Lipid Therapy and Evolving Targets: Looking into the Future

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Unstable Fibrous Plaques in Atherosclerosis Contribute to Residual Risk of CV Events

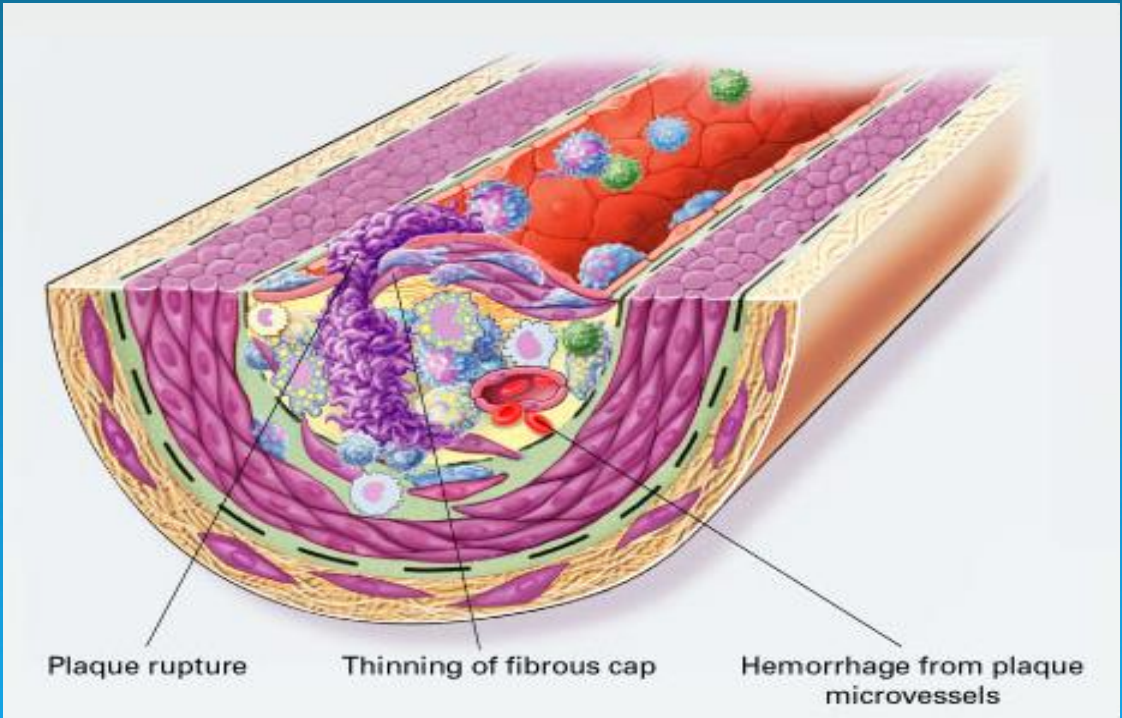


Image used with permission from: Ross R. *N Engl J Med* 1999; 340:115–126.

Approaches to Achieve Additional Reductions in Risk for CVD Events

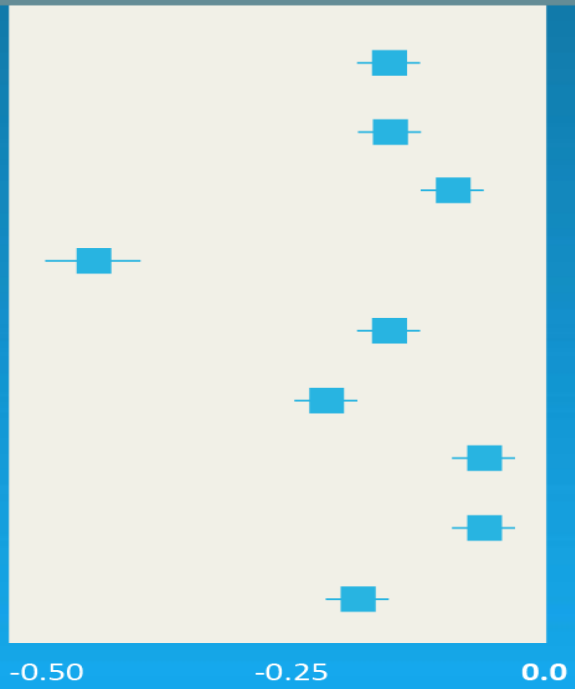
1. Target lipoprotein metabolism: LDL, HDL, triglycerides
2. Target inflammation
3. Target thrombosis
4. Tobacco, obesity, and lifestyle
5. Diabetes control
6. More intensive blood pressure control

Kones R. *Vasc Health Risk Manag*. 2013;9:617-70.

Multiple Single-Nucleotide Polymorphisms (SNPs) Are Associated With a Lower LDL-C Level

Associations with LDL-C

Gene	SNP	Sample Size (N)	LDL-C Effect (95% CI) mmol/L	LDL-C Effect (95% CI) mg/dl
SORT 1	rs599839	116,164	**-0.15** (-0.16, -0.14)	**-5.96** (-6.31, -5.56)
	rs646776	111,538	**-0.15** (-0.16, -0.16)	**-5.67** (-6.08, -5.31)
PCSK9	rs11206510	62,496	**-0.08** (-0.09, -0.06)	**-2.96** (-3.45, -2.48)
	rs11591147	140,952	**-0.44** (-0.47, -0.41)	**-16.9** (-18.0, -15.8)
LDLR	rs2228671	74,661	**-0.15** (-0.16, -0.13)	**-5.63** (-6.28, -4.98)
	rs6511720	124,350	**-0.19** (-0.20, -0.17)	**-7.18** (-7.72, -6.63)
HMGCR	rs12916	122,069	**-0.07** (-0.08, -0.06)	**-2.60** (-2.90, -2.30)
ABCG8	rs4299376	107,391	**-0.07** (-0.08, -0.06)	**-2.80** (-3.26, -2.45)
APOE	rs4420638	120,455	**-0.18** (-0.20, -0.17)	**-7.12** (-7.60, -6.63)



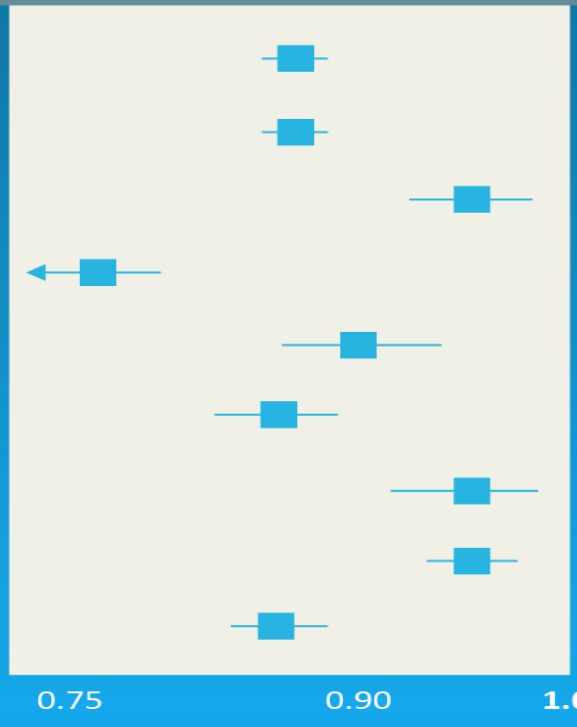
Ference BA et al. *J Am Coll Cardiol*. 2012;60:2631-9.

Plot adapted from: Ference BA, et al. *J Am Coll Cardiol.* 2012;60:2631-9.

SNPs Associated With Low LDL-C Are Also Associated With a Reduction in CHD Risk

Associations with CHD

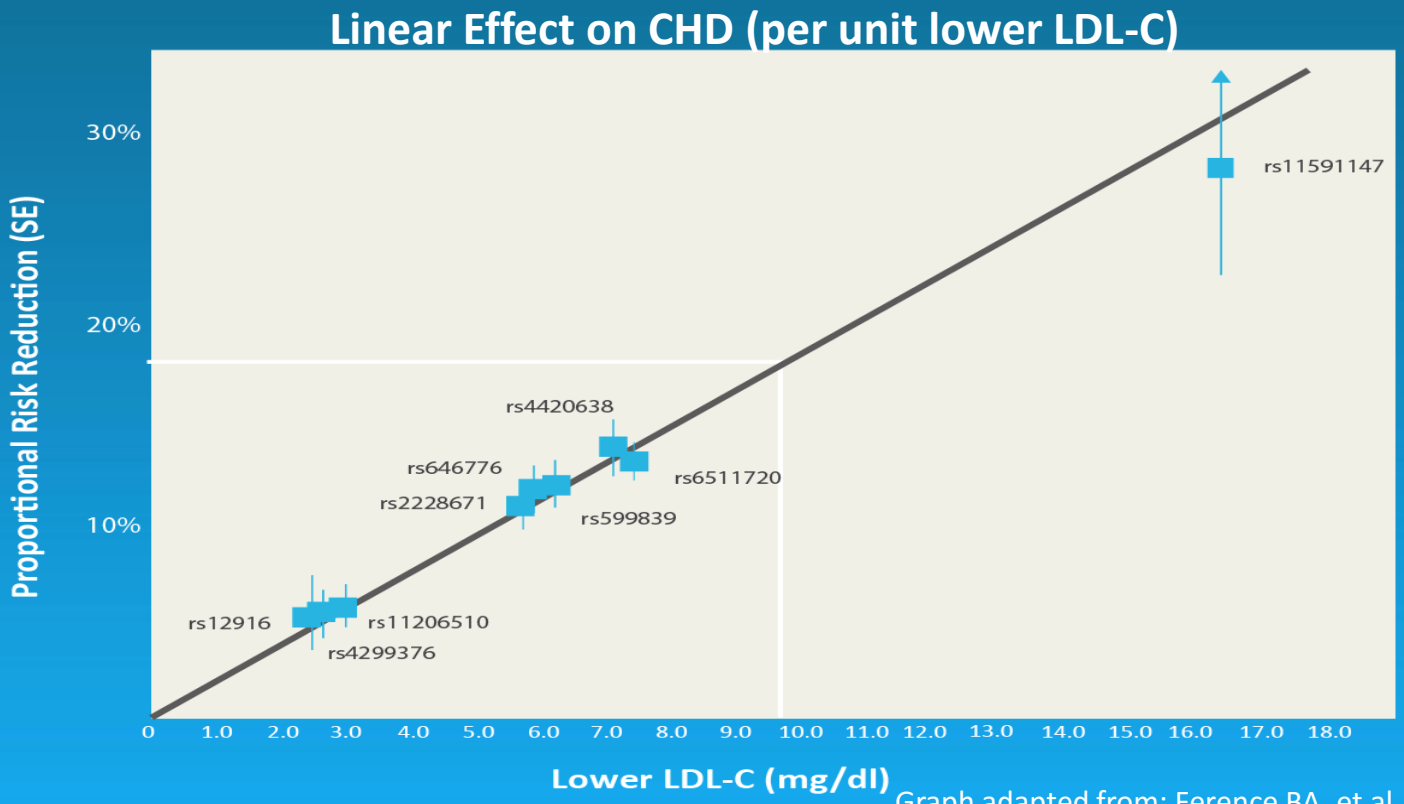
Gene	SNP	Sample Size (N)	OR (95% CI)	RRR
SORT 1	rs599839	151,039	**0.88** (0.87-0.90)	12%
	rs646776	124,040	**0.88** (0.85-0.90)	12%
PCSK9	rs11206510	190,083	**0.94** (0.92-0.97)	6%
	rs11591147	128,244	**0.73** (0.66-0.80)	27%
LDLR	rs2228671	83,305	**0.90** (0.86-0.94)	10%
	rs6511720	80,024	**0.87** (0.83-0.92)	13%
HMGCR	rs12916	49,160	**0.94** (0.90-0.98)	6%
ABCG8	rs4299376	118,842	**0.94** (0.92-0.96)	6%
APOE	rs4420638	78,470	**0.86** (0.83-0.89)	14%
Total		**1,003,207**		



Ference BA et al. *J Am Coll Cardiol*. 2012;60:2631-9.

Plot adapted from: Ference BA, et al. *J Am Coll Cardiol.* 2012;60:2631-9.

