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# Small dense LDL: An underestimated driver of atherosclerosis (Review)

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**Abstract.** Cardiovascular disease remains the leading cause of death globally, despite advances in lipid-lowering strategies. A distinct subfraction of low-density lipoprotein (LDL) particles, known as small LDL (sdLDL; particle size, 15-20 nm), has been found to play a disproportionately large role in atherogenesis and residual cardiovascular risk when present at elevated concentrations, particularly in individuals with normocholesterolemia but underlying metabolic disorders. The present review critically examines the pathophysiological characteristics that render sdLDL highly atherogenic. These include increased permeability, prolonged circulation and heightened susceptibility to oxidative modification. The review also explores how sdLDL promotes endothelial dysfunction, foam cell formation, inflammation and plaque instability. Furthermore, it emphasizes the diagnostic challenges of sdLDL measurement, its clinical relevance in high-risk populations and the limitations of current lipid panels in capturing its contribution to disease progression. Elevated sdLDL levels are commonly observed among individuals with metabolic syndrome, insulin resistance, type 2 diabetes and obesity. Multiple epidemiological studies indicate that elevated sdLDL levels are an independent predictor of cardiovascular events. Targeted lifestyle and pharmacological strategies to reduce sdLDL levels are also reviewed, including statins, fibrates, niacin, w-3 fatty acids, proprotein convertase subtilisin/kexin type 9 inhibitors and RNA-targeting agents. The greater incorporation of sdLDL testing into risk assessment tools and clinical guidelines is recommended, and strategies for advancing diagnostics, including artificial intelligence-driven prediction models and advanced lipid profiling are proposed.

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**Contents**

## 1. Introduction

Low-density lipoprotein cholesterol (LDL-C) has long been recognized as a central contributor to atherosclerosis, the underlying pathology of most cases of cardiovascular disease (CVD). Globally, CVD is the leading cause of morbidity and mortality (1). For several decades, elevated LDL-C levels have provided the cornerstone of our understanding of atherogenesis, and LDL-C has been the principal target of lipid-lowering therapies (2).

In the management of atherosclerotic CVD (ASCVD), European and American guidelines differ regarding the preferred lipid markers for risk assessment and therapeutic targets. European guidelines, particularly those from the European Society of Cardiology (ESC) and the European Atherosclerosis Society, have increasingly advocated for the use of non-high density lipoprotein cholesterol (non-HDL-C) and apolipoprotein B (ApoB) as superior indicators of atherogenic lipoprotein burden (3-5). Non-HDL-C encompasses all atherogenic particles, including LDL, very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL) and lipoprotein(a) [Lp(a)]. Therefore, non-HDL-C is a more comprehensive marker than LDL-C, particularly in patients with hypertriglyceridemia or metabolic syndrome. ApoB, which directly reflects the number of atherogenic lipoprotein particles, offers additional precision in risk stratification, especially when discordance exists between LDL-C levels and particle number (6). By contrast, the American College of Cardiology (ACC) and American Heart Association guidelines emphasize LDL-C as the primary target of lipid-lowering therapy, largely due to its extensive historical validation in randomized controlled trials (7,8).

Although non-HDL-C and ApoB are both acknowledged as secondary or optional markers, they are not routinely prioritized in clinical practice in the USA. This divergence reflects differences in clinical emphasis: European guidelines prioritize a comprehensive assessment of atherogenic risk, particularly in complex cases, whereas American guidelines maintain a simpler, population-level focus based primarily on LDL-C. However, as evidence continues to accumulate regarding the prognostic value of non-HDL-C and ApoB, clinical practices may converge in future guideline updates.

Despite the widespread use of statins and aggressive LDL-C reduction strategies, a considerable number of patients continue to experience cardiovascular events, a phenomenon referred to as residual risk (9,10). This has prompted researchers and clinicians to look beyond total LDL-C and explore the heterogeneity of LDL particles, particularly the role of small dense LDL (sdLDL), in the pathogenesis of CVD (10,11).

sdLDL is a subfraction of LDL where the particles are smaller in size, more compact in structure, and more atherogenic compared with their larger, more buoyant LDL counterparts (12-14). Although sdLDL comprises a relatively small proportion of the total LDL mass, it has a disproportionately large impact on vascular health (15,16). Its unique metabolic and physicochemical characteristics, including increased arterial wall penetration, prolonged plasma half-life and heightened susceptibility to oxidative modification, render it particularly potent in promoting endothelial dysfunction, foam cell formation, inflammation and plaque instability (12). Unlike total LDL-C, which provides a general estimate of cholesterol load, sdLDL is reflective of vascular injury via an insidious lipid-driven mechanism (17,18).

The clinical significance of sdLDL is clearly apparent in individuals with metabolic disorders (18). Patients with type 2 diabetes, insulin resistance, obesity and metabolic syndrome often present with a so-called lipid paradox, defined as having relatively normal LDL-C levels but a high burden of sdLDL particles (19). In such cases, traditional lipid profiles may underestimate cardiovascular risk, resulting in missed opportunities for preventive intervention. This growing recognition of sdLDL as a key contributor to residual cardiovascular risk has started to challenge existing paradigms in cardiovascular risk stratification and treatment, leading to the suggestion that a more detailed, particle-based approach to lipidology is necessary (20,21).

Despite the burgeoning evidence of its atherogenic potential, sdLDL remains underutilized in routine clinical practice. Its more widespread adoption has been restricted by a number of barriers, including limited access to advanced lipid testing, a lack of standardized measurement protocols and inadequate integration into clinical guidelines (15,22). Nevertheless, given advances in diagnostic technology, the increasing availability of targeted therapies, and a shift towards precision medicine, sdLDL is on the cusp of transitioning from being primarily a research interest to recognition as a clinically actionable biomarker.

The present review aims to provide a comprehensive overview of sdLDL as an underestimated driver of atherosclerosis. It explores the mechanistic underpinnings of sdLDL-induced vascular damage, evaluates its diagnostic value and limitations in clinical settings, and examines current and emerging treatment strategies aimed at reducing sdLDL burden. Furthermore, the review discusses future directions and the integration of sdLDL into risk assessment models and personalized therapeutic pathways. Via this approach, it highlights the importance of reconsidering how lipid-associated cardiovascular risk should be assessed and treated.

## 2. The atherogenicity of sdLDL

sdLDL particles represent a highly atherogenic subfraction of LDL-C that contributes disproportionately to the initiation and progression of atherosclerosis (13,23). Although these particles are a minor component of total LDL, their biological behavior renders them potent drivers of vascular pathology (24). Understanding the atherogenic nature of sdLDL requires consideration of the structural features of these particles, along with their metabolic characteristics, interactions with the arterial wall, and role in endothelial dysfunction and plaque formation (24-26).

There is currently no universally accepted cut-off for defining an elevated sdLDL particle concentration. This lack of standardization complicates the interpretation of sdLDL elevation in different populations and clinical contexts (26). Metabolic remodeling of LDL results in sdLDL particles that are cholesterol-depleted, triglyceride-rich and prone to oxidation (24). Critically, sdLDL particles have a prolonged half-life in plasma due to reduced affinity for the LDL receptor. This leads to the particles existing for a prolonged time in circulation, thereby increasing the likelihood of them undergoing further atherogenic modifications (27,28) (Table I).

A defining feature of sdLDL is its enhanced ability to penetrate the endothelial barrier and accumulate within the subendothelial space of arteries. Beyond their smaller size, sdLDL particles exhibit altered surface characteristics-such as reduced sialic acid content, increased negative charge, and lower phospholipid content-that facilitate passage across the endothelium (14,29). Once within the arterial intima, these modifications also confer a stronger binding affinity to proteoglycans in the extracellular matrix, promoting their retention and thereby amplifying their atherogenic potential.

The particles become trapped by arterial wall proteoglycans and, once retained, are highly susceptible to oxidative modification, a key initiating event in atherogenesis (15). This susceptibility to oxidation is further increased by a relative lack of endogenous antioxidants such as vitamin E, and by a lipid core enriched in polyunsaturated fatty acids that are prone to peroxidation (30).

Oxidized sdLDL (oxLDL) has been shown to exert a range of pathological effects (13,16,31) (Table II). It promotes endothelial dysfunction by reducing nitric oxide bioavailability and increasing the expression of vascular adhesion molecules, including vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 (22,30,32). The adhesion molecules facilitate the recruitment of circulating monocytes, which then migrate into the arterial intima and differentiate into macrophages. These macrophages then internalize oxLDL via scavenger receptors, becoming lipid-laden foam cells that form the basis of early atherosclerotic plaques (32-35).

