

Cholesterol Paradox: Understanding and Implications for Clinical Practice and Education

Rodney G. Bowden^{1,*}, Tanvir Ahmed²

¹Professor and Brown Foundation Endowed Chair, Department of Public Health, Baylor University, USA

²Research Assistant, Department of Public Health, Baylor University, USA

*Correspondence should be addressed to Rodney G. Bowden, Rodney_Bowden@baylor.edu

Received date: November 27, 2024, **Accepted date:** January 22, 2025

Citation: Bowden RG, Ahmed T. Cholesterol Paradox: Understanding and Implications for Clinical Practice and Education. J Clin Cardiol. 2025;6(1):18-22.

Copyright: © 2025 Bowden RG, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Cholesterol has long been recognized as a major risk factor for cardiovascular diseases with traditional guidelines emphasizing the reduction of LDL cholesterol and triglycerides, and the increase of HDL cholesterol to lower morbidity and mortality. However, recent studies have questioned the predictive value of these traditional cholesterol measures in coronary artery disease. The concept of the cholesterol paradox has emerged, highlighting instances where elevated LDL cholesterol or high HDL levels have an inverse relationship with cardiovascular risk, particularly in certain diseased populations. This paradox has sparked significant debate in the scientific community. Explanations for the paradox include nutritional deficiencies, inflammation, and variations in cholesterol particle characteristics such as size, number, and quality. For instance, smaller, denser LDL particles and dysfunctional HDL may contribute more to atherosclerosis and cardiovascular risk than traditional lipid measures indicate. Inflammation, commonly seen in chronic diseases, can also alter lipid metabolism and reduce cholesterol levels while increasing CAD risk. These findings suggest a need for updated clinical guidelines that incorporate more comprehensive cholesterol measures, including particle size and number, and account for other factors such as inflammation and nutritional status. Further research and improved clinical practices are essential to better predict and manage cardiovascular disease risk.

Keywords: Cholesterol paradox, HDL, LDL, Reverse epidemiology

Introduction

Cholesterol has long been regarded as a significant risk factor for cardiovascular diseases, leading to widespread guidelines recommending lower cholesterol and triglyceride levels and increased high density lipoprotein (HDL) levels to reduce morbidity and mortality [1]. Historically, numerous studies have established a correlation between elevated levels of low density lipoprotein (LDL) cholesterol, low levels of HDL and elevated triglycerides being associated with increased risk of coronary artery disease (CAD) [2-4]. Traditional lipoprotein profiles have been used for risk assessment, stratification and treatment therapies, relying on these measures in clinical practice. Additionally, a number of studies have not reported a strong association with LDL or HDL and CAD [5-7]. More recent findings regarding cholesterol and CAD have been attempting to understand why LDL and HDL, in some instances are less predictive of morbidity and mortality [1,8,9]. It should be noted that traditional lipid measures of cholesterol content may not

account for variations in cholesterol particle characteristics and quality, which has been reported to play a significant role in atherosclerosis and CAD events [10].

A new term labeled cholesterol paradox has emerged in an attempt to understand some findings that demonstrate a protective effect of elevated LDL cholesterol [11]. Cholesterol paradox refers to the observation that certain health outcomes exhibit an inverse relationship with traditional cholesterol risk factors when examined in specific populations. Study authors have reported that normal levels of LDL and high levels of HDL are linked with increased mortality in older adults [12]. It should be noted that this term has created significant controversy in the scientific literature and created significant debate [13-15].

There have been a number of suggestions, with clinical evidence, as to why cholesterol levels have been less predictive of morbidity and mortality in recent studies [16]. Explanations include nutritional deficiencies, inflammatory processes,

cholesterol particle number and size, cholesterol quality and other factors. More recent explanations for a cholesterol paradox are presented in this commentary.

Nutritional Deficiencies

One such reason that has been presented is nutritional deficiencies in patients presenting with CAD. Many of the recent studies have focused on lower levels of LDL and increased levels of HDL and paradoxical findings. One study [6] examined data from over 40,000 patients with CAD in a hospital in China with the reported findings revealing an association between non-HDL cholesterol concentration and long term all-cause mortality. Yet, when controlling for nutritional status, non-HDL cholesterol was still considered a risk factor for all-cause mortality suggesting nutritional status is likely playing a role in lowered cholesterol levels yet may not be attenuating the risk associated with non-HDL cholesterol [17,18]. An additional large study of over 40,000 participants reported a cholesterol paradox occurred in patients with CAD but also was attenuated when nutritional status was measured and controlled for in the analysis [19]. Malnutrition was also identified as predictor of clinically normal total cholesterol levels and increased levels of CAD in a geriatric population [20]. It should be noted that nutritional deficiencies may contribute to lower total cholesterol and LDL cholesterol, yet with these clinically normal levels of cholesterol may be more likely to be contributing to higher rates of mortality and morbidity. It could be that nutritional deficiencies, especially in active disease states, may cause biomarkers like cholesterol to no longer be predictors of CAD [18].

