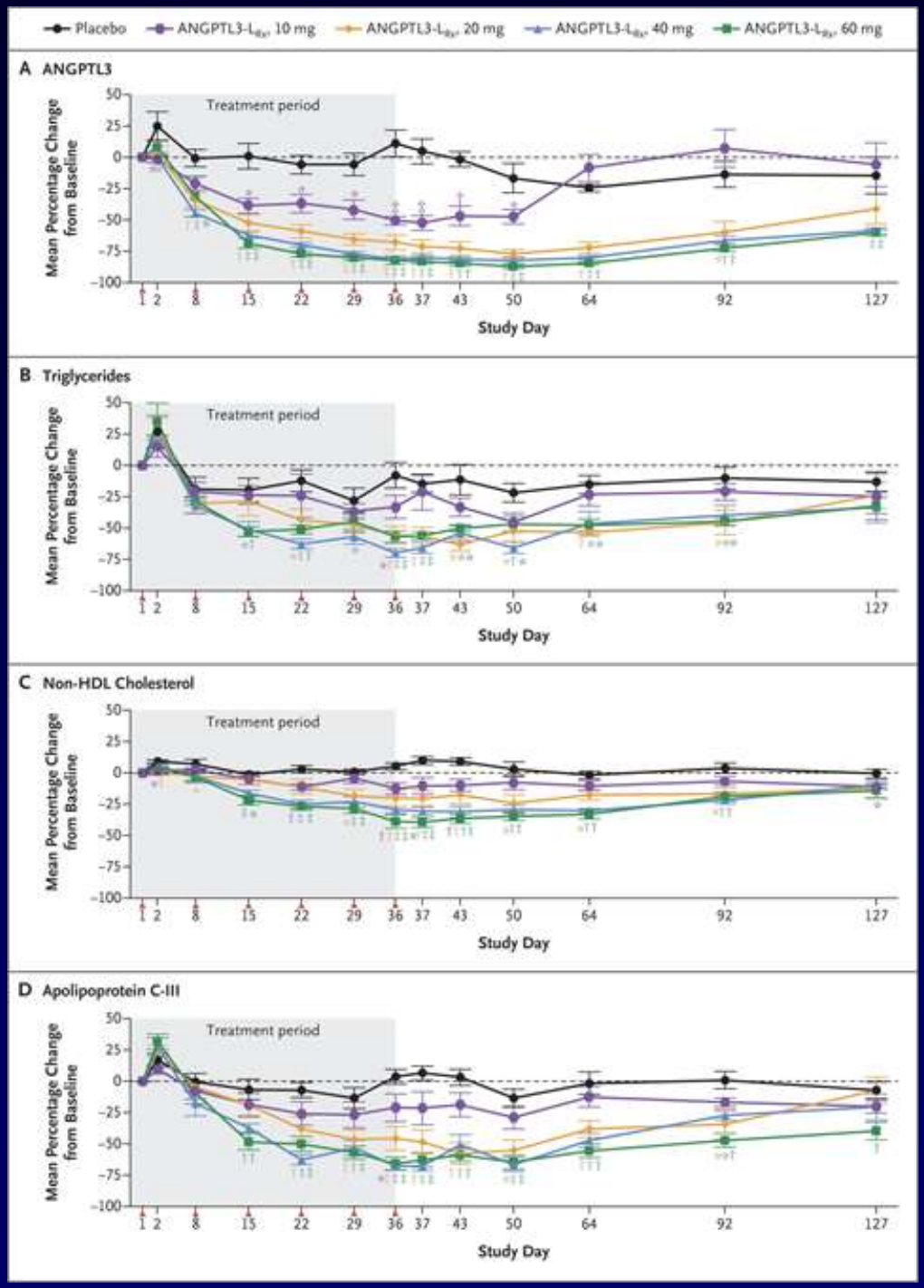
Figure S3. Effects of Inhibition of ANGPTL3 with a Monoclonal Antibody in Human Volunteers on LDL-C.

