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LDL-C: Is 160 the New 190?

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What We Already Know

Low-density lipoprotein cholesterol (LDL-C) has long been recognized as a risk factor for atherosclerotic cardiovascular disease (ASCVD). Although the current treatment guidelines clearly state that formal global cardiovascular risk assessment should be performed in most individuals without established ASCVD, the guidelines do not recommend risk assessment in those with marked elevation of LDL-C levels.[1] This "marked" elevation in LDL-C is generally defined as LDL-C ≥190 mg/dL (mean LDL-C level in US adults is 113 mg/dL[2]). The risk of coronary heart disease (CHD) is accelerated by 10–20 years in men and 20–30 years in women with LDL-C levels ≥190 mg/dL.[3] While the risk of CHD events has been described as 22-fold higher among those with familial hypercholesterolemia (FH)–defining mutations (because of lifetime exposure to elevated LDL-C levels), the future risk of CHD remains 6-fold higher in those with LDL-C ≥190 mg/dL and no FH-related mutations.[4] Statin therapy significantly lowers risk of ASCVD events in these patients.[5] It is important to note that although the prevalence of heterozygous FH may be 1 in 250, the prevalence of LDL-C ≥190 mg/dL may be as high as 5–7% in the general population.[3,6]

Long-term ASCVD risk associated with more moderate elevations in LDL-C levels is not well described, especially among young individuals and those without other major ASCVD

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risk factors. In this population, 10-year ASCVD risk using current risk assessment tools may be low.

What Does This Study Show?

The study by Abdullah et al[7] in this issue of *Circulation* fills this gap. In a group of relatively low-risk individuals (n=36,375) with 10-year ASCVD risk <7.5% (median 1.3% 10-year ASCVD risk) using the Pooled Cohort Risk Equation and without history of ASCVD or diabetes mellitus at baseline, the association between fasting LDL-C (or non–high-density lipoprotein cholesterol [non-HDL-C]) levels and ASCVD mortality was evaluated over a median follow-up of 26.8 years. Compared with those with LDL-C <100 mg/dL, individuals with LDL-C levels of 160–189 mg/dL (hazard ratio [HR] 1.7, 95% confidence interval [CI] 1.4–2.2) and those with LDL-C ≥190 mg/dL (HR 1.5, 95% CI 1.2–2.1) had increased risk for CVD mortality. This would roughly equate to mean reductions in years free of CVD death of 4.3 and 3.9, respectively. Similarly, non-HDL-C levels of 160–189 mg/dL (HR 1.3, 95% CI 1.1–1.6), 190–219 mg/dL (HR 1.8, 95% CI 1.4–2.2), and ≥220 mg/dL (HR 1.5, 95% CI 1.2–2.0) were significantly associated with CVD death compared with non-HDL-C levels <130 mg/dL. Results were qualitatively similar when analyses were restricted to those with 10-year ASCVD risk ≤5% (89% of the cohort).

Several observations can be made from these important analyses in otherwise low-risk individuals. First, even moderately elevated LDL-C levels in the range of 160–189 mg/dL over a 27-year follow-up were associated with increased risk of CVD death, with roughly 4.3 years' reduction in years free of CVD. Second, non-HDL-C levels showed an association with CVD death (and all-cause mortality) that was more robust at even lower levels compared with the corresponding LDL-C levels. This is not surprising, as non-HDL-C includes the cholesterol content of all atherogenic lipoproteins including LDL, intermediate density lipoprotein, very-low-density lipoprotein, lipoprotein(a), and chylomicron remnants.[8] Therefore, non-HDL-C calculation captures the risk associated with both cholesterol-rich lipoproteins and triglyceride-rich remnant lipoproteins. This observation reemphasizes that non-HDL-C is superior to LDL-C in identifying future ASCVD risk.

