

West Webinar:

Optimizing HCP/Patient Conversation About the Importance of LDL-C Lowering for Patients With Recent MI

This disease awareness program is presented on Amgen's behalf, and has been reviewed consistent with Amgen's internal review policies.

Agenda

- Role of Interventional Cardiologist and General Cardiologist in the Acute Setting
- Multiple Contact Points During the Patient Journey
- Patient Education

Role of Interventional Cardiologist and General Cardiologist in the Acute Setting



RJ is a 66 yo male who presented to the ER with chest pain, SOB, and back pain

He is admitted to the ER →
diagnosed with STEMI



Initiated on: oxygen, antiplatelet therapy, anticoagulation, pain medication, nitrates, and beta-blockers

Taken to Cath Lab for PCI

PMHx: NSTEMI (2018); hypertension; dyslipidemia; BMI = 30 kg/m²

Relevant Medications: Maximally tolerated statin and ACEi (same dose for the past 5 years)

Pertinent Labs (4 months ago): TC 158 mg/dL, TG 165 mg/dL, HDL-C 40 mg/dL,
LDL-C 107 mg/dL, A1C 5.5%, BP: 122/83

PCI = percutaneous intervention.

Communication Between RJ and His Cardiologists

In-hospital Care

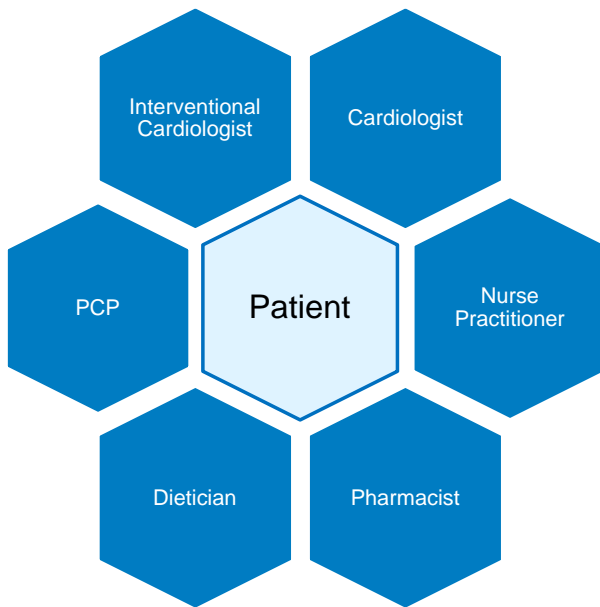
- RJ was admitted
- He underwent PCI
- Cardiac cocktail (anti-coagulant/anti-platelet, BP, cholesterol, nitrates, beta-blockers)
- **Interventional cardiologist can help begin to educate on:**
 - why the MI occurred
 - explain how PCI and medications are helping the patient
 - explain the role of LDL-C and the link to atherosclerosis and MI

Interventional cardiologist and treating cardiologist work together to educate the patient

- After procedure, patient is referred to treating cardiologist
- Treating cardiologist will prescribe discharge medication regimen and set up follow up appointments to ensure patient compliance
- **Treating cardiologist serves as a second touch point and has the opportunity to reiterate:**
 - why the MI occurred and how to help prevent a future event
 - reason for discharge medication and why compliance is important
 - reemphasize the role of LDL-C and the link to atherosclerosis and MI

Multiple Contact Points During the Patient Journey

Several HCPs Took Care of RJ on His Road to Recovery



There are Several Points in the Patient Journey Where HCPs Can Emphasize the Importance of Lowering LDL-C to Help Prevent a Future Event

In-hospital Care¹

- Managed by **interventional cardiologist** then transitioned to a **treating cardiologist**

Hospital Discharge¹

- Patient receives discharge summary & brochures
- **Advanced practice providers (NP/Pharmacist)** will review discharge notes and medications with patient
- Patient may receive **referral to cardiac rehab and/or lipid clinic**

Follow up^{1,2}

- Patient typically sees **treating cardiologist** (after 2-3 weeks, 3 months, 6 months, 12 months)
- Care may then be transitioned to **PCP** after 12 months
- Patient may continue **cardiac rehab and/or management at lipid clinic**

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Patient Education

Important Topics to Reiterate With Patients

- Link between lowering LDL-C, atherosclerosis and MI
- Imaging - “A picture is worth a thousand words”
- Guideline recommended treatment for lowering LDL-C
- Physiology of Low LDL-C

Reviewing Risk Factors With the Patient

RJ is a 66 yo male with hx of NSTEMI (2018), hypertension, hyperlipidemia, hospitalized for STEMI

LDL-C 107 mg/dL on maximally tolerated statin

Very High-Risk ASCVD

Includes history of multiple major ASCVD events, or 1 major event and multiple high-risk conditions