N Engl J Med. 2017 Jul 20;377(3):211-221

Inhibition of mRNA by Antisense Oligonucleotides



Sathiyakumar V et al Trends Pharmacol Sci. 2018 Aug;39(8):733-747

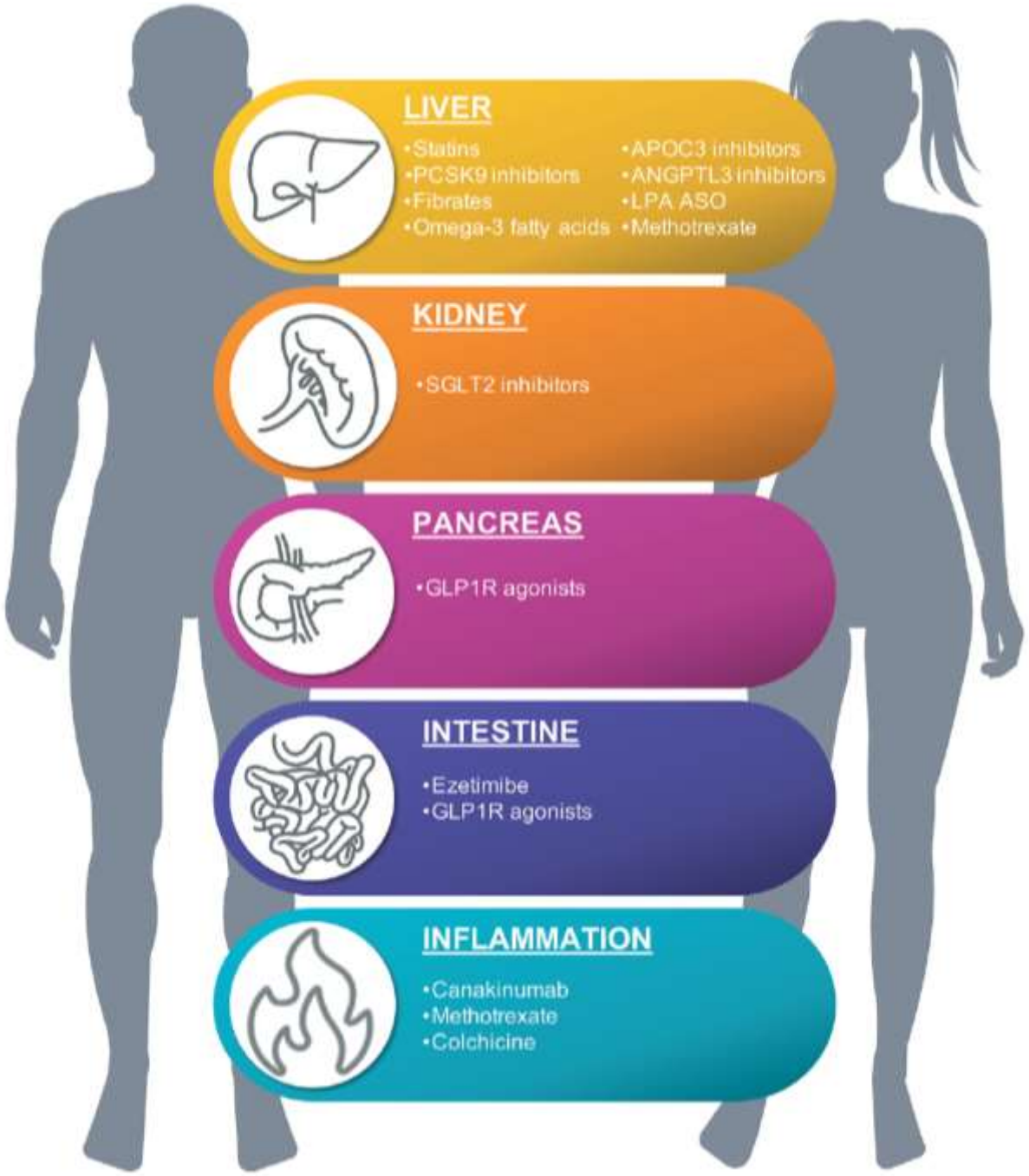


ORIGINAL ARTICLE

Cardiovascular and Metabolic Effects of *ANGPTL3* Antisense Oligonucleotides

Mark J. Graham, M.S., Richard G. Lee, Ph.D., Teresa A. Brandt, Ph.D., Li-Jung Tai, M.D., Ph.D., Wuxia Fu, M.S., Raechel Peralta, M.S., Rosie Yu, Ph.D., Eunju Hurh, Ph.D., Erika Paz, Bradley W. McEvoy, D.P.H., Brenda F. Baker, Ph.D., Nguyen C. Pham, B.S., Andres Digenio, M.D., Steven G. Hughes, M.B., B.S., Richard S. Geary, Ph.D., Joseph L. Witztum, M.D., Rosanne M. Crooke, Ph.D., and Sotirios Tsimikas, M.D.

Effect of ANGPTL3-L_{Rx} on Levels of ANGPTL3 Protein, Apo C-III, Triglycerides, and Non-HDL C in the Multiple-Dose Groups.



Overview of new and emerging targets for the prevention and treatment of atherosclerotic cardiovascular diseases

Arsenault B et al CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 104 NUMBER 2 | AUGUST 2018