Am J Cardiovasc Dis 2026;16(4):234-246
www.AJCD.us /ISSN:2160-200X/AJCD0173705

Review Article

Residual cardiovascular risk beyond LDL-cholesterol control: what remains unaddressed?

Mohammed Taha[1], Buraq Al-Ghaieb[1], Muntadher Al-Bulanee[2]

[1]Department of Internal Medicine, Baptist Health-UAMS Internal Medicine Residency Program, 3116 N Hills BLVD, Apt 10322, North Little Rock, AR 72116, USA; [2]Department of Internal Medicine, Al-Shaheed Dhari Al-Fayadh General Hospital, Baghdad, Iraq

Received April 29, 2026; Accepted July 22, 2026; Epub August 15, 2026; Published August 30, 2026

Abstract: Statins, ezetimibe, and PCSK9 inhibitors have enabled LDL-cholesterol to be lowered to levels previously thought very hard to achieve. However, even after achieving low levels, some patients continued to have cardiovascular events, a phenomenon known as residual cardiovascular risk. This phenomenon indicates the complexity of atherosclerosis, not limited to a simple LDL-driven process. Vascular inflammation persists even in the presence of well-controlled lipids and is largely mediated by the NLRP3-interleukin-1β-interleukin-6 signaling pathway, which has been shown to be a viable therapeutic target in the CANTOS, COLCOT, and LoDoCo2 trials. Triglyceride-rich lipoproteins and remnant cholesterol accumulate in the arterial intima and drive atherogenesis independent of LDL-C, with icosapent ethyl showing meaningful cardiovascular benefit in the REDUCE-IT trial. Apolipoprotein B reflects the true number of circulating atherogenic particles that LDL-C alone fails to identify, especially in patients with metabolic disease. Lipoprotein(a) is an inherited risk factor that statins barely affect, and it carries a well-established association with myocardial infarction, stroke, and aortic stenosis; RNA-based therapies targeting it are now in late-stage trials. The 2026 ACC/AHA Dyslipidemia Guideline now carries a Class I recommendation for universal Lp(a) measurement at least once in all adults. Impaired HDL function, insulin resistance, and a prothrombotic environment provide further risk. GLP-1 receptor agonists and SGLT2 inhibitors have emerged as important contributors to residual cardiovascular risk reduction in patients with metabolic dysfunction, showing consistent cardiovascular benefit on top of their background of statin therapy, with mechanisms that extend far beyond glycemic control. Coronary imaging, such as coronary calcium scoring and coronary CT angiography, can identify high-risk plaque features that persist despite aggressive lipid-lowering. Taken together, these findings make the case that LDL-C treatment is important but incomplete. A more comprehensive approach is required to meaningfully reduce the residual risk, one that considers apoB, remnant cholesterol, inflammation, lipoprotein(a), and metabolic risk.

Keywords: Residual cardiovascular risk, LDL-cholesterol, apolipoprotein B, lipoprotein(a), vascular inflammation

Introduction

Reduction of low-density lipoprotein cholesterol (LDL-C) is the basic principle of atherosclerotic cardiovascular disease (ASCVD) prevention. Evidence from large trials demonstrates a proportional, log-linear relationship exists between the magnitude of LDL-C reduction and cardiovascular events across various patient populations [1, 2]. This association is consistent regardless of how LDL-C was reduced, supporting LDL-C as a primary causal driver of atherosclerosis rather than only a risk marker.

The pathophysiological basis of this association begins with the retention of ApoB-containing lipoproteins in the arterial intima. This trapping will trigger a cascade of events, resulting in endothelial dysfunction, immune activation, and, ultimately, chronic inflammation. These events lead to the formation and destabilization of atherosclerotic plaque [3, 4]. Even at relatively modest concentrations, LDL-C particles cross the arterial wall and accumulate within it. The long-term risk of coronary artery disease has been shown to be determined by the cumulative LDL-C exposure over a lifetime [5].