These results should be interpreted in the context of the limitations of the analyses. No information on baseline or follow-up lipid-lowering therapies was available. Also, age was not adjusted for in the main analyses because of violation of the proportional-hazards assumption. It is quite possible that given such a long follow-up, some would reach a threshold of 7.5% 10-year ASCVD risk because of age or the development of age-dependent risk factors, and therefore, would meet the guideline-recommended risk threshold of 7.5% 10-year ASCVD risk for discussion regarding statin therapy.

What Are the Implications of the Findings?

First, these analyses indicate that there is no "threshold" at which atherogenic lipoproteins increase ASCVD risk. Even moderate elevations in atherogenic lipoproteins, without other risk factors and with low 10-year ASCVD risk, are associated with increased long-term risk of CVD mortality and possibly all-cause mortality. This raises questions of whether 10-year

or lifetime ASCVD risk assessment should be performed first in individuals with LDL-C 160–189 mg/dL, or whether they should begin lipid-lowering treatments based on long-term risk similar to individuals with LDL-C levels ≥190 mg/dL. As noted in the current analyses, the association between LDL-C levels and CHD mortality (or CVD mortality) was not significant when analyses were truncated at 10 years.

Second, should patients with LDL-C 160–189 mg/dL be treated early? Most primary-prevention trials[9,10,11] (**Table**) include a low-risk population, and some included patients with LDL-C ≥160 mg/dL; however, the baseline age in those trials was higher than the mean of 42 years in the current study. Although treating those with LDL-C 160–189 mg/dL but low 10-year ASCVD risk early in life sounds promising, this would lead to treating a much larger number of individuals than the current recommendation of treating those with LDL-C ≥190 mg/dL. For example, individuals with LDL-C 160–189 mg/dL comprised 13% of the overall study population. The 2013 ACC/AHA cholesterol guideline notes that statin therapy may be considered (Class IIb recommendation with Level of Evidence C) in individuals with LDL-C ≥160 mg/dL who are otherwise not considered for statin therapy based on the statin benefit groups.[1] The current analyses could substantiate updating the level of evidence for this recommendation, which when combined with clinical trial evidence (**Table**), could support early initiation of statin therapy in at least some of these individuals. At least two of these primary-prevention trials[9,11] (**Table**) showed benefit in individuals with LDL-C levels ~160 mg/dL and 10-year ASCVD risk <7.5%. It is unlikely that clinical trials of statin therapy will be performed in a population of this age with few risk factors because of the large sample size and long-term follow-up required. How then should observational data such as this study be used for joint decision making with our patients?

Third, these analyses reemphasize the importance of calculating non-HDL-C. Although the Adult Treatment Panel III guideline recommended non-HDL-C as a secondary treatment target especially among individuals with elevated triglycerides,[12] the 2013 ACC/AHA cholesterol guideline did not include non-HDL-C for treatment decisions since trials of statin therapy mostly used LDL-C levels for eligibility.[1] The analyses in the current study show that non-HDL-C levels were associated with CHD and CVD mortality at much lower levels (130–159 mg/dL) than the corresponding LDL-C levels. It is important to note that all recent outcomes trials of PCSK9 inhibitors (most of which included secondary-prevention patients) used both LDL-C and non-HDL-C thresholds for eligibility[13,14] and could therefore include patients with elevated non-HDL-C levels despite LDL-C below the eligibility criterion. Should clinicians use non-HDL-C in addition to LDL-C when making decisions regarding lipid-lowering therapy?

What Are the Remaining Gaps?

Although the authors evaluated elevation of LDL-C and non-HDL-C levels in mid-life, there are other clinical circumstances in which LDL-C levels may be elevated but the duration of exposure may not be as long. One example would be perimenopausal elevation of LDL-C.[15] Menopause can lead to elevated LDL-C which in some cases may approach 160–189 mg/dL. Should these women be treated with lipid-lowering therapy? Although they may have elevated LDL-C levels, their risk may not as high as individuals in the current analyses,

because overall risk is likely a combination of the degree of elevation of atherogenic lipoproteins and the duration of exposure (shorter in women with perimenopausal LDL-C elevation). Lastly, although imaging, especially coronary calcium score, has shown to stratify risk in intermediate-risk individuals,[16] can imaging be used for risk stratification in individuals with moderate LDL-C elevation? Can therapy be withheld with a coronary calcium score of 0 when LDL-C levels are 160–189 mg/dL, especially when one considers the limitations of coronary calcium scores in young individuals? This would be important given the considerable number of individuals with LDL-C 160–189 mg/dL, the need for lifelong treatment once lipid-lowering therapy is started, and possibly a higher risk for statin-associated side effects given the longer duration of therapy.

