Will guidelines still pertain in the era of PCSK9i?

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Disclosures: Consulting/Research/Speaking

- Amgen
- Regeneron/Sanofi
- Aegerion
- Merck
- Esperion
- Akcea
- Ionis
- AstraZeneca
- Boehringer Ingelheim
- Madrigal

“You can only know where you're going if you know where you've been.”

- James Burke

History's lessons…

- **Higher LDL-C = Higher CV Risk and Lower LDL-C = Lower CV Risk.**
- **From Epidemiology to Outcomes trials**
  - Evidence from outcomes studies shows a consistent linear relationship between the extent of low-density lipoprotein cholesterol (LDL-C) lowering with a statin and the relative reduction in risk of ASCVD events.[1] **Mendelian Randomization** studies confirm this relationship.
- **Statins are cheap, and effective**
  - Moreover, the low cost of statins means that treatment is also cost effective even in patients at lower risk (including those with a 7.5% 10-year calculated cardiovascular disease risk).[2]

[1]Laufs U, Descamps OS, Catapano AL, Packard CJ. Understanding IMPROVE-IT and the cardinal role of LDL-C lowering in CVD prevention. Eur Heart J 2014;35:1996-2000.
[2]National Institute for Health and Clinical Excellence. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease (July 2014). https://www.nice.org.uk/guidance/indevelopment/GID-CGWAVER123

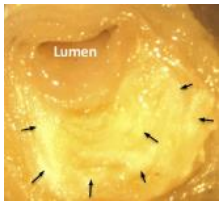
Understanding Cholesterol Metabolism

Where we've been

History of Cholesterol Understanding

1908–1913

Cholesterol related to atherosclerosis[1]

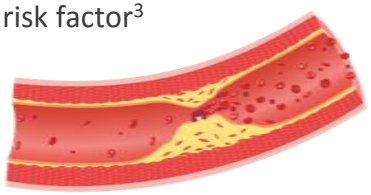


1948

Framingham Heart Study begins[2]

1961

Cholesterol identified as cardiovascular risk factor[3]

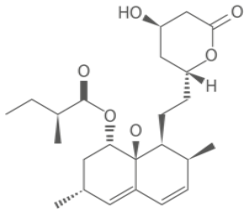


1985

Brown and Goldstein awarded nobel prize for cholesterol metabolism (LDL receptor)[4]

1987

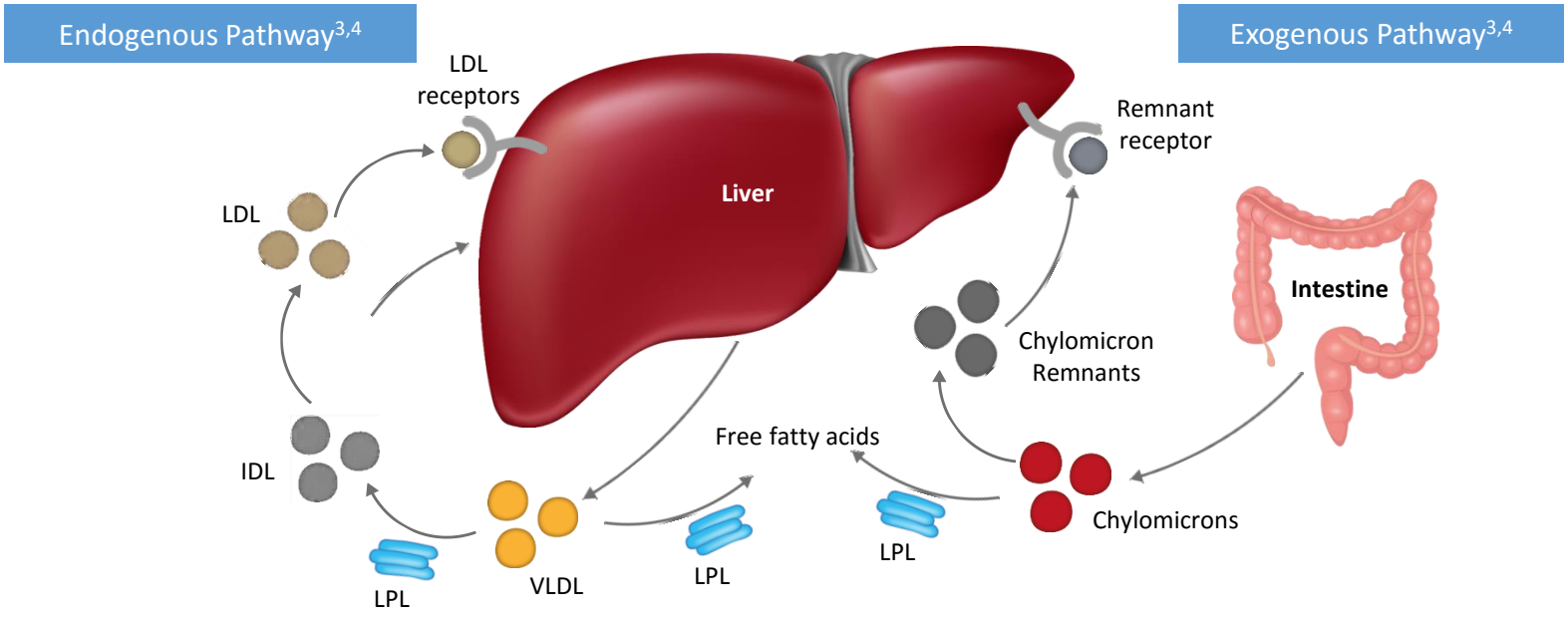
First statin approved[5]



1. Konstantinov IE, et al. *Tex Heart Inst J.* 2006;33:417-423. 2. Framingham Heart Study. https://www.framinghamheartstudy.org/about-fhs/index.php. Accessed January 13, 2016. 3. Kannel WB, et al. *Ann Intern Med*. 1961;55:33-50. 4. Brown MS, Goldstein JL. Nobel lecture 1985. http://www.med.harvard.edu/md_phd/news/Brown%20and%20Goldstein%20Nobel%20Lecture.pdf. Accessed January 13, 2016. 5. Tobert JA. *Nat Rev Drug Discov*. 2003;2:517-526. 5. Nobelprize.org. The Nobel prize in physiology or medicine 1985. http://www.nobelprize.org/nobel_prizes/medicine/laureates/1985/. Accessed January 13, 2016.

LDL-C and LDL-P are the End Products of Endogenous Lipoprotein Metabolism[1]

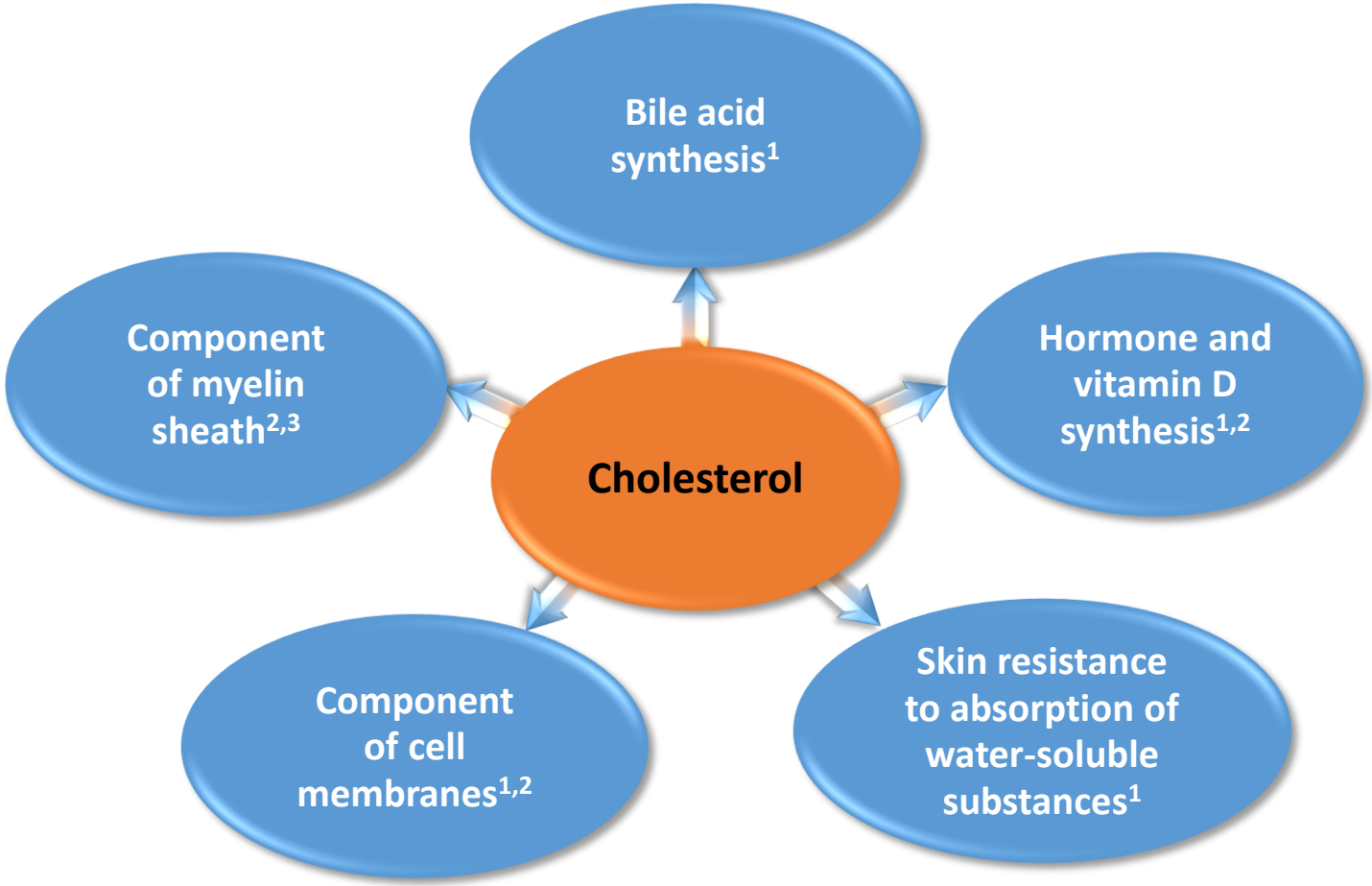
- LDL receptors remove LDL from the circulatory system[1]
- LDL, to a minor degree, delivers cholesterol to peripheral tissues[2]



HDL = high-density lipoprotein; IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; LPL = lipoprotein lipase; VLDL = very low-density lipoprotein

1. Goldstein JL, Brown MS. *Arterioscler Thromb Vasc Biol*. 2009;29;431-438. 2. Rader DJ, et al. *J Clin Invest*. 2003;111:1795-1803.
3. Dietschy JM, Turley SD. *J Lipid Res.* 2004;45:1375-1397; 4. Mc Auley MT, et al. *BMC Syst Biol*. 2012;6:130.

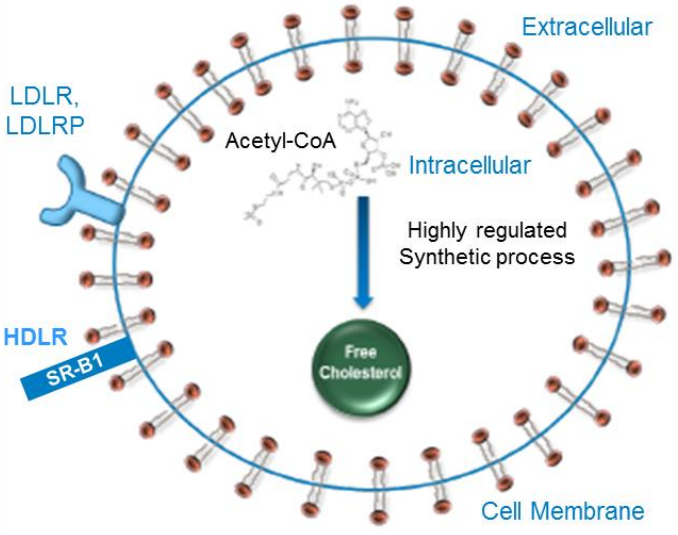
Cholesterol Plays a Role in Many Important Physiologic Functions



1. Hall JE, Guyton AC. In: *Guyton and Hall Textbook of Medical Physiology*. 12th ed. Philadelphia, PA: Saunders; 2011:819-830.
2. Goldstein JL, Brown MS. *Arterioscler Thromb Vasc Biol*. 2009;29:431-438. 3. Saher G, et al. *Nat Neurosci*. 2005;8:468-475.