Beyond foam cell formation, sdLDL also contributes to a pro-inflammatory and pro-thrombotic vascular

Table I. Summary of key concepts in the atherogenicity of sdLDL.

| Aspect | Key points | Advantages | Challenges | (Refs.) |
|---|---|---|---|---|
| Definition and relevance | sdLDL is a small, dense subfraction of LDL-C with disproportionately high atherogenic potential | Recognizing sdLDL explains residual cardiovascular risk despite normal LDL-C | Not routinely measured in clinical practice | (14) |
| Size and structure | 18-20.5 nm diameter; dense, triglyceride-rich, cholesterol-poor particles with prolonged plasma residence time | Explains enhanced atherogenic potential compared with that of larger LDL | Requires specialized testing, e.g., NMR or gradient gel electrophoresis | (26) |
| Metabolic characteristics | Poor LDL receptor affinity; more likely to remain in circulation and undergo oxidative modification | Identifies patients with increased oxidative risk and prolonged lipid exposure | No standardized thresholds across populations; high variability | (24) |
| Endothelial penetration | Easily traverses the endothelium and binds arterial wall proteoglycans | Helps explain early subendothelial retention in atherogenesis | Challenging to assess or visualize directly *in vivo* | (24) |
| Susceptibility to oxidation | Enriched in polyunsaturated fats and depleted in antioxidants such as vitamin E, making it prone to oxidation | Oxidized sdLDL triggers immune and inflammatory responses | Not distinguished by standard lipid panels; requires indirect evidence | (31) |
| Pathological effects of oxLDL | Promotes endothelial dysfunction, inflammation and foam cell formation | Target for anti-inflammatory and antioxidant therapies | Lack of specific inhibitors of sdLDL oxidation in current practice | (32) |
| Inflammatory and thrombotic role | Activates NF-κB, promotes the release of cytokines, e.g., IL-6 and TNF-α, and promotes platelet aggregation | Links lipid abnormalities with systemic inflammation and thrombosis | Mechanistic complexity makes therapeutic targeting challenging | (36) |
| Endothelial dysfunction | Reduces nitric oxide production; increases oxidative stress and vascular tone loss | Early marker of vascular injury; potential target for early interventions | Few treatments directly reverse endothelial dysfunction associated with sdLDL | (29) |
| Plaque instability | Associated with thin fibrous caps, large necrotic cores, and macrophage-rich plaques, which are features of rupture-prone lesions | Provides insight into acute coronary syndrome pathogenesis | Imaging or detecting sdLDL-rich plaques *in vivo* is limited | (48) |
| Clinical associations | Elevated in metabolic syndrome, type 2 diabetes, insulin resistance and obesity, even when LDL-C appears normal | Identifies patients with hidden high-risk beyond LDL-C levels | Frequently missed in standard risk assessments | (93) |
| Epidemiological evidence | Independently associated with cardiovascular events, e.g., in the Quebec Cardiovascular study and ARIC study | Strong justification for inclusion in future risk prediction models | Longitudinal data required to determine whether sdLDL reduction improves outcomes | (52) |
| Clinical implications | Should be considered a therapeutic and diagnostic target in modern cardio-metabolic care | Guides precision medicine strategies and residual risk management | Integration into guidelines, broader awareness among clinicians, and cost-effective testing are necessary | (24) |

ARIC, Atherosclerosis Risk in Communities; IL-6, interleukin 6; LDL, low-density lipoprotein; LDL-C, LDL cholesterol; NF-κB, nuclear factor-κB; NMR, nuclear magnetic resonance; oxLDL, oxidized LDL; sdLDL, small dense LDL; TNF-α, tumor necrosis factor-α.

Table II. Summary of the cellular and molecular mechanisms of sdLDL in atherogenesis.

| Mechanism | Key features | Molecular players and outcomes | (Refs.) |
|---|---|---|---|
| Structural features | Small size (15-20 nm), dense core, triglyceride-rich, cholesterol-depleted | Increased arterial permeability; prolonged circulation due to reduced LDL receptor affinity | (24) |
| Endothelial dysfunction | Enhanced endothelial penetration via proteoglycan binding | ↑ Oxidative stress; ↓ nitric oxide bioavailability; ↑ VCAM-1/ICAM-1 expression | (51) |
| Oxidative susceptibility | Lipid core rich in polyunsaturated fatty acids; low antioxidant content | Rapid oxidation to oxLDL; activation of scavenger receptors, e.g., LOX-1 and CD36 | (40) |
| Foam cell formation | Macrophage uptake of oxidized sdLDL via scavenger receptors | Lipid-laden foam cells; NLRP3 inflammasome activation; ↑ IL-1β and IL-6 | (35) |
| Inflammatory signaling | NF-κB activation; cytokine release | ↑ TNF-α, MCP-1; recruitment of monocytes/ macrophages; vascular inflammation | (42) |
| Plaque instability | Promotion of necrotic core formation; thin fibrous cap | Metalloproteinase activation; smooth muscle cell apoptosis; ↑ plaque rupture risk | (47) |
| Prothrombotic effects | Platelet activation; tissue factor expression | ↑ Fibrinogen; ↑ PAI-1; thrombus formation post-plaque rupture | (41) |
| Metabolic interactions | Association with insulin resistance, hypertriglyceridemia | ↑ ApoC-III; ↓ LDL receptor clearance; CETP-mediated lipid exchange | (39) |

ApoC-III, apolipoprotein C-III; CETP, cholesteryl ester transfer protein; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; LDL, low-density lipoprotein; LOX-1, lectin-like oxLDL receptor-1; MCP-1, monocyte chemoattractant protein-1; NF-κB, nuclear factor-κB; NLRP3, NLR family pyrin domain containing 3; oxLDL, oxidized LDL; PAI-1, plasminogen activator inhibitor-1; sdLDL, small dense LDL; TNF-α, tumor necrosis factor-α; VCAM-1, vascular cell adhesion molecule-1.

environment (22,24,26,36) (Table II). It activates transcription factors such as nuclear factor-κB (NF-κB), leading to the upregulation of inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-α and monocyte chemoattractant protein-1 (37-42). This inflammatory response drives further immune cell infiltration, promotes smooth muscle cell proliferation, and contributes to extracellular matrix remodelling (37,43,44).

In addition, sdLDL induces platelet aggregation and promotes a pro-coagulant state, thereby increasing the risk of thrombotic events, including myocardial infarction and ischemic stroke (37,43).

Elevated levels of sdLDL are closely associated with endothelial dysfunction (29), an early marker of vascular injury. sdLDL impairs vasodilation by reducing the synthesis of nitric oxide and increasing oxidative stress within endothelial cells (38). This disruption of vascular homeostasis facilitates further lipoprotein infiltration and immune cell activation, thereby sustaining a self-reinforcing cycle of injury and repair (45).

In a study by Miceli *et al* (46), the histological analysis of human atherosclerotic plaques confirmed that lesions enriched in sdLDL are more likely to exhibit features of instability, including thin fibrous caps, large necrotic lipid cores and extensive inflammatory cell infiltration (47). Such features increase the likelihood of plaque rupture, an event that can trigger acute coronary syndrome (ACS) and sudden cardiovascular death (48).

Clinically, sdLDL concentrations are often elevated in individuals with metabolic syndrome, type 2 diabetes, obesity and insulin resistance, all of which are conditions characterized by atherogenic dyslipidemia (39,40,49-51). Notably, patients with these metabolic disturbances may present with normal or near-normal LDL-C levels, while harboring a predominance of sdLDL particles, thereby evading conventional risk stratification. Epidemiological studies, including the Quebec Cardiovascular Study and the Atherosclerosis Risk in Communities (ARIC) Study, have demonstrated that elevated sdLDL levels are independently associated with an increased cardiovascular risk, even after adjustment for total LDL-C and other traditional risk factors (52).

Given its distinct biological behaviour and strong association with residual cardiovascular risk, sdLDL should be considered a critical target for both diagnostic assessment and therapeutic intervention in modern cardio-metabolic care.

## 3. Diagnostic significance and limitations in clinical practice

Although total LDL-C has long been a cornerstone of cardiovascular risk assessment and lipid-lowering strategies, the recognition of sdLDL as a highly atherogenic subfraction has prompted a critical re-evaluation of traditional diagnostic paradigms. Increasing evidence suggests that conventional lipid panels, which typically measure total cholesterol, LDL-C, HDL-C and triglycerides, may not sufficiently capture the full spectrum of lipoprotein-associated cardiovascular risk, particularly in individuals with metabolic dysregulation (53,54). In this context, sdLDL has emerged as a powerful and independent predictor of ASCVD, especially in populations that may appear to be at low risk according to conventional criteria (55-57) (Table III).