SNPs Associated With Low LDL-C Were Associated With a Highly Consistent Reduction in the Risk of CHD Per Unit Lower LDL-C



Ference BA et al. *J Am Coll Cardiol*. 2012;60:2631-9.

Graph adapted from: Ference BA, et al. *J Am Coll Cardiol* 2012;60:2631-9.

Relationship Between HDL-C and CHD Risk Is Less Clearly Established

THE LANCET

Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study

Benjamin F Voight, Gina M Peloso*, Marju Orho-Melander, Ruth Frikke-Schmidt, Maja Barbalic, Majken K Jensen, George Hindy, Hilma Hólm, Eric L Ding, Toby Johnson, Heribert Schunkert, Nilesh J Samani, Robert Clarke, Jemma C Hopewell, John F Thompson, Mingyao Li, Gudmar Thorleifsson, Christopher Newton-Cheh, Kiran Musunuru, James P Pirruccello, Danish Saleheen, Li Chen, Alexandre F R Stewart, Arne Schillert, Unnur Thorsteinsdottir, Gudmundur Thorgeirsson, Sonia Anand, James C Engert, Thomas Morgan, John Spertus, Monika Stoll, Klaus Berger, Nicola Martinelli, Domenico Girelli, Pascal P McKeown, Christopher C Patterson, Stephen E Epstein, Joseph Devaney, Mary-Susan Burnett, Vincent Mooser, Samuli Ripatti, Ida Surakka, Markku S Nieminen, Juha Sinisalo, Marja-Liisa Lokki, Markus Perola, Aki Havulinna, Ulf de Faire, Bruna Gigante, Erik Ingelsson, Tanja Zeller, Philipp Wild, Paul I W de Bakker, Olaf H Klungel, Anke-Hilse Maitland-van der Zee, Bas J M Peters, Anthonius de Boer, Diederick E Grobbee, Pieter W Kamphuisen, Vera H M Deneer, Clara C Elbers, N Charlotte Onland-Moret, Marten H Hofker, Cisca Wijmenga, W M Monique Verschuren, Jolanda M A Boer, Yvonne T van der Schouw, Asif Rasheed, Philippe Frossard, Serkalem Demissie, Cristen Willer, Ron Do, Jose M Ordovas, Gonçalo R Abecasis, Michael Boehnke, Karen L Mohlke, Mark J Daly, Candace Guiducci, Noël P Burtt, Aarti Surti, Elena Gonzalez, Shaun Purcell, Stacey Gabriel, Jaume Marrugat, John Peden, Jeanette Erdmann, Patrick Diemert, Christina Willenborg, Inke R König, Marcus Fischer, Christian Hengstenberg, Andreas Ziegler, Ian Buysschaert, Diether Lambrechts, Frans Van de Werf, Keith A Fox, Nour Eddine El Mokhtari, Diana Rubin, Jürgen Schrezenmeir, Stefan Schreiber, Arne Schäfer, John Danesh, Stefan Blankenberg, Robert Roberts, Ruth McPherson, Hugh Watkins, Alistair S Hall, Kim Overvad, Eric Rimm, Eric Boerwinkle, Anne Tybjaerg-Hansen, L Adrienne Cupples, Muredach P Reilly, Olle Melander, Pier M Mannucci, Diego Ardissino, David Siscovick, Roberto Elosua, Kari Stefansson, Christopher J O'Donnell, Veikko Salomaa, Daniel J Rader, Leena Peltonen, Stephen M Schwartz, David Altshuler, Sekar Kathiresan*

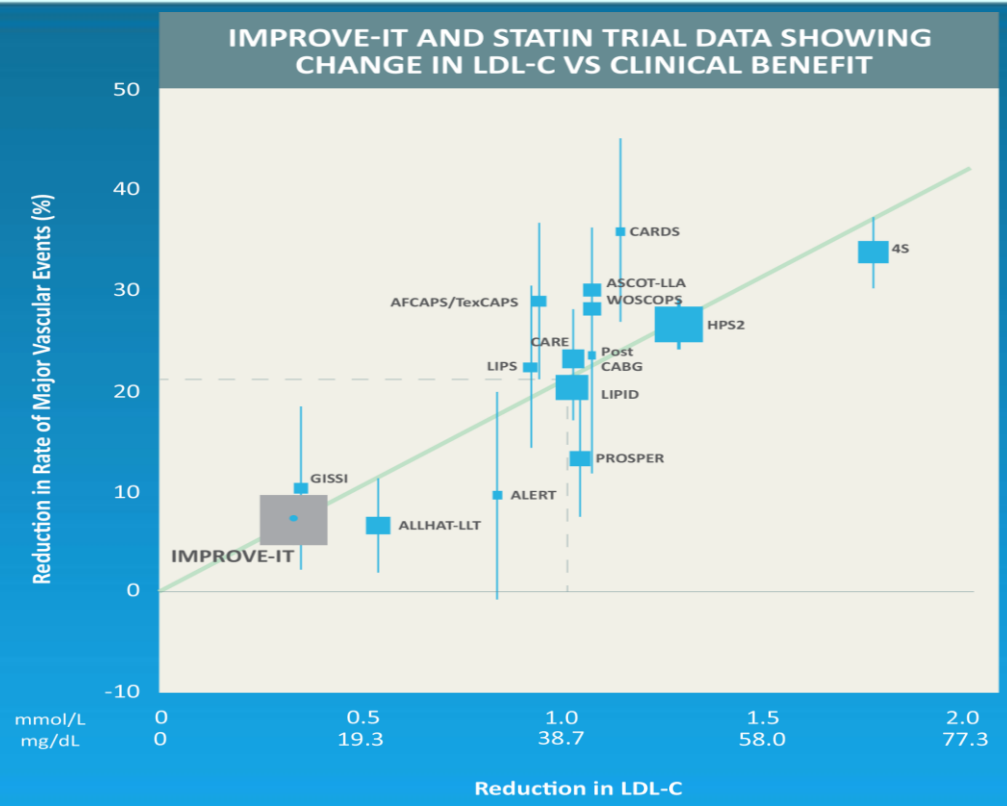
Voight BF et al. *Lancet*. 2012;380(9841):572-80.

Genetic Variants Associated Only With HDL-C Were Not Associated With a Lower Risk of MI

Gene(s) of interest within or near associated interval	Major allele, minor allele (minor allele frequency)*	Modelled allele	Effect of modelled allele on plasma HDL cholesterol (mmol/L)*	Effect of modelled allele on plasma triglycerides (mmol/L)*	Effect of modelled allele on plasma LDL cholesterol (mmol/L)*	Sample size (MI cases/ MI-free controls)	For modelled allele, observed change in MI risk (%; 95% CI)	For modelled allele, p value for association with MI
LPL†	G, T (0·10)	T	0·08	−0·24	..	19 139/50 812	−12% (−16 to −7)	4×10^{-7}†
TRIB1†	A, G (0·45)	G	0·02	−0·11	−0·05	19 139/50 812	−7% (−9 to −4)	2×10^{-6}†
APOA1-APOC3-APOA4-APOA5†	A, G (0·07)	A	0·05	−0·27	−0·09	18 310/49 897	−10% (−15 to −5)	8×10^{-5}†
GALNT2†	A, G (0·40)	A	0·02	−0·03	..	19 139/50 812	−3% (−6 to −1)	0·02†
ANGPTL4†	C, T (0·16)	C	0·05	−0·07	..	13 595/16 423	−5% (−10 to −1)	0·03†
CETP†	C, A (0·32)	A	0·10	..	−0·03	16 503/46 576	−4% (−7 to 0)	0·04†
LIPG	A, G (0·015)	G	0·14‡	..	..	17 165/49 077	−6% (−18 to 9)	0·41
MLXIPL	C, T (0·11)	T	0·03	−0·15	..	19 139/50 812	−1% (−4 to 3)	0·61
ABCA1	G, A (0·14)	G	0·03	..	0·05	19 139/50 812	−1% (−5 to 4)	0·76
MMAB, MVK	G, C (0·46)	G	0·03	..	..	19 139/50 812	0% (−3 to 3)	0·85
TTC39B	T, C (0·12)	T	0·03	..	..	15 693/47 098	0% (−5 to 5)	0·97
LCAT	G, A (0·11)	A	0·03	..	..	19 139/50 812	4% (−1 to 8)	0·10
FADS1-FADS2-FADS3	T, C (0·33)	T	0·03	−0·06	..	19 139/50 812	3% (−1 to 6)	0·11
LIPC	C, T (0·22)	T	0·05	0·07	..	17 917/49 514	4% (0 to 7)	0·04
HNF4A	C, T (0·01)	T	0·01	..	..	17 041/20 137	31% (12 to 54)	9×10^{-4}

Voight BF et al. *Lancet*. 2012;380(9841):572-80.

IMPROVE-IT Demonstrated CV Benefit Consistent With Statin Trials Through LDL-C Lowering With a Non-statin (Ezetimibe) With LDL-C of 54 vs 70 mg/dL

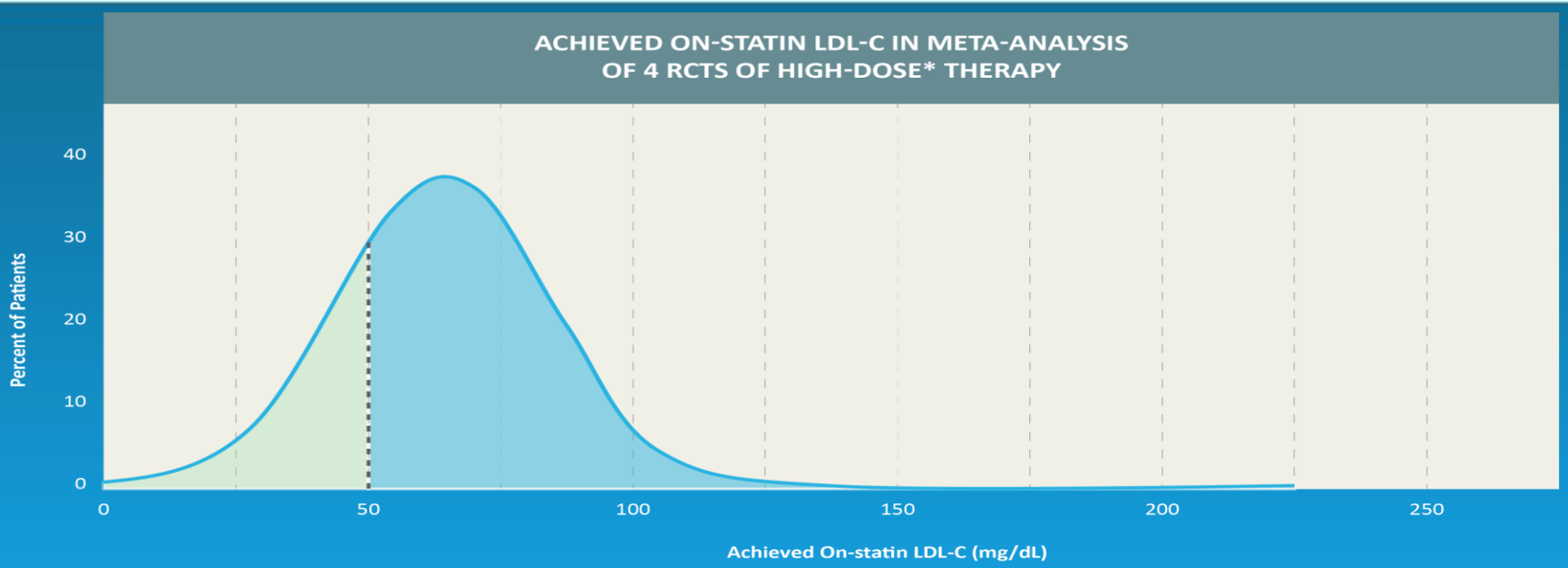


CV benefit of statin–ezetimibe combination in IMPROVE-IT was consistent with that seen in previous statin trials, with a similar reduction in CV events according to the degree of LDL-C lowering

Cannon CP, et al. *N Engl J Med*. 2015;372(25):2387-97.

Graph adapted from: Cannon CP, et al. *N Engl J Med*. 2015;372(25):2387-97.