Cellular Acquisition of Cholesterol Can Be From Multiple Sources

- Cholesterol for cellular physiologic functions can be from intra and/or extracellular pathways[1–5]
  - Systemic distribution of cholesterol is important, but cells are not dependent on circulating plasma LDL-C[3]

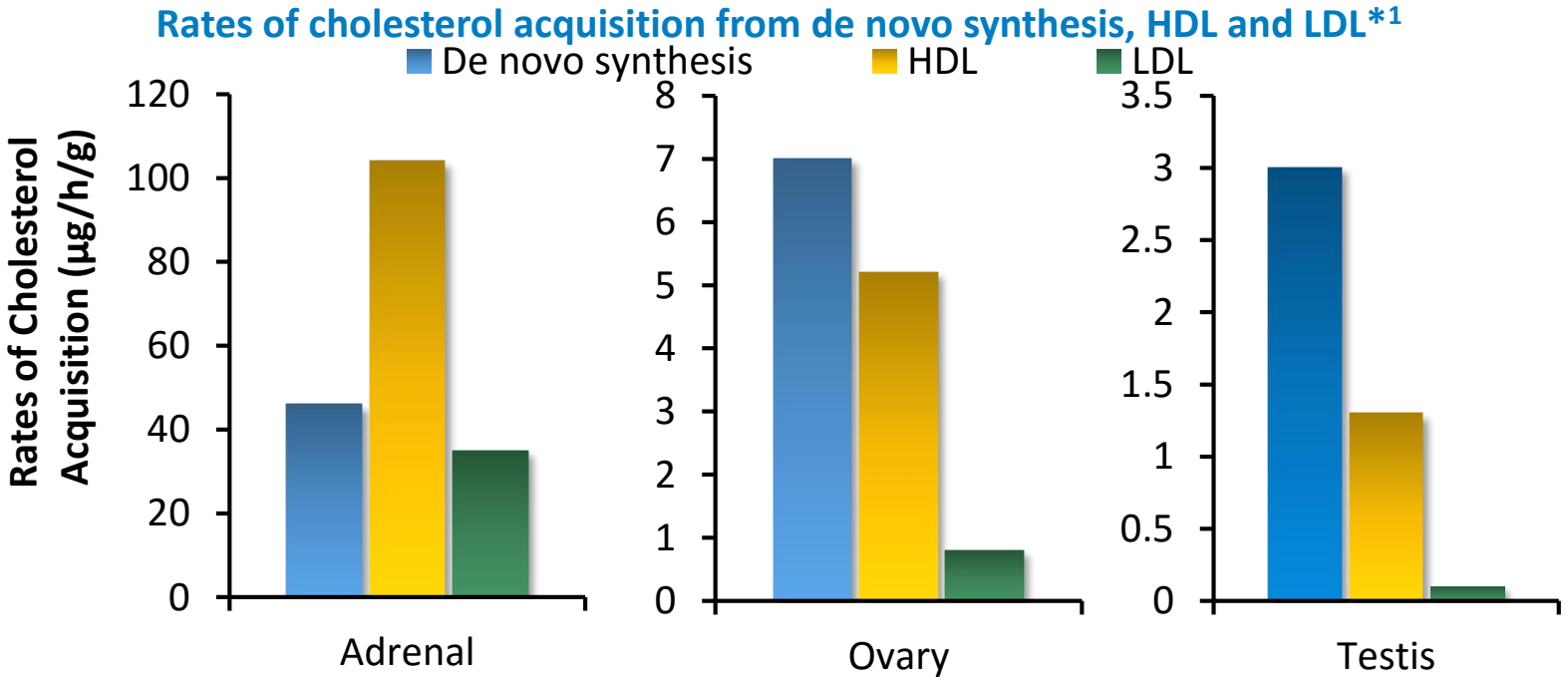


HDLR = high-density lipoprotein cholesterol receptor; LDL-C = low-density lipoprotein cholesterol; LDL-R = LDL receptor; LDLRP = LDLR protein; SR-B1 = scavenger receptor class B type 1.

1. Mc Auley MT, et al. *BMC Syst Biol.* 2012;6:130. 2. Xie C, et al. *J Lipid Res.* 2006;47:953-963. 3. Hu J, et al. *Nutr Metab (Lond).* 2010;7:47. 4. Orth M, Bellosta S. *Cholesterol.* 2012;2012:292598. 5. Dietschy JM, Turley SD. *J Lipid Res.* 2004;45:1375-1397.
Figure adapted from Dietschy 2004.

Animal Data Demonstrate Steroidogenic Tissues Acquire Cholesterol via HDL-C and De Novo Synthesis[1,2]

- Adrenal, ovarian, and testicular tissues can acquire cholesterol via LDL, HDL, and de novo synthesis
  - Predominant pathway is HDL and de novo synthesis[1,2]



*Data were calculated from measurements made in 49-day-old control mice with LDL receptor activity.

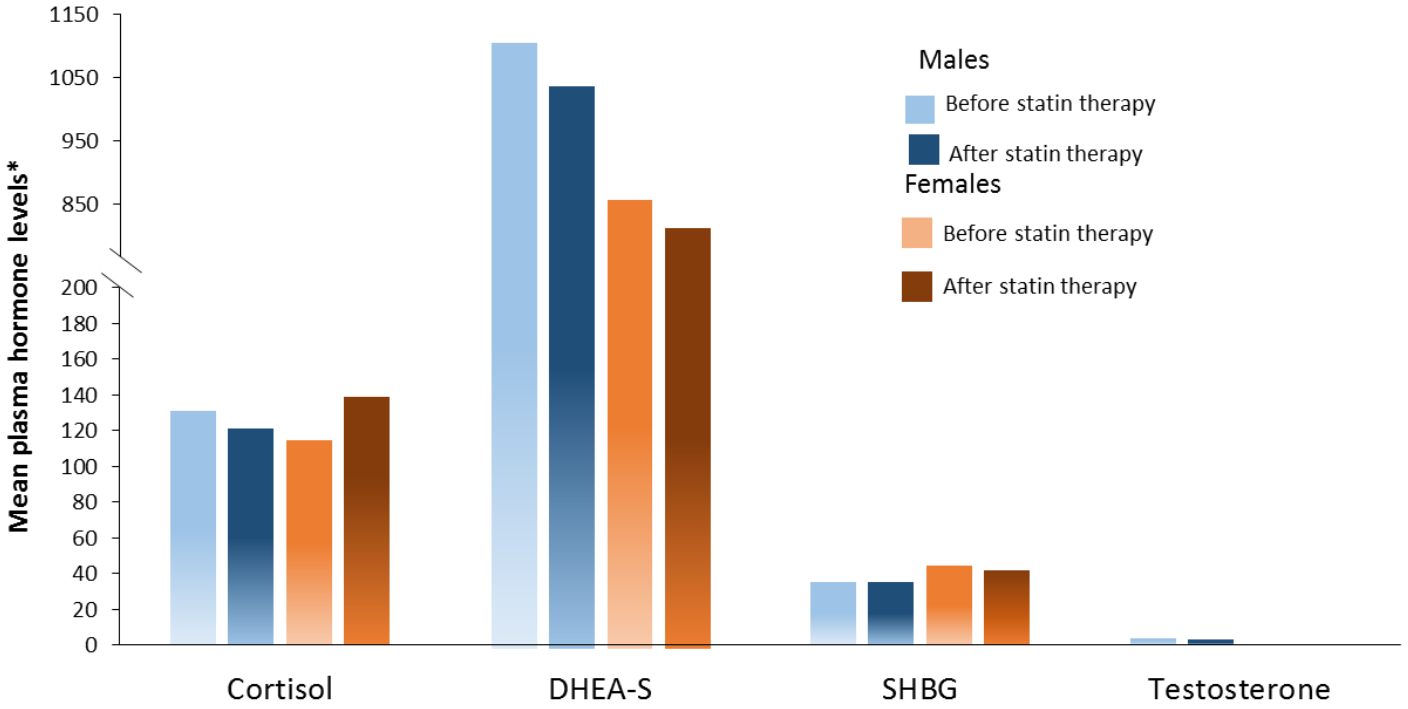
HDL = high-density lipoprotein; LDL = low-density lipoprotein.

1. Xie C, et al. *J Lipid Res.* 2006;47:953-963. 2. Hu J, et al. *Nutr Metab (Lond).* 2010;7:47.

Despite Reducing LDL-C, Statins Do Not Alter Gonadal or Adrenal Steroid Hormones in Humans

Plasma hormone levels before and 3 months after treatment with statin[1]

- Reduction in LDL-C with statins without changing steroid hormones has been consistently shown[1–3]



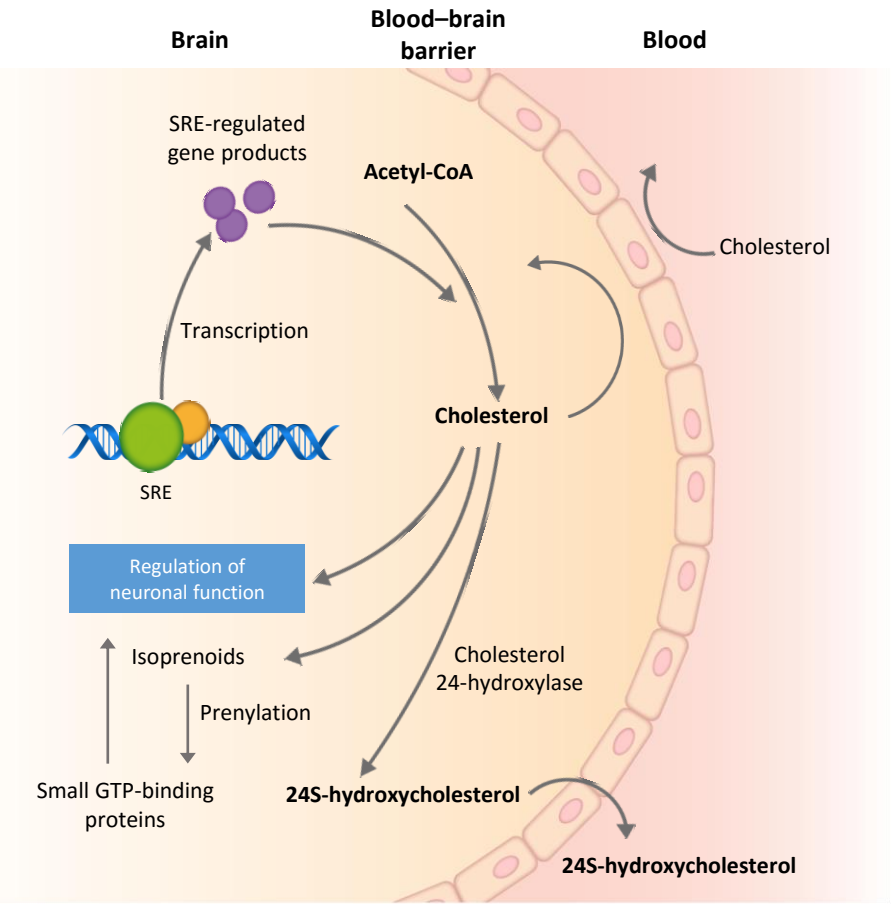
*ng/mL for cortisol, DHEA-S and testosterone and nmol/L for SHBG. Effect of statin on gonadal and adrenal hormones studied on 24 patients with type 2 diabetes, studied before and after a 3-month treatment with statin.