Table III. Diagnostic relevance and clinical limitations of sdLDL.

| Aspect | Key insights and clinical relevance | Limitations and challenges | Solutions and opportunities | (Refs.) |
|---|---|---|---|---|
| Clinical importance | sdLDL is a highly atherogenic subfraction linked to residual cardiovascular risk, even in patients with normal LDL-C | Often overlooked in standard lipid panels and clinical guidelines | Use sdLDL to improve risk stratification, particularly in patients with metabolic syndrome or diabetes | (14) |
| Risk stratification | Independently predicts ASCVD events and coronary calcification; validated in large cohorts, e.g., Quebec, ARIC and MESA | Predictive value may vary by population or sdLDL threshold | Combine sdLDL with other markers, e.g., apoB, LDL-P and/or HDL-C, for a more comprehensive lipid risk profile | (56) |
| Measurement methods | Techniques include NMR, electrophoresis, precipitation, and enzymatic assays; direct methods are becoming more accessible | High cost, low availability, and lack of inter-laboratory standardization | Use validated, standardized methods and maintain consistency across serial testing | (20) |
| Cut-off values | sdLDL thresholds differ by method and population; no universal reference ranges exist | Lack of standard cut-offs limits clinical decision-making | Develop and adopt population-specific reference values; interpret results contextually | (62) |
| Association with diabetes | sdLDL is commonly elevated in type 2 diabetes and contributes to cardiovascular risk | Not all diabetic patients show increased risk from sdLDL; context matters | Interpret alongside glycemic control and other lipid metrics; use as an adjunct, not a replacement | (58) |
| Therapeutic use | Helps identify residual risk in statin-treated patients; may inform therapy intensification | No defined target levels or verified benefits from lowering sdLDL directly | Use sdLDL to guide treatment in high-risk patients pending outcome data | (78) |
| Pre-analytical considerations | Stable in frozen serum for up to 30 days; fasting preferred for accuracy | Hemolysis, lipemia or icterus can compromise results; non-fasting samples reduce accuracy | Standardize patient preparation and reject samples that are compromised | (59) |
| Indirect surrogates | Non-HDL-C and apoB correlate with sdLDL and are practical for routine use | Not specific to sdLDL and may underrepresent sdLDL burden in certain cases | Use when sdLDL testing is unavailable; supplement with direct sdLDL if necessary | (57) |
| Emerging tools | Tools such as the LP-IR index and advanced sub-fraction profiling aid in precision risk assessment | Limited clinical validation and lack of interpretative guidelines | Investigate in research; potential role in individualized therapy | (94) |
| Clinical integration | sdLDL testing adds value in selected patients with unexplained residual risk or complex lipid profiles | Not incorporated into current guidelines or risk calculators | Use as a supplemental test, particularly in metabolic syndrome, lean obesity, or discordant lipid phenotypes | (61) |

ApoB, apolipoprotein B; ARIC, Atherosclerosis Risk in Communities; ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; LDL-C, LDL cholesterol; LDL-P, LDL particle number; LP-IR, lipoprotein insulin resistance index; MESA, Multi-Ethnic Study of Atherosclerosis; NMR, nuclear magnetic resonance; sdLDL, small dense LDL.

Numerous epidemiological studies have shown that elevated sdLDL levels are strongly associated with an increased risk of major adverse cardiovascular events, even after adjustment for total LDL-C and other conventional risk factors (25,52,58,59). This predictive strength is particularly notable in individuals with metabolic syndrome, type 2 diabetes and insulin resistance, in whom sdLDL concentrations are often elevated despite normal LDL-C levels. In these populations, sdLDL is frequently accompanied by high triglyceride and low HDL-C levels, forming a pro-atherogenic lipid profile that accelerates plaque development and increases the risk of plaque instability and cardiovascular events (20,39,60,61).

The clinical utility of sdLDL as a risk marker is closely associated with its sensitivity and specificity. sdLDL demonstrates a high sensitivity for detecting an increased ASCVD risk in patients with metabolic dysfunction or residual risk, even when LDL-C is optimally controlled (56,62). Its small particle size, greater arterial wall penetration and heightened susceptibility to oxidation allow sdLDL to reflect early vascular injury and subclinical atherosclerosis that may not be captured by standard lipid panels. However, the specificity of sdLDL is context-dependent (61). Although elevated sdLDL is highly specific for increased cardiovascular risk in high-risk groups such as diabetics and individuals with metabolic syndrome, its specificity may be lower in the general population, where sdLDL levels can overlap between healthy and at-risk individuals (24,60,63). Furthermore, assay variability and lack of standardized cut-off values can affect both sensitivity and specificity, underscoring the requirement for harmonized measurement protocols.

The diagnostic performance of sdLDL is enhanced when combined with other biomarkers, such as ApoB, or inflammatory markers, such as high-sensitivity C-reactive protein (hs-CRP), which can improve sensitivity and specificity when identifying individuals with the highest risk (64,65).

Despite its clear prognostic value, the routine measurement of sdLDL in clinical practice remains limited, largely due to technical barriers, a lack of standardization and its absence from most current guidelines. Nevertheless, in select high-risk populations, particularly those with persistent cardiovascular risk despite optimal LDL-C levels, the quantification of sdLDL may provide valuable additional prognostic information to guide personalized treatment strategies. These factors indicate that sdLDL may be considered as a sensitive and clinically meaningful marker for ASCVD risk, particularly in patients with metabolic abnormalities or unexplained residual risk. Standardizing sdLDL assays and integrating sdLDL measurement into risk assessment algorithms may facilitate early detection and enable more targeted interventions for those patients at the greatest risk of cardiovascular events.

A major diagnostic implication of sdLDL is that it can identify individuals with elevated residual cardiovascular risk, specifically those whose total LDL-C levels fall within the normal or near-normal range but who harbour a high concentration of small, dense and highly atherogenic LDL particles. This situation is frequently observed in patients with type 2 diabetes, insulin resistance, obesity, metabolic syndrome and certain individuals with so-called 'lean' metabolic obesity (66). In such cases, relying on the standard LDL-C metric may give a false sense of security, while elevated sdLDL levels silently contribute to subclinical atherosclerosis (67).

Numerous epidemiological and clinical studies have demonstrated the independent prognostic value of sdLDL (68-70). For example, the Quebec Cardiovascular Study showed that high concentrations of sdLDL were strongly associated with an increased risk of ischemic heart disease, even after adjusting for LDL-C and other conventional risk factors (71,72). Similar associations were observed in the ARIC study and the Multi-Ethnic Study of Atherosclerosis, where sdLDL predicted coronary artery calcium progression and cardiovascular events (73,74).

These findings underscore the importance of moving beyond a simple assessment of total cholesterol, and also considering lipoprotein quality and particle size distribution when performing a clinical evaluation (75,76).

Importantly, sdLDL may contribute to residual cardiovascular risk in patients with otherwise normal LDL-C levels. Numerous studies have shown that individuals with elevated sdLDL levels can experience major adverse cardiovascular events, even when standard lipid metrics appear to be well controlled (77-79).

This has spurred interest in sdLDL as a potential marker of hidden risk, particularly in patients with premature coronary artery disease, recurrent events or a poor response to statin therapy (78,80).

In addition, sdLDL has been associated with specific clinical manifestations of ASCVD, including ACS and coronary artery calcification (81,82). Higher sdLDL concentrations have been shown to be associated with greater plaque burden, more extensive coronary stenosis and higher levels of circulating inflammatory markers, including hs-CFP and IL-6.

These associations suggest that sdLDL is not merely a marker of risk but may also play an active role in the progression and destabilization of atherosclerotic plaques. Despite compelling evidence, the adoption of sdLDL measurement in routine clinical practice remains limited. Current guidelines continue to prioritize LDL-C, non-HDL-C and ApoB, partly due to the lack of standardization in sdLDL assays and the scarcity of outcome-based intervention trials. However, in select high-risk populations, particularly those with metabolic dysfunction or persistent cardiovascular risk despite optimal LDL-C control, sdLDL quantification may offer additional prognostic value and support more personalized treatment strategies.

As already discussed, despite its clinical importance, the routine measurement of sdLDL remains limited in practice (Table III). A key barrier is the lack of standardization in analytical techniques. Several methods are available to quantify sdLDL, including gradient gel electrophoresis, ultracentrifugation, nuclear magnetic resonance (NMR) spectroscopy and ion mobility analysis (83). Each technique has its own advantages and limitations in terms of cost, accessibility, resolution and reproducibility. Among these, gradient gel electrophoresis and NMR spectroscopy are the most commonly applied in research settings (84); however, these techniques are not widely available in standard clinical laboratories and are often cost-prohibitive for routine use. Furthermore, there is currently no universally accepted cut-off value for defining elevated sdLDL concentrations. This lack of standardization complicates interpretation across different populations and clinical contexts. In addition, sdLDL levels are dynamic and can be influenced by diet, insulin sensitivity, weight changes, physical activity and pharmacological interventions (85). Consequently, interpreting a single measurement in isolation may not reflect long-term cardiovascular risk, unless values are monitored longitudinally or assessed alongside other metabolic parameters.