Most Patients With Elevated CV Risk Are Not Able to Achieve Very Low LDL-C on Intensive Statin Therapy



78.3% of statin trial participants assigned to high-dose therapy did not reach an LDL-C concentration below 50 mg/dL

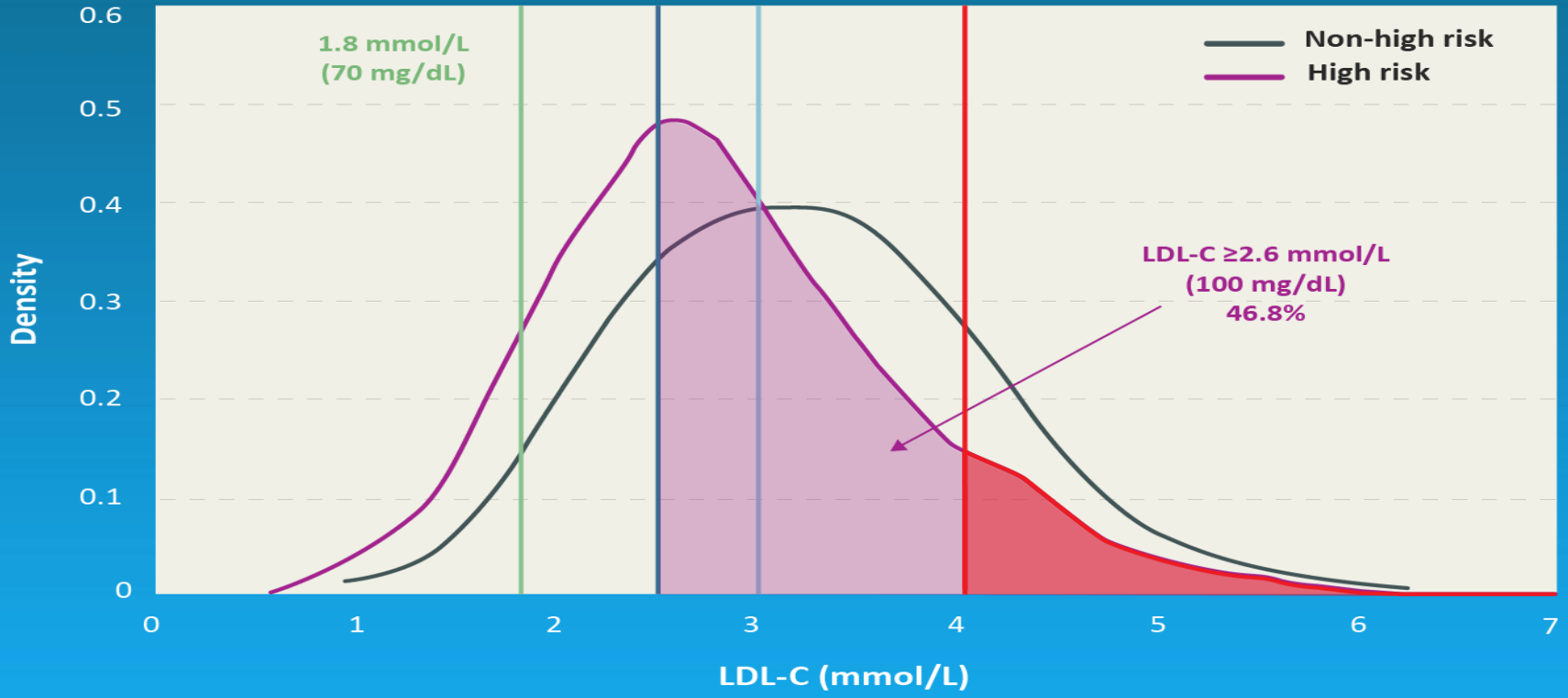
*High-dose statin therapy was defined as either atorvastatin 80 mg or rosuvastatin 20 mg; High-dose RCTs included in meta-analysis: TNT, IDEAL, SPARCL, JUPITER.

Boekholdt SM, et al. *J Am Coll Cardiol.* 2014 Aug 5;64(5):485-494.

Graph adapted from: Boekholdt SM, et al. *J Am Coll Cardiol*. 2014 Aug 5;64(5):485-494.

Despite Statin Therapy, Many High-Risk Patients Have Marked LDL Elevations

DYSIS
Dyslipidemia International Study



Gitt AK, *et al. Eur J Prev Cardiol.* 2012;19:221–30.

Graph adapted from: Gitt AK, et al. *Eur J Prev Cardiol*. 2012;19:221–30.

Critical Questions in Regard to Therapy Targeting Atherogenic Lipoproteins

1. How aggressively should we lower LDL-C in high-risk patients? If 54 mg/dL (1.4 mmol/L) led to better outcomes than 70 mg/dL (1.8 mmol/L), would achieving 30 mg/dL (0.8 mmol/L) lead to even better outcomes?
2. Are there any adverse effects with reducing LDL-C to very low levels (ie, < 20 mg/dL [0.5 mmol/L])?
3. Does lowering Lp(a) provide additional benefits beyond lowering LDL-C?
4. Which therapies can be added to statins to achieve the greatest benefit with the least risk?
5. How do we use genomics and biotechnology to pick targets and accelerate drug development?

Human Genetics and Drug Targets for Lipoprotein-Related Therapies

Therapy	Human Genetics Data Supporting Target	LDL-C Reduction	Safety	CHD Event Reduction
Statins (HMG-CoA reductase)	+	+++	+++	Yes
Ezetimibe (NPC1L1)	++	+	+++	Yes
Lp-PLA_2 inhibition	—	—	+++	No
sPLA_2 inhibition	—	+	Harm	No

Kathiresan S, et al. *Nat Genet*. 2009;41(1): 56–65.; Cholesterol Treatment Trialists' Collaboration. *Lancet.* 2005;366:1267.; Ference BA, et al. *J Am Coll Cardiol*. 2015;65:1552–61.; Cannon CP, et al. *N Engl J Med*. 2015;372(25):2387-97.; Polfus LM, et al. *N Engl J Med*. 2015;372(3):295-6.; O'Donoghue ML, et al. *JAMA*. 2014;312(10):1006-15. ; White HD, et al. *N Engl J Med*. 2014;370(18):1702-11. ; Holmes MV, et al. *Circ* ***Cardiovasc Genet*****. 2014;7:144-150.;** Nicholls SJ, et al. *JAMA*. 2014;311(3):252-62.

Human Genetics and Drug Targets for Lipoprotein-Related Therapies

Therapy	Human Genetics Data Supporting Target	LDL-C Reduction	Safety	CHD Event Reduction
PCSK9 inhibitors*	+++	+++	Looks good so far	Outcomes trials in progress
CETP inhibitors	++**	++	Looks good so far	Outcomes trials in progress
ETC-1002	no data	+	Limited data	?
Apo C-III antisense	+++	?	?	?
Apo(a) antisense	+++	?	?	?

Alirocumab has been approved for use by the U.S. FDA and has received a positive opinion from the CHMP.

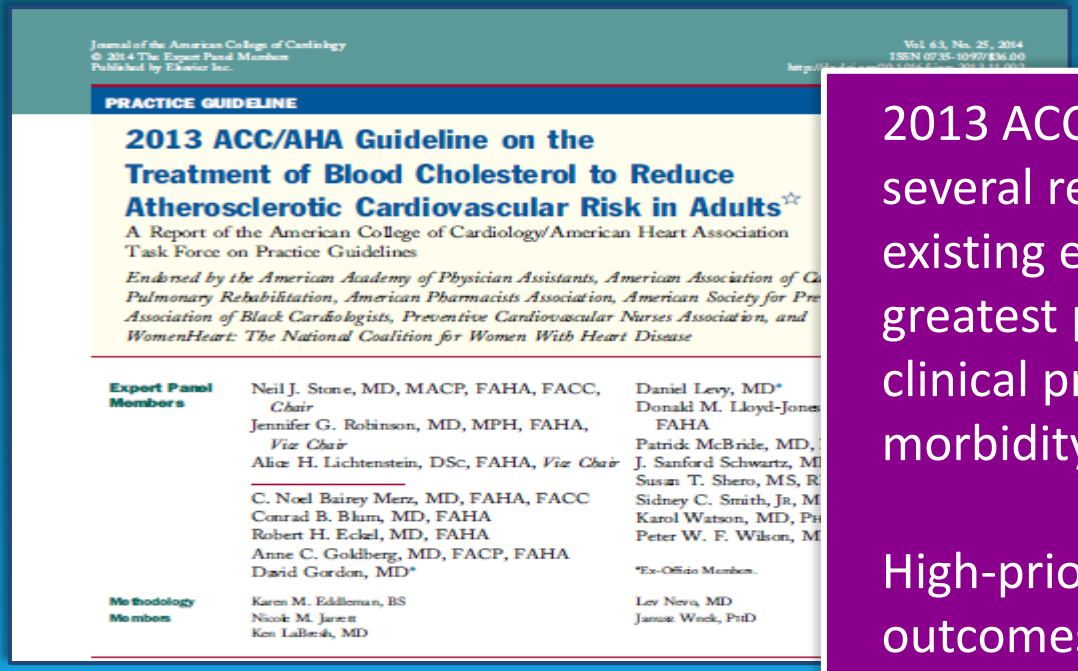
Evolocumab has been approved for use by the U.S. FDA and EC .

Bococizumab is an investigational compound.

**SNP data with reduced function; unclear Asian data for null mutation.

Cohen JC, et al. *N Engl J Med.* 2006; 354:1264-72.; Ballantyne CM, et al. *Am J Cardiol.* 2015;115:1212e1221.; https://clinicaltrials.gov.; Ridker PM, et al. *Circ Cardiovasc Genet*. 2009;2(1):26-33.; Inazu A, et al. *J Clin Invest*. 1994 Nov;94(5):1872-82.; Cannon CP, et al. *N Engl J Med.* 2010;363:2406-15.; Nicholls SJ, et al. *JAMA*. 2011 Nov 16;306(19):2099-109. Thompson PD, et al. *J Clin Lipidol*. 2015;9(3):295-304. Crosby J, et al. *N Engl J Med*. 2014;371:22-31.; Jorgenson AB, et al. *N Engl J Med.* 2014;371:32-41.; Kathiresan S, et al. *Nat Genet*. 2009;41(1): 56–65.

2013 ACC/AHA Lipid Guidelines Suggest High Research Priorities to Include CV Outcome Trials of New Lipid-Lowering Agents



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PRACTICE 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 Academy of Physician Assistants, American Association of Cardiovascular and Pulmonary Rehabilitation, American Pharmacists Association, American Society for Preventive Cardiology, National Association of Black Cardiologists, Preventive Cardiovascular Nurses Association, and WomenHeart: The National Coalition for Women With Heart Disease