Inflammation

Inflammatory states, common in chronic diseases, can alter lipid metabolism resulting in lower cholesterol levels while simultaneously increasing the risk of mortality [21]. In clinical practice inflammation is measured more readily as high sensitivity C-reactive protein (hs-CRP) with inflammation and cholesterol contributing to both CAD and all-cause mortality [21]. A large sample of over 30,000 research participants demonstrated that inflammation may play a larger role in CAD than LDL cholesterol [22]. The study authors reported that patients receiving statin therapy for cholesterol control reported higher risk for future CAD morbidity and mortality based on hs-CRP rather than LDL cholesterol. The inflammatory process may in fact reduce cholesterol values to the point of having a normal lipid profile, but due to the increased inflammation, more patients may have more CAD events. Additionally, it is important to remember that statin therapy may also have an effect on non-cardiac related all-cause mortality, which could possibly be associated with the cholesterol paradox [23]. Finally, inflammatory diseases and infections that can effect cholesterol levels resulting in a cholesterol paradox have included chronic kidney disease [24], COVID-19 [25], bacterial infections [26].

Cholesterol Particle Number and Size

Cholesterol particle number (CPN) refers to the total number of lipoprotein particles carrying cholesterol in the circulation with cholesterol particle size referring to the diameter of these lipoprotein particles. Smaller, denser LDL particles have been linked to a higher risk of cardiovascular events compared to larger, less dense LDL particles [27]. This is primarily due to smaller and more dense LDL particles more easily penetrating the arterial wall causing arterial stenosis and greater susceptibility to oxidative modification [28]. In clinical practice the assays used to measure CAD risk via cholesterol is based on cholesterol that is found in lipoproteins. Though normal cholesterol levels can be present, it may be that the cholesterol lipoproteins such as LDL may be smaller, more dense and higher in number all of which increase the risk for CAD events even though cholesterol values as traditionally measured may be normal [29]. Additionally, research has demonstrated that CPN and particle size can independently predict cardiovascular risk beyond traditional lipid measures. For instance, study authors have reported that individuals with high CPN, even with normal LDL cholesterol levels, may still have a significantly elevated risk of CAD [30]. Conversely, individuals with larger, buoyant LDL particles may exhibit lower risk, despite elevated LDL cholesterol levels [31].

Lipid Quality

HDL levels, especially elevated HDL levels have been associated with decreased CAD, but there are some studies where higher levels of HDL do not provide a protective effect [32]. More recent studies outcomes have reported the functionality of HDL, rather than its quantity, is an important determinant of cardiovascular protection. Recent studies have reported that HDL quality or a term know as HDL dysfunction may play a role in the development of CAD [33] with increasing evidence suggesting that HDL dysfunction, rather than HDL levels, may play a significant role in the pathogenesis of CAD [34]. HDL particles can become dysfunctional and lose their protective properties despite normal and elevated levels of HDL lipoproteins in circulation. HDL dysfunction can result from alterations in HDL particle composition, structure, and function, and is often driven by systemic factors such as inflammation, oxidative stress, and metabolic diseases [35].

Several factors can be associated with dysfunctional HDL. Oxidative modifications of Apo A-I, the major apolipoprotein in HDL, reduces its ability to mediate cholesterol efflux from macrophages and impair HDL antioxidant properties [36]. Additionally, decreased phospholipid content in HDL can affect the stability and structure of the particles, limiting their ability to engage in reverse cholesterol transport and enhance endothelial function [37]. Another factor in HDL dysfunction is elevated triglyceride levels in HDL lipoproteins are associated with increased hepatic lipase activity, which can lead to the formation of small, dense HDL particles that are less efficient in cholesterol efflux and have pro-inflammatory properties [38].

