CLINICAL VIGNETTE

Highly Elevated Low-Density Lipoprotein in a Patient with No Coronary Calcium

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Introduction

It has been known since the 1960s that serum levels of cholesterol and its lipoprotein carriers (low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), and high-density lipoprotein (HDL)) are related to atherosclerotic cardiovascular disease (ASCVD). Long-term ASCVD risk for US adults with the severe hypercholesterolemia, defined as LDL ≥190 mg/dL) is elevated up to ~5-fold compared with adults with average LDL levels, even after adjustment for other CVD risk factors.[1] Coronary artery calcium (CAC) as measured by CT angiography is a marker of coronary atherosclerosis burden and its presence is strongly associated with future ASCVD events. We present a case of a 58-year-old woman with severe hypercholesterolemia and a CAC score of zero.

Case Presentation

A 58-year-old woman with paroxysmal atrial fibrillation and impaired glucose tolerance was referred to cardiology for evaluation and treatment of hypercholesterolemia. She had hyperlipidemia noted for more than ten years and was resistant to medical management. She had tried lifestyle modification prior to her consultation. Her initial lipid panel after consultation showed: total cholesterol 380 mg/dL, HDL-cholesterol 65 mg/dL, LDL-cholesterol 285 mg/dL and triglycerides 148 mg/dL. These results were reviewed with the patient and initiation of statin therapy was recommended. The American Heart Association/American College of Cardiology Risk Assessment was not calculated, because her total cholesterol exceeded the range for inclusion, 130-320. Citing concerns about side effects of this class of medications and wanting to pursue "natural" therapies, the patient asked for additional information about her cardiovascular risk, and a CT coronary calcium scan was scheduled. Her total coronary artery calcium score of 0, placing the patient within the less than 25th percentile range of gender and age-matched controls.

Discussion

This patient with highly elevated LDL had no measurable coronary artery calcium. Current guidelines using the ASCVD risk calculator recommend high intensity statin treatment for patients with LDL-C levels of >190 mg/dL without atherosclerotic cardiovascular disease.[2] This case highlights an interesting clinical conundrum – what is one to do when well-validated markers of atherosclerotic cardiovascular disease (ASCVD) risk guide the clinician in opposing directions?

The role of cholesterol as a contributor to the formation of atherosclerosis was suggested over 100 years ago, in 1913 with Antischkow paper reporting feeding of rabbits with cholesterol caused atherosclerosis.[3] That same year, Bacmeister and Henes, demonstrated that elevated blood levels of cholesterol were associated with atherosclerosis.[4] During the 1940s Bloch and Lynen revealed the mechanism of synthesis and regulation of cholesterol and fatty acid in the body, for which they received the Nobel Prize. In the 1950s, the pathway of cholesterol synthesis had been fully revealed, and the rate-limiting step had been shown to be the transformation of β-hydroxy-β-methyl glutaryl-CoA (HMG-CoA) to mevalonate.[4] Scientists in Japan and the United States identified fungus species that produced a potent inhibitor of HMG-CoA reductase which led to reduction of cholesterol synthesis in rats.[4] In 1984, the first report of statin use in patients with heterozygous familial hypercholesterolemia, which was approved on compassionate grounds, was published.[5] Over the past six decades, numerous population based studies have identified LDL-C as a key risk factor for ASCVD. Many intervention trials have shown that statin therapy routinely inhibits cholesterol synthesis and reduces cardiovascular events. Based on this evidence, the most current American College of Cardiology/American Heart Association Guideline on the Primary Prevention of Cardiovascular Disease, calls for statin therapy as first-line treatment for primary prevention of ASCVD in patients with elevated LDL-C (≥190 mg/dL).[6]

Reports from the early 1990s showed mural coronary artery calcium to be diagnostic of atherosclerotic coronary artery disease.[7] The total CAC score represents an anatomic measure of overall cardiac plaque burden, and presence of CAC is strongly associated with future CVD events.[8] Absence of CAC has been shown to be a powerful negative risk marker for the development of coronary heart disease.[9] Accordingly, the 2018 American College of Cardiology/American Heart Association guidelines assigned a Class IIa recommendation for CAC testing in select patients with borderline to intermediate-risk, acknowledging that it is reasonable to withhold statin therapy for patients with CAC = 0.[2]

Ordinarily, given the conflicting assessments of risk, a clinician would be inclined to pursue a conservative, middle-of-the-road strategy. In this case, one may be inclined to initiate a low-dose statin therapy for this patient. However, our patient was highly resistant to taking a statin citing concerns of muscle pain, diges-

tive problems and mental fuzziness. Our question was whether it was necessary to encourage the patient to begin statin therapy or if she could be safely followed without a medical intervention.