In clinical practice, several indirect markers have been proposed as surrogates for sdLDL burden. These include non-HDL-C, which has gained particular attention as a more comprehensive risk marker compared with LDL-C alone. By encompassing the total concentration of atherogenic lipoproteins, including LDL, VLDL, IDL and Lp(a), non-HDL-C correlates moderately well with sdLDL levels, and has been shown to more reliably reflect the overall atherogenic risk (86).

ApoB100 is another widely used surrogate. ApoB100 is a structural protein present on all liver-derived atherogenic lipoproteins, including VLDL, IDL and LDL. Since each of these particles carries a single molecule of ApoB100, its measurement serves as a reliable proxy for the total number of circulating atherogenic particles. However, an important but often overlooked limitation is that ApoB100 does not account for all atherogenic lipoproteins, particularly those of intestinal origin (87,88).

For example, VLDL remnants, which are partially lipolyzed derivatives obtained during VLDL metabolism, contain ApoB100 and have well-documented atherogenic potential (88). These remnants can bind to arterial wall proteoglycans, become retained in the subendothelial space, and are subsequently internalized by macrophages. This process activates Toll-like receptors 2 and 4 (TLR2 and TLR4), leading to localized inflammation and the progression of atherosclerosis. By contrast, chylomicron remnants, which originate from dietary fat metabolism in the intestine, carry ApoB48 rather than ApoB100 (89). Although not detected by ApoB100-based assays, chylomicron remnants contribute to atherogenesis through distinct, yet equally pathogenic mechanisms. They have been shown to activate TLR4 and the downstream NF-κB signaling pathway, thereby promoting endothelial dysfunction, monocyte adhesion and foam cell formation, which are key features of early atheromatous plaque development (90,91).

This highlights a fundamental limitation of relying solely on ApoB100 as a marker of atherogenic particle burden. Although ApoB100 reliably quantifies liver-derived lipoproteins, it fails to reflect the contribution of intestinally derived particles, such as chylomicron remnants. Consequently, a more nuanced approach to lipoprotein profiling may be necessary in specific clinical contexts, particularly in patients with postprandial dyslipidemia, insulin resistance or metabolic syndrome, where chylomicron remnants may play a disproportionately larger role in atherogenesis (92,93). While these markers are not specific to sdLDL, they are practical and cost-effective tools for the estimation of atherogenic risk in settings where direct sdLDL quantification is not possible.

Emerging approaches, such as use of the Lipoprotein Insulin Resistance Index and advanced lipoprotein subfraction testing using ion mobility or NMR spectroscopy, may soon provide clinicians with more nuanced insights into lipoprotein metabolism (94). However, these technologies must be carefully integrated into clinical workflows, with the establishment of clear guidelines for their interpretation and application in clinical decision-making.

The role of sdLDL in risk stratification and treatment intensification is a critical factor requiring consideration (95). Although current guidelines prioritize LDL-C as the primary target for lipid-lowering therapy, individuals with high sdLDL may benefit from more aggressive lifestyle and pharmacological interventions, even when their LDL-C levels appear to be acceptable. This raises the question of whether sdLDL should be incorporated into risk calculators or treatment algorithms, an area that remains underexplored in current cardiovascular guidelines.

In summary, the diagnostic significance of sdLDL is substantial and growing, particularly in the context of cardiometabolic diseases. Its presence signifies a hidden yet potent atherogenic threat that may be undetected by standard lipid screening. However, limitations in measurement standardization, cost, accessibility and clinical integration continue to hinder its routine application. As our understanding of lipidology deepens, and precision medicine becomes more central to cardiovascular prevention, sdLDL is likely to gain prominence as both a biomarker and a therapeutic target. Bridging the gap between scientific evidence and clinical implementation is essential to harness the full diagnostic power of sdLDL in the fight against atherosclerosis and CVD.

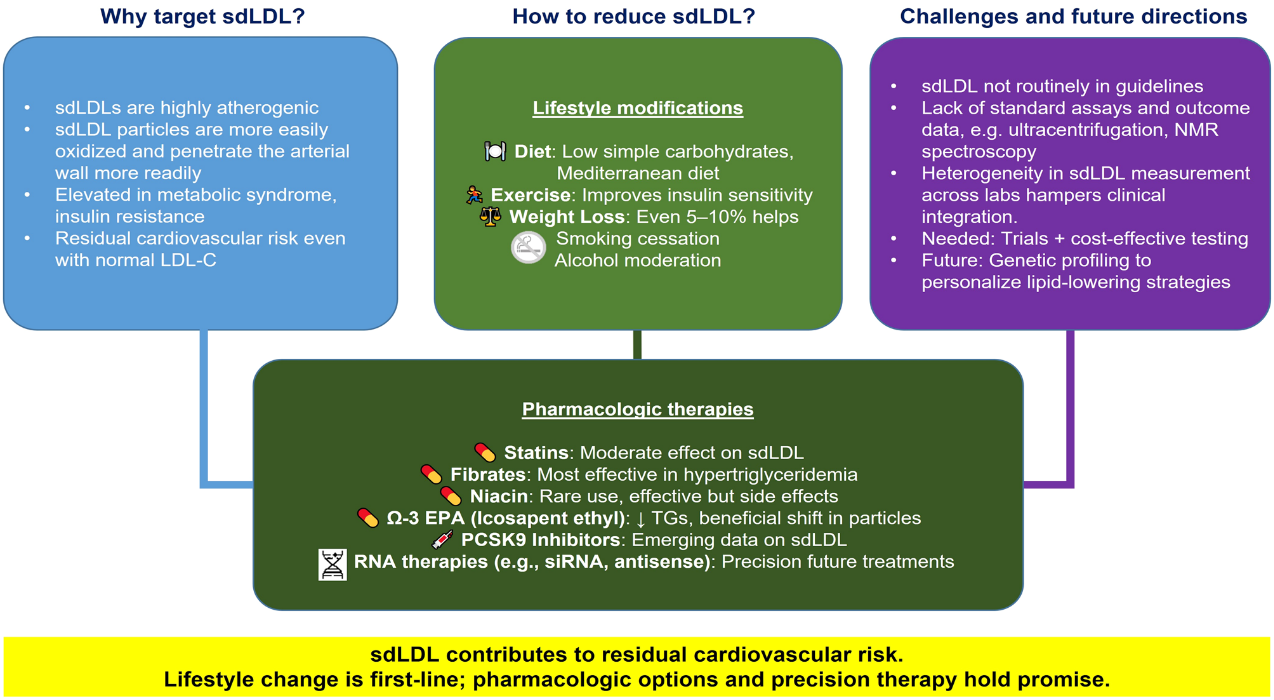
## 4. Targeted treatment strategies for sdLDL reduction

The clinical recognition of sdLDL as a highly atherogenic lipoprotein subclass has prompted growing interest in the development and refinement of therapeutic strategies that specifically address elevated sdLDL concentrations. Traditional lipid-lowering therapies have largely focused on the reduction of total LDL-C, although a burgeoning body of evidence suggests that not all therapies exert equivalent effects on sdLDL concentrations or particle composition (67,96). As our understanding of the role of sdLDL in atherogenesis deepens, a more nuanced and tailored approach to treatment is likely to become both necessary and feasible (Fig. 1).

Lifestyle modification remains the primary strategy for managing increases in sdLDL levels. Among non-pharmacological interventions, dietary changes, particularly those that reduce simple carbohydrate intake and improve insulin sensitivity, have been shown to significantly impact sdLDL particles (97). Diets low in refined sugars and rich in monounsaturated fats, such as the Mediterranean diet, can induce a change in the LDL particle distribution towards larger, less atherogenic forms (98). A modest weight loss of 5-10% body weight and increased physical activity substantially reduce sdLDL levels, particularly in insulin-resistant individuals (99). These findings reinforce the suggestion that sdLDL is not merely a lipid abnormality but also a marker of broader metabolic dysfunction.

Pharmacologically, statins remain the cornerstone of lipid-lowering therapy, as they can effectively reduce total LDL-C and sdLDL concentrations to a certain extent (100) (Fig. 1). However, their effect on sdLDL is variable, and often less pronounced than their effect on larger LDL particles (101,102). Statins primarily act by upregulating LDL receptors, which preferentially clear larger, less dense LDL particles, leaving some sdLDL particles in circulation (103,104). Nevertheless, when combined with other agents or used in high-intensity regimens, statins can contribute meaningfully to sdLDL reduction (105).