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Methodology Members

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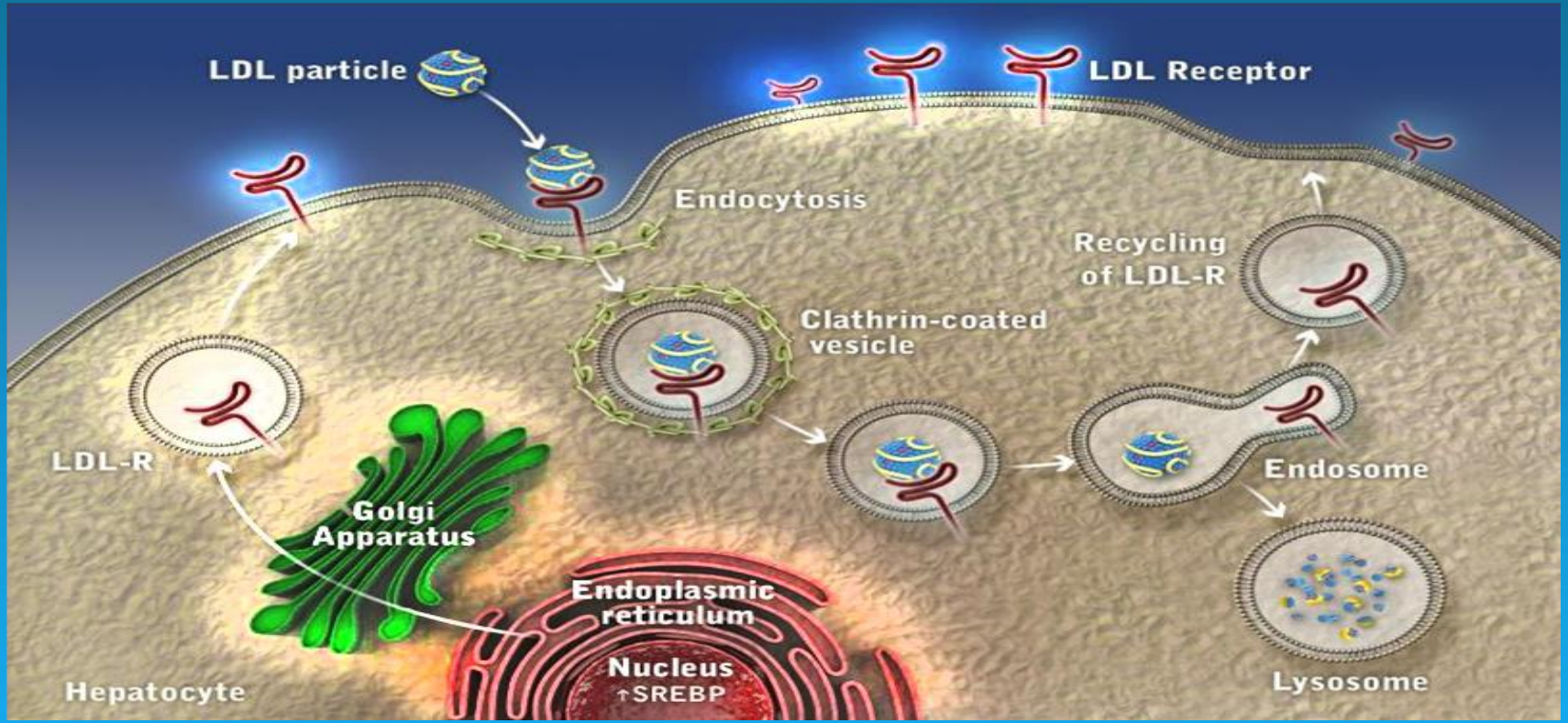
Nicole M. Jarrett
Ken LaBresh, MD
Lev Nevo, MD
Janusz Wnek, PhD

2013 ACC/AHA Lipid Guidelines identify several research priorities that address existing evidence gaps and offer the greatest potential to inform and influence clinical practice and reduce ASCVD morbidity and mortality.

High-priority research areas include CV outcomes trials of ***"…new lipid-modifying agents to determine the incremental ASCVD event-reduction benefits when added to evidence-based statin therapy."***

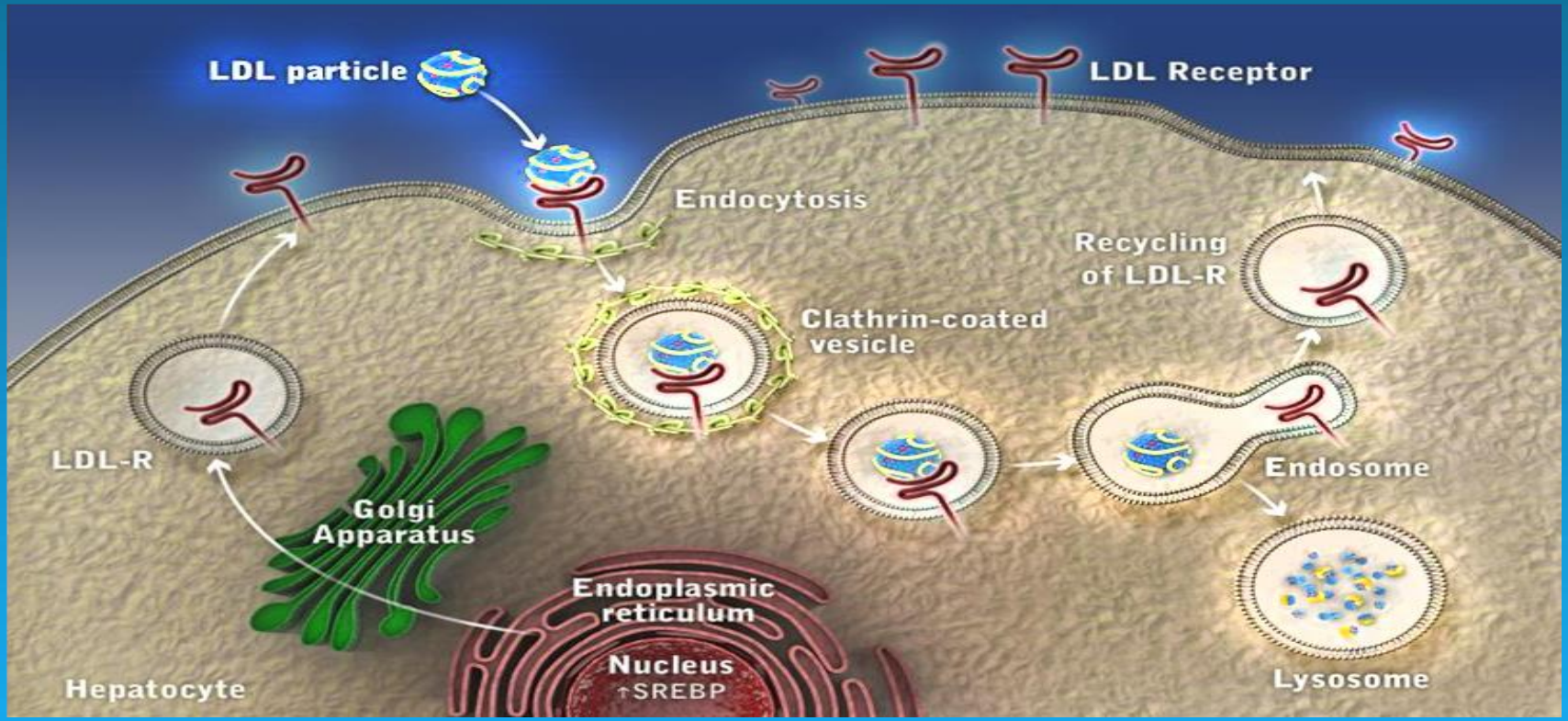
Stone NJ, et al. *J Am Coll Cardiol*. 2014 Jul 1;63:2889-934.

LDL-Receptor Function and Life Cycle



Lambert et al. *J Lipid Res*. 2012. 53:2515–2524.

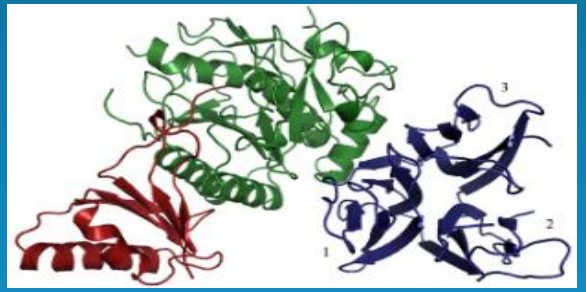
LDL-Receptor Function and Life Cycle



Lambert et al. *J Lipid Res*. 2012. 53:2515–2524.

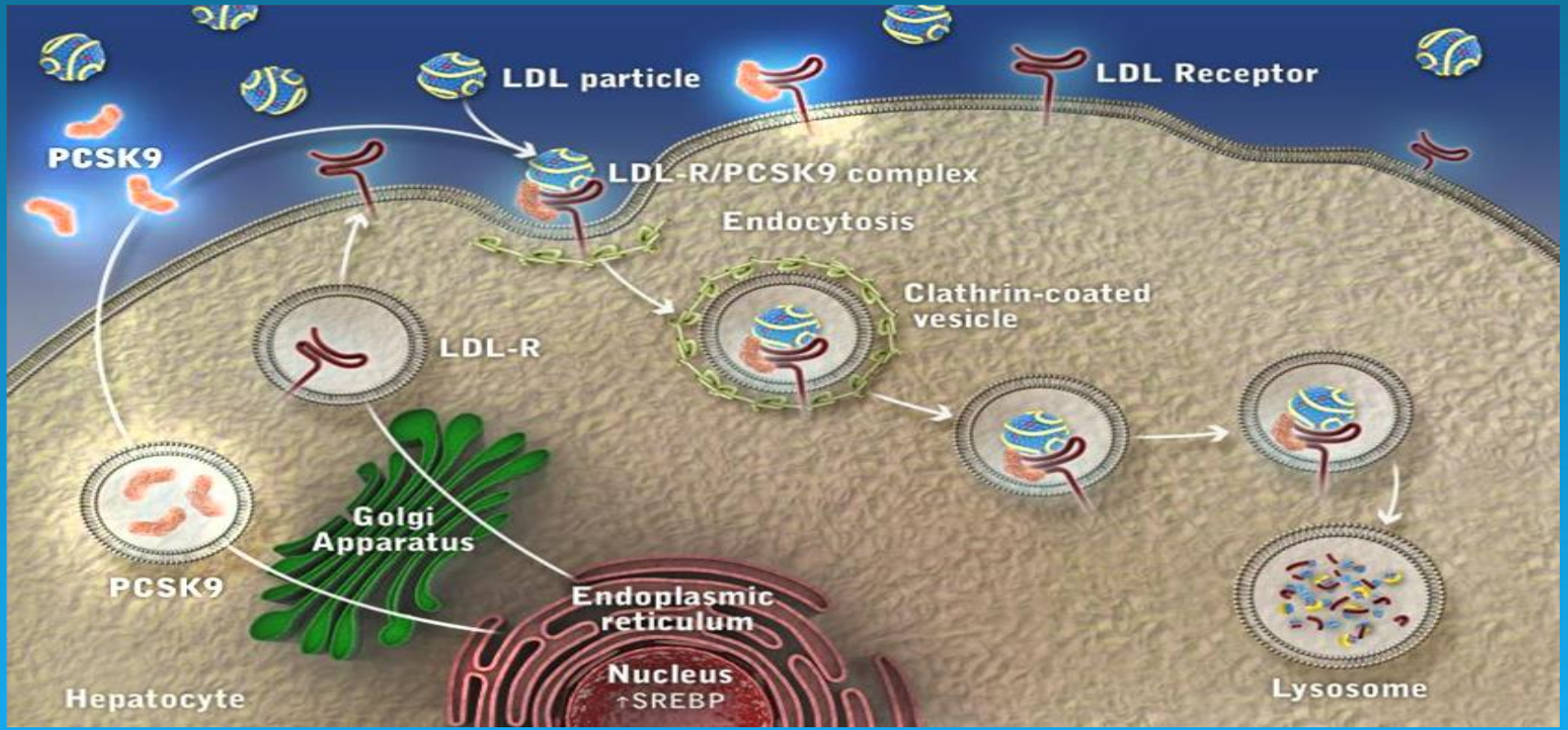
PCSK9: Proprotein Convertase Subtilisin/Kexin Type 9

- A secreted protease (692 amino acids), consisting of a prodomain, a catalytic and C-terminal domain
- Primarily expressed in the liver, and to a lesser extent in the intestine and the kidney. Also found in the adrenal gland, lung, spleen, thymus, and cerebellum



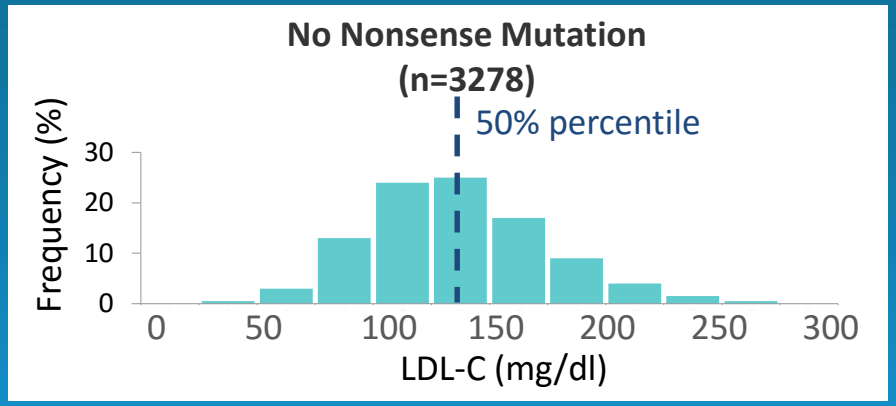
Lambert et al. *Atherosclerosis.* 2009;20(203):1-7.
Seidah NG, et al. *Proc Natl Acad Sci U S A*. 2003;100(3):928-33.
Tavori H, et al. *Circulation*. 2013;127(24):2403-13.