Given the importance of lowering LDL-C, several therapeutic strategies have been identified to reduce it effectively. Statins, HMG-CoA

reductase inhibitors, lower LDL by decreasing hepatic LDL-C production and upregulating hepatic LDL receptors. Moderate to high-intensity statins are the cornerstone of treatment. In cases where statins alone are not enough, ezetimibe can be used to block cholesterol absorption in the intestines. This has been shown in the IMPROVE-IT trial, in which adding ezetimibe to statin therapy resulted in further reductions in cardiovascular events compared with statin therapy alone [6]. For patients who continue to be at high risk despite maximum doses of statin and ezetimibe, PCSK9 inhibitors are a potential additional option. These agents block proprotein convertase subtilisin/kexin type 9, which is responsible for LDL receptor degradation and therefore markedly increases LDL-C clearance. The FOURIER trial demonstrated that evolocumab reduced LDL-C by approximately 59% and significantly decreased the risk of major adverse cardiovascular events [7], while the ODYSSEY OUTCOMES trial demonstrated similar benefits with alirocumab after acute coronary syndromes [8].

Even with this progress, cardiovascular events continued to occur at a high event rate in people who already achieved guideline-recommended targets for LDL-cholesterol [9]. Even in some high-risk patients treated with statins, with LDL-C reduced to less than 70 mg/dL, event rates remained significant, particularly in secondary prevention populations [6-8, 10]. Meta-analyses have confirmed that although the greater the LDL-C lowering, the greater the risk reduction, a significant residual risk remains even at the lowest achieved LDL-C levels [2, 11]. Therefore, the concept of residual cardiovascular risk has emerged and is defined as the residual risk of ASCVD events that remain after optimal LDL-C control [12], reflecting the complex, multifactorial biology of atherosclerosis. It also highlights that atherosclerosis is associated with both lipid- and non-lipid-related mechanisms, which are not fully captured by LDL-C measurement alone [12, 13]. Subsequent studies suggest that residual inflammation, triglyceride-rich lipoproteins (TRLs) and remnant cholesterol, apolipoprotein B (apoB) particle burden, lipoprotein(a) [Lp(a)], metabolic dysfunction, and thrombotic pathways are important contributors to ongoing cardiovascular risk [13-16] (**Table 1**).

In addition to LDL cholesterol buildup, the atherosclerosis process is now recognized as a chronic inflammatory and thrombotic disease involving complex interactions among lipoprotein retention, endothelial dysfunction, immune activation, and plaque instability [3, 4]. An important point to note is that even after LDL-C is brought into the desired range, cholesterol crystals and modified apoB-containing lipoproteins can persist within the arterial wall, causing local inflammation, sustained macrophage signaling [17], and plaque instability [3, 17, 18]. Although LDL-C reduction stabilizes plaque, it does not eliminate cardiovascular events [6-8, 18]. These findings support a broader pathophysiological model in which residual cardiovascular risk is driven by ongoing arterial wall pathology rather than circulating lipid levels alone [3].

Therefore, this review summarizes the evidence supporting persistent cardiovascular risk despite LDL-C control and discusses the dominant biological mechanisms contributing to residual risk.

Residual inflammatory risk

Inflammatory signaling plays a central role in both plaque development and destabilization. A well-recognized marker of vascular inflammation is high-sensitivity C-reactive protein (hs-CRP). Elevated hs-CRP identifies patients at increased risk even when LDL-C is well controlled [19].

Observational studies have demonstrated that patients with controlled LDL-C and elevated inflammatory markers experience higher event rates than those with both low LDL-C and low inflammatory burden [20].

Residual inflammatory risk is largely driven by activation of the NLRP3 inflammasome and subsequent interleukin-1β signaling, leading to interleukin-6 production and hepatic C-reactive protein synthesis [4, 21]. This chronic inflammatory signaling favors macrophage foam cell formation, weakens the fibrous cap of atherosclerotic plaques, and predisposes to atherosclerotic plaque rupture and acute thrombosis, the final common pathway of most acute coronary syndromes [4, 21].