Fibrates, which activate peroxisome proliferator-activated receptor (PPAR)-α, are among the most effective agents for lowering sdLDL, particularly in individuals with hypertriglyceridemia and mixed dyslipidemia (106-108). By reducing triglyceride-rich lipoproteins and promoting lipolysis, fibrates



**Why target sdLDL?**

- sdLDLs are highly atherogenic
- sdLDL particles are more easily oxidized and penetrate the arterial wall more readily
- Elevated in metabolic syndrome, insulin resistance
- Residual cardiovascular risk even with normal LDL-C

**How to reduce sdLDL?**

**Lifestyle modifications**

**Diet**: Low simple carbohydrates, Mediterranean diet
**Exercise**: Improves insulin sensitivity
**Weight Loss**: Even 5–10% helps
Smoking cessation
Alcohol moderation

**Challenges and future directions**

- sdLDL not routinely in guidelines
- Lack of standard assays and outcome data, e.g. ultracentrifugation, NMR spectroscopy
- Heterogeneity in sdLDL measurement across labs hampers clinical integration.
- Needed: Trials + cost-effective testing
- Future: Genetic profiling to personalize lipid-lowering strategies

**Pharmacologic therapies**

**Statins**: Moderate effect on sdLDL
**Fibrates**: Most effective in hypertriglyceridemia
**Niacin**: Rare use, effective but side effects
**Ω-3 EPA (Icosapent ethyl)**: ↓ TGs, beneficial shift in particles
**PCSK9 Inhibitors**: Emerging data on sdLDL
**RNA therapies (e.g., siRNA, antisense)**: Precision future treatments

**sdLDL contributes to residual cardiovascular risk.**
**Lifestyle change is first-line; pharmacologic options and precision therapy hold promise.**

Figure 1. Targeted treatment strategies for sdLDL reduction. EPA, eicosapentaenoic acid; lab, laboratory; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; sdLDL, small dense low-density lipoprotein; TG, triglycerides. [167] [183]

shift the LDL particle distribution from small dense particles to larger and more buoyant forms. Clinical studies, such as the Veterans Affairs High-Density Lipoprotein Intervention Trial (109) and the Fenofibrate Intervention and Event Lowering in Diabetes trial (110) have demonstrated cardiovascular benefits in high-risk patients, although the use of pioglitazone must be balanced against potential side effects, including weight gain, edema and an increased risk of heart failure (111).

Niacin, also known as vitamin B3, has historically been effective in reducing sdLDL levels, raising HDL-C levels, and improving overall lipoprotein particle size. However, it is no longer frequently used due to its side-effect profile and lack of outcome benefits in clinical trials (24,112). Its use may still be considered in select cases of severe atherogenic dyslipidemia, particularly when other therapeutic options are insufficient or contraindicated.

Formulations of ω-3 fatty acids, particularly icosapent ethyl, a highly purified form of eicosapentaenoic acid (EPA) marketed as Vazkepa, have demonstrated consistent benefits in lowering triglyceride levels and improving lipoprotein quality (113). Beyond triglyceride reduction, treatment with icosapent ethyl has been shown to shift the LDL particle distribution toward larger, more buoyant LDL particles, thereby decreasing the proportion of small dense LDL (sdLDL), which are strongly associated with atherogenic risk. Subanalyses of the REDUCE-IT trial and subsequent lipidomic studies confirmed that EPA therapy not only reduces residual cardiovascular risk in statin-treated patients but also exerts favorable effects on LDL particle size and composition, contributing to a less atherogenic lipid profile (114,115). These changes in lipoprotein remodeling may represent one of the mechanistic pathways through which icosapent ethyl provides cardiovascular protection, independent of triglyceride lowering (116,117).

The Reduction of Cardiovascular Events With Icosapent Ethyl-Intervention Trial reported significant reductions in cardiovascular events in patients treated with EPA therapy, suggesting that modulation of sdLDL levels and inflammation may have contributed to the observed clinical benefits (118).

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, including alirocumab and evolocumab, primarily lower LDL-C levels by enhancing receptor-mediated clearance. Emerging evidence suggests they may also reduce sdLDL levels, particularly when used in combination with statins (119-121). However, their high cost is a barrier to widespread use, although they are increasingly recommended for high-risk patients who have persistent dyslipidemia despite receiving statin therapy.

Antisense oligonucleotides and small interfering RNA therapies targeting apoB or angiopoietin-like protein 3 are under investigation for their ability to modulate atherogenic lipoproteins, including sdLDL (122). These experimental approaches highlight the potential of precision lipid therapy, where targeting specific molecular pathways may enable the individualized management of atherogenic lipoprotein profiles.

While lowering sdLDL concentrations represents a promising strategy for the reduction of ASCVD risk, it is essential to consider potential side effects of intensive sdLDL-lowering therapies, particularly with regard to the risk of bleeding. Most traditional lipid-lowering agents, including statins, fibrates and PCSK9 inhibitors, are not strongly associated with increased bleeding. However, the broader impact that targeting sdLDL has on hemostasis and vascular integrity is not completely understood, especially given that novel pharmacological agents and combination therapies are currently undergoing development. Probucol, an antioxidative and lipid-lowering drug, exemplifies the complexity of this issue. Historically used to treat atherosclerosis and xanthomas, probucol effectively reduces LDL-C and sdLDL levels, largely through its antioxidant properties and its effects on LDL particle size and oxidation (123,124). Notably, a recent study by Lang *et al* (125) suggested that probucol may offer unique benefits for patients at high risk of hemorrhage. The study suggested that probucol has potential as a novel therapeutic option for cerebral infarction in patients with a high risk of bleeding, as it appears to exert protective effects on the vasculature without significantly increasing hemorrhagic complications (125). This observation is clinically relevant, as aggressively lowering the lipid level, particularly with agents that alter platelet function or endothelial stability, has sometimes been associated with an increased risk of bleeding, particularly in patients receiving concomitant antithrombotic therapy or those with cerebrovascular disease (126,127).

The apparent safety of probucol in this context may be attributed to its antioxidant effects, which stabilize endothelial function and reduce oxidative stress, potentially counteracting pro-hemorrhagic mechanisms. Nevertheless, it is essential to carefully evaluate the safety profile of sdLDL-targeting therapies in diverse patient populations. Although probucol may be a potential therapeutic option for patients with ASCVD and a high risk of bleeding, its use is limited by concerns such as QT prolongation and other non-hemorrhagic adverse effects. Furthermore, is is unclear whether the protective profile of probucol can be generalized to other sdLDL-lowering agents.

Despite these therapeutic advances, the integration of sdLDL-focused strategies into clinical practice guidelines remains limited. Major guidelines, such as those from the ACC and ESC, continue to prioritize LDL-C, non-HDL-C and apoB as primary targets of therapy (128). While sdLDL is recognized to increase cardiovascular risk, it has not yet been incorporated into routine risk calculators or treatment algorithms. This may be partly due to the lack of standardization in sdLDL measurement, as well as limited outcome data directly associating reductions in sdLDL concentration with hard cardiovascular endpoints.

Despite its limited integration into guidelines, there is growing support for the consideration of sdLDL measurements in certain clinical scenarios. These include patients with residual cardiovascular risk despite optimal LDL-C control, individuals with metabolic syndrome or type 2 diabetes, and those with premature or familial atherosclerotic disease. In such cases, the presence of an increased concentration of sdLDL may justify the intensification of therapy or the use of combination treatment approaches, even in the absence of overt LDL-C elevation.

Targeted reduction of sdLDL is most effective and clinically relevant during the chronic phase of ASCVD or in individuals at high long-term risk, such as those with metabolic syndrome, type 2 diabetes or persistent residual risk despite optimal LDL-C control (20,129).

Chronic management allows sufficient time for lifestyle modifications and pharmacological therapies, including statins, fibrates, PCSK9 inhibitors, probucol and w-3 fatty acids, to be implemented in order to exert their full lipid-modifying and anti-atherogenic effects.

Sustained lowering of sdLDL concentration during the chronic phase of disease has been associated with limited atherosclerosis progression, the stabilization of vulnerable plaques and a reduced incidence of major adverse cardiovascular events (25,60).

By contrast, the acute phase of ASCVD, such as acute coronary syndrome or stroke, is not the primary window for sdLDL-targeted interventions. Although lipid-lowering therapy is often initiated or intensified during acute events for secondary prevention, the specific impact of sdLDL reduction in this setting is less well established, as acute interventions are focused on patient stabilization, and the management of thrombosis and immediate complications. Nevertheless, the early initiation of sdLDL-lowering therapy during hospitalization for an acute event may lay the foundation for effective long-term risk reduction (130,131).