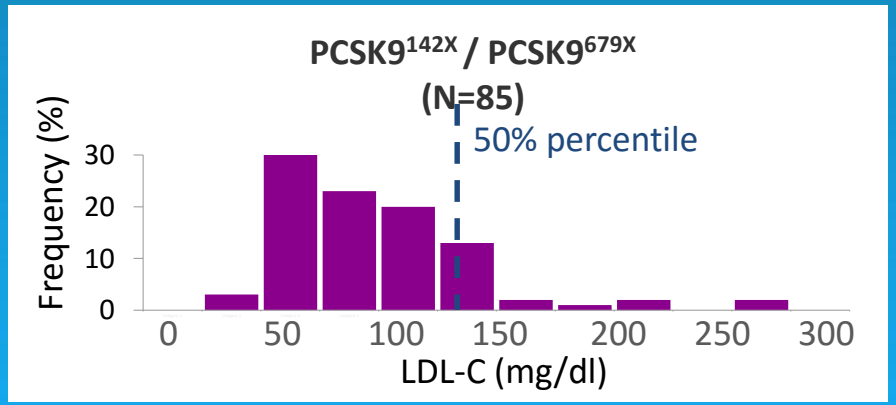
PCSK9: A Natural Circulating Inhibitor of the LDLR

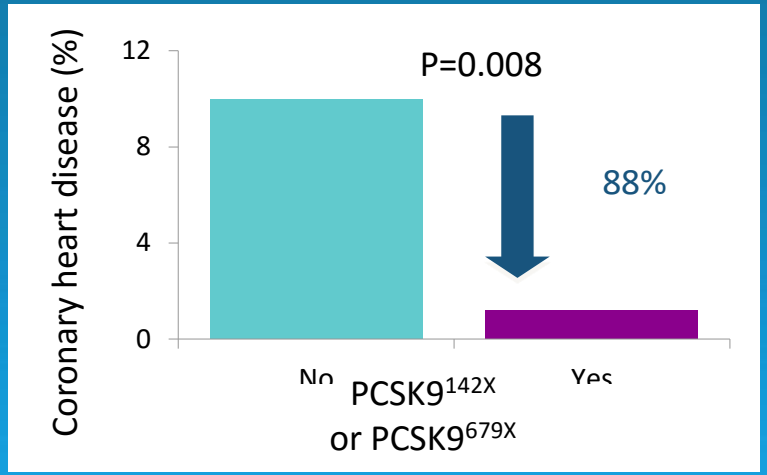


Lambert et al. *J Lipid Res*. 2012. 53:2515–2524.

Genetic Evidence: Loss-of-Function Mutations in PCSK9 Associated With Low LDL-C Levels and Reduced CHD Risk







Cohen JC, et al. *N Engl J Med* 2006; 354:1264-72.

Emerging Therapy: PCSK9 Inhibitors

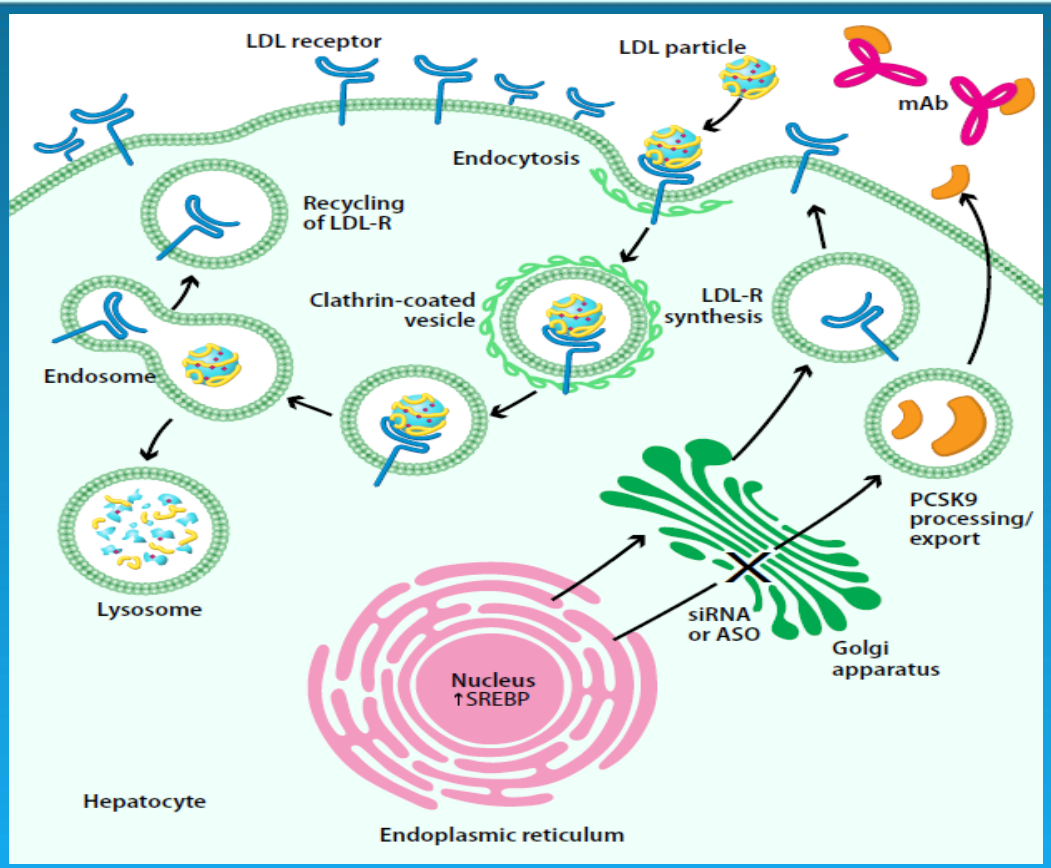
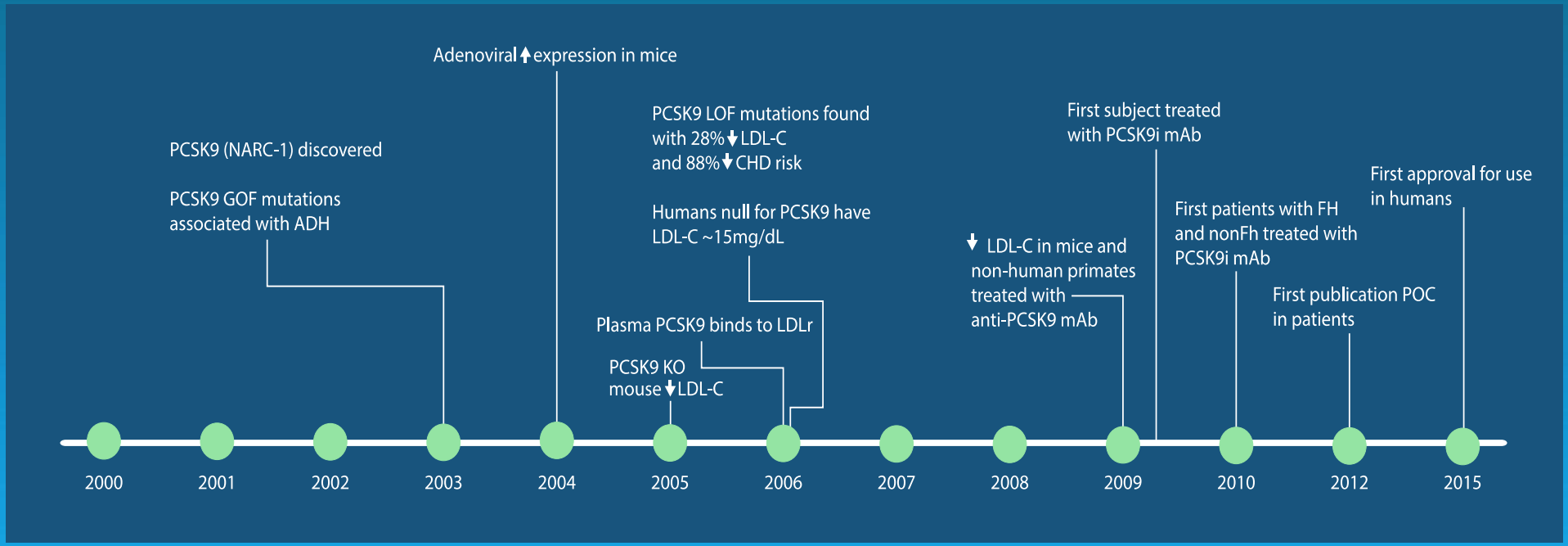


Image adapted from: Lambert et al. *J Lipid Res*. 2012. 53:2515–2524.

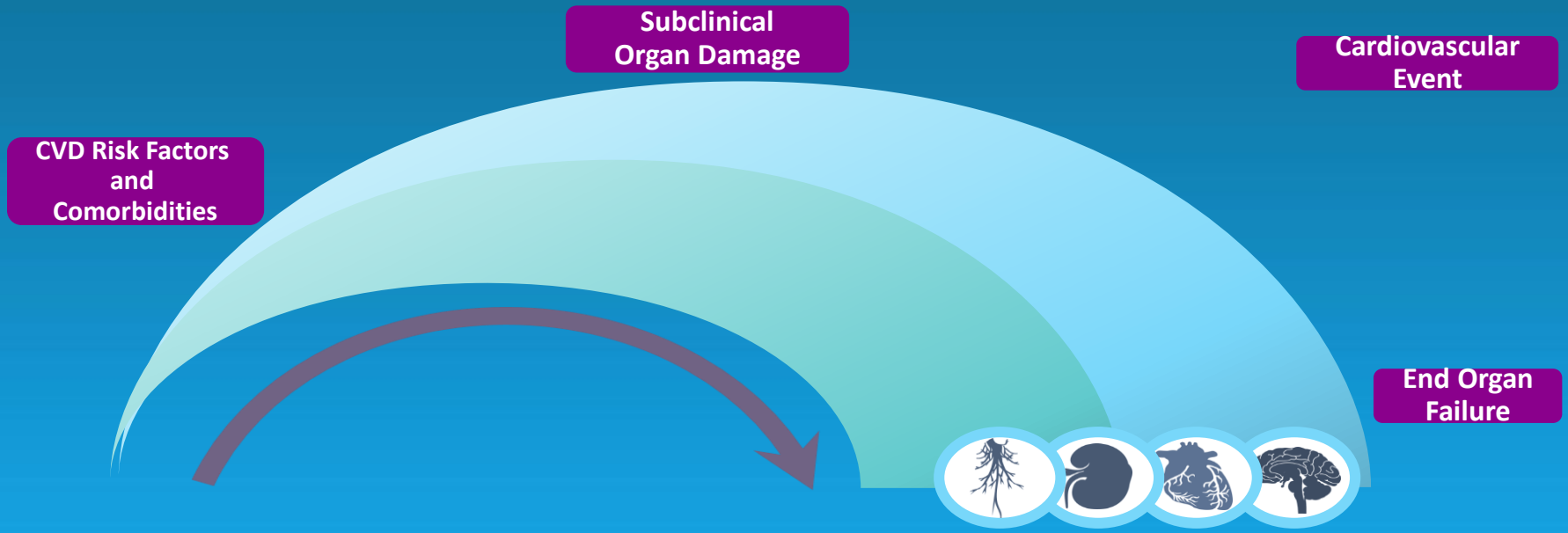
PCSK9i: Rapid Progress From Discovery to Clinic



PCSK9i = PCSK9 inhibition.

Seidah NG. *Proc Natl Acad Sci US.* 2003;100(3):928-33. Abifadel M. *Nat Genet.* 2003;34(2):154-6. Maxwell KN. *Proc Natl Acad Sci US.* 2004;101(18):7100-5. Rashid S. *Proc Natl Acad Sci US.* 2005;102(15):5374-79. Lagace TA et al. *JCI.* 2006;116:2995-3005. Cohen JC. *N Engl J Med.* 2006;354(12):1264-72. Zhao Z. *Am J Hum Genet.* 2006;79(3):514-23. Hooper AJ. *Atherosderosis.* 2007;193(2):445-8. Chan JC. *Proc Natl Acad Sci US.* 2009;106(24):9820-5. Stein et al. *N Engl J Med.* 2012;366:1108-18. European Medicines Agency. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003766/smops/Positive/human_smop_000828.jsp&mid=WC0b01ac058001d127.