DHEA-S = dehydroepiandrosterone sulfate; SHBG = sex hormone binding globulin.

1. Santini SA, et al. *J Atheroscler Thromb*. 2003;10:160-164. 2. Sezer K, et al. *J Endocrinol Invest*. 2008;31:1075-1078.
3. Bohm M, et al. *Z Kardiol*. 2004;93:43–48.

The Central Nervous System Synthesizes Cholesterol De Novo

- The central nervous system synthesizes cholesterol de novo[1,2]
- The blood–brain barrier prevents the uptake of systemic lipoprotein cholesterol[1,2]
- This segregation ensures that cholesterol metabolism within the brain is isolated from changes in the circulating lipid levels[2]



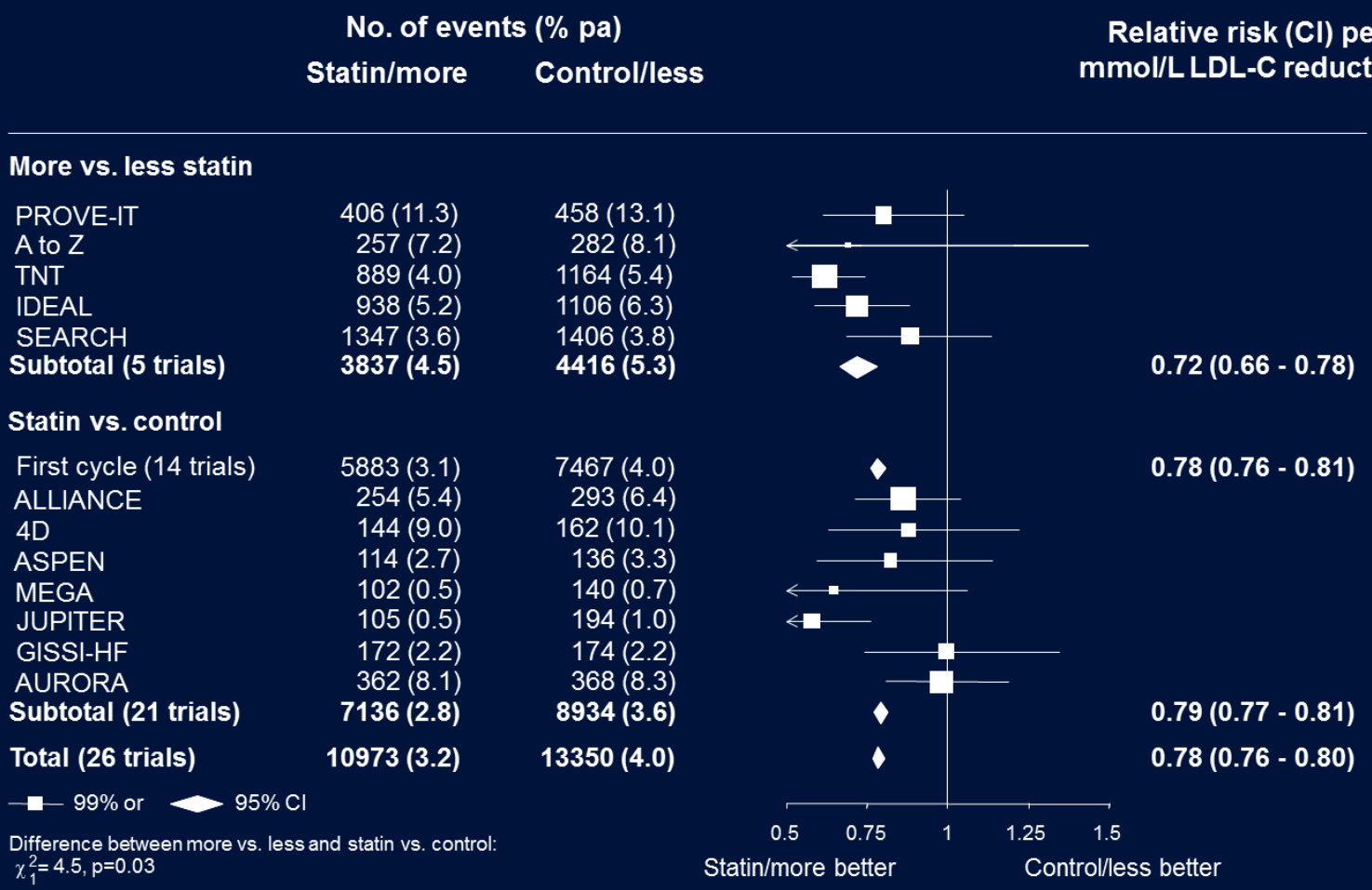
1. Björkhem I, Meaney S. *Arterioscler Thromb Vasc Biol.* 2004;24:806-815. 2. Katsuno M, et al. *Nat Med*. 2009;15:253-254.
Figure adapted from Katsuno M et al. 2009.

Cholesterol Kinetics in Humans: What We Now Know

- Knowledge of cholesterol's role and trafficking mechanisms has dramatically evolved over the last century
- Cholesterol plays a role in various vital physiologic functions
- Cellular cholesterol is minimally dependent on extracellular acquisition; and not at all in the brain
- LDL is an insignificant source of cholesterol for steroid hormone synthesis
- Statins do not impact vital hormones
- LDL carries cholesterol destined for excretion

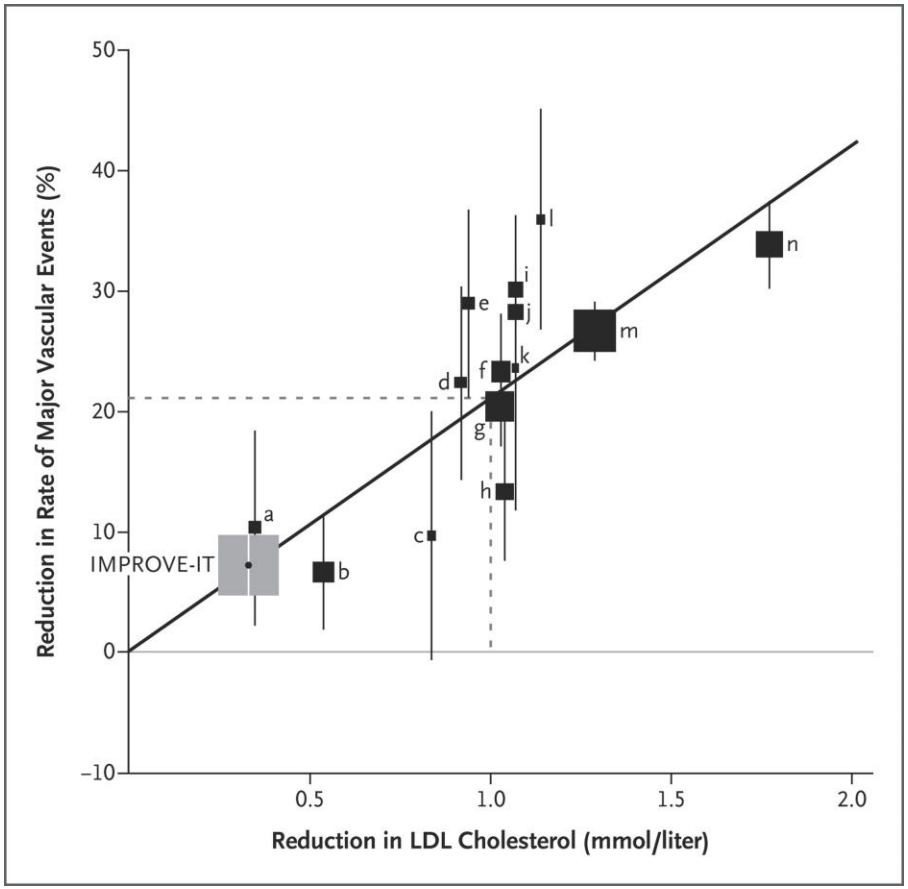
A summary of RCTs proving statin effectiveness

Proportional effects on major vascular events per mmol/L LDL-C reduction



Lancet 2010; **376**: 1670–81.