Major ASCVD Events

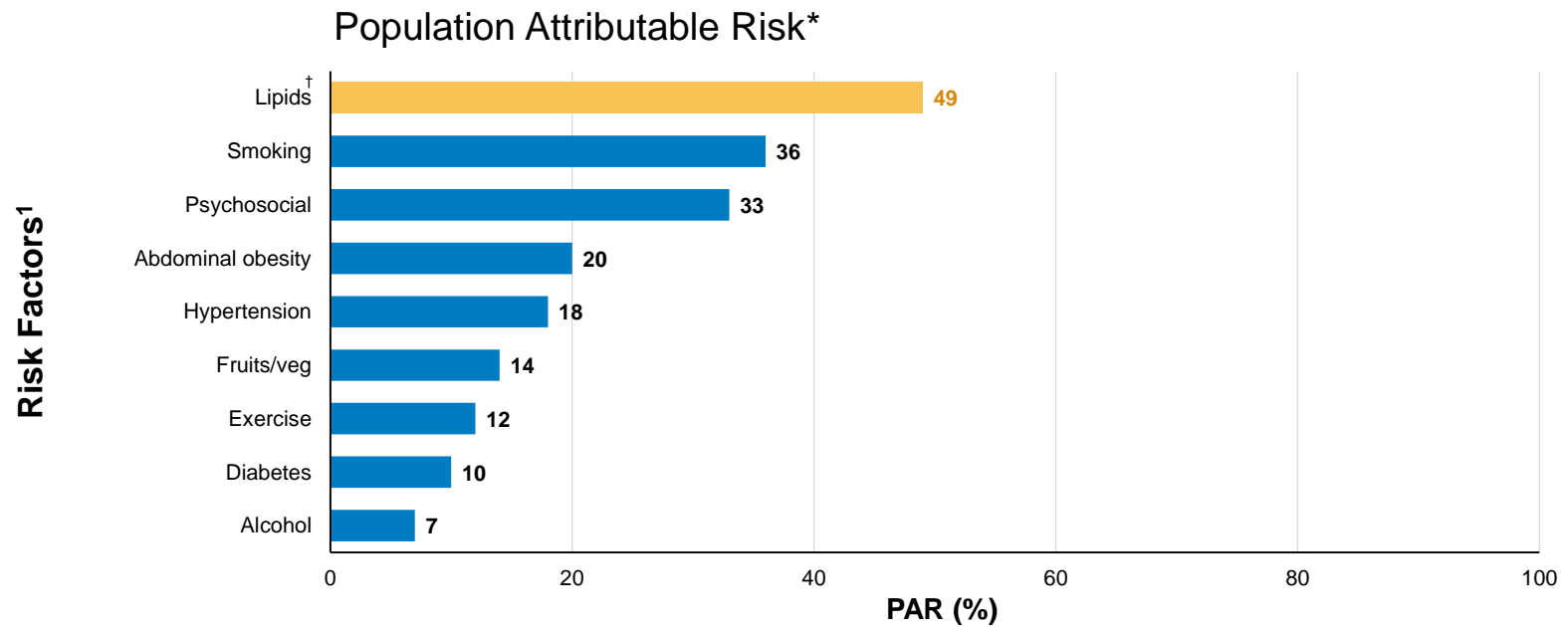
- Recent ACS (within past 12 months)
- History of MI (other than recent ACS event above)
 - History of ischemic stroke
 - Symptomatic PAD (history of claudication with ABI < 0.85, or previous revascularization or amputation)

High-Risk Conditions

- Age \geq 65 years
 - Heterozygous FH
 - Prior CABG or PCI outside of major ASCVD event(s)
 - Diabetes mellitus
 - History of congestive HF
- Hypertension
 - CKD (eGFR 15-59 mL/min/1.73m²)
 - Currently smoking
 - Persistent LDL-C \geq 100 mg/dL despite maximal tolerated statin therapy and ezetimibe

RJ is Very High-Risk ASCVD

Lipids Are One of the Most Critical Modifiable Risk Factors for an Acute MI¹



INTERHEART: 9 modifiable factors account for 90% of first-MI risk worldwide, N = 15,152 patients and 14,820 controls in 52 countries.¹ *Proportional reduction in population disease that would occur if exposure to a risk factor were reduced to an alternative ideal exposure scenario (eg. no tobacco use).² [†]Lipids = ApoB/ApoA1 Ratio.¹

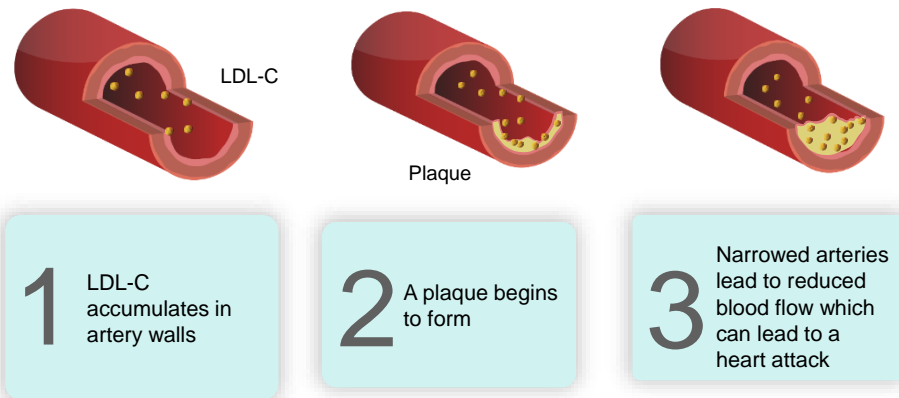
1. Yusuf S, et al. *Lancet*. 2004;364:937-952. 2. World Health Organization. https://www.who.int/healthinfo/global_burden_disease/metrics_paf/en/. Accessed October 7, 2019.

Example Patient Education Slide: Link Between LDL-C, Atherosclerosis and MI

What is LDL-C and Why Treat It?