Ongoing CVOTs Will Evaluate the Impact of PCSK9 Inhibition on CV Events in Distinct Populations Throughout the CVD Continuum

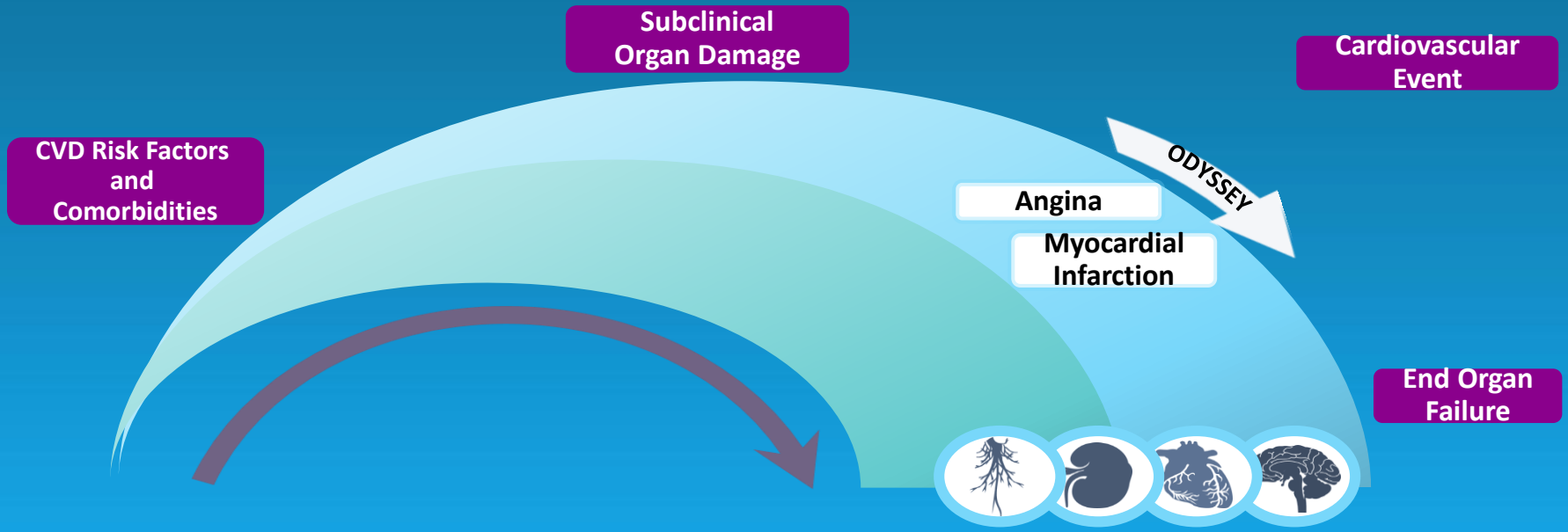


The CV-renal disease continuum represents a continuous development of disease initiated by risk factors and comorbidities, progressing through several stages that contribute to CV events and eventual organ failure

Dzau VJ, et al. *Circulation*. 2006;114:2850-70; Dzau VJ, et al. *Circulation*. 2006;114:2871-91.

Ongoing CVOTs Will Evaluate the Impact of PCSK9 Inhibition on CV Events in Distinct Populations Throughout the CVD Continuum

Alirocumab has been approved for use by the U.S. FDA and has received a positive opinion from the CHMP



ODYSSEY Outcomes will determine whether the addition of alirocumab to intensive statin therapy 4 to 52 weeks after ACS reduces cardiovascular morbidity and mortality

Dzau VJ, et al. *Circulation*. 2006;114:2850-70; Dzau VJ, et al. *Circulation*. 2006;114:2871-91; Schwartz GG, et al. *Am Heart J.* 2014;168(5):682-9.

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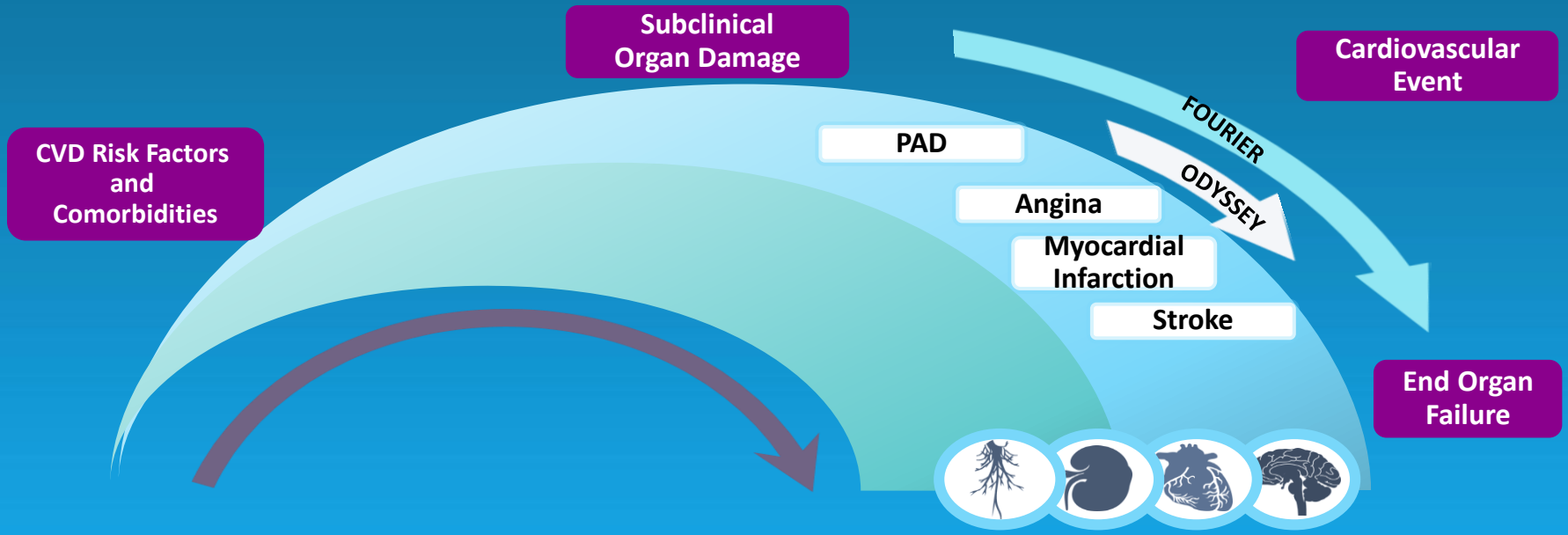
Evolocumab has been approved for use by the U.S. FDA and EC



FOURIER is a secondary prevention study that is assessing CV outcomes when evolocumab is used in combination with effective statin therapy in patients with clinically evident CVD

Dzau VJ, et al. *Circulation*. 2006;114:2850-70; Dzau VJ, et al. *Circulation*. 2006;114:2871-91; Schwartz GG, et al. *Am Heart J.* 2014;168(5):682-9.; https://clinicaltrials.gov.; Sabatine MS, et al. Presented at the American College of Cardiology Congress, San Diego, CA, 2015.

Ongoing CVOTs Will Evaluate the Impact of PCSK9 Inhibition on CV Events in Distinct Populations Throughout the CVD Continuum

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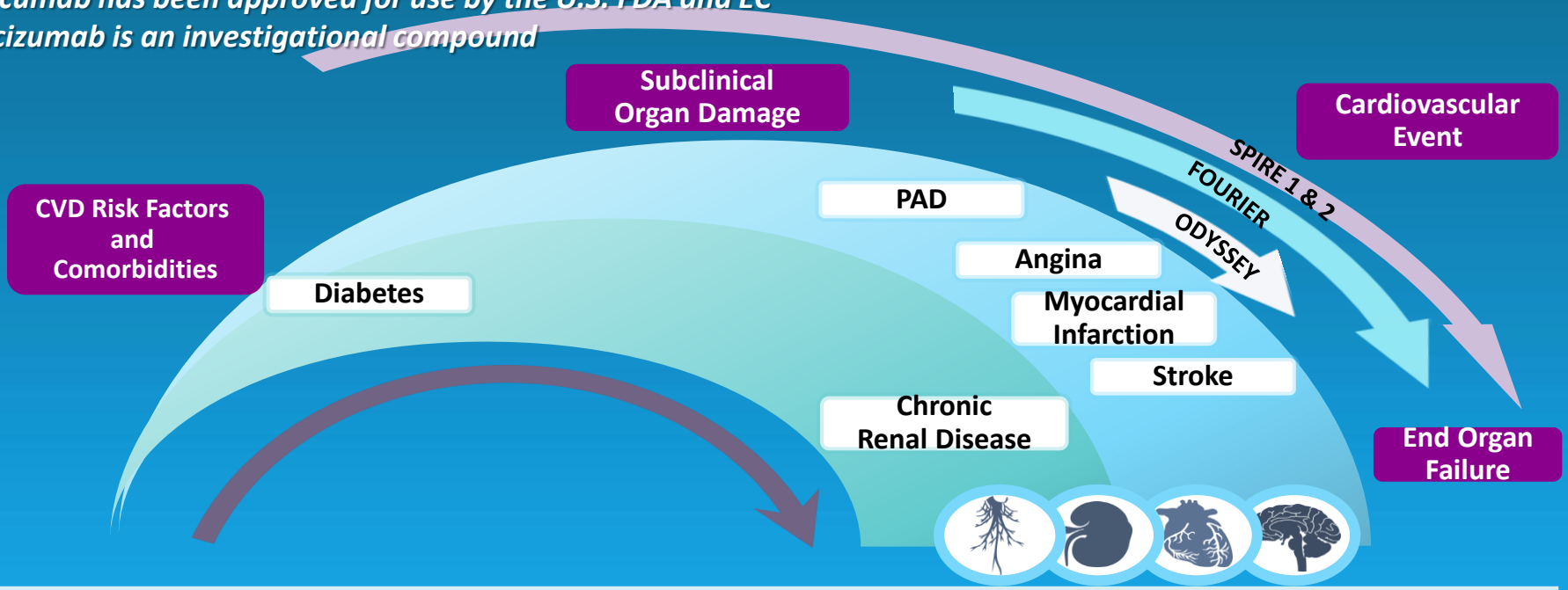
Bococizumab is an investigational compound