Cholesterol and Extracellular Vesicles

Extracellular vesicles (EV) are membrane-bound particles that vary in size and density and are released into the extracellular space. EVs carry molecules such as proteins, RNA, DNA and importantly for this paper, lipids. Though studies regarding EVs and the cholesterol paradox are wanting, the emerging understanding of EVs, inflammation and CAD demonstrates promising findings regarding a better understanding of the cholesterol paradox [39,40].

Clinical Implications for the Cholesterol Paradox

Despite the most recent understandings of cholesterol, most of the emphasis in clinical practice is on traditional cholesterol measurement that measure cholesterol content only and does not consider other measures such as particle number, size and functionality. There is need for an update to clinical guidelines that include the inclusion of these new measures of LDL and HDL and how other factors such as inflammation and disease states affect CAD morbidity and mortality. More advanced lipid testing is available yet is not used routinely in clinical practice. Reasons include laboratories not running the assays as they are expensive and presently are rarely reimbursed by insurance plans. Additionally, there is need for provider and patient education regarding changes in our understanding of cholesterol and CAD prevention. As such the following is proposed for the inclusion of more predictive measures of cholesterol in clinical practice.

1. Updated clinical guidelines: The National Cholesterol Education Program (NCEP) should update their ATPIII guidelines [41] that address the latest understanding of cholesterol, cholesterol measurement and prediction.
2. New risk stratification categories: New ATPIII guidelines would need to create new stratification categories for CAD prediction based on non-traditional measures of cholesterol.
3. Increased access and affordability: With the creation of new guidelines by the NCEP there would need to be an investment in others means of cholesterol measurement and reimbursement models by US government and private insurance providers.
4. Provider training: Continuing medical education should focus on increased awareness among clinicians about changes in our understanding of cholesterol and disease predictions including an increased understanding of forms of measurement for cholesterol. This could include more personalized treatment strategies inclusive of statin therapy and lifestyle interventions
5. Patient Awareness: Education programs are needed for patient and general populations about the new understanding of cholesterol prediction and measurement.

6. Monitoring of outcomes: Continued monitoring of treatment strategies to have a better understanding of how new measures of cholesterol predict CAD outcomes.
7. Patient education: Educating patients about the significance of cholesterol particle characteristics can empower them to engage in discussions with their healthcare providers.
8. Patient and general population outreach: More information about cardiovascular risk through screening programs and educational campaigns is needed.
9. Research: Increased research funding to gain a better understanding of new ways to measure cholesterol and the implication on various chronic diseases.
10. Inclusion of cholesterol particle number, size and quality in federal databases such as the National Health and Nutrition Examination Survey.

As more studies are being published that suggest our traditional understanding of cholesterol measurement and prediction are counterintuitive in the associations with CAD, more emphasis is needed on education and changes in clinical practice. A renewed focus on creating new cholesterol guidelines and risk stratification is warranted to lower morbidity and mortality outcomes related to CAD.

References

1. Gidding SS, Allen NB. Cholesterol and Atherosclerotic Cardiovascular Disease: A Lifelong Problem. *J Am Heart Assoc.* 2019 Jun 4;8(11):e012924.
2. Lee Y, Park S, Lee S, Kim Y, Kang MW, Cho S, et al. Lipid profiles and risk of major adverse cardiovascular events in CKD and diabetes: A nationwide population-based study. *PLoS One.* 2020 Apr 9;15(4):e0231328.
3. Yang JK, Kim YJ, Jeong J, Kim J, Park JH, Ro YS, Shin S, et al. Low serum cholesterol level as a risk factor for out-of-hospital cardiac arrest: a case-control study. *Clin Exp Emerg Med.* 2021 Dec;8(4):296-306.
4. Lee YB, Koo M, Noh E, Hwang SY, Kim JA, Roh E, et al. Myocardial Infarction, Stroke, and All-Cause Mortality according to Low-Density Lipoprotein Cholesterol Level in the Elderly, a Nationwide Study. *Diabetes Metab J.* 2022 Sep;46(5):722-32.
5. Bowden RG, Griggs J, Wilson RL, Gentile M. Cholesterol values are poor markers of disease risk in a chronic disease population. *Clinical Lipidology and Metabolic Disorders.* 2009 Oct 1;4(5):545.
6. Wang B, Guo Z, Li H, Zhou Z, Lu H, Ying M, et al. Non-HDL cholesterol paradox and effect of underlying malnutrition in patients with coronary artery disease: A 41,182 cohort study. *Clin Nutr.* 2022 Mar;41(3):723-30.
7. Kumthekar GV, Mondhe SD, Hedau S, Naidu S, Chakravarthi RM. Reverse Epidemiology for Lipid Disorders in Hemodialysis-