Therefore, sdLDL-lowering strategies should be prioritized for long-term risk reduction and the prevention of recurrent events, with their main benefits being realized during ongoing, chronic management.

To facilitate the broader adoption of sdLDL-guided therapy, it is necessary to integrate sdLDL measurements into the risk stratification frameworks outlined in clinical guidelines, supported by randomized trials and real-world data demonstrating the predictive value and therapeutic responsiveness of sdLDL levels. In addition, the development of cost-effective standardized assays for sdLDL quantification is essential to ensure clinical feasibility. Table IV summarizes both established and emerging strategies for sdLDL reduction, highlighting their mechanisms of action, clinical roles and other key considerations.

The targeting of sdLDL is an important evolution in the management of dyslipidemia and cardiovascular disease prevention. While traditional therapies influence sdLDL levels indirectly, emerging pharmacological agents and lifestyle strategies provide more specific and effective approaches. Bridging the gap between sdLDL recognition and its inclusion in clinical practice guidelines will be a key step toward precision cardiovascular medicine. As the evidence base expands, incorporating sdLDL into diagnostics and treatment may enhance our ability to address residual risk and improve outcomes for patients at high risk of atherosclerotic disease.

## 5. Artificial intelligence (AI) and machine learning (ML) in sdLDL research

The rapid evolution of AI and ML is profoundly transforming cardiovascular research, particularly in the study of sdLDL, a key but often underestimated driver of atherosclerosis. Historically, the measurement and clinical interpretation of sdLDL have faced substantial challenges. Standard lipid panels do not directly quantify sdLDL, and conventional estimation equations, such as the Friedewald or Martin equations, often yield imprecise results, especially in patients with elevated triglyceride levels or atypical lipid profiles (132,133). These limitations have limited the integration of sdLDL metrics into the routine clinical risk assessment and management of ASCVD (Table V).

AI and ML technologies are now bridging these gaps by leveraging large-scale, multidimensional datasets that include

Table IV. Targeted treatment strategies for reducing sdLDL levels.

| Treatment | Type | Effect on sdLDL | Mechanism of action | Notes and clinical considerations | (Refs.) |
|---|---|---|---|---|---|
| Lifestyle modification | Non-pharmacologic | Reduces sdLDL concentrations; shifts to larger LDL particles | Improves insulin sensitivity; reduces refined carbohydrate intake; increases physical activity | Foundation of all therapies; particularly effective in metabolic syndrome | (24) |
| Statins | Pharmacologic | Modest and variable reduction in sdLDL | Upregulate LDL receptors, preferentially clearing larger LDL particles | Optimum results in combination or high-intensity regimens | (60) |
| Fibrates | Pharmacologic | Significant reduction in sdLDL | Activate PPAR-α; reduce triglycerides; enhance lipolysis; shift LDL to larger particles | Particularly effective in patients with high TG and low HDL-C | (108) |
| Pioglitazone | Pharmacologic | Reduces sdLDL; improves lipoprotein profile | Activates PPAR-γ; enhances insulin sensitivity; reduces inflammation; lowers TG and increases HDL-C | Benefits high-risk patients; side effects include weight gain and edema | (54) |
| Niacin/vitamin B3 | Pharmacologic | Reduces sdLDL; increases HDL-C; improves LDL particle size | Decreases hepatic VLDL production; reduces lipolysis of adipose tissue | Limited use due to side effects and lack of outcome benefit | (24) |
| w-3 Fatty acids (EPA) | Pharmacologic | Modulates sdLDL and reduces TG | Reduces hepatic TG synthesis; alters LDL particle composition | Reduced cardiovascular events in the REDUCE-IT phase III trial | (113) |
| PCSK9 inhibitors | Pharmacologic | May reduce sdLDL when combined with statins | Increase LDL receptor recycling; enhance LDL clearance | High cost; recommended for high-risk patients with residual dyslipidemia | (121) |
| Antisense/siRNA therapies, e.g., targeting apoB or ANGPTL3 | Experimental | Potential for sdLDL reduction | Inhibit synthesis of apoB or ANGPTL3; reduce atherogenic lipoprotein production | Emerging tools in precision lipid management | (141) |

ANGPTL3, angiopoietin-like protein 3; apoB, apolipoprotein B; EPA, eicosapentaenoic acid; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; PCSK9, proprotein convertase subtilisin/kexin type 9; PPAR, peroxisome proliferator-activated receptor; REDUCE-IT, Reduction of Cardiovascular Events with Icosapent Ethyl - Intervention Trial; sdLDL, small dense LDL; siRNA, small interfering RNA; TG, triglyceride; VLDL, very low-density lipoprotein.

clinical, biochemical, genetic and imaging data (134). ML algorithms can identify complex, non-linear relationships among lipid parameters that are not detected by traditional statistical methods (133). Advanced models, such as gradient boosting machines and deep neural networks, can predict sdLDL concentrations with high accuracy, even in the presence of confounding factors such as elevated triglyceride levels or metabolic syndrome. These models demonstrate substantially reduced prediction errors compared with legacy equations, and maintain a high performance across diverse patient subgroups (Table V).

Han *et al* (135) developed and validated a number of ML models, including XGBoost, Random Forest and Logistic Regression, to predict the likelihood of LDL-C target levels being achieved in patients with coronary artery disease treated with moderate-dose statins. These models, trained on a large hospital dataset, achieved respectable area under the receiver operating characteristic curve values of ~0.695, even following significant dimensionality reduction. Notably, SHapley Additive exPlanations (SHAP) analysis was included to interpret the predictions made by the models, providing transparency and clinical insight that can guide individualized treatment strategies.

Similarly, Olmo *et al* (136) applied ML-driven decision tree algorithms to cluster patients based on LDL-C levels, family history of coronary heart disease and age. This led to

Table V. Summary of in sdLDL research.

| Domain | AI/ML contribution | Details and examples | Challenges and limitations | (Refs.) |
|---|---|---|---|---|
| Measurement and estimation | Accurate prediction of sdLDL levels | ML models, e.g., gradient boosting and deep neural networks, outperform Friedewald/Martin equations, even with high TGs | Variability in sdLDL measurement techniques, e.g., NMR vs. ultracentrifugation | (133) |
| Risk stratification | Enhanced cardiovascular risk prediction | AI integrates sdLDL with apoB, Lp(a) and inflammation markers; outperforms Framingham Risk Score (AUC >0.85) | Lack of standardization and validation across population subgroups | (164) |
| Explainability | Interpretable models via SHAP | sdLDL shown to contribute comparably to systolic blood pressure and age in predictive models | 'Black box' concerns reduce clinician trust in complex models | (154) |
| Personalized medicine | Tailored therapy for sdLDL reduction | AI predicts individual responses to statins, PCSK9 inhibitors and lifestyle changes | Requires integration of high-resolution genetic and lipidomic data | (134) |
| Therapeutic optimization | Adaptive treatment planning | Reinforcement learning guides drug/lifestyle interventions; neural nets track plaque via coronary CT angiography | Longitudinal, multimodal datasets are limited; high computational costs | (145) |
| Clinical trials and interventions | AI-guided lifestyle interventions show rapid sdLDL reduction | Customized diet/exercise plans reduce sdLDL in weeks | Scalability and cost of implementing AI-driven personalization in real-world settings | (144) |
| Challenges | Data heterogeneity, generalizability, ethical concerns | Inconsistent sdLDL assays, bias in training data, lack of model transparency | Data privacy, underrepresentation of certain demographic groups | (149) |
| Emerging solutions | Federated learning, explainable AI, digital twins | Cross-institutional model training, transparent decision-making, virtual simulations of sdLDL progression | Early stage of development; limited clinical integration and regulatory guidance | (155) |
| Future outlook | AI positions sdLDL as central in precision cardiology | Transition from niche biomarker to a core element in personalized atherosclerosis prevention | Large-scale validation studies and harmonization with clinical workflows are necessary | (156) |

AUC, area under the curve; AI, artificial intelligence; apoB, apolipoprotein B; CT, computed tomography; Lp(a), lipoprotein(a); ML, machine learning; NMR, nuclear magnetic resonance; PCSK9, proprotein convertase subtilisin/kexin type 9; sdLDL, small dense low-density lipoprotein; SHAP, SHapley Additive exPlanations; TGs, triglycerides.

the identification of distinct risk groups with progressively higher levels of Lp(a). Their study of >2,300 patients from a multicenter Spanish registry revealed that nearly 39% of patients had elevated Lp(a) levels, defined as >50 mg/dl, highlighting the importance of using ML to stratify patients and identify those at higher cardiovascular risk.