In conclusion, these analyses solidify the evidence that even moderately elevated atherogenic lipoprotein levels, especially when present over a long-term follow-up, are associated with an increased risk of CVD death and possibly overall mortality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

AFCAPS/TexCAPS	Air Force/Texas Coronary Atherosclerosis Prevention Study[9]
ASCVD	atherosclerotic cardiovascular disease
JUPITER	Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin[10]
HDL-C	high-density lipoprotein cholesterol
hs-CRP	high-sensitivity C-reactive protein
LDL-C	low-density lipoprotein cholesterol
MEGA	Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese[11]
RRR	relative risk reduction

References

1. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC, Jr., Watson K, Wilson PW, Eddleman KM, Jarrett NM, LaBresh K, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC, Jr., Tomaselli GF. 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. Circulation 2014;129:S1-45. [PubMed: 24222016]
2. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, Chiuve SE, Cushman M, Delling FN, Deo R, de Ferranti SD, Ferguson JF, Fornage M, Gillespie C, Isasi CR, Jimenez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Lutsey PL, Mackey JS, Matchar DB, Matsushita K, Mussolino ME, Nasir K, O'Flaherty M, Palaniappan LP, Pandey A, Pandey DK, Reeves MJ, Ritchey MD, Rodriguez CJ, Roth GA, Rosamond WD, Sampson UKA, Satou GM, Shah SH, Spartano NL, Tirschwell DL, Tsao CW, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P, on behalf of the American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2018 update: A report from the American Heart Association. Circulation 2018;137:e67-e492. [PubMed: 29386200]
3. 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;134:9–19. [PubMed: 27358432]
4. Khera AV, Won HH, Peloso GM, Lawson KS, Bartz TM, Deng X, van Leeuwen EM, Natarajan P, Emdin CA, Bick AG, Morrison AC, Brody JA, Gupta N, Nomura A, Kessler T, Duga S, Bis JC, van Duijn CM, Cupples LA, Psaty B, Rader DJ, Danesh J, Schunkert H, McPherson R, Farrall M, Watkins H, Lander E, Wilson JG, Correa A, Boerwinkle E, Merlini PA, Ardissino D, Saleheen D, Gabriel S, Kathiresan S. Diagnostic yield and clinical utility of sequencing familial hypercholesterolemia genes in patients with severe hypercholesterolemia. J Am Coll Cardiol 2016;67:2578–2589. [PubMed: 27050191]
5. Vallejo-Vaz AJ, Robertson M, Catapano AL, Watts GF, Kastelein JJ, Packard CJ, Ford I, Ray KK. Low-density lipoprotein cholesterol lowering for the primary prevention of cardiovascular disease among men with primary elevations of low-density lipoprotein cholesterol levels of 190 mg/dl or above: analyses from the WOSCOPS (West of Scotland Coronary Prevention Study) 5-year randomized trial and 20-year observational follow-up. Circulation 2017;136:1878–1891. [PubMed: 28877913]
6. Abul-Husn NS, Manickam K, Jones LK, Wright EA, Hartzel DN, Gonzaga-Jauregui C, O'Dushlaine C, Leader JB, Lester Kirchner H, Lindbuchler DM, Barr ML, Giovanni MA, Ritchie MD, Overton JD, Reid JG, Metpally RP, Wardeh AH, Borecki IB, Yancopoulos GD, Baras A, Shuldiner AR, Gottesman O, Ledbetter DH, Carey DJ, Dewey FE, Murray MF. Genetic identification of familial hypercholesterolemia within a single U.S. health care system. Science 2016;354:aaf7000.
7. Abdullah SM, Defina LF, Leonard D, Barlow CE, Radford NB, Willis BL, Rohatgi A, McGuire DK, de Lemos JA, Grundy SM, Berry JD, Khera A. Long-term association of LDL cholesterol with cardiovascular mortality in individuals at low 10-year risk of atherosclerotic cardiovascular disease: results from the Cooper Center Longitudinal Study. Circulation In press.
8. Virani SS. Non-HDL cholesterol as a metric of good quality of care: opportunities and challenges. Tex Heart Inst J 2011;38:160–162. [PubMed: 21494527]
9. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Kruyer W, Gotto AM, Jr., for the AFCAPS/TexCAPS Research Group. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. JAMA 1998;279:1615–1622. [PubMed: 9613910]
10. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM, Jr., Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, Macfadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ.

Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195–2207. [PubMed: 18997196]

11. Nakamura H, Arakawa K, Itakura H, Kitabatake A, Goto Y, Toyota T, Nakaya N, Nishimoto S, Muranaka M, Yamamoto A, Mizuno K, Ohashi Y, for the MEGA Study Group. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. Lancet 2006;368:1155–1163. [PubMed: 17011942]
12. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486–2497. [PubMed: 11368702]
13. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR, for the FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376:1713–1722. [PubMed: 28304224]
14. Ridker PM, Revkin J, Amarenco P, Brunell R, Curto M, Civeira F, Flather M, Glynn RJ, Gregoire J, Jukema JW, Karpov Y, Kastelein JJP, Koenig W, Lorenzatti A, Manga P, Masiukiewicz U, Miller M, Mosterd A, Murin J, Nicolau JC, Nissen S, Ponikowski P, Santos RD, Schwartz PF, Soran H, White H, Wright RS, Vrablik M, Yunis C, Shear CL, Tardif JC, for the SPIRE Cardiovascular Outcome Investigators. Cardiovascular efficacy and safety of bococizumab in high-risk patients. N Engl J Med 2017;376:1527–1539. [PubMed: 28304242]
15. Matthews KA, Crawford SL, Chae CU, Everson-Rose SA, Sowers MF, Sternfeld B, Sutton-Tyrrell K. Are changes in cardiovascular disease risk factors in midlife women due to chronological aging or to the menopausal transition? J Am Coll Cardiol 2009;54:2366–2373. [PubMed: 20082925]
16. Nasir K, Bittencourt MS, Blaha MJ, Blankstein R, Agatson AS, Rivera JJ, Miedema MD, Sibley CT, Shaw LJ, Blumenthal RS, Budoff MJ, Krumholz HM. Implications of coronary artery calcium testing among statin candidates according to American College of Cardiology/American Heart Association cholesterol management guidelines: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol 2015;66:1657–1668. [PubMed: 26449135]

Table:

Randomized clinical trials of statin monotherapy as primary prevention

Trial	Treatment	Age/sex eligibility criteria	Lipid/other eligibility criteria (mg/dL)	Mean LDL-C reduction and absolute reduction vs. placebo at 1 year	RRR for ASCVD	Estimated 10-year "hard" ASCVD risk
MEGA	Pravastatin 10–20 mg	Men aged 40–70 y; postmenopausal women aged 40–70 y	Total cholesterol 220–279 (LDL-C ≈ 160–210)	−17% 128 vs. 156 (−28 mg/dL)	24%	5.1%
AFCAPS/ TexCAPS	Lovastatin 20–40 mg	Men aged 45–73 y; postmenopausal women aged 55–73 y	LDL-C 130–190; triglycerides <400; HDL-C <45 for men and <47 for women	−27% 115 vs. 156 (−41 mg/dL)	26%	6.9%
JUPITER	Rosuvastatin 20 mg	Men aged >50 y; women aged ≥60 y	hs-CRP >2 mg/L; LDL-C <130; triglycerides <500	−50% 55 vs. 110 (−55 mg/dL)	44%	7.6%