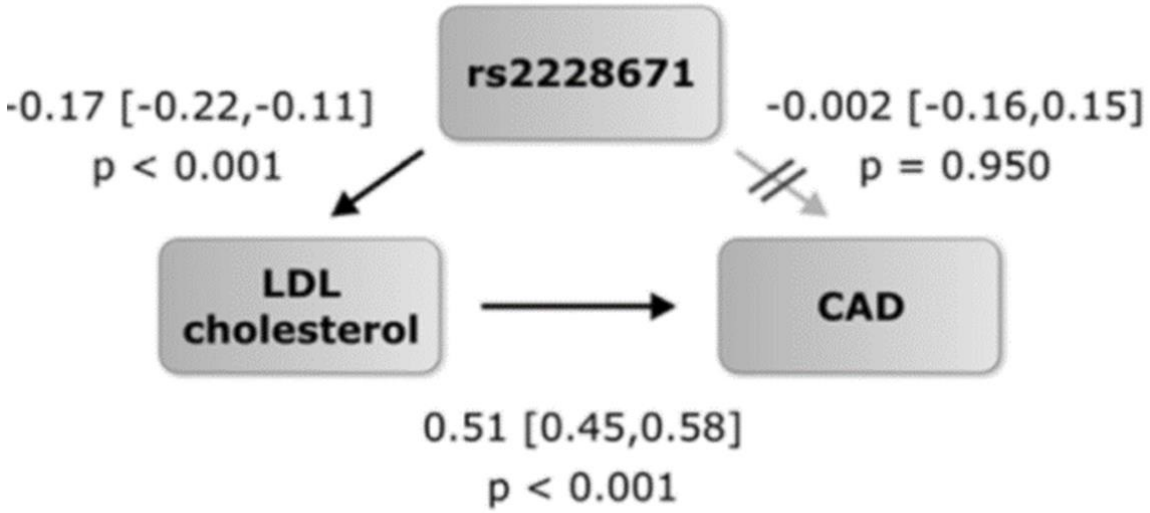
IMPROVE-IT: Another piece of the puzzle



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

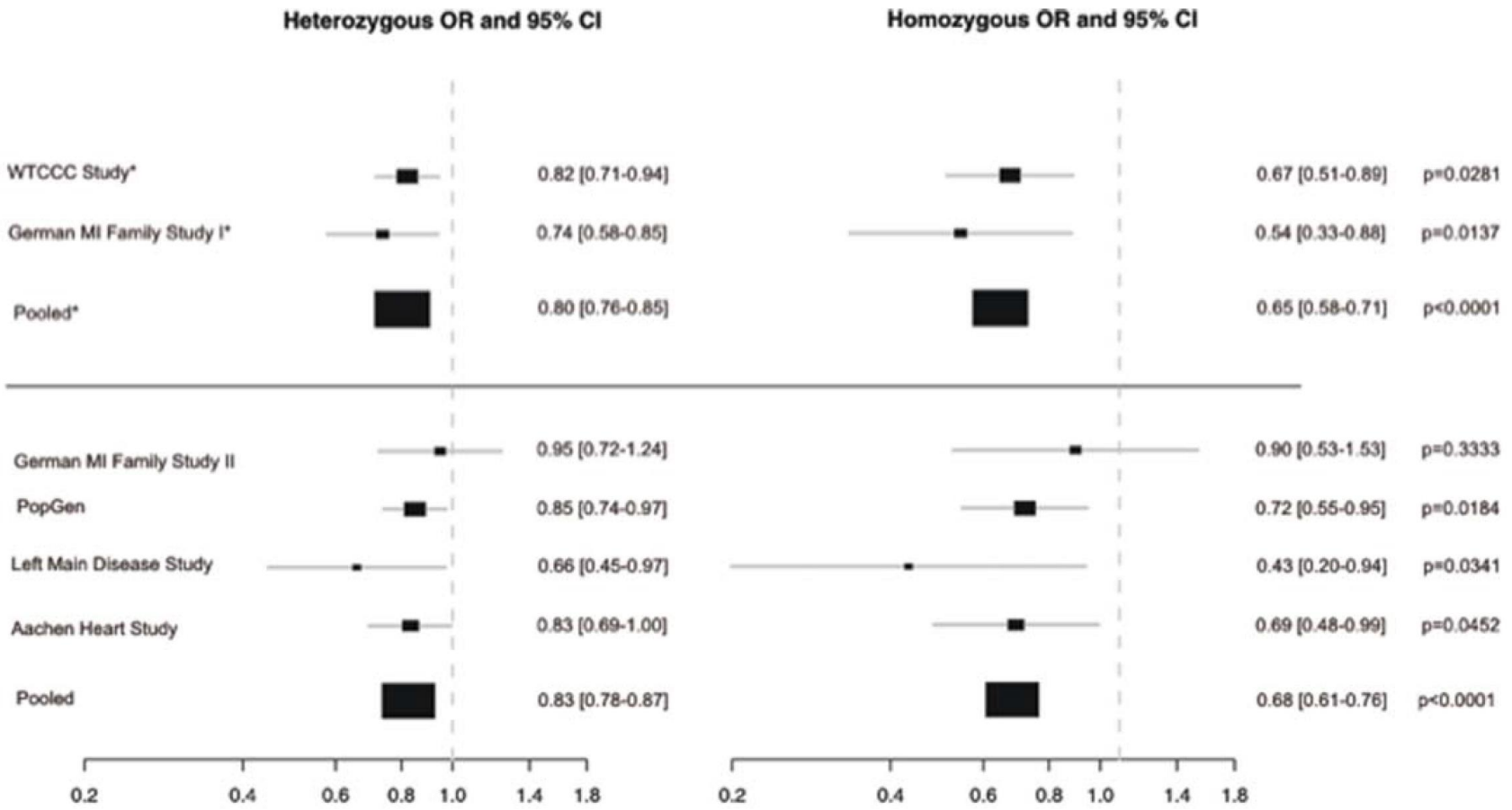
From Statin Trials and EZ to Mendelian Randomization: Confirmation that LDL is causally related to vascular disease

- Mendelian randomization study
- Exploration of the causal relationship between LDL-C associated with rs2228671 and CAD



Linsel-Nitschke P et al. PLoS. 2008; 3: e2986.

Association of rs2228671 with risk of CAD in six case-control studies



Linsel-Nitschke P et al. PLoS. 2008; 3: e2986.

“LDL Hypothesis” is no longer “Hypothetical”; it is Reality

- LDL biology and pathophysiology
- Epidemiology
- Statin trials
- IMPROVE-IT
- Mendelian Randomization Studies

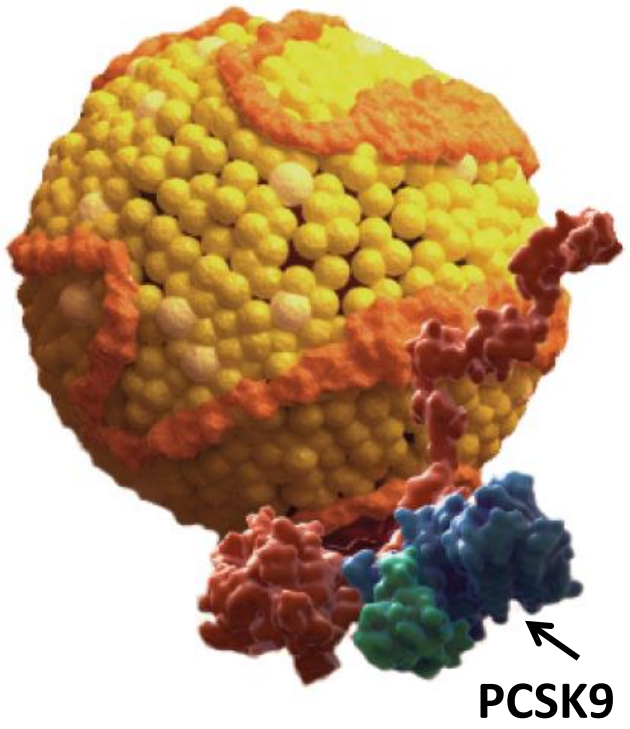
Yet, statins remain underutilized. Consequently LDL-C is inadequately treated.

- Clinician Inertia/Patient resistance
- Under-use of high-intensity, high dose statins
- Guideline pressure *against* combination therapy
- Guideline Discord
- Prescribing issues: $$$, Insurance requirements
- Poor compliance & Statin Intolerance

Enter PCSK9

PCSK9: Major modulator in LDL-C Metabolism

PCSK9 is a regulator of LDL metabolism

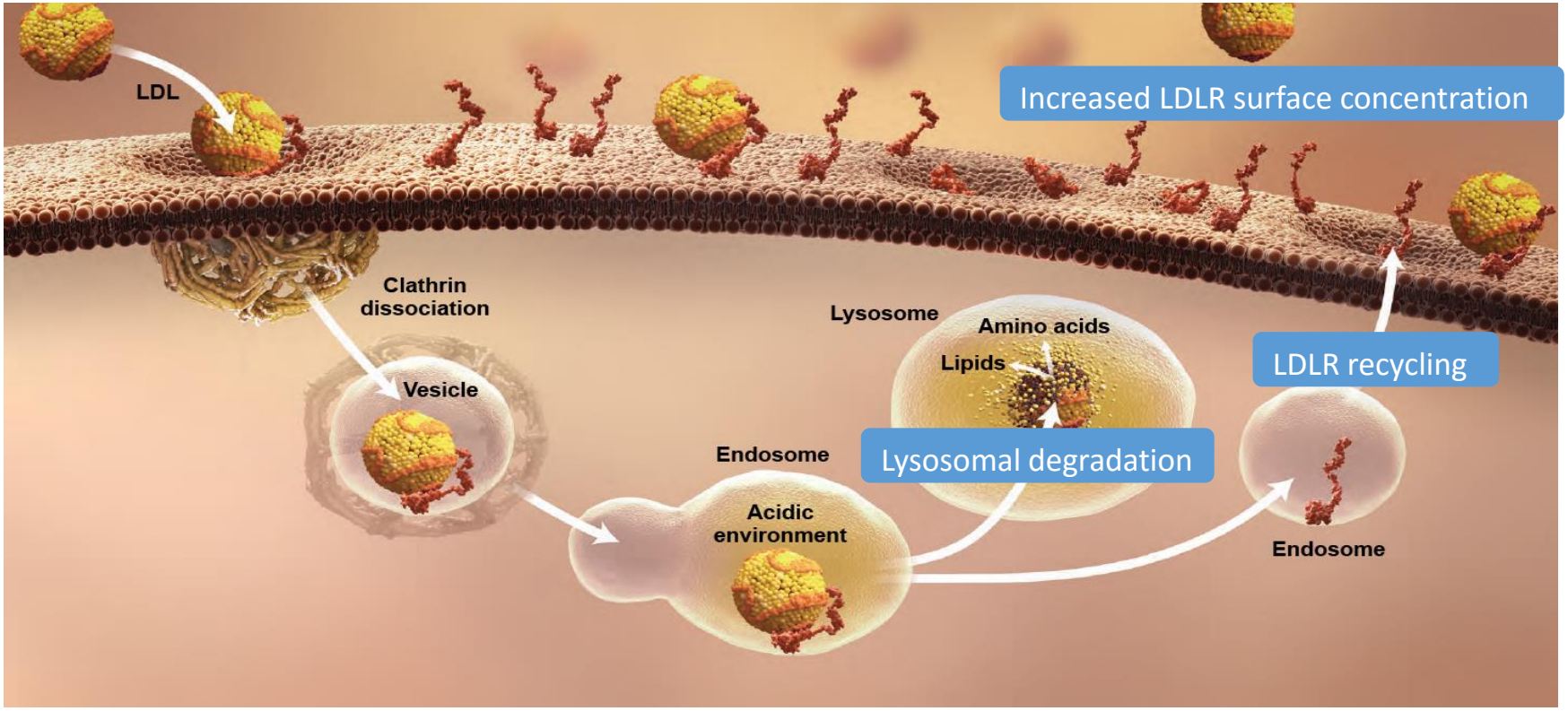


PCSK9

- Proprotein convertase subtilisin/kexin type 9[1]
- Secreted by liver into plasma[1]
- Binds LDL receptor on surface of hepatocyte[1,2]
- Targets LDL receptor for degradation[1,2]

1. Seidah NG, et al. *Circ Res.* 2014;114:1022-1036. 2. Steinberg D, Witztum JL. *Proc Natl Acad Sci U S A.* 2009;106:9546-9547.

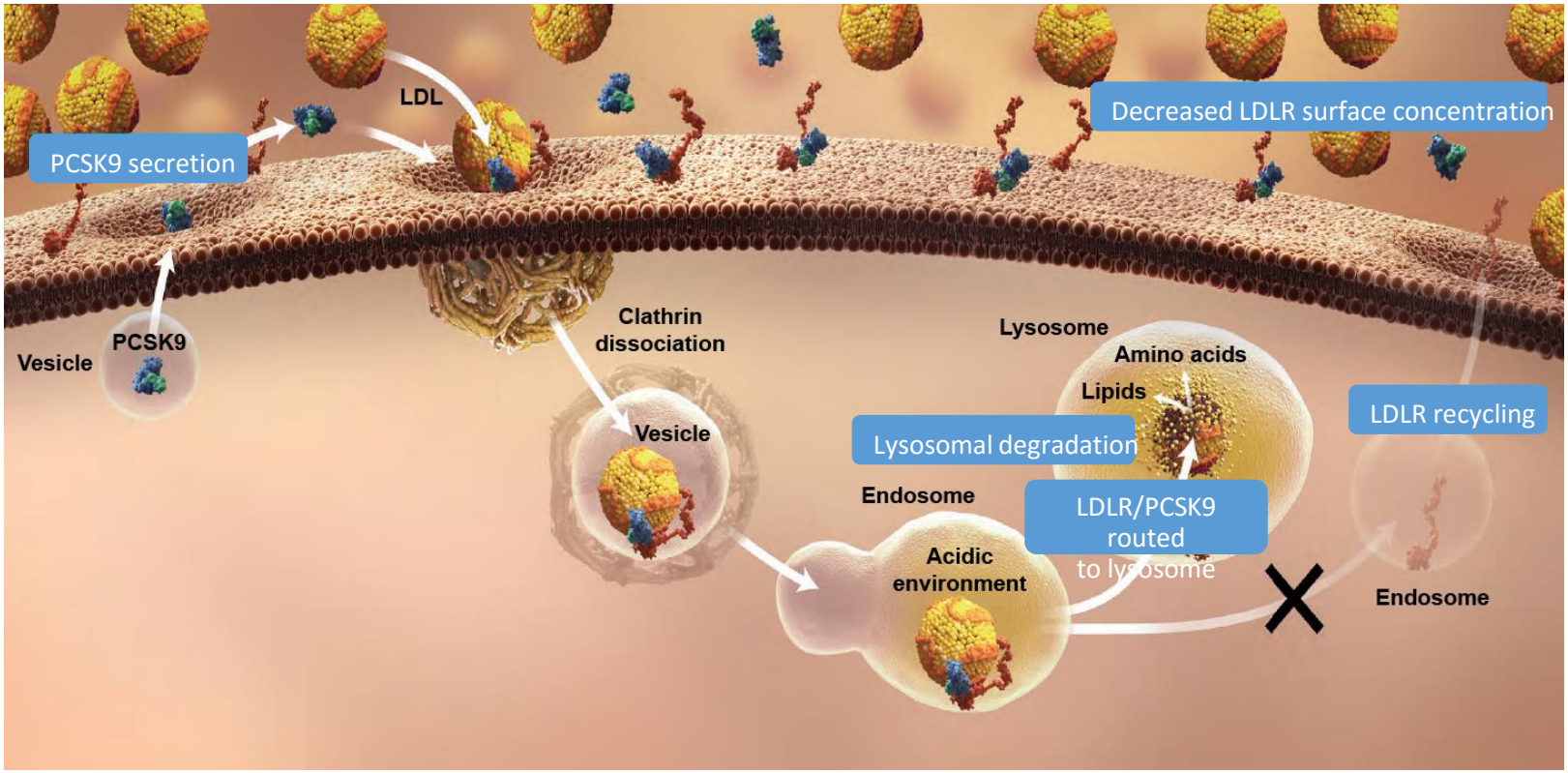
LDL particles are cleared from the plasma by binding to LDLR receptors and being internalized by the hepatocyte[1-3]



Recycled LDL receptors continue to clear plasma LDL

1. Brown MS, Goldstein JL. *Proc Natl Acad Sci U S A.* 1979;76:3330-3337. 2. Brown MS, Goldstein JL. *Science*. 1986;232:34-47. 3. Steinberg D, Witztum JL. *Proc Natl Acad Sci U S A.* 2009;106:9546-9547.