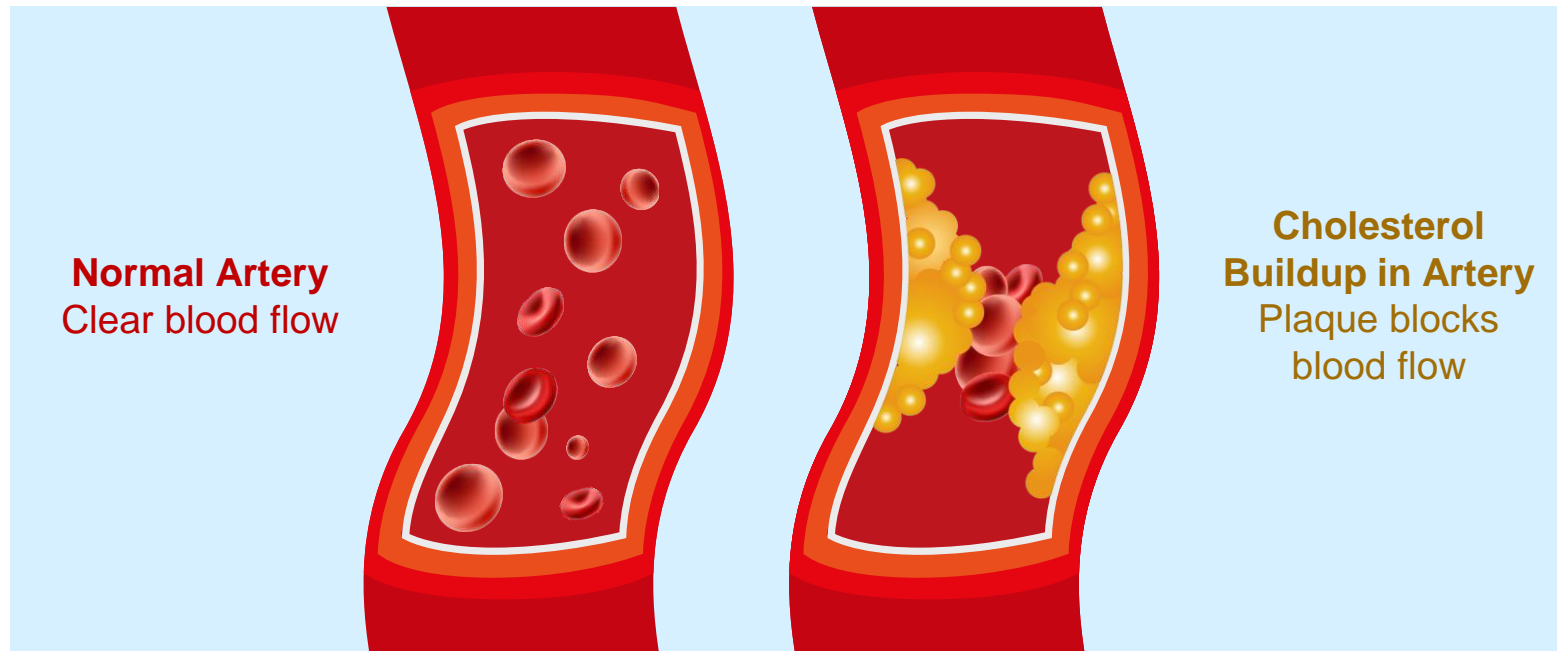
LDL-C is often called “bad cholesterol”

- Builds up in the walls of your arteries and forms plaque
- Plaque reduces blood flow through your arteries (the blood vessels that carry blood from your heart to other parts of the body)
- Restriction of blood flow puts you at risk of a heart attack, stroke, stent, open heart surgery, or other heart problems



Example Patient Education Visual Animation: Link Between LDL-C, Atherosclerosis and MI^{1,2}

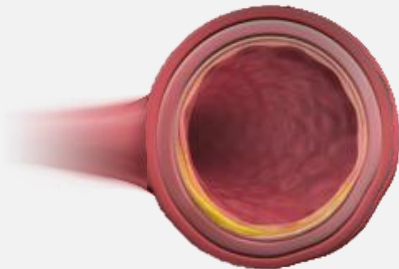
What Happens in Your Vessels When You Have Too Much Bad Cholesterol?



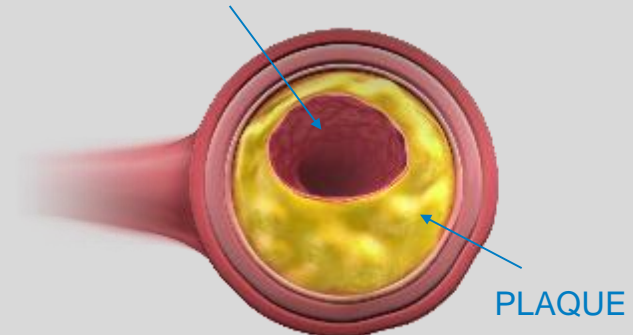
1. Grundy SM, et al. *J Clin Lipidol*. 2014;8:29-60. 2. Mayo Clinic. www.mayoclinic.org. Accessed September 26, 2019.

