REVIEW

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The role of low- and high-density lipoprotein profiles in acute coronary syndrome

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ABSTRACT

Acute coronary syndrome (ACS) represents the most severe manifestation of ischaemic heart disease and remains a leading cause of cardiac mortality, carrying a particularly significant and growing burden in Indonesia, where regional prevalence continues to exceed the national average. Dyslipidemia, specifically elevated low-density lipoprotein cholesterol (LDL-C) and reduced high-density lipoprotein cholesterol (HDL-C), is among the most critical modifiable risk factors for the atherosclerotic process that underlies ACS, yet the holistic preventive significance of managing both lipid fractions simultaneously remains underemphasized in clinical practice. This narrative review synthesizes current evidence on the atherogenic role of LDL-C, the cardioprotective function of HDL-C, their combined and interactive contribution to coronary risk, and lifestyle-based preventive strategies that can favorably modify both parameters. The evidence reviewed demonstrates that elevated LDL-C and low HDL-C operate through distinct yet complementary pathways, lipid deposition and oxidative plaque destabilization on one hand, and loss of reverse cholesterol transport and endothelial protection on the other, and that their coexistence compounds atherogenic risk disproportionately. A holistic preventive approach integrating dietary modification, regular physical activity, smoking cessation, and weight management is proposed as the most sustainable strategy for simultaneously addressing both lipid abnormalities and reducing the burden of ACS at the individual and population level.

Keywords: acute coronary syndrome, cholesterol, HDL, LDL, prevention.
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INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of death globally, accounting for an estimated 17.8 million deaths annually according to the World Health Organization (WHO) in 2022.[1] Among the spectrum of cardiovascular diseases, ACS encompassing unstable angina pectoris (UAP), non-ST elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI) represents the most severe and life-threatening manifestation of ischaemic heart disease.[2,3] Epidemiologically, ACS carries an overall mortality of approximately 30%, with nearly half of deaths occurring before the patient reaches hospital, and its incidence continues to rise in developing countries.[4,5] In Indonesia, ACS-related deaths account for 66.6% of all cardiac deaths, and the Province of Bali records a prevalence of ischaemic heart disease of 1.0%, placing it fourth nationally and above the national average of 0.85%.[2,6]

The principal underlying cause of ACS is atherosclerosis, driven by subendothelial accumulation of lipids and inflammatory cells, leading to fibrous plaque formation and eventual rupture with thrombotic occlusion of the coronary lumen.[7,8] Among modifiable risk factors, lipid imbalance particularly elevated LDL-C and reduced HDL-C has been identified as a principal contributor to atherogenesis.[9,10] Despite this well-established basis, published studies have yielded inconsistent findings on the association of these lipid fractions with ACS, reflecting differences in populations, settings, and analytic approaches.[11–14] This narrative review therefore aims to synthesise evidence on the roles of LDL-C and HDL-C in ACS and the holistic preventive strategies that address both parameters.

RESULTS

Role of LDL in Atherogenesis

LDL-C is the primary lipid mediator of atherosclerosis and the most extensively studied atherogenic risk factor in coronary artery disease. When circulating LDL-C exceeds the endothelium's regulatory capacity, particles infiltrate the subendothelial space and undergo oxidative modification, producing oxidised LDL (Ox-LDL).[8,9] Ox-LDL activates endothelial cells to upregulate adhesion molecules including VCAM-1 and ICAM-1 which recruit monocytes that differentiate into macrophages and internalise Ox-LDL via scavenger receptors, transforming into lipid-laden foam cells.[9,12] The aggregation of foam cells forms the fatty streak, the earliest atherosclerotic lesion, which progressively evolves into fibrous plaques that narrow the coronary lumen and, upon rupture, precipitate ACS.[7,15]