PCSK9 binds to the LDL receptor, targeting it for degradation[1-3]



Fewer LDL receptors on hepatocyte surface result in increased plasma LDL-C

1. Abifadel M, et al. *Hum Mutat.* 2009;30:520-529. 2. Seidah NG, et al. *Circ Res.* 2014;114:1022-1036. 3. Steinberg D, Witztum JL. *Proc Natl Acad Sci U S A.* 2009;106:9546-9547.

The NEW ENGLAND JOURNAL of MEDICINE

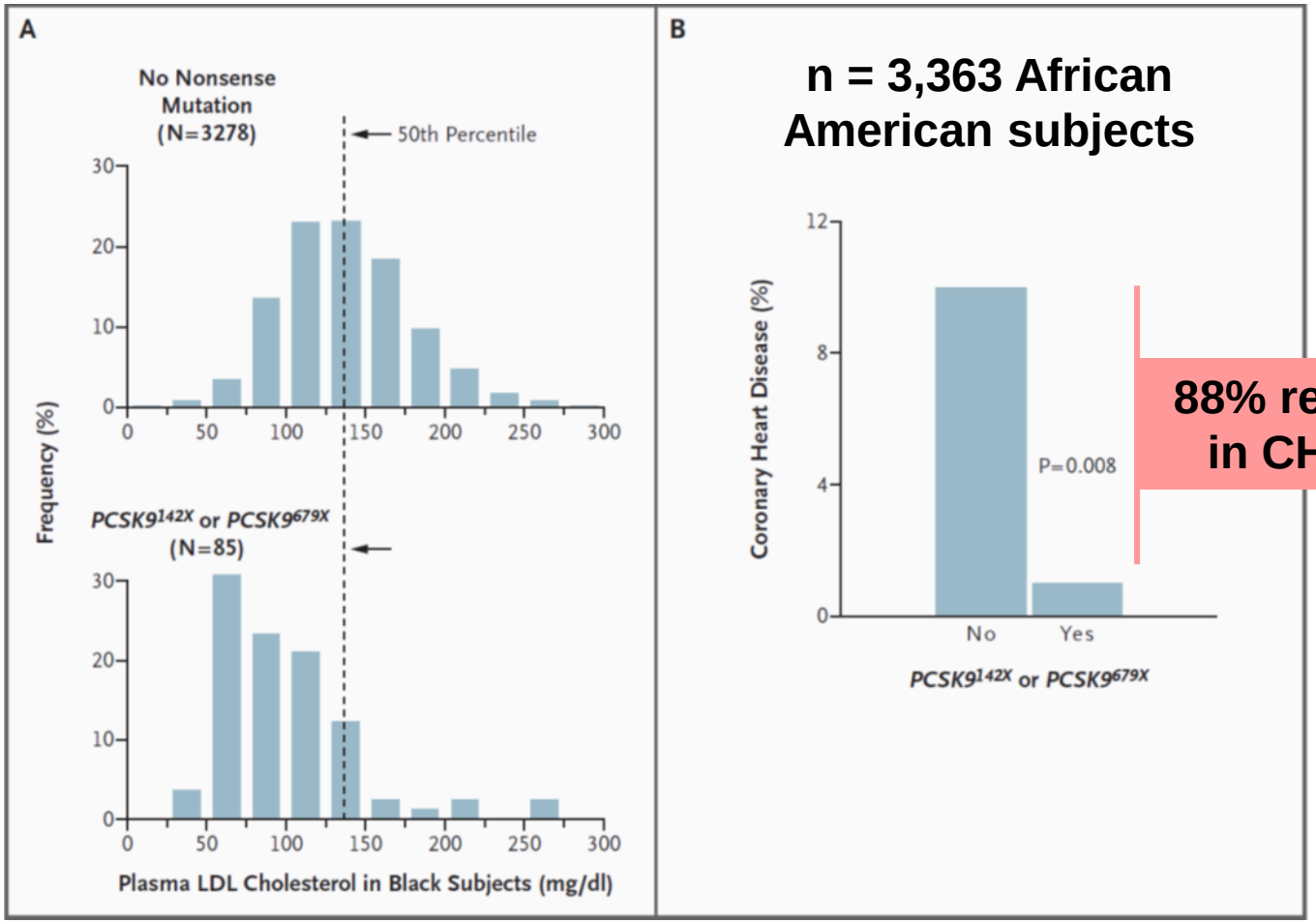
ORIGINAL ARTICLE

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.

Compared the incidence of CHD (MI, fatal CHD, or coronary revascularization) over a 15-year interval in the ARIC study according to the presence or absence of sequence variants in the PCSK9 gene that are associated with reduced plasma levels of LDL cholesterol.

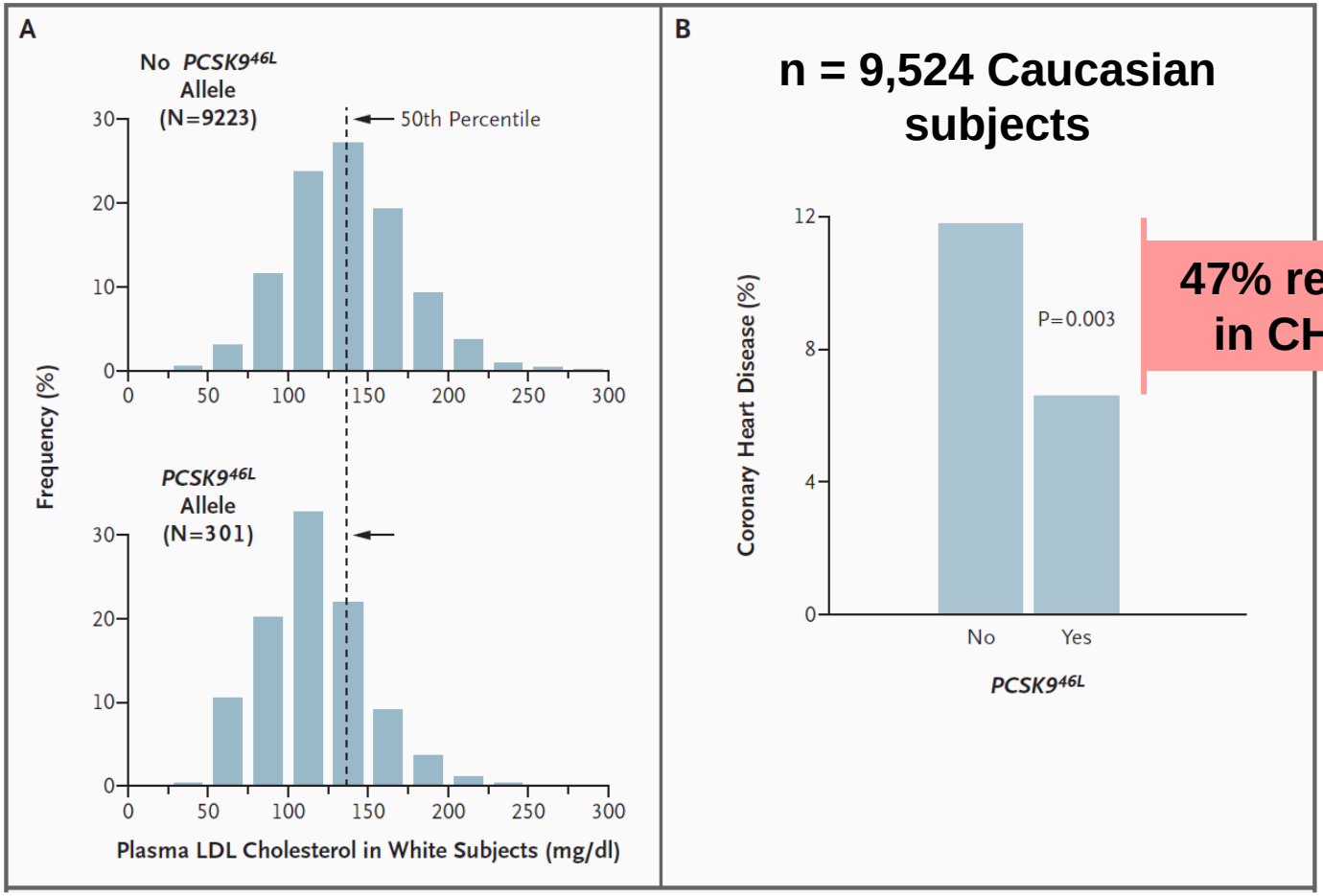
Plasma LDL cholesterol levels and incidence of CHD in African Americans



88% reduction in CHD risk

Cohen JC et al. *N Engl J Med*. 2006; 354: 1264-1272.

Plasma LDL cholesterol levels and incidence of CHD in Caucasians



47% reduction in CHD risk

Cohen JC et al. *N Engl J Med*. 2006; 354: 1264-1272.

Loss-of-Function Mutations in PCSK9 Are Associated With Decreased LDL-C

PCSK9 Variant	Population	LDL-C
R46L	ARIC[1], DHS[2]	↓ 15%[1]
Y142X or C679X	ARIC[1], DHS[2]	↓ 28%–40%[1]
R46L	CGPS[3]	↓ 11%[3]

- Heterozygous LOF mutations found in 1% to 3% of representative populations[1,3]
- Associated with
  - Lower serum LDL-C[1]
- PCSK9 null individual identified (compound heterozygote for two inactivating mutations)
  - No detectable circulating PCSK9 with strikingly low LDL-C (14 mg/dL)[4]

LOF = loss of function
ARIC = Atherosclerosis Risk in Communities (N ~ 4,000); DHS = Dallas Heart Study (N = 3,553);
CGPS = Copenhagen General Population Study (N = 26,013)

1. Cohen JC, et al. *N Engl J Med*. 2006;354:1264-1272. **2.** Cohen J, et al. *Nat Genet*. 2005;37:161-165
3. Benn M, et al. *J Am Coll Cardiol*. 2010;55:2833-2842. **4.** Zhao Z, et al. *Am Journal of Hum Gen*. 2006;79:514-534.