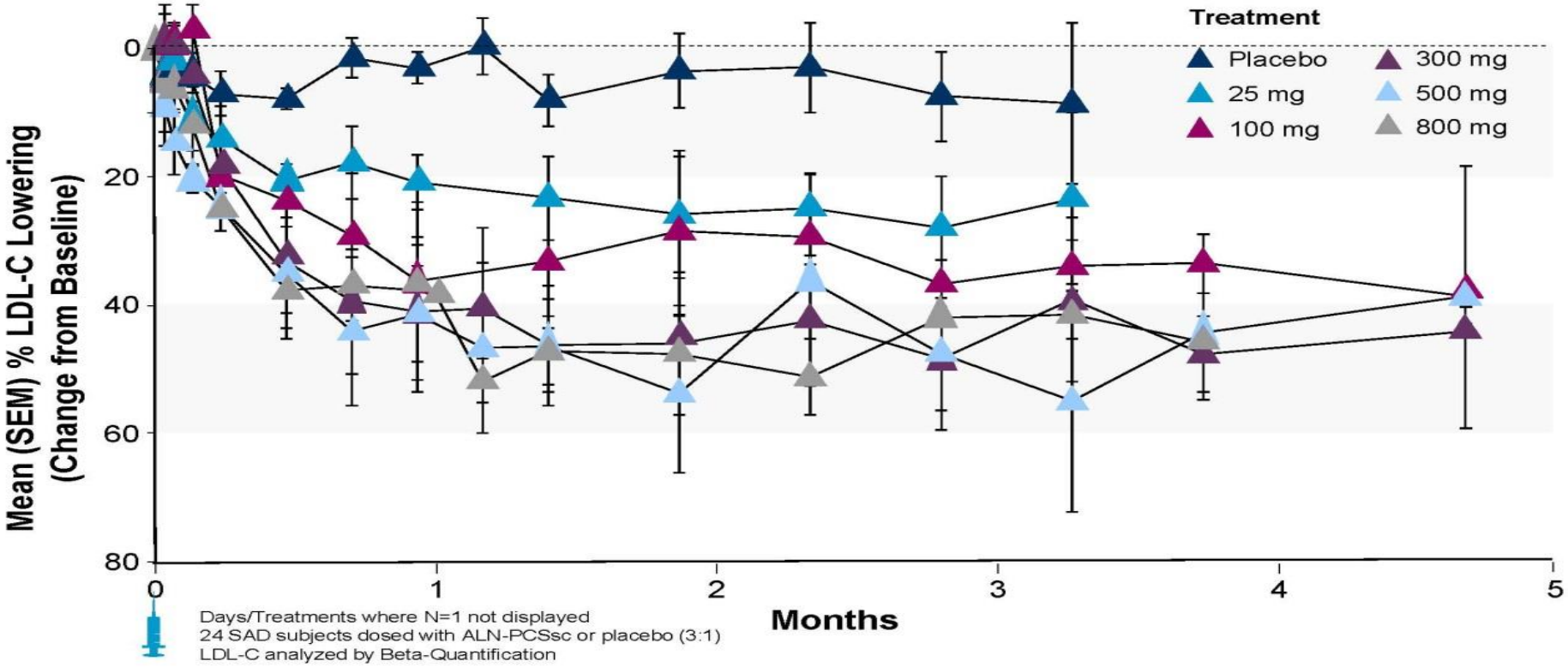


SPIRE 1 and 2 will evaluate CV outcomes in patients on lipid-lowering therapy* that have combinations of CVD comorbidities and risk factors that create a high risk of a first CV event OR have had a prior CV event or related procedure

Dzau VJ, et al. *Circulation*. 2006;114:2850-70; Dzau VJ, et al. *Circulation*. 2006;114:2871-91; Schwartz GG, et al. *Am Heart J.* 2014;168(5):682-9.; https://clinicaltrials.gov.; Sabatine MS, et al. Presented at the American College of Cardiology Congress, San Diego, CA, 2015.

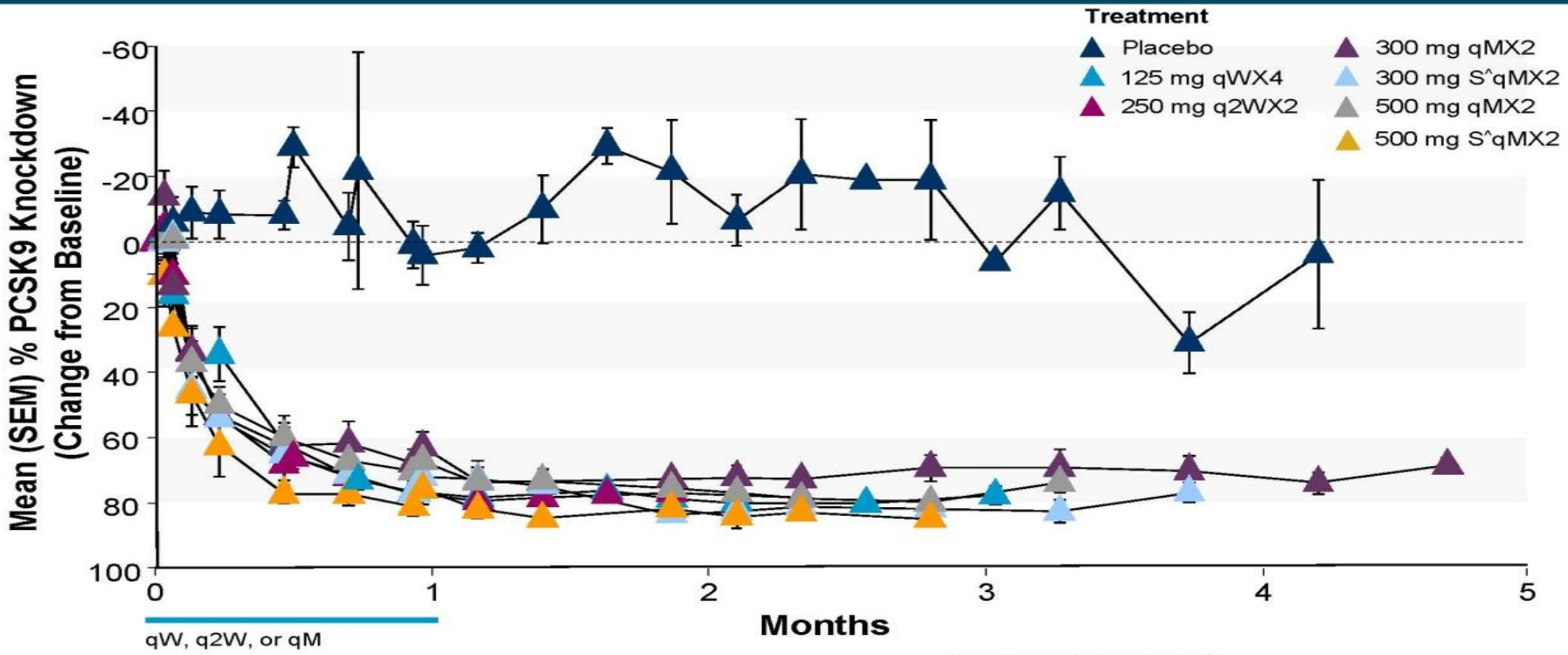
*Includes highly effective statins unless statin intolerant.

Initial ALN-PCSsc Phase 1 Study Results
SAD LDL-C Lowering Relative to Baseline



Fitzgerald K et al. *Lancet* 2014;383:60-8.

Initial ALN-PCSsc Phase 1 Study Results
MD PCSK9 Knockdown Relative to Baseline



S ^=On stable dose of statin
45 MD subjects dosed with ALN-PCSsc or placebo (3:1)
Two subjects excluded from all MD analyses:
One placebo subject elected to discontinue;
One subject in 300 mg statin group was incarcerated on Day 14

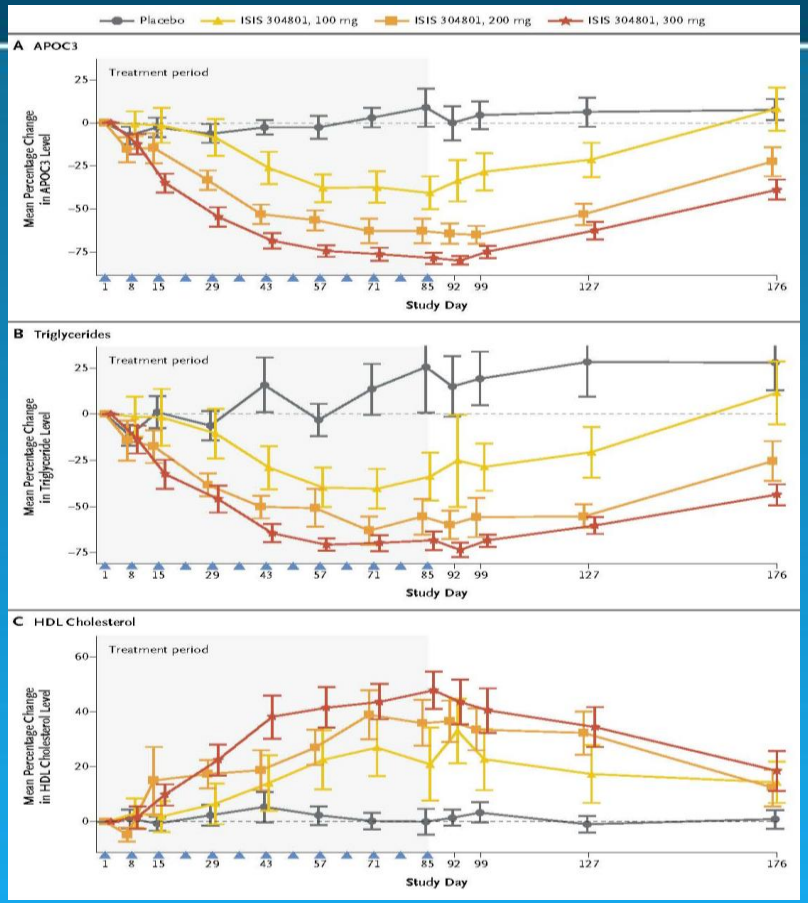
Fitzgerald K et al. *Lancet* 2014;383:60-8.

What's Next for CETP Inhibitors?

- **Anacetrapib**
  - HDL-C increased by 138% compared with placebo (from 41 to 101 mg/dL) [1]
  - LDL-C reduced by 40% compared with placebo (from 81 to 45 mg/dL) [1]
  - Outcomes trial (REVEAL) continues after DSMB meeting [2]
- **Evacetrapib**
  - HDL-C increased by 54–129% (from 55 mg/dL; dose dependent) vs –3% with placebo
  - LDL-C reduced by 14–36% (from 144 mg/dL; dose dependent) vs +4% with placebo [3]
  - Outcomes trial (ACCELERATE) stopped for futility [4]

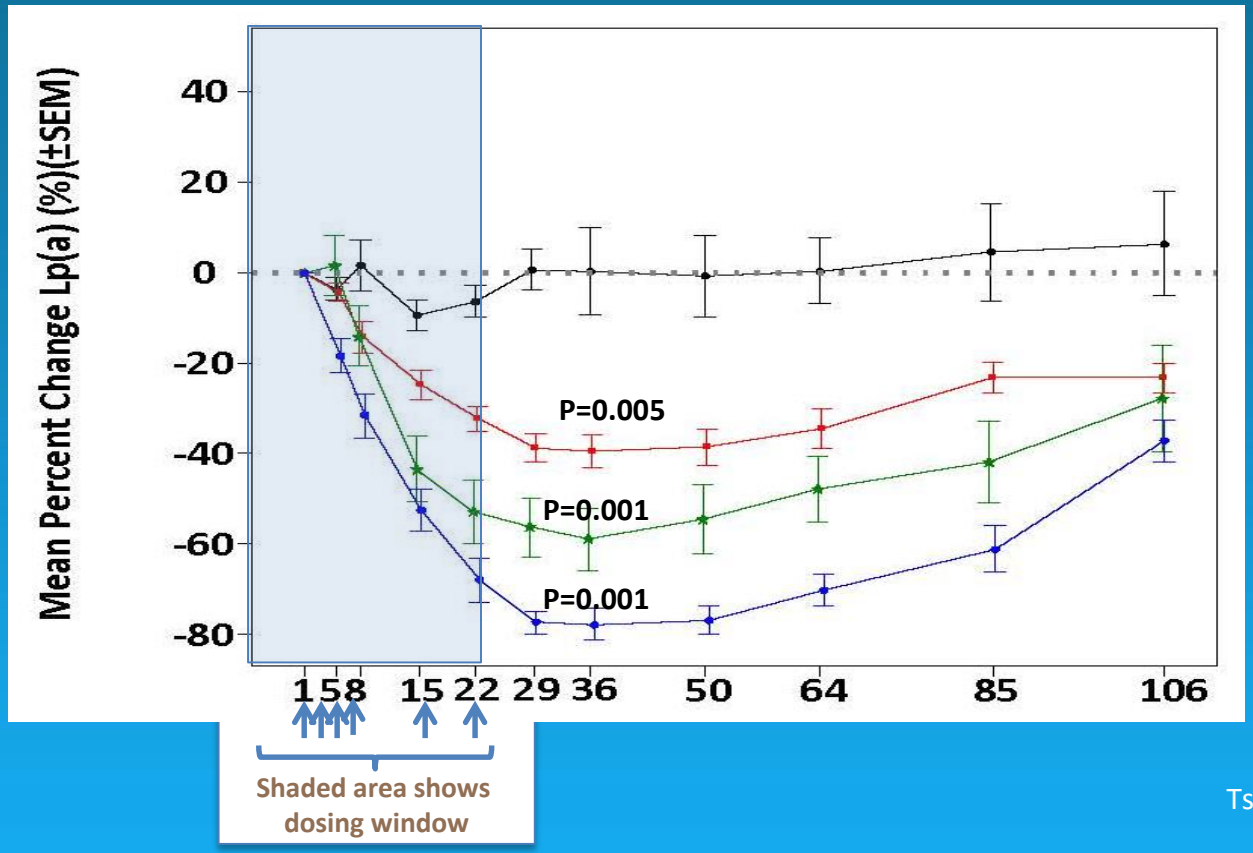
1. Cannon CP et al. N Engl J Med 2010;363:2406–2415; 2. http://clinicaltrials.gov/ct2/show/NCT01252953;3. Nicholls SJ et al. *JAMA* 2011;306:2099–2109; 4. http://clinicaltrials.gov/ct2/show/NCT01687998

ISIS-304801: Changes from Baseline in Levels of Apo C-III, TGs, and HDL-C



Gaudet D et al. *N Engl J Med* 2015;373:438-47.