Link Between LDL-C, Atherosclerosis and MI

NORMAL BLOOD FLOW

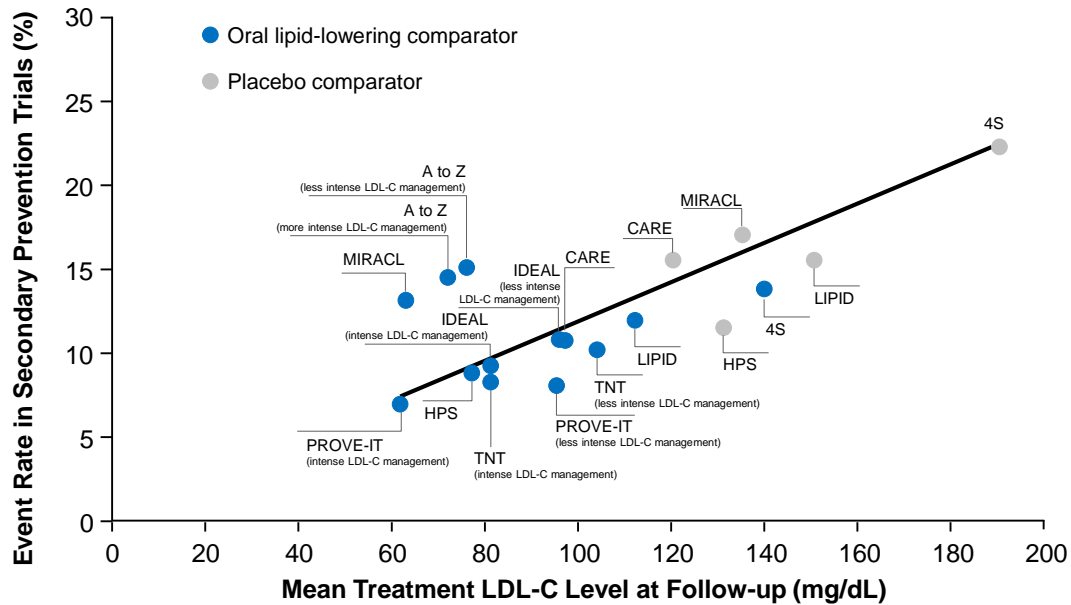


SIGNIFICANT NARROWING OF ARTERY



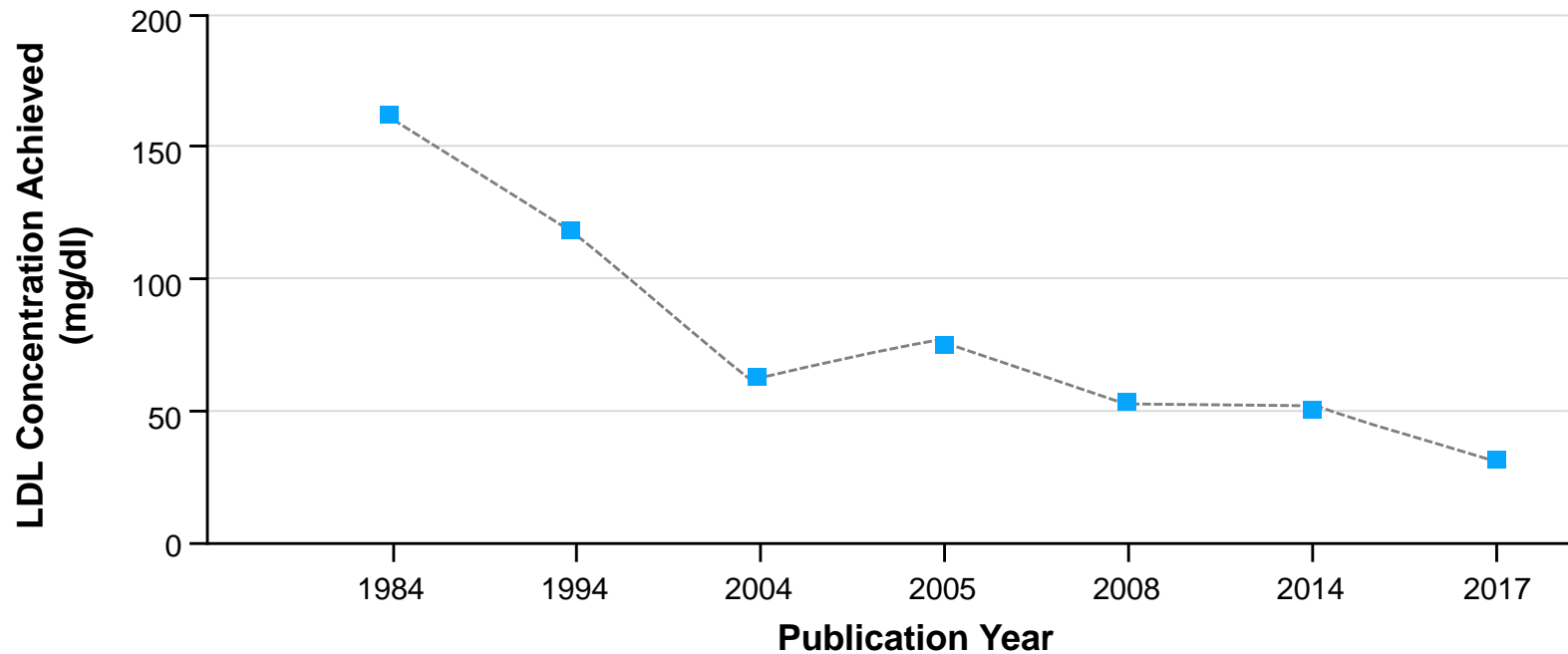
There Is a Linear Correlation Between LDL-C Lowering and Lowering Risk of CV Events in Statin Trials^{1,2}

CTTC Meta-analysis of major lipid secondary prevention statin trials conducted in 2010:
Median follow-up ~ 5 years, N = 169,138²



1. Raymond C, et al. *Clev Clin J Med*. 2014;81:11-19. 2. Cholesterol Treatment Trialists' (CTT) Collaboration. *Lancet*. 2010;376:1670-1681.

Lipid-Lowering Trials Over The Years Have Achieved Progressively Lower LDL-C Levels