Gain-of-Function Mutations in PCSK9 Cause Familial Hypercholesterolemia*†

PCSK9 Variant	Population	Clinical/Biochemical Characteristics
D374Y[1]	British, Norwegian families, 1 Utah family	Tendon xanthomas, severe hypercholesterolemia
S127R[1]	French, South African, Norwegian families	Tendon xanthomas
R218S[2]	French families	Tendon xanthomas, arcus corneae

- Associated with:
  - High serum LDL-C[1]
  - In vitro testing in many identified mutations shows decreased levels of LDLRs[3]

*Autosomal Dominant Hypercholesterolemia

1. Abifadel M, et al. *Hum Gen*. 2009;30:520-529. **2.** Lopez D. *Biochem Biophys Acta*. 2008;1781:184-191.
3. Cameron J, et al. *Hum Mol Genet*. 2006;15:1551-1558.

†*For a full list of ADH mutations, please refer to Abifadel reference.*

Genetic Variants Establish PCSK9 as a Modulator of LDL-C

- Increased plasma levels of TC and LDL-C[1]
- FH-associated physical abnormalities[1]

Increasing PCSK9 (GOF)

- Fewer LDL receptors[1,2]
- Higher LDL-C[1,2]

Plasma LDL-C

Decreasing PCSK9 (LOF)

- More LDL receptors[1,2]
- Lower LDL-C[1,2]

- Reduced plasma levels of TC and LDL-C[1,3]

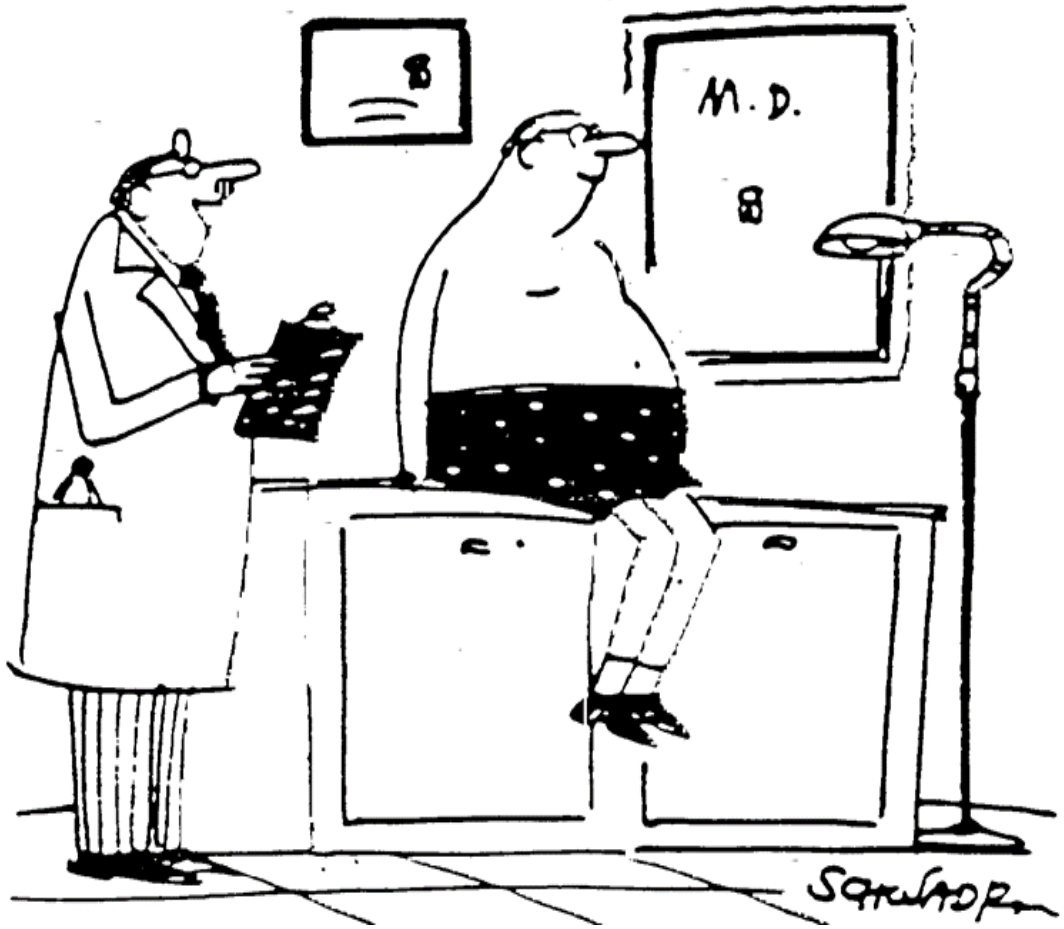
FH = familial hypercholesterolemia; GOF = gain of function; LDL-C = low-density lipoprotein cholesterol; LOF = loss of function; TC = total cholesterol.

1. Abifadel M, et al. *Hum Mutat*. 2009;30:520-529. 2. Seidah NG, et al. *Circ Res.* 2014;114:1022-1036. 3. Benn M, et al. *J Am Coll Cardiol.* 2010;55:2833:2842.

Summary

- PCSK9 regulates hepatic surface expression of LDLR and, in turn, systemic LDL-C levels
- Mutations in PCSK9 (both GOF and LOF) influence LDL-C levels as well as ASCVD risk
- Revelation: PCSK9 represents an excellent therapeutic target for LDL reduction

Cholesterol Guidelines: Un-harmonized



“I have some bad news. While your cholesterol level has remained the same, the research findings have changed.”

ACC/AHA Guidelines (2013)

Three (3) critical questions (The questions we ask, provide particular answers)

- **CQ1:** What is the evidence for LDL-C and non-HDL-C goals for the secondary prevention of ASCVD?
- **CQ2:** What is the evidence for LDL-C and non-HDL-C goals for the primary prevention of ASCVD?
- **CQ3:** For primary and secondary prevention, what is the impact on lipid levels, effectiveness, and safety of specific cholesterol-modifying drugs used for lipid management in general and in selected subgroups?

Stone NJ et al. 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. *J Am Coll Cardiol*. 2014; 63: 2889-2934.

ACC/AHA Guidelines (2013)

Solely RCT Data were considered.

Treatment targets:
"The Expert Panel makes no recommendations for or against specific LDL-C or non-HDL-C targets for the primary or secondary prevention of ASCVD."
Translation: Do not use treatment targets!

Stone NJ et al. 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. *J Am Coll Cardiol*. 2014; 63: 2889-2934.

Case 1: Secondary Prevention

- Patients **≥21** years old with **Clinical Atherosclerotic Cardiovascular Disease (ASCVD),** defined as **acute coronary syndromes**, **myocardial infarction**, stable or unstable **angina pectoris**, coronary or other **arterial revascularization**, **stroke**, **transient ischemic attack**, or **peripheral arterial disease** presumed to be of atherosclerotic origin.
- These patients are to receive **high-intensity statins**.

Case 2: Primary Prevention

- **Primary elevations** of low-density lipoprotein cholesterol **(LDL-C) ≥190 mg/dL** (consistent with **familial hypercholesterolemia**).
- These patients are to receive **high-intensity statins**

Case 3: Primary Prevention

- **Diabetic patients between the ages of 40 and 75** with **LDL-C 70 to 189 mg/dL** and **no history of ASCVD**.
- Patients with **10-year risk ≥ 7.5%** receive **high-intensity statins**
- Patients with **10-year risk < 7.5%** receive **moderate-intensity statins**

Case 4: Primary Prevention

- Patients **without clinical ASCVD or diabetes mellitus between the ages of 40 and 75**, having an **LDL-C 70 to 189 mg/dL** and **10-year ASCVD risk of ≥ 7.5%**.
- These patients are to receive **moderate- to high intensity statins**

ACC/AHA Guidelines (2013)

Conclusions

- Abandon LDL-C Goals
- Adopt treatment strategy based upon statin strength
- Apply statin strength recommendations based upon absolute ASCVD risk

Limitations

- Damaging to long-held practice using LDL targets
- RCTs were sole source of evidence
- Lack of adequate f/u of LDL – not all patients respond the same; some will be undertreated
- Failure to ask the “right” questions
- “De-harmonization” of Guidelines

European Atherosclerosis Society Guidelines on CVD Prevention in Clinical Practice (2012)

CVD Risk Category	Target LDL-C (mg/dL)
Low or moderate	≤115
High	≤100
Very high	≤70 (or a ≥50% LDL-C reduction when target level unattainable)

- All FH patients must be recognized as high risk and treated with lipid-lowering therapy
- For ACS patients, statin treatment in high does must be initiated while the patients are in the hospital

European Heart Journal. 2012: 33: 1635-1701.
European Journal of Preventive Cardiology. 2012; 19: 4: 585-667.

International Atherosclerosis Society (IAS) Guidelines

- Favors non-HDL-C as the major target of LLT
- Does not specifically prescribe “treatment goals” for atherogenic lipoproteins.
- Instead identifies optimal levels of atherogenic cholesterol making the general statement that the intensity of cholesterol-lowering therapy should be based on long-term risk.
- Potency of cholesterol-lowering therapy must be left to clinical judgment.
- Framingham is the core estimate with re-calibration for individual countries

Grundy SM et al. An International Atherosclerosis Society Position Paper: Global recommendations for the management of dyslipidemia-Full report. *J Clin Lipidol*. 2014; 8: 29-60.

International Atherosclerosis Society (IAS) Guidelines

- Statins: first line therapy for achieving the optimal levels of atherogenic cholesterol in high risk individuals
- If statin intolerant, consider:
  - Switching statin
  - Reducing statin dose
  - Prescribing QOD dosing
  - Using alternate drugs alone or in combination
  - Maximizing lifestyle intervention

Grundy SM et al. An International Atherosclerosis Society Position Paper: Global recommendations for the management of dyslipidemia-Full report. *J Clin Lipidol*. 2014; 8: 29-60.

National Lipid Association Recommendations (2014)

Major conclusions

1. An elevated level of cholesterol carried by circulating ApoB-containing lipoproteins (non-high-density lipoprotein cholesterol and LDL-C) is a root cause of atherosclerosis.
2. Reducing elevated levels of atherogenic cholesterol will lower ASCVD risk in proportion to the extent that atherogenic cholesterol is reduced. This benefit is presumed to result from atherogenic cholesterol lowering through multiple modalities, including lifestyle and drug therapies.
3. The intensity of risk-reduction therapy should generally be adjusted to the patient's absolute risk for an ASCVD event.

Jacobson TA et al. National lipid association recommendations for patient-centered management of dyslipidemia: Part 1--full report. *J Clin Lipidol*. 2015; 9: 129-169.

National Lipid Association Recommendations (2014)

Major conclusions (cont'd)

4. Atherosclerosis is a process that often begins early in life and progresses for decades before resulting a clinical ASCVD event. Therefore, both intermediate-term and long-term or lifetime risk should be considered when assessing the potential benefits and hazards of risk-reduction therapies.
5. For patients in whom lipid-lowering drug therapy is indicated, statin treatment is the primary modality for reducing ASCVD risk.
6. Non-lipid ASCVD risk factors should also be managed appropriately (high BP, cigarette smoking, and diabetes mellitus).
7. The measurement and monitoring of atherogenic cholesterol levels remain an important part of a comprehensive ASCVD prevention strategy.

Jacobson TA et al. National lipid association recommendations for patient-centered management of dyslipidemia: Part 1--full report. *J Clin Lipidol*. 2015; 9: 129-169.

2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk

"The ACC recognized that clinicians and patients may seek firmer and more specific guidance on the adequacy of statin therapy and whether or when to use non-statin therapies if response to statins is deemed inadequate."

Lloyd-Jones DM et al. 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk. 2016. *J Am Coll Cardiol*; XX-XXX-XX.

"The Committee therefore judged that it was appropriate to provide levels of LDL-C, or "thresholds", ***in terms of both percentage LDL-C reduction from baseline and absolute on-treatment LDL-C measurement, which, if not achieved by adherent patients, would serve as factors to consider in decision making regarding further therapy.***

The Writing Committee emphasizes that these are not firm triggers for adding medication but factors that may be considered within the broader context of an individual patient's clinical situation."

