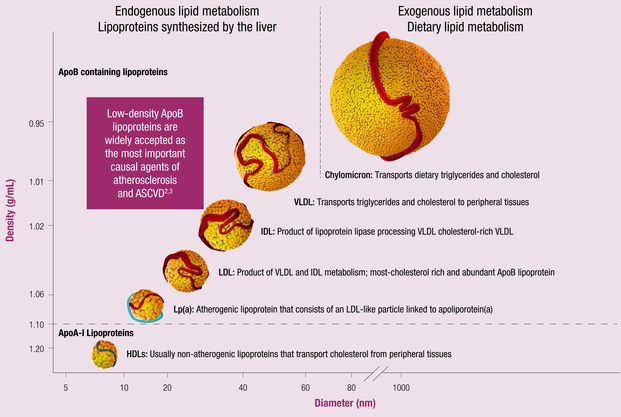
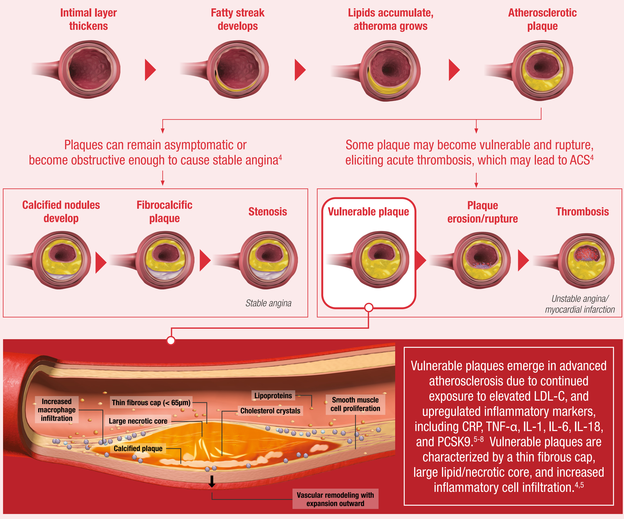
The Science and Clinical Management of ASCVD

Cholesterol-rich ApoB Lipoproteins Are Responsible For Atherosclerotic Plaque Formation[1-3]



Atherogenic lipoproteins cause atherosclerosis by infiltrating the arterial wall, which leads to arterial inflammation, endothelial dysfunction and plaque formation[1-3]

Progression of Atherosclerosis and ASCVD[4]



Vulnerable plaques emerge in advanced atherosclerosis due to continued exposure to elevated LDL-C, and upregulated inflammatory markers, including CRP, TNF-α, IL-1, IL-6, IL-18, and PCSK9.[5-8] Vulnerable plaques are characterized by a thin fibrous cap, large lipid/necrotic core, and increased inflammatory cell infiltration.[4,5]

LDL-C Is A Major Modifiable Risk Factor For Cardiovascular Events[1-3]

More can be done to achieve lower LDL-C levels to reduce the risk of CV risk in ASCVD patients.

In Statin Trials, LDL-C Reduction is Proportional to a Decrease in the Incidence of CV Events[9]
There was a proportional **21% reduction** in major CV events per each **39 mg/dL** (1 mmol/L) LDL-C reduction in patients with CHD[9]

Many ASCVD Patients Do Not Achieve Recommended LDL-C Levels[10]

Among ASCVD patients on LLT followed over a 2-year period in GOULD registry (N = 5,006)[10]:

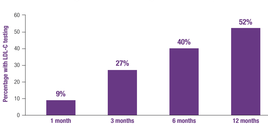
Only 32% of patients achieved LDL-C < 70 mg/dL and only **15% achieved** LDL-C < 55 mg/dL

Lipid-lowering therapy intensification occurred in **17% of patients**

21% of patients had only one lipid panel in 2 years, and **11% did not have** a lipid panel

Even in Patients with Prior MI, Lipid Testing and LDL-C Levels Remain Suboptimal[11,12]

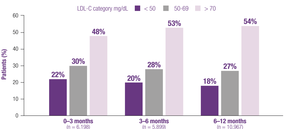
LDL-C Testing Rates Following Post-MI Hospitalization[11]



Only **50%** of patients received LDL-C testing in the year following MI hospitalization

Retrospective study (N = 389,367) using claims data from a large US population with Medicare supplemental or commercial insurance.

LDL-C Distribution by Recency of MI[12]



Only **45%** of patients achieved LDL-C levels < 70 within 6-12 months

Retrospective cohort study (N = 22,807) using the Medicare fee-for-service claims linked to the Prognos LDL-C database.

Clinical Guidelines Define Patients Who Are at Increased Risk of CV Events and Advise Intensive LDL-C Lowering with Non-Statin Therapies[13-17]

2018 AHA/ACC Guidelines[13]

Very High-Risk ASCVD:

Multiple major ASCVD events
ACS < 12 months, history of MI (other than ACS event) or IS, symptomatic PAD

OR

1 major ASCVD event and multiple high-risk conditions
Age ≥ 65, heFH, history of CABG or PCI outside of major ASCVD events, DM, HTN, CKD, current smoker, persistently elevated LDL-C despite maximally tolerated statin therapy and ezetimibe, history of congestive HF

2019 ESC/EAS Guidelines[14]

Very High-Risk for ASCVD*:

Documented ASCVD, including previous ACS (MI or UA), stable angina, coronary revascularization†, stroke, TIA, and PAD