Beyond foam cell formation, elevated LDL-C suppresses endothelial nitric oxide synthase (eNOS) activity, reducing nitric oxide (NO) bioavailability and thereby impairing vasodilation and promoting a pro-thrombotic milieu through increased platelet activation.[10] The clinical literature consistently supports a positive relationship between LDL-C concentration and ACS risk: Rachman (2022) found that 67% of ACS patients had suboptimal

LDL-C and demonstrated a significant association with ACS occurrence,[11] while Karo et al. (2020) showed that elevated LDL-C was significantly associated with increased ACS severity.[12] Azzahra (2024) further corroborated these findings, reporting that LDL-C was substantially higher in ACS patients versus non-ACS controls with a large effect size (Cohen's d = 1.174),[16] and Aswara (2022) similarly documented significantly higher LDL-C levels in coronary artery disease patients compared with non-cardiac controls.[15]

Protective Role of HDL

HDL-C is the principal anti-atherogenic lipoprotein, exerting its cardioprotective effects primarily through reverse cholesterol transport (RCT), a process by which excess cholesterol is retrieved from peripheral tissues and returned to the liver for excretion.[8,10] HDL is secreted by hepatocytes and enterocytes as nascent, disc-shaped particles enriched in apolipoprotein A-I (ApoA-I). Upon reaching the arterial wall, ApoA-I binds to the ATP-binding cassette transporter A1 (ABCA1) on macrophage membranes, triggering the efflux of intracellular cholesterol and phospholipids to the extracellular space. The cholesterol-laden particles are then packaged into mature HDL and transported to the liver, where they are taken up via scavenger receptor class B type I (SR-BI) and the cholesterol is excreted into bile.[10,17] An indirect pathway further expands HDL's cholesterol-clearing capacity: lecithin-cholesterol acyltransferase (LCAT), carried on the HDL surface, esterifies free cholesterol to cholesteryl esters, which are subsequently transferred to other lipoprotein classes via cholesteryl ester transfer protein (CETP), allowing hepatic clearance through the LDL receptor pathway.[8,17]

Beyond RCT, HDL exerts direct endothelial protection through its associated enzyme paraoxonase-1 (PON1), which prevents the oxidative modification of LDL particles, thereby blocking a key step in foam cell formation and atherogenesis.[8,10] PON1 also inhibits the expression of endothelial adhesion molecules, reduces monocyte recruitment to the subendothelial space, and stimulates the synthesis of prostacyclin,