Lloyd-Jones DM et al. 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk. 2016. *J Am Coll Cardiol*; XX-XXX-XX.

Expert Consensus Decision Pathway addresses current gaps in care for LDL-C lowering to reduce ASCVD risk

1. In what patient populations should non-statin therapies be considered?
2. In what situations should non-statin therapies be considered, i.e., when is the amount of LDL-C lowering (percent LDL-C reduction or LDL-C range achieved on therapy) less than anticipated, less than desired, or inadequate, and which treatment options should be considered in patients who are truly statin intolerant?
3. If non-statin therapies are to be added, which agents or therapies should be considered and in what order?

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Strategies and non-statin agents considered for management of LDL-related ASCVD risk

- Both PCSK9i and ezetimibe included as add-on Rx
- Refer to lipid specialist
- Ezetimibe
  - Monotherapy: 18%
  - Combination therapy with statin (incremental reduction): 25%
- PCSK9i effects on LDL-C
  - Combination therapy - **Alirocumab** (75 mg and 150 SQ every 2 weeks) with maximally tolerated statin (incremental reduction): **43%** and **47%**, respectively
  - Combination therapy - **Evolocumab** (140 mg every 2 weeks and 420 mg SQ every 4 weeks) with maximally tolerated statin (incremental reduction): **64%** and **58%**, respectively

Lloyd-Jones DM et al. 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk. 2016. *J Am Coll Cardiol*; XX-XXX-XX.

Additional considerations: Strategies and non-statin agents considered for management of LDL-related ASCVD risk

- Bile acid sequestrants
- Phytosterols
- Soluble/viscous fiber
- Mipomersen
- Lomitapide
- LDL apheresis

Lloyd-Jones DM et al. 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk. 2016. *J Am Coll Cardiol*; XX-XXX-XX.

The single common denominator in ALL Cholesterol Guidelines brings us back to where we started:

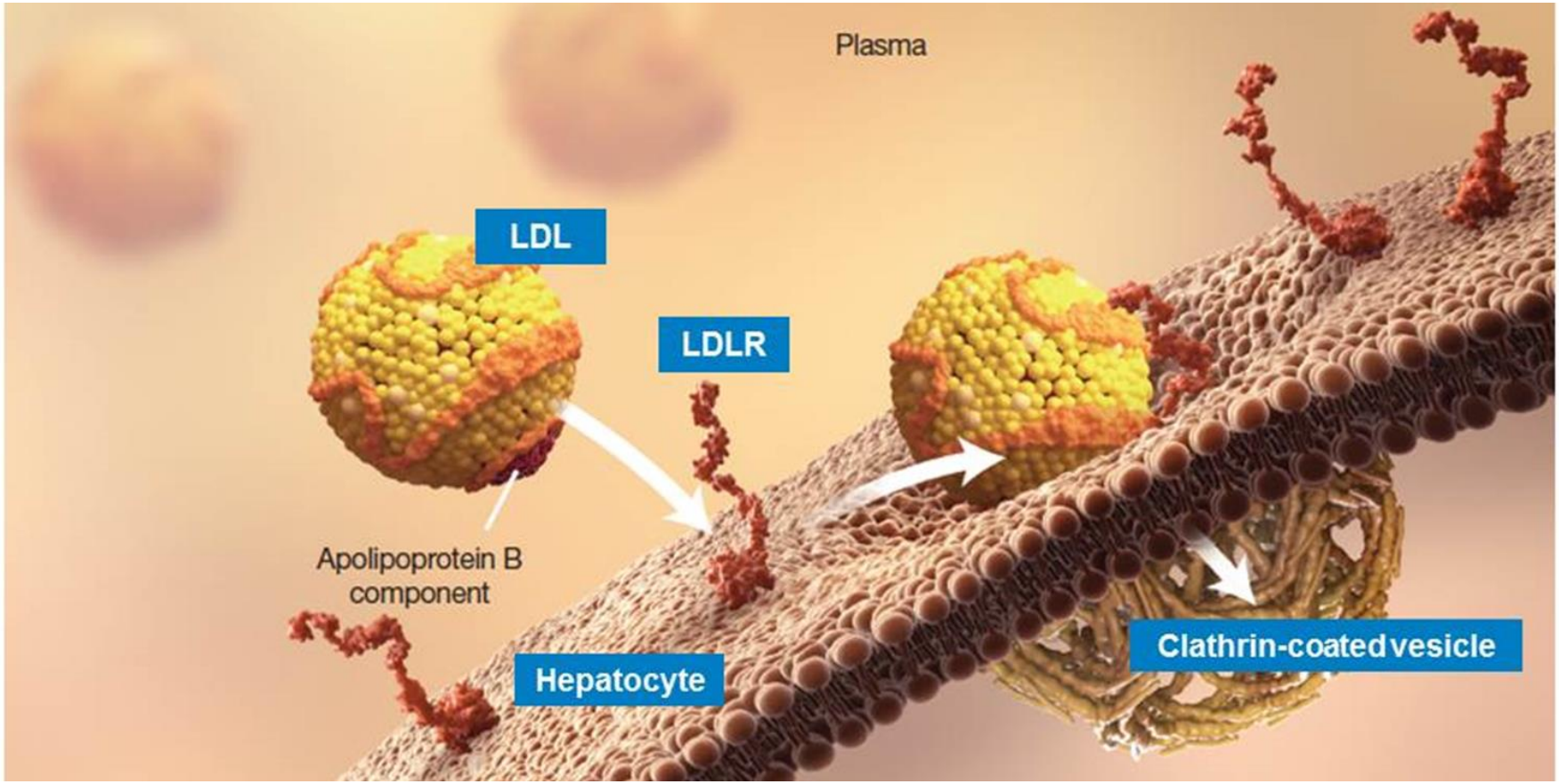
- LDL is causally related to ASCVD
- LDL is our central target in lipid-related risk reduction
- Wipe “LDL Hypothesis” from our Lexicon

PCSK9 Inhibitors: A revolution in lipid control

A new era of LDL-C reduction: PCSK9i

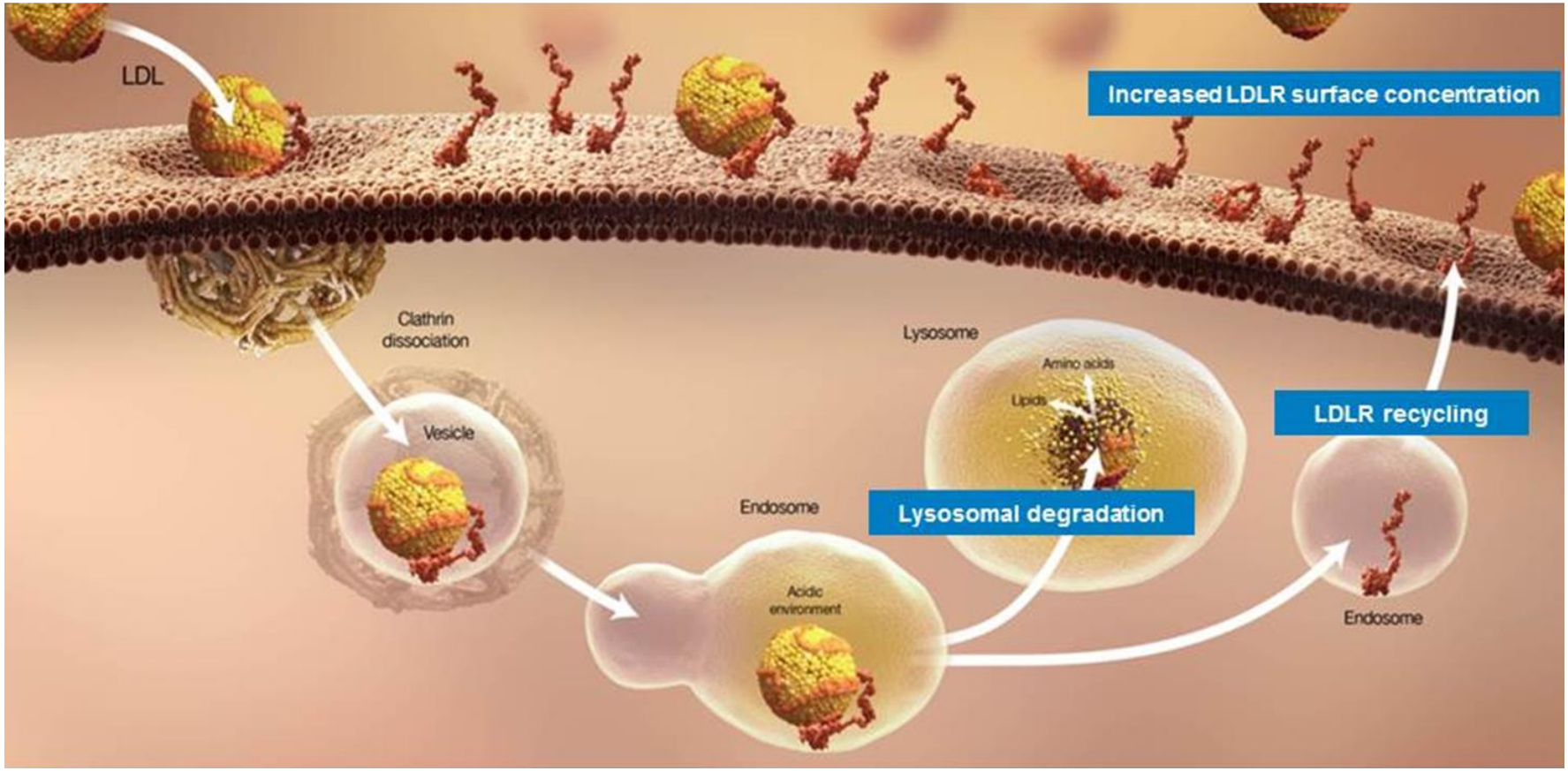
- **Evolocumab** and **Alirocumab**
  - Both are monoclonal antibodies that bind to PCSK9 and inhibit its interaction with LDL receptors
  - When PCSK9 binds to the LDL receptor, the receptor is degraded and can no longer remove LDL cholesterol from the blood.
  - If PCSK9 is blocked, more LDL receptors will be present on the surface of the liver and will remove more LDL cholesterol from the blood.
  - Both FDA approved for clinical ASCVD & HeFH when maximally tolerated statin is insufficient