In another recent application of AI in lipidomics, Tavaglione *et al* (137) leveraged neural network models to assess the contribution of lipoproteins to liver fat accumulation and inflammation, particularly in the context of metabolic dysfunction-associated steatotic liver disease (MASLD; formerly known as non-alcoholic fatty liver disease) and metabolic dysfunction-associated steatohepatitis. Using data from the UK Biobank, the research team found that the ability of isolated hypertriglyceridemia to predict MASLD was stronger than that of isolated hypercholesterolemia, a finding with potential implications for targeted screening and early intervention in dyslipidemic populations (54).

Sezer *et al* (138) investigated both AI and explainable AI (XAI) techniques, including Random Forests and Gradient Boosting, for the prediction of LDL-C from standard lipid panels. By applying SHAP and Local Interpretable Model-agnostic Explanations techniques, they demonstrated how XAI can bridge the gap between predictive accuracy and clinical interpretability. Their findings further suggested that AI-based LDL-C predictions may offer more reliable and cost-effective alternatives to traditional estimation formulas, particularly in large-scale screening scenarios.

Collectively, these studies highlight a growing trend toward the adoption of AI and ML methods in the diagnosis and management of lipid disorders. The integration of explainable models with clinical variables such as LDL-C, Lp(a) and triglycerides is supporting a shift from population-based approaches to precision cardiovascular medicine. Notably, SHAP analysis and XAI frameworks are enhancing the ability of clinicians to trust and act on AI-driven outputs, a critical factor for successful clinical adoption.

Beyond estimation methods, AI-driven approaches are redefining cardiovascular risk stratification by incorporating sdLDL as a dynamic, actionable biomarker. Unlike static risk scores, ML models can account for the cumulative burden of sdLDL exposure over time and integrate it with other risk factors, including ApoB, Lp(a) and inflammatory markers. In large cohort studies, these AI-enhanced risk models have consistently outperformed traditional tools such as the Framingham Risk Score, achieving area under the curve values >0.85 (139). Notably, XAI techniques, such as SHAP analysis, have shown that the sdLDL percentage contributes as much to risk prediction as do established factors such as systolic blood pressure or age, thereby highlighting its clinical significance (140).

The impact of AI is increasingly extending into the realm of personalized medicine. Reinforcement learning and other adaptive algorithms are being used to tailor interventions that specifically target sdLDL reduction. These systems can model individual responses to statins, PCSK9 inhibitors and lifestyle modifications, thereby optimizing treatment regimens based on the unique lipidomic and genetic profile of each patient (141). Clinical trials using AI-generated dietary and exercise recommendations have already reported significant reductions in sdLDL levels within weeks, demonstrating the potential for rapid, individualized risk mitigation (142-144). In addition, neural networks that analyze longitudinal imaging data, such as coronary computed tomography angiography, can identify optimal windows for intervention by tracking the progression of atherosclerotic plaques in relation to sdLDL fluctuations (145,146).

Despite these advances, several challenges remain that must be addressed before AI and ML can be fully integrated into routine sdLDL management (147,148).

Data heterogeneity remains a major barrier, as different measurement techniques, for example, ultracentrifugation and NMR spectroscopy, may produce inconsistent results, complicating model training and validation. Concerns about the generalizability of AI models also persist, particularly when they are trained on datasets that do not adequately represent diverse populations. Ethical considerations, including algorithmic bias and data privacy, also require ongoing attention to ensure equitable and responsible deployment of these technologies. In addition, the opaque nature of certain deep learning models may undermine the trust of clinicians and hinder their clinical adoption, thereby underscoring the requirement for transparent and interpretable AI systems (149).

Looking ahead, the AI and ML field is moving towards federated learning frameworks that enable collaborative model development across institutions without compromising patient privacy (150,151).

The integration of XAI should further enhance clinician confidence by making the decision-making process clearer. In addition, so-called 'digital twins' or virtual patient models are emerging that may simulate sdLDL trajectories under various treatment scenarios, and have the potential to revolutionize individualized care and preventative strategies (152-155).

The convergence of AI, ML and sdLDL research represents a paradigm shift in the fight against atherosclerosis (156). By enabling precise estimation, robust risk prediction and personalized intervention, these technologies are poised to elevate sdLDL from an emerging biomarker to a central pillar of precision cardiology. As validation studies progress and implementation barriers are addressed, AI-driven approaches have the potential to transform the science and practice of CVD prevention and management.

## 6. Future directions

As cardiovascular medicine enters an era increasingly defined by precision and personalization, the recognition of sdLDL as a critical contributor to residual atherosclerotic risk opens numerous avenues for future research, scientific innovation and clinical integration. The body of evidence associating sdLDL with heightened cardiovascular morbidity and mortality, despite standard lipid control, highlights the necessity of redefining our understanding of lipoprotein pathology and risk assessment (18,27). In the future, several key areas must be addressed to fully harness the clinical potential of sdLDL-focused strategies (Fig. 2).

First and foremost, it is essential to standardize sdLDL measurements and increase their accessibility. Although advanced techniques, including NMR spectroscopy, ion mobility analysis and density gradient ultracentrifugation, have provided invaluable insights into lipoprotein subfractions, these tools remain largely confined to research settings (157,158). The development of affordable, automated and reproducible assays for sdLDL detection is necessary for widespread adoption in clinical practice (18,159). Furthermore, establishing universally accepted cut-off values and reference ranges, stratified by age, sex, ethnicity and comorbidities, will enhance the interpretability and clinical relevance of sdLDL metrics.

Another critical priority is the integration of sdLDL into existing cardiovascular risk prediction models. Current tools, such as the ASCVD Risk Calculator and SCORE2, primarily consider traditional lipid markers and broad demographic factors (160). Incorporating sdLDL concentrations into multi-parametric indices alongside ApoB, triglycerides and inflammatory biomarkers, may substantially improve the accuracy of risk stratification, particularly in individuals with metabolic syndrome or type 2 diabetes, or those with normal LDL-C levels but persistent vascular disease.

At the therapeutic level, the evolution of precision medicine approaches is necessary. Although current lipid-lowering therapies, including statins and fibrates, partially reduce sdLDL levels, more selective and sdLDL-targeted interventions are