Mean Percent Change Lp(a) Over Time by Treatment Groups
Multiple-Dose Cohorts (N=29)*



Placebo
100 mg
200 mg
300 mg

*Excludes 2 subjects who received < 3 doses of Study Drug

P=0.003
P=0.18
P=0.001

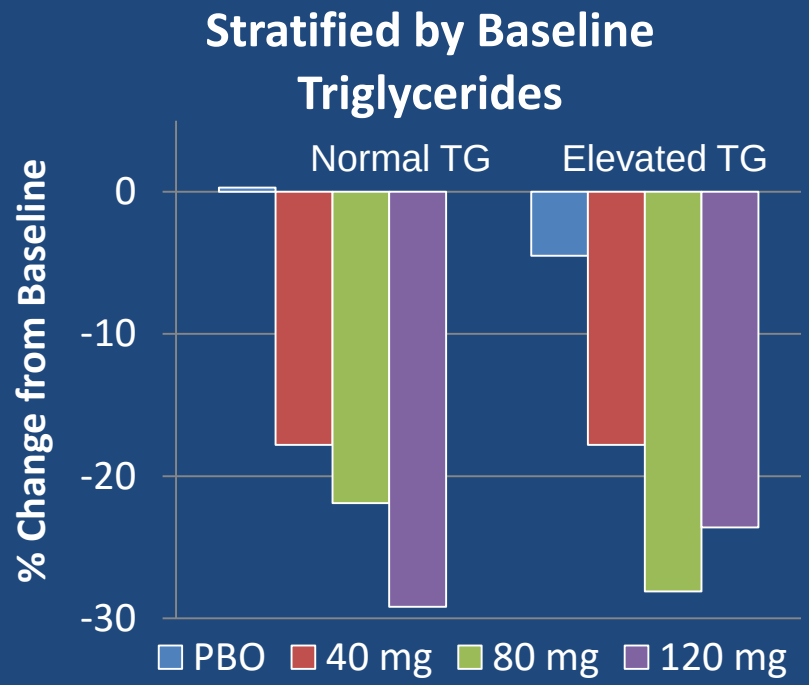
Wilcoxon Rank Sum Test p-value

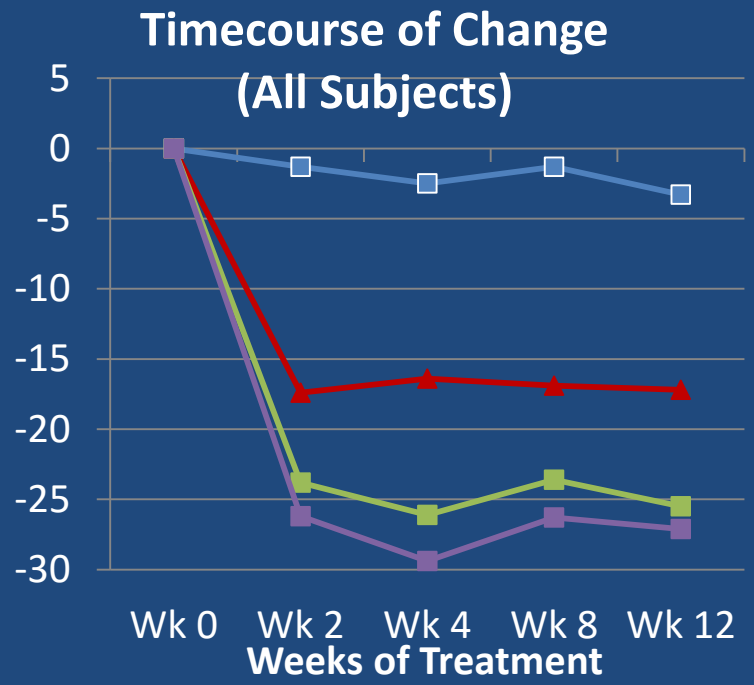
Tsimikas S. *Lancet* 2015;386:1472-83.

ETC-1002 (Bempedoic Acid) Pharmacologic Properties

- Oral, once-daily small molecule
- Half-life: 15-24 hours
- Target organ: Liver
  - Minimal metabolism in preclinical and clinical studies
  - Primary biliary and minimal kidney excretion
- No competitive liver uptake with statins (e.g. OATP1B1)
- MOA: Inhibits ATP-citrate lyase (ACL) and activates AMP-activated protein kinase (AMPK)

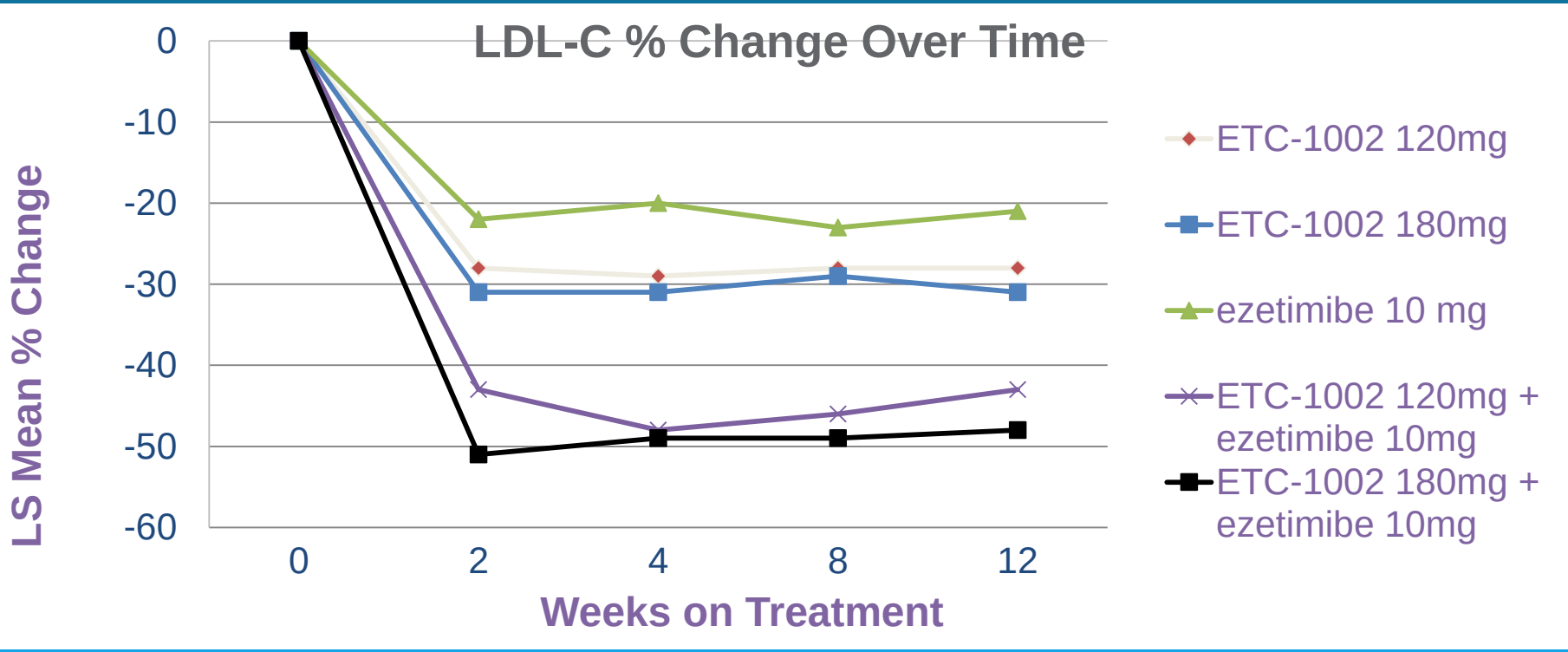
ETC-1002-003 (Bempedoic Acid): Percent Change from Baseline in LDL-C





Ballantyne CM et al. *J Am Coll Cardiol* 2013;62:1154-62.

ETC-1002 (Bempedoic Acid) ± Ezetimibe



Thompson PD. Presented at ACC, San Diego, 14 Mar 2015 (moderated poster #116M-03).

Few Recent Secondary Prevention Lipid Treatment Trials Have Demonstrated a CV Outcomes Benefit

Fibrates	FIELD	Fenofibrate	Neutral
	ACCORD	Fenofibrate	Neutral
Niacin	AIM-HIGH	Niacin	Neutral
	HPS2-THRIVE	Niacin / Laropiprant	Neutral
Chol Absorption Inhibition	IMPROVE-IT	Ezetimibe	Positive
CETP Inhibition	ILLUMINATE	Torcetrapib	Negative
	Dal-OUTCOMES	Dalcetrapib	Neutral
sPLA2 Inhibition	VISTA-16	Varespladib	Negative
Lp-PLA2 Inhibition	SOLID	Darapladib	Neutral
	STABILITY	Darapladib	Neutral

Fenofibrate, niacin and ezetimibe are licensed products, dalcetrapib is under investigation, and niacin/laropiprant, torcetrapib, varespladib, and darapladib are no longer under investigation.

The Field Study Investigators. *Lancet*. 2005;366:1849.
The ACCORD Study Group. *N Engl J Med.* 2010;362:1563.
Boden WE et al. *N Engl J Med.* 2011;365:2255.
HPS2-TRIVE Collaborative Group. *N Engl J Med*. 2014;371(3):203-12.
Cannon CP, et al. American Heart Association Scientific Sessions, Chicago, IL, November 17, 2014.
Barter PJ, et al. *N Engl J Med*. 2007;357(21):2109-22.
Schwartz GG, et al. *N Engl J Med*. 2012;367(22):2089-99.
Nicholls SJ, et al. *JAMA*. 2014 Jan 15;311(3):252-62.
O'Donoghue ML, et al. *JAMA*. 2014;312(10):1006-15.
White HD, et al. *N Engl J Med*. 2014;370(18):1702-11.
https://clinicaltrials.gov.

Ongoing CV Outcomes Trials May Expand Understanding of the Role of Lipid Modulation in CV Risk Reduction

CETP Inhibition	REVEAL	Anacetrapib	Enrolled
	ACCELERATE	Evacetrapib	HALTED
IL-1-B Inhibition	CANTOS	Canakinumab	Enrolled
Low-Dose MTX	CIRT	Low-Dose Methotrexate	Enrolling
PCSK9 Inhibition	ODYSSEY OUTCOMES	Alirocumab	Enrolled
	FOURIER	Evolocumab	Enrolled
	SPIRE 1	Bococizumab	Enrolling
	SPIRE 2	Bococizumab	Enrolling

Alirocumab has been approved for use by the U.S. FDA and has received a positive opinion from the CHMP
Evolocumab has been approved for use by the U.S. FDA and EC
Bococizumab and anacetrapib are investigational compounds; Evacetrapib is no longer under investigation
Canakinumab and methotrexate are licensed products with indications outside CV medicine

- What will the long-term safety profile be of very low levels of LDL-C, and will this offer an improvement in CV outcomes?
- What is the evidence supporting LDL-C reduction even when levels are low?
- Is LDL-C lowering without inflammation inhibition effective?
- Will our patients live longer and more productive lives?

https://clinicaltrials.gov.

Conclusions

- Statins reduce CV events in proportion to the amount of LDL-C reduction
- Considerable residual CV risk remains despite statin therapy
- Many high-risk patients may benefit from further LDL-C reduction, including those at high risk despite a statin, those with a suboptimal response to statins, and those who are statin intolerant
- Human genetics may be helpful in selecting targets for drug development that have a greater chance for success in CV outcomes trials, which ultimately must be done to understand the full risk-benefit profile of new therapies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