Hepatic LDLRs play a central role in cholesterol homeostasis



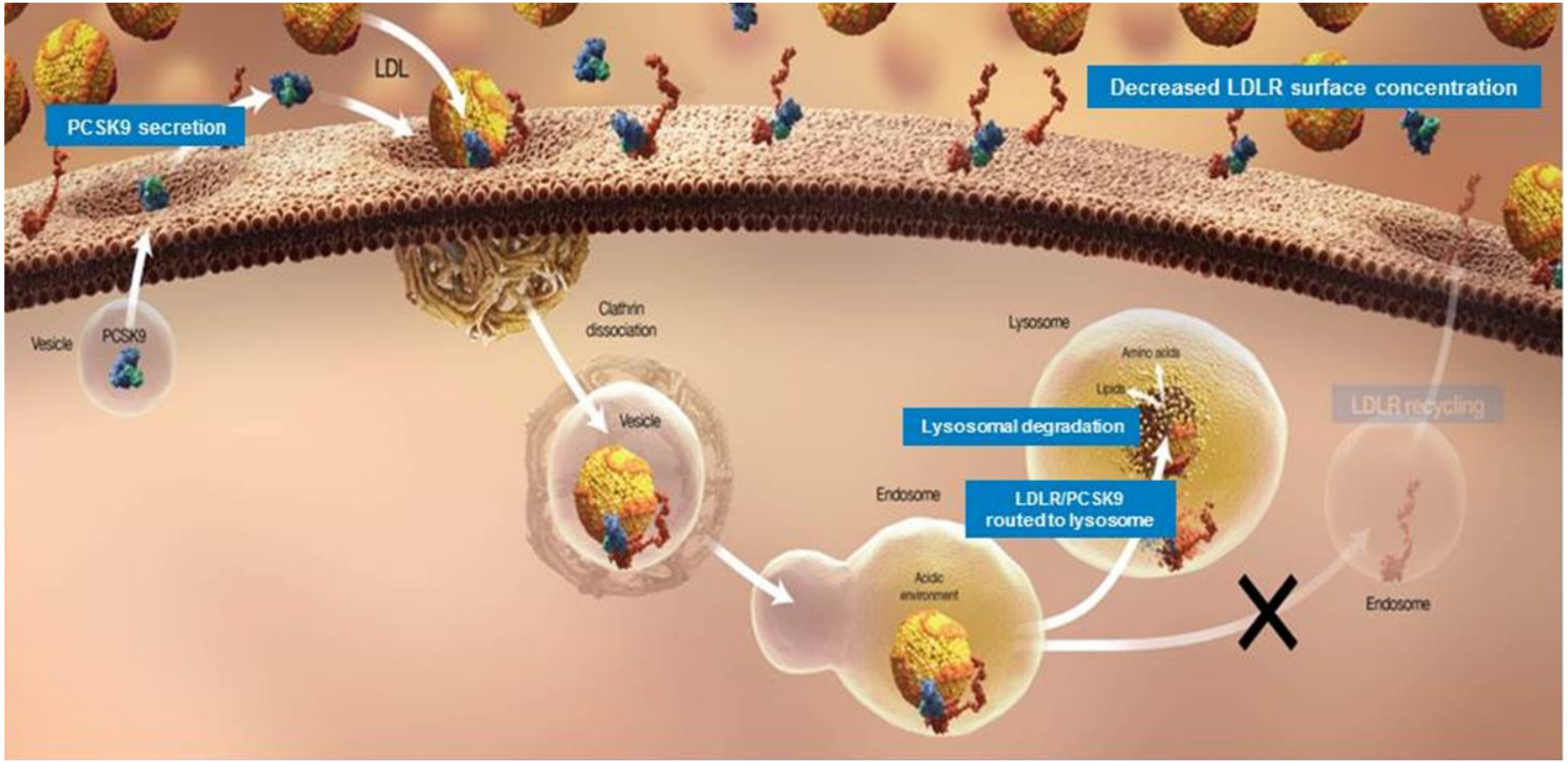
Steinberg D et al. *Proc Natl Acad Sci*. 2009; 106: 9546-9547.
Brown MS et al. *J Lipid Res*. 2009; 50: S15-S27.

Recycling of LDLRs enables efficient clearance of LDL-C particles



Steinberg D et al. *Proc Natl Acad Sci*. 2009; 106: 9546-9547.
Goldstein JL et al. *Arterioscler Thromb Vasc Biol*. 2009; 29: 431-438.
Brown MS et al. *Proc Natl Acad Sci*. 1979; 76: 3330-3337.

PCSK9 regulates the surface expression of LDLRs by targeting them for lysosomal degradation

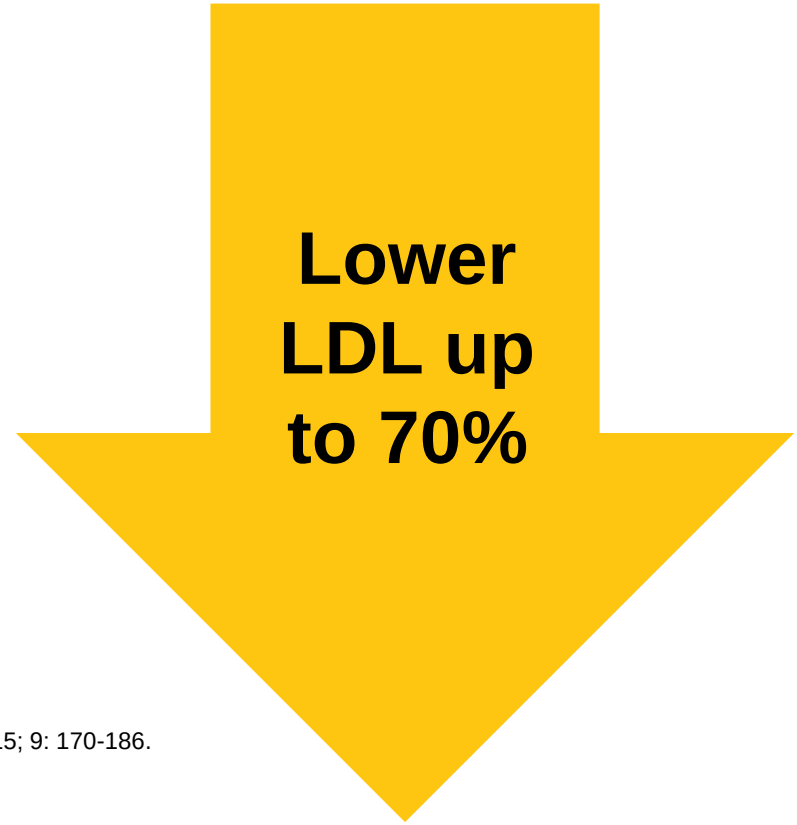


Qian YW et al. *J Lipid Res*. 2007; 48: 1488-1498.
Horton JD et al. *J Lipid Res*. 2009; 50: S172-S177.
Brown MS et al. Proc Natl Acad Sci. 1979; 76: 3330-3337.
Steinberg D et al. *Proc Natl Acad Sci*. 2009; 106: 9546-9547.
Goldstein JL et al. *Arterioscler Thromb Vasc Biol*. 2009; 29: 431-438.
Zhang DW et al. *J Biol Chem*. 2007; 282: 18602-18612.

Both PCSK9i predictably and intensively reduce LDL-C alone or when added to statin therapy in short term studies

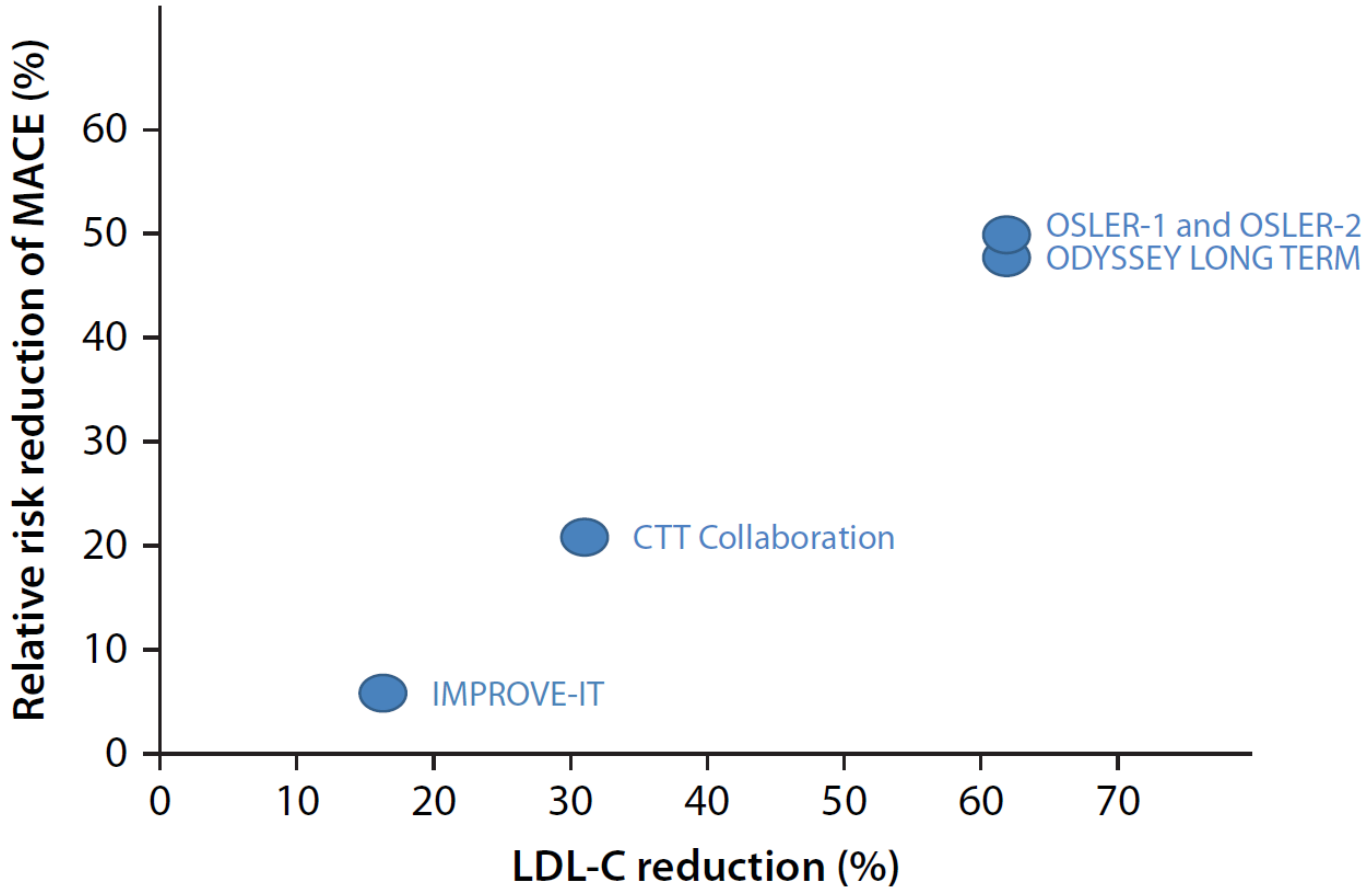
Acting Alone

Acting together with statins



McKenney JM. Understanding PCSK9 and anti-PCSK9 therapies. *J Clin Lipidol*. 2015; 9: 170-186.

Effectiveness of LDL-lowering therapies (statins, ezetimibe and PCSK9i)



Hassan M. *Global Cardiology Science and Practice. 2015: 20:.*

PCSK9i are effective; yet, there is enormous insurance pushback

- Despite being effective at lowering LDL-C, PCSK9i are expensive (theoretically cost roughly $14,000/year).
- Insurance barriers are among the top reasons for not prescribing the PCSK9 inhibitors
  - Either insurer does not cover one or both drugs, or
  - Insurer requires patients to first try other medicines (prior authorization)
  - To date, 90% of prescriptions have been denied!

Where does this leave us?

Conclusions: PCSK9i and current guidelines

- LDL is causally related to ASCVD
- To date, statin therapies have proved to be a cost-effective approach to lowering LDL-C and reducing ASCVD risk
- All Guidelines are LDL-centric, and with good reason. However, the Guidelines are not harmonized, are in flux, and always lag the literature.
- While the most effective at reducing LDL-C, the prescribing of PCSK9i is being battled by insurance providers. But, the ACC now includes them and soon we will have outcomes trials…

Conclusions: PCSK9i and current guidelines

- PCSK9i - and other emerging therapies - will never neutralize the cholesterol guidelines, but they certainly do change their value…
  - LDL is now known to cause ASCVD
  - Lower LDL translates into lower risk
  - PCSK9i are the most effective LDL lowering therapy available
  - PCSK9i outcomes data are on the way
  - We will all want to prescribe PCSK9i

  So, guidelines will always have a place, though that place is becoming more and more nebulous and less and less defining for doctors. Biology and pathophysiology are gaining ground.

  N.B. Insurance providers on the other hand do use Guidelines to their advantage so we must be careful when writing them.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