Table 1. Residual cardiovascular risk pathways beyond LDL-cholesterol control

Residual Risk Pathway	Key Biomarker (s)	Pathophysiologic Role	Therapeutic Strategies (Key Evidence)	Key Limitations
ApoB Particle Burden	ApoB, non-HDL-C	Total atherogenic particle number; superior risk marker vs LDL-C	Statins ± Ezetimibe ± PCSK9 Inhibitors (IMPROVE-IT, FOURIER, ODYSSEY); apoB-guided risk assessment	Residual risk persists; trials target LDL-C, not apoB
TRLs & Remnant Cholesterol	Triglycerides, remnant cholesterol	Arterial wall penetration, inflammation, plaque progression	Icosapent ethyl (REDUCE-IT); TRL-targeted therapy	Benefit agent-specific; no benefit with mixed omega-3 or niacin
HDL Dysfunction	HDL-C, efflux capacity	Impaired cholesterol efflux and anti-inflammatory function	No direct therapies; address upstream risk factors	Raising HDL-C ineffective; no therapies improve HDL function
Residual Inflammatory Risk	hs-CRP	Chronic inflammation drives plaque instability and thrombosis	Statins (JUPITER); IL-1β inhibition (CANTOS); colchicine (COLCOT, LoDoCo2)	Infection risk (canakinumab); colchicine intolerance; methotrexate ineffective
Lipoprotein(a)	Lp(a)	Genetic apoB lipoprotein promoting atherothrombosis	Lifetime screening; emerging antisense/siRNA therapies	Outcome benefit unproven; modest PCSK9 effect
Metabolic Dysfunction	Insulin resistance, diabetes, obesity	↑ apoB production, inflammation, prothrombotic state	Lifestyle + cardiometabolic risk reduction; GLP-1 receptor agonists (Galli et al.); SGLT2 inhibitors; combination GLP-1 RA + SGLT2 (Neuen et al.)	Multifactorial; outcome data for combination therapy still emerging

This table summarizes the major pathways contributing to residual cardiovascular risk despite optimal LDL-cholesterol lowering, including key biomarkers, pathophysiologic mechanisms, therapeutic strategies with supporting trial evidence, and current limitations of each approach.

Although LDL-C-lowering therapies may indirectly reduce inflammation, many patients have persistently elevated inflammatory markers despite intensive lipid control. This discordance between lipid and inflammatory pathways explains why hs-CRP remains a powerful predictor of recurrent cardiovascular events regardless of achieved LDL-C levels. These findings further support the concept that residual inflammatory risk constitutes a distinct therapeutic target in ASCVD prevention [21].

The JUPITER trial demonstrated that statin therapy in patients with normal LDL cholesterol but elevated hs-CRP levels significantly reduced cardiovascular events, with a 44% reduction in major cardiovascular events and a 47% reduction in the composite of cardiovascular death, myocardial infarction, and stroke [22]. This trial highlights inflammation as a targetable factor that can reduce cardiovascular risk.

The CANTOS trial provided clearer evidence that inflammation continues to drive cardiovascular risk. This study used canakinumab, an interleukin-1β inhibitor, as an anti-inflammatory. The trial demonstrated a reduction in recurrent cardiovascular events without affecting lipid levels, with a 15% reduction in major adverse cardiovascular events (HR 0.85) and a 37% reduction in hs-CRP levels [23].

Additional trials, such as COLCOT and LoDoCo2, were conducted for further anti-inflammatory therapy evaluation. These trials used low-dose colchicine. The results suggested a limited but significant reduction in cardiovascular events when colchicine was added to standard care, with COLCOT demonstrating a 23% reduction in cardiovascular events (HR 0.77) [24] and LoDoCo2 demonstrating a 31% reduction (HR 0.69) [25].