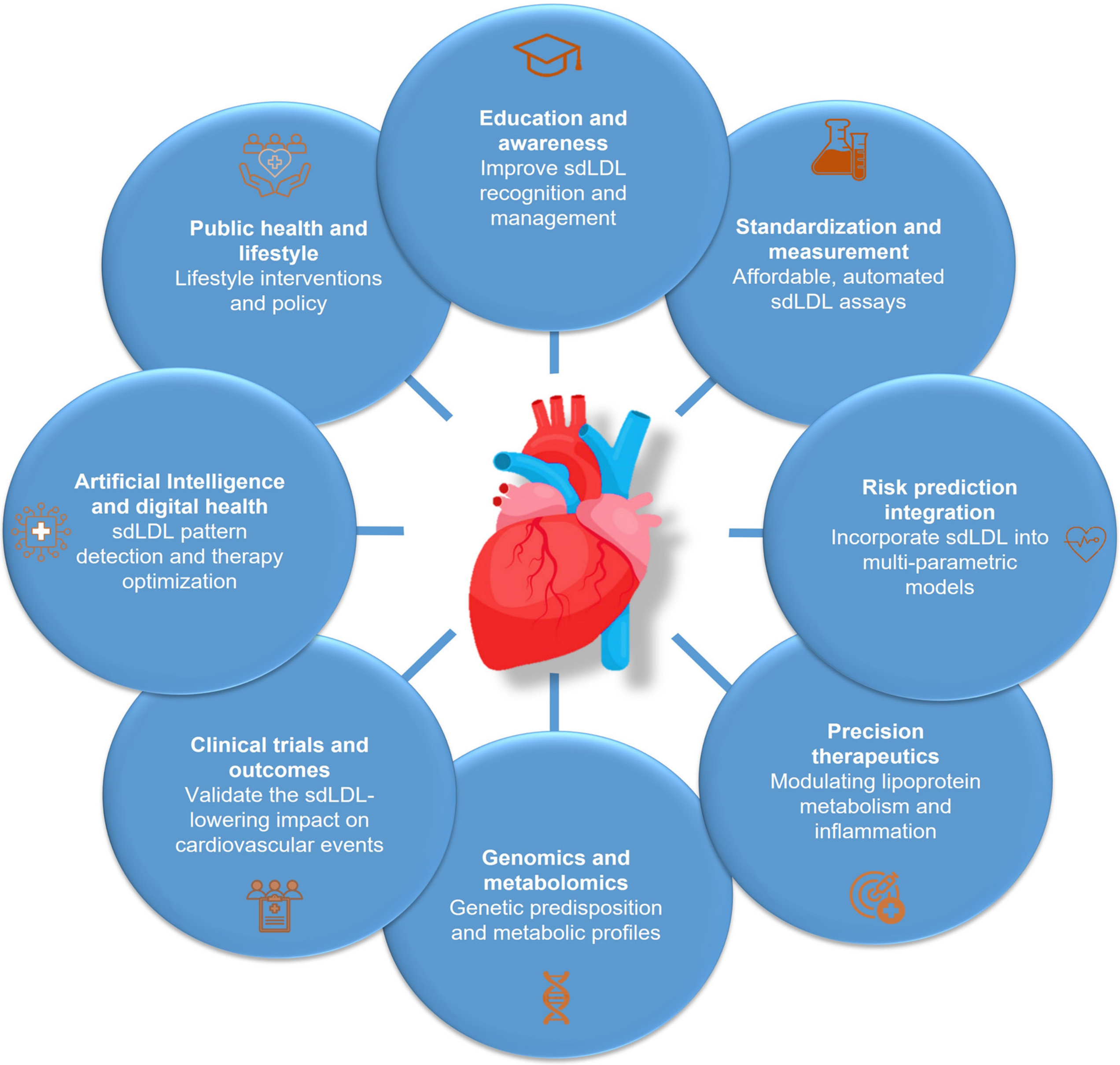


Figure 2. Future directions in sdLDL research and clinical applications. sdLDL, small dense low-density lipoprotein.

required (161,162). Future pharmacological studies should prioritize agents that modify hepatic lipoprotein secretion, lipolysis and receptor-mediated lipoprotein to preferentially reduce sdLDL formation and persistence. Furthermore, combinatorial therapies addressing both lipid and inflammatory signaling pathways may yield synergistic benefits for patients with a high sdLDL burden.

Personalized treatment algorithms that incorporate genetic and metabolic profiling could further enhance the targeting of sdLDL. Advances in genomics and metabolomics may help to identify individuals who are genetically predisposed to overproduce or inefficiently clear sdLDL. This information, combined with real-time lipidomic and glycemic monitoring, may guide individualized therapeutic regimens and dynamic risk tracking over time.

Longitudinal and interventional studies are required to clarify the clinical benefits of lowering sdLDL levels. Although the atherogenicity of sdLDL has been well documented, conclusive evidence that reducing sdLDL leads to improvements in cardiovascular outcomes remains elusive. Large, well-powered randomized controlled trials are necessary to determine whether targeting sdLDL levels, either through lifestyle or pharmacological means, leads to measurable reductions in myocardial infarction, stroke and cardiovascular death, particularly in high-risk populations (Fig. 2).

The integration of AI and digital health technologies in routine sdLDL assessment and management is a promising strategy. ML algorithms could be trained to detect patterns of sdLDL elevation based on indirect clinical and biochemical markers, thereby reducing dependence on direct measurement. AI-driven platforms may also leverage patient-specific data streams from electronic health records and wearable devices to optimize therapy selection, adherence and monitoring (134,163,164).

Lipidomics, an emerging discipline within the broader field of metabolomics, focuses on the comprehensive analysis of cellular lipid profiles using advanced analytical chemistry techniques and high-throughput technological platforms. Unlike traditional lipid panels that measure only a small number of lipid classes, such as total cholesterol, LDL-C, HDL-C and triglycerides, lipidomics enables the simultaneous identification and quantification of hundreds to thousands of distinct lipid species within biological samples (165). This comprehensive approach is achieved using sophisticated tools, including mass spectrometry, NMR spectroscopy and liquid chromatography, which together provide high resolution and sensitivity in lipid analysis (166,167).

The application of lipidomics in cardiovascular research has enhanced our understanding of lipid metabolism and its role in atherosclerosis (168). Specifically, lipidomics allows for the detailed characterization of lipoprotein subfractions, including sdLDL (157,169). By profiling the molecular composition of sdLDL particles, including their enrichment in triglycerides, depletion of cholesterol, and susceptibility to oxidative modifications that increase atherogenicity, lipidomics can reveal mechanistic links between specific lipid species and the pathogenesis of ASCVD (170,171).

Lipidomics offers the potential to identify novel lipid biomarkers that may improve risk stratification beyond conventional measures (165). For example, recent studies have uncovered unique lipid signatures that are associated with increased sdLDL levels in patients with metabolic syndrome, type 2 diabetes and insulin resistance (172-174). These signatures include specific oxidized phospholipids, ceramides and sphingolipids, which have been implicated in endothelial dysfunction, inflammation and plaque instability. Integrating such lipidomic data with clinical and genetic information may increase the precision and individualization of risk assessment, as well as the development of targeted therapies aimed at modulating pathogenic lipid species.

Despite its promise, the clinical implementation of lipidomics is hindered by a lack of standardized protocols, robust data interpretation frameworks and cost-effective analytical platforms. However, as technology advances and a deeper understanding of lipid biology is obtained, lipidomics is poised to become an indispensable tool in research and clinical practice, particularly in the context of sdLDL and its role in residual cardiovascular risk. Future studies leveraging lipidomic profiling are likely to yield new insights into the molecular mechanisms of atherogenesis, facilitating the transition towards precision cardiovascular medicine.

Finally, promoting greater awareness and education among clinicians and patients is paramount. Despite its clinical significance, sdLDL remains under-recognized in numerous healthcare settings. Medical curricula, continuing education programs and clinical guidelines should be updated to reflect the evolving understanding of sdLDL, ensuring that healthcare providers are equipped to interpret, communicate and act on sdLDL-associated information effectively.

In summary, the future of sdLDL research and application lies in the convergence of technological innovation, translational science and personalized care. By advancing measurement techniques, integrating sdLDL into risk models, validating targeted therapies and implementing health system-level changes, insights into the pathophysiological role of sdLDL can be translated into actionable clinical strategies. In so doing, cardiovascular prevention may become both more comprehensive and more precisely targeted.

## 7. Conclusion

Over the last few decades, our understanding of atherosclerosis has evolved from a simplistic cholesterol-centric view to a complex appreciation of lipid subfractions, inflammation, endothelial dysfunction and metabolic interactions. Among these factors, sdLDL has emerged as a critical, yet under-recognized, contributor to CVD. Its unique physicochemical properties, such as elevated arterial wall permeability, prolonged circulation time and heightened susceptibility to oxidation, result in its atherogenicity being greater than that of larger LDL particles. A growing body of evidence demonstrates that sdLDL plays a central role in promoting endothelial injury, foam cell formation, inflammation and plaque instability, all of which are key features of progressive atherosclerosis.

Despite these insights, sdLDL remains insufficiently addressed in clinical diagnostics and practice guidelines. Traditional lipid panels do not detect sdLDL, and so potentially overlook high-risk individuals, particularly those with metabolic syndrome, type 2 diabetes or normocholesterolemia. The absence of routine sdLDL measurement may lead to suboptimal risk assessment and missed opportunities for early intervention. Integrating sdLDL into diagnostic protocols, either directly through specialized testing or indirectly via surrogate markers such as ApoB and non-HDL-C, could refine cardiovascular risk prediction and guide personalized treatment strategies.

Therapeutically, although conventional lipid-lowering agents such as statins and fibrates can reduce sdLDL levels, emerging therapies, including w-3 fatty acid formulations, PCSK9 inhibitors and RNA-targeting agents, have the potential to provide more targeted and effective sdLDL modulation. Additional clinical trials are required to determine whether specific sdLDL-lowering strategies translate into improved long-term cardiovascular outcomes. Alongside pharmacological innovations, lifestyle modifications, particularly those aimed at improving insulin sensitivity and reducing the levels of triglyceride-rich lipoproteins, remain crucial for managing sdLDL-associated risk.

Looking ahead, the future management of sdLDL must be grounded in an integrative approach that combines advanced diagnostics, precision therapeutics and population-level interventions. Efforts should focus on standardizing measurement techniques, educating clinicians and updating clinical guidelines to reflect the evolving understanding of the pathophysiological role of sdLDL.

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## Availability of data and materials

Not applicable.

## Authors' contributions

MB was responsible for writing, reviewing and editing the manuscript, supervision and project administration. TS was responsible for writing the original draft of the manuscript, defining the scope and focus of the review, devising a literature search strategy, formal analysis and conceptualization. TIR was responsible for collecting data. SA was responsible for writing the manuscript, methodology, analysis and conceptualization. AK was responsible for reviewing and editing the manuscript, formal analysis, methodology and conceptualization. GM was responsible for editing the manuscript, methodology and formal analysis. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

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## Competing interests

The authors declare that they have no competing interests.

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