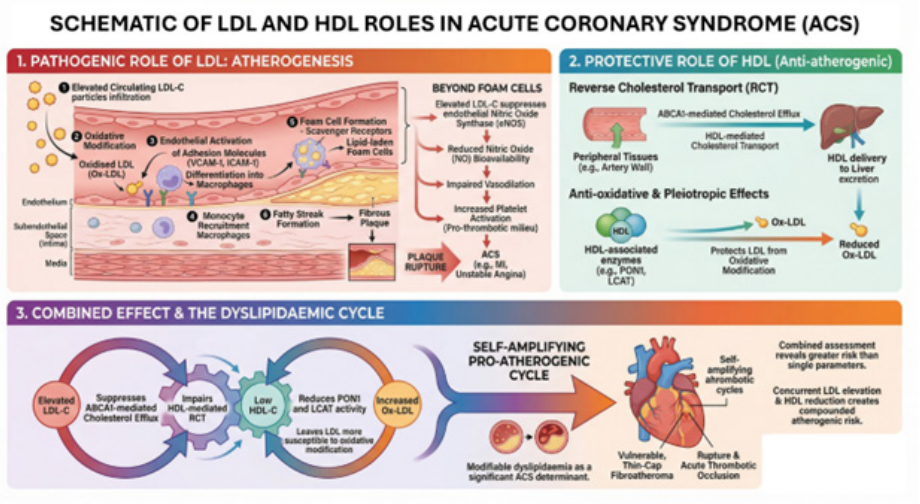

Figure 1. Roles of LDL and HDL in ACS

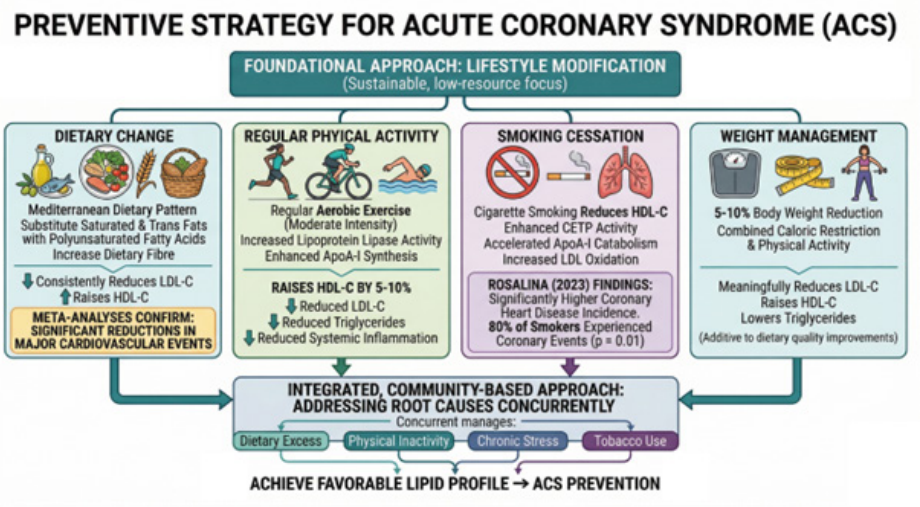

Figure 2. Preventive strategy for acute coronary syndrome

a potent vasodilator and platelet aggregation inhibitor that maintains vascular homeostasis.[10] Collectively, these mechanisms position HDL as a multifunctional anti-atherogenic particle whose protective value extends well beyond simple cholesterol removal. However, HDL function is not determined by concentration alone: under conditions of chronic oxidative stress or systemic inflammation, HDL particles can become dysfunctional, losing their antioxidant and anti-inflammatory properties and, paradoxically, acquiring pro-inflammatory characteristics that may actively accelerate atherogenesis.[8,18]

The clinical literature consistently supports an inverse relationship between HDL-C concentration and ACS risk. Low HDL-C was significantly associated with STEMI events (p = 0.019),[13] and a study reported that 87.5% of 80 ACS patients had low HDL-C (≤40–50 mg/dL), indicating that a substantially reduced HDL-C level is a near-universal feature of the ACS lipid profile.[19] Dharayani (2024) further confirmed a significant relationship between low HDL-C and ACS in a Balinese hospital cohort,[14] and Karani and Erizon (2020) underscored that HDL concentrations below 40 mg/dL are independently associated with accelerated atherogenesis and elevated coronary risk.[10] According to the Indonesian Endocrinologist Association guideline, an HDL-C level below 40 mg/dL is classified as low, while a level of 60 mg/dL or above is considered optimal for cardiovascular risk reduction.[20]

Combined Effect of LDL and HDL

The cardiovascular risk associated with LDL-C and HDL-C cannot be fully appreciated when each is assessed in isolation. The simultaneous presence of elevated LDL-C and low HDL-C creates a self-amplifying pro-atherogenic cycle: high LDL-C suppresses ABCA1-mediated cholesterol efflux impairing HDL-mediated RCT at its most critical point while low HDL-C reduces PON1 and LCAT activity, leaving LDL particles more susceptible to oxidative modification.[17,18] Together, this interaction promotes the development of vulnerable, thin-cap fibroatheromas the lesion subtype most prone to rupture and acute thrombotic occlusion to a degree disproportionately greater than either abnormality alone (**Figure 1**).[12,21]