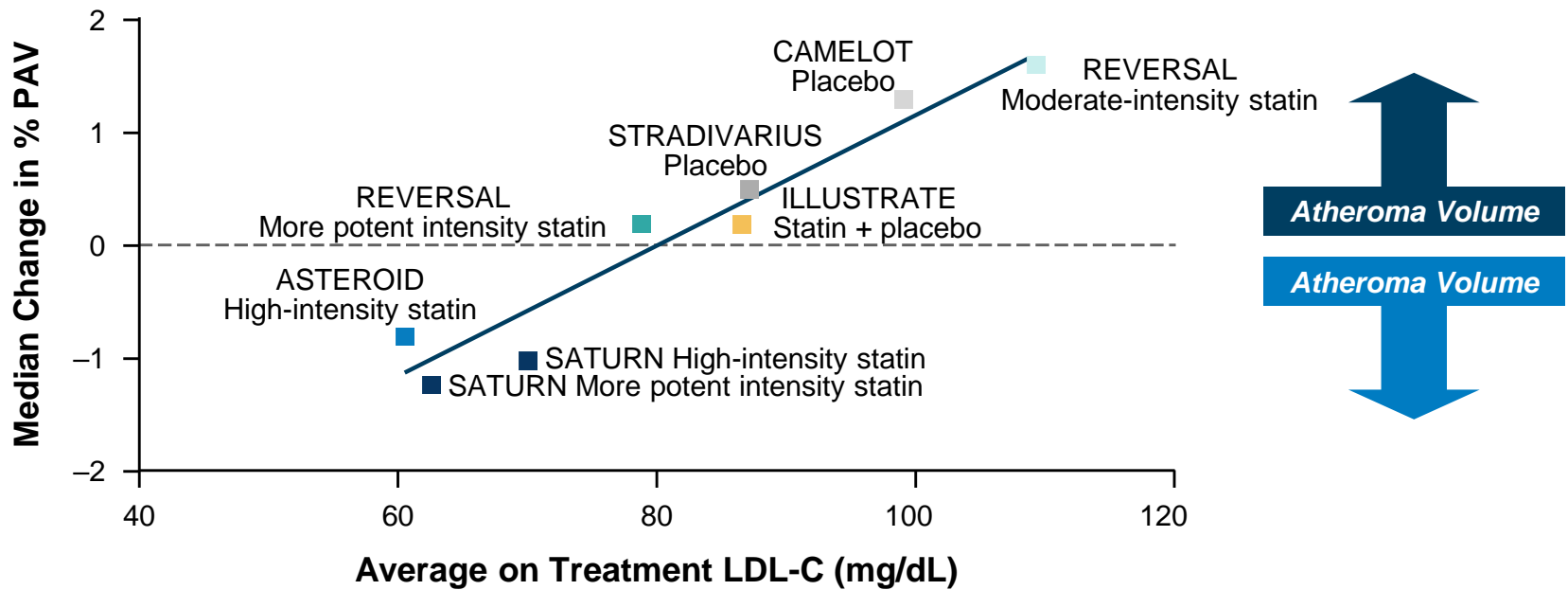


LDL-C values from the Lipid Research Clinics are extrapolated from total cholesterol. Mean LDL-C decrease obtained in the study. LDL-C values from the Lipid Research Clinics (LRC) are extrapolated from total cholesterol.

Studies include: LRC, 4S, PROVE-IT, TNT, JUPITER, IMPROVE-IT, Recent CV Outcomes Trial.

Modified from Masana L, et al. *J Clin Lipidol*. doi: 10.1016/j.jacl.2017.12.018.

Reductions in Plaque Volume Have Been Shown With LDL-C Lowering



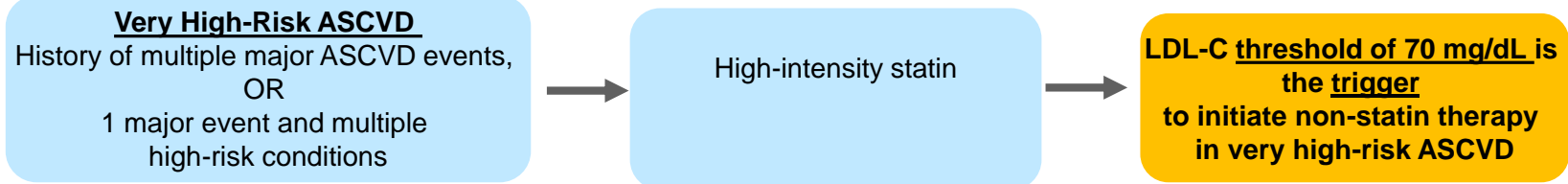
Median changes in PAV vs average on-treatment LDL-C in serial coronary IVUS trials.

Reviewing Guideline Recommended Treatment With the Patient

RJ is a 66 yo male with hx of NSTEMI (2016), hypertension, hyperlipidemia, hospitalized for STEMI

LDL-C 107 mg/dL on maximally tolerated statin

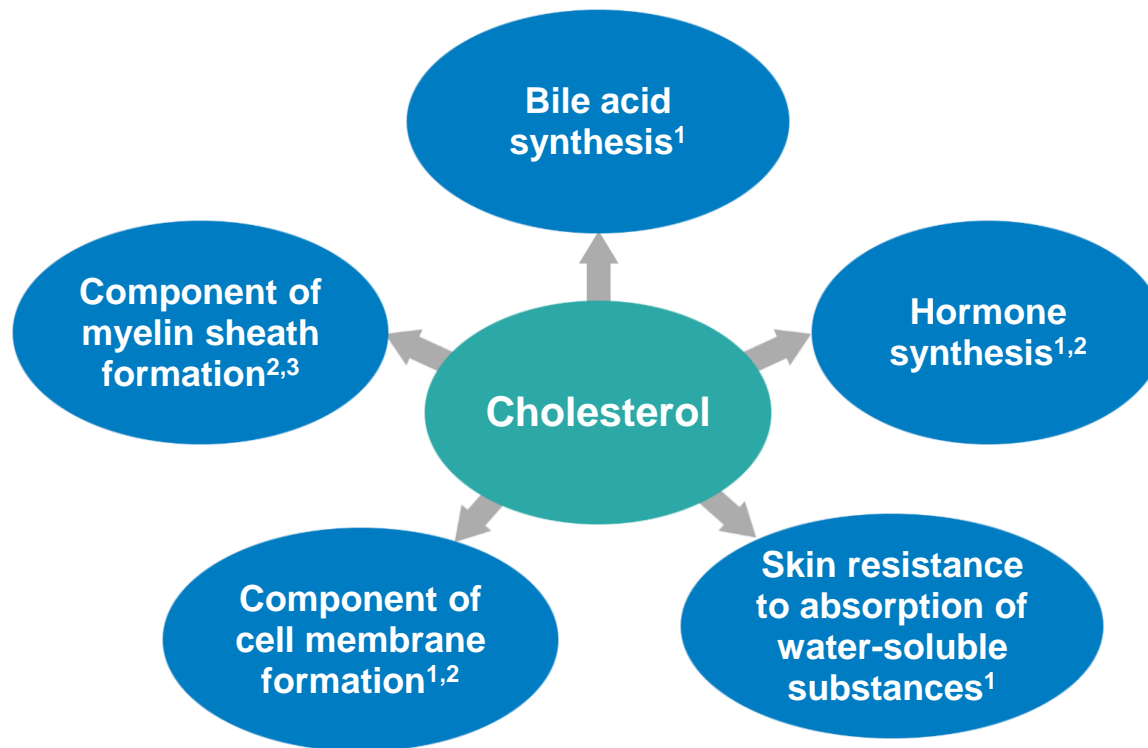
2018 ACC/AHA Multi-Society Guideline Overview of Cholesterol Management