- Dependent Patients: Role of Dilutional Hypolipidemia. *Indian J Nephrol.* 2022 Mar-Apr;32(2):104-9.
8. Fröhlich H, Raman N, Täger T, Schellberg D, Goode KM, Kazmi S, et al. Statins attenuate but do not eliminate the reverse epidemiology of total serum cholesterol in patients with non-ischemic chronic heart failure. *Int J Cardiol.* 2017 Jul 1;238:97-104.
9. Ravnskov U, Diamond DM, Hama R, Hamazaki T, Hammarskjöld B, Hynes N, et al. Lack of an association or an inverse association between low-density-lipoprotein cholesterol and mortality in the elderly: a systematic review. *BMJ Open.* 2016 Jun 12;6(6):e010401.
10. Richardson KA, Richardson LT, Bowden RG. Association of High-Density Lipoprotein Cholesterol, Renal Function, and Metabolic Syndrome: An Assessment of the 2013–2018 National Health and Nutrition Examination Surveys. *Kidney and Dialysis.* 2022 Jul 12;2(3):419-32.
11. Meng J, Bhalraam U, Merinopoulos I, Eccleshall S, Tsampasian V, Vassiliou V. Cholesterol paradox for cardiac events: is age the missing link? *European Journal of Preventive Cardiology.* 2024;31(Supplement_1):zwae175.367.
12. Wang SS, Yang SS, Pan CJ, Wang JH, Li HW, Chen SM, et al. Cholesterol paradox in the community-living old adults: is higher better? *J Geriatr Cardiol.* 2023 Dec 28;20(12):837-44.
13. Attia P. "The cholesterol paradox": a catchy phrase for an idea with no substance. Peter Attia. May 27, 2023. Accessed September 23, 2024. <https://peterattiamd.com/issues-with-the-cholesterol-paradox/>
14. Kalantar-Zadeh K. What is so bad about reverse epidemiology anyway? *Semin Dial.* 2007 Nov-Dec;20(6):593-601.
15. Orkaby AR. The Highs and Lows of Cholesterol: A Paradox of Healthy Aging? *J Am Geriatr Soc.* 2020 Feb;68(2):236-7.
16. Huang Y, Yan MQ, Zhou D, Chen CL, Feng YQ. The U-shaped association of non-high-density lipoprotein cholesterol with all-cause and cardiovascular mortality in general adult population. *Front Cardiovasc Med.* 2023 Feb 8;10:1065750.
17. Hariri Z, Kord-Varkaneh H, Alyahya N, Prabakar K, Găman MA, Abu-Zaid A. Higher Dietary Vitamin D Intake Influences the Lipid Profile and hs-CRP Concentrations: Cross-Sectional Assessment Based on The National Health and Nutrition Examination Survey. *Life (Basel).* 2023 Feb 19;13(2):581.
18. Fernandez ML, Murillo AG. Is There a Correlation between Dietary and Blood Cholesterol? Evidence from Epidemiological Data and Clinical Interventions. *Nutrients.* 2022 May 23;14(10):2168.
19. Wang B, Liu J, Chen S, Ying M, Chen G, Liu L, et al. Malnutrition affects cholesterol paradox in coronary artery disease: a 41,229 Chinese cohort study. *Lipids Health Dis.* 2021 Apr 19;20(1):36.
20. Zhang Z, Pereira SL, Luo M, Matheson EM. Evaluation of Blood Biomarkers Associated with Risk of Malnutrition in Older Adults: A Systematic Review and Meta-Analysis. *Nutrients.* 2017 Aug 3;9(8):829.
21. Jukema RA, Ahmed TAN, Tardif JC. Does low-density lipoprotein cholesterol induce inflammation? If so, does it matter? Current insights and future perspectives for novel therapies. *BMC Med.* 2019 Nov 1;17(1):197.
22. Ridker PM, Bhatt DL, Pradhan AD, Glynn RJ, MacFadyen JG, Nissen SE, et al. Inflammation and cholesterol as predictors of cardiovascular events among patients receiving statin therapy: a collaborative analysis of three randomised trials. *Lancet.* 2023 Apr 15;401(10384):1293-301.
23. Nowak MM, Niemczyk M, Florkczyk M, Kurzyńska M, Pączek L. Effect of Statins on All-Cause Mortality in Adults: A Systematic Review and Meta-Analysis of Propensity Score-Matched Studies. *J Clin Med.* 2022 Sep 25;11(19):5643.
24. Kaysen GA, Ye X, Raimann JG, Wang Y, Topping A, Usvyat LA, et al. Lipid levels are inversely associated with infectious and all-cause mortality: international MONDO study results. *J Lipid Res.* 2018 Aug;59(8):1519-28.
25. Chidambaram V, Kumar A, Majella MG, Seth B, Sivakumar RK, Voruganti D, et al. HDL cholesterol levels and susceptibility to COVID-19. *EBioMedicine.* 2022 Aug;82:104166.
26. Kissinger D. Are bacterial infections a major cause of cardiovascular disease? *Front Cardiovasc Med.* 2024 Sep 4;11:1389109.
27. Allaire J, Vors C, Couture P, Lamarche B. LDL particle number and size and cardiovascular risk: anything new under the sun? *Curr Opin Lipidol.* 2017 Jun;28(3):261-6.
28. Chen L, Chen S, Bai X, Su M, He L, Li G, et al. Low-Density Lipoprotein Cholesterol, Cardiovascular Disease Risk, and Mortality in China. *JAMA Netw Open.* 2024 Jul 1;7(7):e2422558.
29. Pichler G, Amigo N, Tellez-Plaza M, Pardo-Cea MA, Dominguez-Lucas A, Marrachelli VG, et al. LDL particle size and composition and incident cardiovascular disease in a South-European population: The Horta-Liposcale Follow-up Study. *Int J Cardiol.* 2018 Aug 1;264:172-8.
30. Nilsson G, Leppert J, Ohrvik J. Enigma of the cholesterol paradox in acute myocardial infarction: lessons from an 8-year follow-up of all-cause mortality in an age-matched and sex-matched case-control study with controls from the patients' recruitment area. *BMJ Open.* 2022 Jul 27;12(7):e057562.
31. Teis A, Cediel G, Amigó N, Julve J, Aranyó J, Andrés-Cordón J, et al. Particle size and cholesterol content of circulating HDL correlate with cardiovascular death in chronic heart failure. *Sci Rep.* 2021 Feb 4;11(1):3141.
32. Pirillo A, Catapano AL, Norata GD. Biological Consequences of Dysfunctional HDL. *Curr Med Chem.* 2019;26(9):1644-64.
33. Bonizzi A, Piuri G, Corsi F, Cazzola R, Mazzucchelli S. HDL Dysfunctionality: Clinical Relevance of Quality Rather Than Quantity. *Biomedicines.* 2021 Jun 25;9(7):729.
34. Bowden RG. The Role of Dysfunctional HDL in Clinical Practice and Research. *Biomed J Sci Tech Res.* 2023;53(4):44969-70.