The clinical literature supports the superiority of combined lipid assessment over single-parameter evaluation. Esmiralda (2023) reported that patients with ACS showed a pattern of concurrent LDL-C elevation and HDL-C reduction compared with non-ACS controls, highlighting the compounded atherogenic risk when both lipid abnormalities coexist.[6] Budiman (2015) similarly demonstrated that dyslipidaemia encompassing both elevated LDL-C and reduced HDL-C was significantly associated with acute myocardial infarction, with the combined effect conferring greater risk than individual lipid derangements.[21] Tall et al. (2022) further emphasised that addressing dyslipidaemic risk beyond LDL-C lowering, specifically by targeting residual risk associated with low HDL-C, represents an important but underutilised therapeutic frontier,[22] while Agung & Anindya (2024) confirmed that modifiable lipid-related risk factors including dyslipidaemia remain significant determinants of ACS in a local Indonesian case-control study.[23]

Preventive Strategy

The modifiable nature of both LDL-C and HDL-C places dyslipidaemia at the centre of ACS prevention strategies. Lifestyle modification encompassing dietary change, regular physical activity, smoking cessation, and weight management is the foundational and most sustainable approach to achieving a favourable lipid profile (**Figure 2**), particularly in lower-resource settings where long-term pharmacotherapy may be difficult to maintain.[20,24,25] Substituting saturated and trans-fatty acids with polyunsaturated fatty acids, increasing dietary fibre, and adhering to a Mediterranean dietary pattern consistently reduce LDL-C and raise HDL-C, with meta-analyses of randomised controlled trials confirming significant reductions in major cardiovascular events.[24,26] Regular aerobic exercise of moderate intensity raises HDL-C by 5–10% through increased lipoprotein lipase activity and enhanced ApoA-I synthesis, while simultaneously reducing LDL-C, triglycerides, and systemic inflammation.[27]

Smoking cessation and weight management further complement dietary and exercise interventions. Cigarette smoking reduces HDL-C through enhanced cholesteryl ester transfer protein (CETP) activity and accelerated ApoA-I catabolism, while increasing LDL oxidation, and Rosalina (2023) reported that smokers had a significantly higher incidence of coronary heart disease compared with non-smokers ($p = 0.01$), with 80% of smokers in the study population experiencing coronary events.[28] A 5–10% reduction in body weight through combined caloric restriction and physical activity meaningfully reduces LDL-C, raises HDL-C, and lowers triglycerides, effects that are additive to dietary quality improvements alone.[24] From a holistic standpoint, dyslipidaemia frequently reflects a broader systemic imbalance across multiple health behaviours dietary excess, physical inactivity, chronic stress, and tobacco use and effective ACS prevention therefore requires integrated, community-based approaches that address these root causes concurrently, as emphasised by Firdaus (2024) and supported by lifestyle medicine evidence.[25,29]

CONCLUSION

This narrative review demonstrates that elevated LDL-C and low HDL-C are both independent and interacting risk factors for acute coronary syndrome, operating through distinct yet complementary atherogenic pathways: LDL-C drives subendothelial lipid deposition, oxidative modification, and plaque destabilisation, while inadequate HDL-C removes the anti-inflammatory, antioxidant, and reverse cholesterol transport mechanisms that would otherwise contain these processes, such that the coexistence of both lipid abnormalities compounds coronary risk beyond the contribution of either alone. From a holistic preventive standpoint, dyslipidaemia is not merely a biochemical finding but a modifiable manifestation of broader lifestyle imbalance, and its management must extend beyond pharmacotherapy to encompass dietary improvement, regular physical activity, smoking cessation, and sustainable community-based health behaviour. It is therefore recommended that combined LDL-C and HDL-C assessment be incorporated into routine cardiovascular risk stratification, that lifestyle-based preventive interventions targeting both lipid fractions be integrated into clinical guidelines and public health programmes across Indonesia, and that future prospective multicentre studies be conducted in local populations to strengthen the evidence base for holistic lipid management in ACS prevention.

CONFLICT OF INTEREST

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All authors contributed equally in the writing process of this article.

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