Since LDL-C is ≥ 70 mg/dL, consider addition of non-statin therapy

Lower LDL-C is better

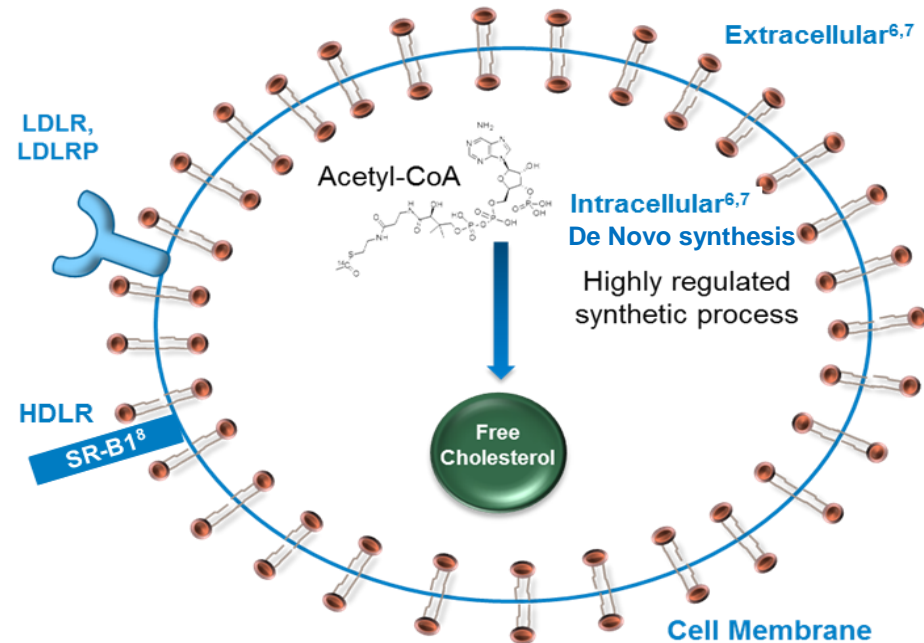
Cholesterol Plays a Role in Many Important Physiologic Functions



1. Hall JE, et al. In: *Guyton and Hall Textbook of Medical Physiology*. 12th ed. Philadelphia, PA: Saunders; 2011:819-830.
2. Goldstein JL, et al. *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 pathways¹⁻⁵
- Systemic distribution of cholesterol is important, but cells are not entirely dependent on systemic LDL-C^{3,4}

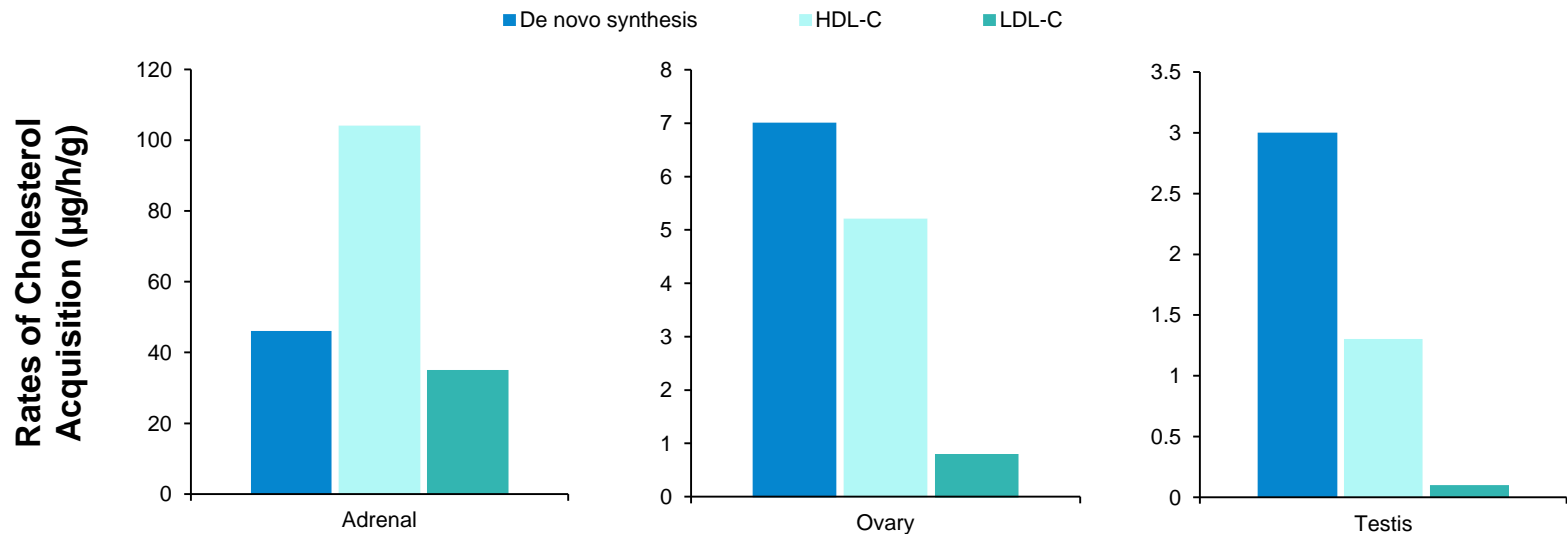


1. McAuley MT, et al. *BMC Syst Biol*. 2012;6:130 doi 10.1186/1752-0509-6-130. 2. Xie C, et al. *J Lipid Res*. 2006;47:953-963.

3. Hu J, et al. *Nutr Metab (Lond)*. 2010;7:47. 4. Orth M, et al. *Cholesterol*. 2012;2012:292598. 5. Dietschy JM, et al. *J Lipid Res*. 2004;45:1375-1397. 6. Hall JE, et al. In: *Guyton and Hall Textbook of Medical Physiology*. 12th ed. 2011:819-830. 7. McAuley MT, et al. *BMC Syst Biol*. 2012;6:130 doi 10.1186/1752-0509-6-130. 8. Dietschy JM, et al. *J Lipid Research*. 2004;45:1375-1397.