35. Mishra M, Muthuramu I, De Geest B. HDL dysfunction, function, and heart failure. *Aging (Albany NY)*. 2019 Jan 17;11(2):293-4.
36. Ossoli A, Pavanello C, Giorgio E, Calabresi L, Gomaraschi M. Dysfunctional HDL as a Therapeutic Target for Atherosclerosis Prevention. <http://www.eurekaselect.com>. Accessed November 19, 2024. <https://www.eurekaselect.com/article/89144>
37. Cao J, Xu Y, Li F, Shang L, Fan D, Yu H. Protein markers of dysfunctional HDL in scavenger receptor class B type I deficient mice. *J Transl Med*. 2018 Jun 7;16(1):155.
38. Madaudo C, Bono G, Ortello A, Astuti G, Mingoia G, Galassi AR, et al. Dysfunctional High-Density Lipoprotein Cholesterol and Coronary Artery Disease: A Narrative Review. *J Pers Med*. 2024 Sep 19;14(9):996.
39. Record M, Silvente-Poirot S, Poirot M, Wakelam MJO. Extracellular vesicles: lipids as key components of their biogenesis and functions. *J Lipid Res*. 2018 Aug;59(8):1316-24.
40. Pfrieger FW, Vitale N. Cholesterol and the journey of extracellular vesicles. *J Lipid Res*. 2018 Dec;59(12):2255-61.
41. Cleeman J. ATP III Guidelines At-A-Glance Quick Desk Reference. National Cholesterol Education Program. U.S. Department of Health and Human Services. 2001.