Sandesara et al, recently published an analysis of the Multi-Ethnic Study of Atherosclerosis (MESA) cohort seeking to examine the predictive value of zero CAC in patients with LDL-C ≥190 mg/dL.[9] Of the 6814 participants from the original MESA cohort, 246 had an LDL-C ≥190 mg/dL. Of these, 90 had CAC of 0. Participants with CAC = 0 had a lower risk for future cardiovascular events (incidence rate per 1000 person-years = 4.7; 10-year risk = 3.7%; risk/year = 0.4%) than those with CAC >0 (incidence rate per 1000 person-years = 26.4; 10-year risk = 20%; risk/year = 2.0%), adjusted HR 0.25 (95%CI = 0.10–0.66). Other studies have demonstrated discordance between risk level and atherosclerosis measured by CAC. Miname et al. reported the utility of CAC scores among asymptomatic patients with molecularly proven heterozygous familial hypercholesterolemia receiving standard lipid-lowering therapy.[10] They studied 206 patients with average baseline LDL-C 269 mg/dL and on-treatment LDL-C 150 mg/dL) who underwent CAC measurement and observed that nearly 50% had a zero CAC score. Similar to the study by Sandesara, absence of CAC was associated with excellent cardiovascular prognosis over nearly 4 years of follow-up.[10]

Conclusion

This case highlights the clinician's task of combining guideline recommendations and validated clinical tools with patient preferences to guide individual patient care. In the case of severe hypercholesterolemia and zero CAC, it seems that it may be safe to withhold statin therapy.

REFERENCES

1. **Perak AM, Ning H, de Ferranti SD, Gooding HC, Wilkins JT, Lloyd-Jones DM**. Long-Term Risk of Atherosclerotic Cardiovascular Disease in US Adults With the Familial Hypercholesterolemia Phenotype. *Circulation*. 2016 Jul 5;134(1):9-19. doi: 10.1161/CIRCULATIONAHA.116.022335. PMID: 27358432; PMCID: PMC4933328.
2. **Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC Jr, Sperling L, Virani SS, Yeboah J**. 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. *Circulation*. 2019 Jun 18;139(25):e1082-e1143. doi: 10.1161/CIR.0000000000000625. Epub 2018 Nov 10. Erratum in: *Circulation*. 2019 Jun 18;139(25):e1182-e1186. PMID: 30586774.
3. **Finking G, Hanke H**. Nikolaj Nikolajewitsch Anitschkow (1885-1964) established the cholesterol-fed rabbit as a model for atherosclerosis research. *Atherosclerosis*. 1997 Nov;135(1):1-7. doi: 10.1016/s0021-9150(97)00161-5. PMID: 9395267.
4. **Pedersen TR**. The Success Story of LDL Cholesterol Lowering. *Circ Res*. 2016 Feb 19;118(4):721-31. doi: 10.1161/CIRCRESAHA.115.306297. PMID: 26892969.
5. **Illingworth DR, Sexton GJ**. Hypocholesterolemic effects of mevinolin in patients with heterozygous familial hypercholesterolemia. *J Clin Invest*. 1984 Dec;74(6):1972-8. doi: 10.1172/JCI111618. PMID: 6569064; PMCID: PMC425384.
6. **Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, Michos ED, Miedema MD, Muñoz D, Smith SC Jr, Virani SS, Williams KA Sr, Yeboah J, Ziaeian B**. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019 Sep 10;140(11):e596-e646. doi: 10.1161/CIR.0000000000000678. Epub 2019 Mar 17. Erratum in: *Circulation*. 2019 Sep 10;140(11):e649-e650. Erratum in: *Circulation*. 2020 Jan 28;141(4):e60. Erratum in: *Circulation*. 2020 Apr 21;141(16):e774. PMID: 30879355.
7. **Rumberger JA, Sheedy PF 2nd, Breen JF, Fitzpatrick LA, Schwartz RS**. Electron beam computed tomography and coronary artery disease: scanning for coronary artery calcification. *Mayo Clin Proc*. 1996 Apr;71(4):369-77. doi: 10.4065/71.4.369. PMID: 8637260.
8. **Latif MA, Budoff MJ**. Role of CT angiography for detection of coronary atherosclerosis. *Expert Rev Cardiovasc Ther*. 2014 Mar;12(3):373-82. doi: 10.1586/14779072.2014.890050. Epub 2014 Feb 10. PMID: 24506476.
9. **Sandesara PB, Mehta A, O'Neal WT, Kelli HM, Sathiyakumar V, Martin SS, Blaha MJ, Blumenthal RS, Sperling LS**. Clinical significance of zero coronary artery calcium in individuals with LDL cholesterol ≥190 mg/dL: The Multi-Ethnic Study of Atherosclerosis. *Atherosclerosis*. 2020 Jan;292:224-229. doi: 10.1016/j.atherosclerosis.2019.09.014. Epub 2019 Sep 27. PMID: 31604582.
10. **Miname MH, Bittencourt MS, Moraes SR, Alves RIM, Silva PRS, Jannes CE, Pereira AC, Krieger JE, Nasir K, Santos RD**. Coronary Artery Calcium and Cardiovascular Events in Patients With Familial Hypercholesterolemia Receiving Standard Lipid-Lowering Therapy. *JACC Cardiovasc Imaging*. 2019 Sep;12(9):1797-1804. doi: 10.1016/j.jcmg.2018.09.019. Epub 2018 Nov 15. PMID: 30448145.