Animal Data Demonstrate Steroidogenic Tissues Predominantly Acquire Cholesterol Via HDL-C and De Novo Synthesis¹⁻³

Rates of cholesterol acquisition from *de novo* synthesis, HDL-C and LDL-C^{1,*}



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

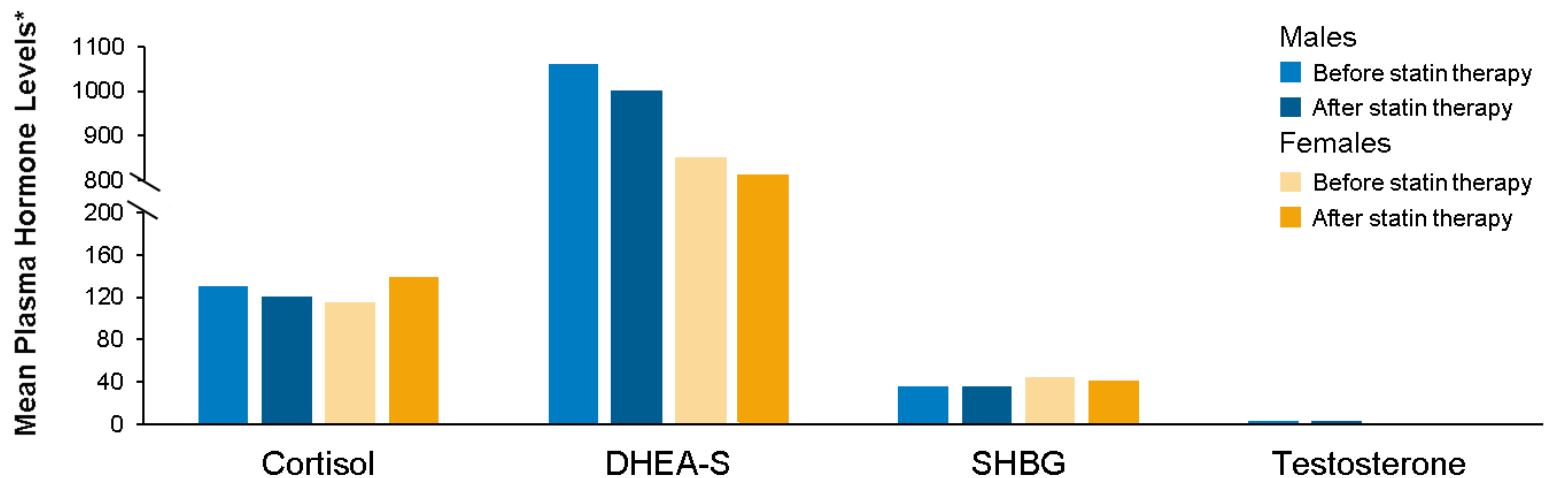
1. Xie C, et al. *J Lipid Res.* 2006;47:953-963. 2. Hu J, et al. *Nutr Metab (Lond).* 2010;7:47. 3. Bochem AE, et al. *J Lipid Res.* 2013;54:1698-1704.

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

Plasma Hormone Levels Before and 3 Months After Treatment with Statin¹



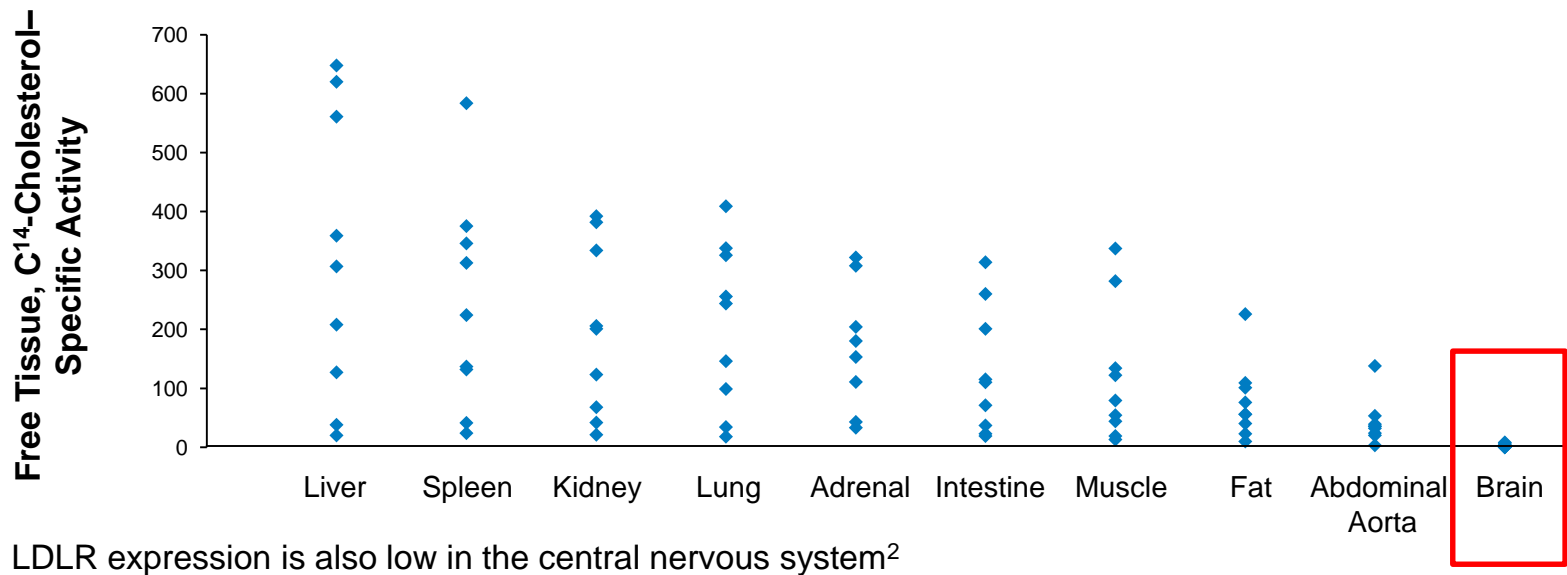
- Reduction in LDL-C with statins without changing steroid hormones has been consistently shown¹⁻³

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

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.