2017 AACE Guidelines[15,16]

Extreme Risk for ASCVD*:

Progressive ASCVD including UA, established clinical ASCVD plus diabetes or CKD ≥ 3 or heFH, history of premature ASCVD (< 55 y, male; < 65 y, female)

Very High-Risk for ASCVD*:

Established clinical ASCVD or recent hospitalization for ACS, carotid, or peripheral vascular disease

Statins are universally recommended as first-line therapy, followed by addition of non-statin therapies[14-17]

LDL-C *THRESHOLD* of 70 mg/dL
First goal to achieve ≥ 50% LDL-C reduction on maximally tolerated statin therapy[13]
Threshold = trigger to intensify therapy by using non-statin medications

LDL-C *GOAL* of < 55 mg/dL AND ≥ 50% reduction from baseline[14]
For patients with ASCVD who have recurrent events within 2 years, a lower LDL-C goal of < 40 mg/dL should be considered

LDL-C *GOAL* of < 55 mg/dL (extreme risk) AND < 70 mg/dL (very high-risk)[15,16]

2022 ACC Expert Consensus Decision Pathway[17]

Very High-Risk ASCVD:

LDL-C *THRESHOLD* of 55 mg/dL AND 50% reduction from baseline

Consider initiating non-statin therapies in very high-risk patients‡‡ with LDL-C ≥ **55 mg/dL** AND/OR < 50% LDL-C reduction from baseline on maximally tolerated statin therapy[11]

Not Very High-Risk ASCVD:

LDL-C *THRESHOLD* of 70 mg/dL AND 50% reduction from baseline

Consider initiating non-statin therapies in ASCVD patients not at very high risk with LDL-C of ≥ **70 mg/dL** AND/OR < 50% LDL-C reduction from baseline on maximally tolerated statin therapy[11]

‡‡Consider initiating non-statin therapies after evaluating and optimizing: lifestyle, adherence to guideline-recommended statin therapy, risk factor control and statin-associated side effects, and escalating to high-intensity statins if not already taking.

*Patients fall into the respective designation if they have one or more of the listed criteria. †PCI, CABG, and other arterial revascularization procedures. **Very high-risk patients have a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions, as previously defined in the 2018 AHA/ACC/Multi-Society cholesterol guideline.

AACE, American Association of Clinical Endocrinology; ACC, American College of Cardiology; ACS, acute coronary syndrome; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; Apo, apolipoprotein; CABG, coronary artery bypass grafting; CHD, coronary heart disease; CKD, chronic kidney disease; CT, computed tomography; CRP, C-reactive protein; CV, cardiovascular; DM, diabetes mellitus; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; FH, familial hypercholesterolemia; GOULD, Getting to an Improved Understanding of Low-Density Lipoprotein Cholesterol and Dyslipidemia Management; HDL, high-density lipoprotein; HF, heart failure; heFH, heterozygous familial hypercholesterolemia; HTN, hypertension; IDL, intermediate-density lipoprotein; IL, interleukin; IS, ischemic stroke; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapies; Lp(a), lipoprotein(a); MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; TIA, transient ischemic attack; TNF-α, tumor necrosis factor alpha; UA, unstable angina; VLDL, very-low-density lipoprotein.

1. Ridker PM. *Lancet*. 2014;384:607-617. 2. Merck Manual: Overview of Lipid Metabolism. http://www.merckmanuals.com/professional/endocrine-and-metabolic-disorders/lipid-disorders/overview-of-lipid-metabolism. Accessed June 30, 2022. 3. Linton MRF, et al. The Role of Lipids and Lipoproteins in Atherosclerosis. [Updated 2019 Jan 3]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK343489/. 4. Sandfort V, et al. *Circ Cardiovasc Imaging*. 2015;8:e003316. 5. Stefanadis C, et al. *J Am Heart Assoc*. 2017; 6:e005543. doi: 10.1161/JAHA.117.005543. 6. Koenig W, Khuseyinova N. *Atheroscler Thromb Vasc Biol*. 2006;27:15-26. 7. Navarese EP, et al. *Ann Internal Med*. 2018;164:600-607. 8. Wu NQ, et al. *Front Cardiovasc Med*. 2022;9:763516. 9. Cholesterol Treatment Trialists' Collaboration. *Lancet*. 2005;366:1267-1278. 10. Cannon CP, et al. *JAMA Cardiol*. 2021;6(9):1060-68. doi:10.1001/jamacardio.2021.1810. 11. Desai NR, et al. *Circulation*. 2019;140:A13945. doi: 10.1161/circ.140.suppl_1.13945. 12. Levinstine DN, et al. *Clin Epidemiol*. 2022; 14:727-748. 13. Grundy SM, et al. *Circulation*. 2019;139(25):e1046-e1081. doi: 10.1161/CIR.0000000000000624. 14. Mach F, et al. *Eur Heart J*. 2020;41(1):111-188. doi: 10.1093/eurheartj/ehz455. 15. Jellinger PS, et al. *Endocr Pract*. 2017;23(suppl2):1-87. 16. Handelsman Y, et al. *Endocr Pract*. 2020;26(10):1196-1224. doi: 10.4158/GS-2020-0490. 17. Lloyd-Jones D, et al. *J Am Coll Cardiol*. 2022;80(14):1366–1418. doi: 10.1016/j.jacc.2022.07.006.

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