In the Central Nervous System, Cholesterol Is Predominantly Obtained by De Novo Synthesis

Postmortem Analysis of Equilibration of Tissue Cholesterol Following Intravenous Injection of C¹⁴-Cholesterol in Nine Hospitalized Patients^{1,*}

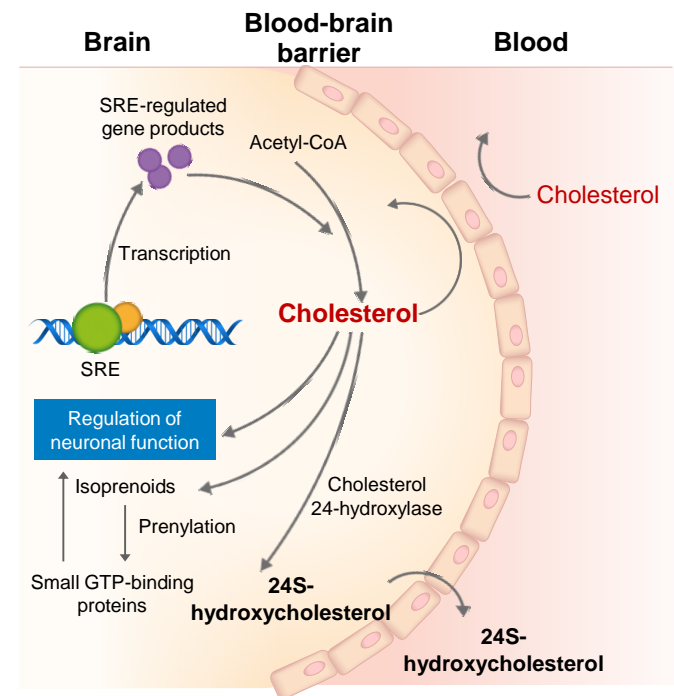


*Patients had no evidence of hypercholesterolemia, DM, thyroid dysfunction, or the nephrotic syndrome.

1. Chobanian A, et al. *J Clin Invest.* 1962;41:1732-1737. 2. The Human Protein Atlas. <https://www.proteinatlas.org/ENSG00000130164-LDLR/tissue>. Accessed October 7, 2019.

The Central Nervous System Predominantly Synthesizes Cholesterol De Novo

- Cholesterol is a major component of the CNS^{1,2}
 - The CNS predominantly synthesizes cholesterol de novo^{1,2}
 - The BBB prevents the uptake of systemic lipoprotein cholesterol from atherogenic lipoproteins^{2,3}
 - However, HDL does appear to cross the BBB³
 - This segregation ensures that cholesterol metabolism within the brain is isolated from changes in the circulating lipid levels due to diet or medication²



1. Björkhem I, et al. *Arterioscler Thromb Vasc Biol.* 2004;24:806-815. 2. Katsuno M, et al. *Nat Med.* 2009;15:253-254.
3. Wang H, et al. *Trends Endocrinol Metab.* 2014;25:8-14.

Case Studies of Genetic Loss of Function Mutations Appear Healthy

Compound Heterozygotes (Homozygote Phenotype)

PCSK9 Compound
Heterozygote^{1,*}

Female
Age: 32 years

TC: 96 mg/dL
LDL-C: 14 mg/dL

PCSK9 Compound
Heterozygote²

Female
Age: 21 years

TC: 85 mg/dL
LDL-C: 15 mg/dL

Case studies of healthy asymptomatic individuals with extremely low LDL-C levels

*Apparently healthy, fertile, normotensive, college-educated woman with normal liver and renal function tests (including urinalysis) who works as an aerobics instructor.
1. Zhao Z, et al. *Am J Hum Genet.* 2006;79:514-523. 2. Hooper AJ, et al. *Atherosclerosis.* 2007;193:445-448.

Thank You!

Abbreviations

- ABI = ankle-brachial index
- ACC = American College of Cardiology
- ACEi = angiotensin-converting enzyme inhibitor;
- ACS = acute coronary syndrome
- AHA = American Heart Association
- ASCVD = atherosclerotic cardiovascular disease
- BBB = blood-brain barrier
- BMI = body mass index
- BP = Blood pressure
- CABG = coronary artery bypass graft
- CKD = chronic kidney disease
- CNS = central nervous system
- CTTC = Cholesterol Treatment Trialists' Collaboration
- CV = cardiovascular
- DHEA-s = dehydroepiandrosterone sulfate
- eGFR = estimated glomerular filtration rate
- ER = emergency room
- FH = familial hypercholesterolemia
- GTP = guanosine triphosphate
- HCP = healthcare professional
- HDL = high-density lipoprotein
- HDL-C = high-density lipoprotein cholesterol
- HDLR = HDL receptor
- HF = heart failure
- Hx = history
- IVAS = intravascular ultrasound
- LDL = low-density lipoprotein
- LDL-C = low-density lipoprotein cholesterol
- LDLR = LDL receptor
- LDLRP = LDLR protein
- MI = myocardial infarction
- mo = month
- NP = Nurse Practitioner
- NSTEMI = Non-ST-elevation myocardial infarction
- PAD = peripheral artery disease
- PAR = population attributable risk
- PAV = percent atheroma volume
- PCI = percutaneous coronary intervention
- PCP = Primary Care Physician
- PMHx = patient medical history
- SHBG = sex hormone binding solution
- SOB = shortness of breath
- SR-B1 = scavenger receptor class B type 1
- SRE = sterol regulatory element =
- STEMI = ST-elevation myocardial infarction
- TC = total cholesterol
- TG = triglyceride
- wk = week
- y = year

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