There are multiple limitations for residual inflammatory risk management. In the CANTOS trial, canakinumab was associated with an increased risk of fatal infections, limiting its clinical applicability [23]. Additionally, low-dose colchicine, although effective in COLCOT and LoDoCo2, gastrointestinal intolerance, drug-drug interactions, and concerns regarding long-term safety remain, particularly in patients with renal dysfunction [24, 25]. While low-dose methotrexate was ineffective, demonstrating that not all anti-inflammatory strategies are effective [26].

Triglyceride-rich lipoproteins and remnant cholesterol

Triglyceride-rich lipoproteins (TRLs) and their remnants are gaining recognition as factors that promote atherosclerosis and increase cardiovascular risk. The cholesterol content of partially metabolized very low-density lipoproteins and chylomicron remnants, referred to as remnant cholesterol, is retained within the arterial intima, where they promote local inflammatory activation [27]. Once retained in the intima, these remnants are phagocytized by macrophages, favoring the formation of foam cells, persistent endothelial dysfunction, and progressive plaque growth, which increases the probability of plaque vulnerability and thrombotic occlusion over time [27, 28].

A strong association between remnant cholesterol and ASCVD risk, independent of LDL-C, was demonstrated in both genetic and epidemiological studies [28].

These particles are often missed by LDL-C measurements, especially in patients with metabolic disease or high triglycerides.

The REDUCE-IT trial showed that patients who were treated with a statin and had high triglyceride levels and were treated with icosapent ethyl (pure EPA) resulted in a significant reduction in cardiovascular events, with a 25% reduction in major cardiovascular events (HR 0.75) and an absolute risk reduction of 4.8% [29]. However, no cardiovascular benefit was seen with other triglyceride-lowering strategies, as seen in the STRENGTH and AIM-HIGH trials, where STRENGTH showed no significant reduction (HR 0.99) and AIM-HIGH was stopped early due to lack of cardiovascular benefit (HR 1.02) [30, 31].

For further discussion, in the REDUCE-IT trial, as described above, the use of high-dose icosapent (pure EPA) was associated with significant clinical benefit, thought to be due to anti-inflammatory effects and mechanisms of plaque and membrane stabilization, regardless of triglyceride reduction. However, studies of mixed omega-3 fatty acids or niacin failed to demonstrate benefit, highlighting the impor-

tance of qualitative differences in lipid biology and downstream inflammatory signaling as a main determinant of risk. These results highlight that remnant cholesterol-related risk is complex and not solely related to lowering triglycerides alone [32].

There are several limitations to triglyceride- and remnant cholesterol-lowering therapies. As discussed, clinical trials of triglyceride-lowering agents have shown mixed results. While the REDUCE-IT trial demonstrated cardiovascular benefit with a 25% relative risk reduction [29], other trials such as STRENGTH and AIM-HIGH did not show similar reductions in cardiovascular events [30, 31].

The role of apolipoprotein B in residual lipid risk

ApoB represents the total number of circulating atherogenic particles, including LDL, intermediate-density lipoproteins, TRLs, and lipoprotein(a). Because every atherogenic lipoprotein carries apolipoprotein B, the apoB level reflects how many atherogenic particles are circulating in the blood [33]. The higher the number of circulating apoB-containing particles, the more likely they are to be retained in the intima and deposited in the subendothelium, triggering the inflammatory cascade and leading to plaque formation, growth, and subsequently, rupture [33, 34].

Compared to LDL-C, LDL-C only measures the amount of cholesterol within these particles, not how many particles are present. Multiple cohort studies have demonstrated that apoB is more closely linked to ASCVD risk than LDL-C, especially in patients receiving statin therapy, with up to 30% of high-risk patients misclassified by LDL-C alone [34].

Studies of lipid discordance demonstrate that even when LDL-C is low, elevated apoB is associated with higher cardiovascular risk, with cardiovascular risk remaining elevated by approximately 35% compared to those with concordantly low levels, indicating that LDL-C may miss ongoing atherogenic risk in some metabolic states [35].

Further Mendelian randomization studies also showed a direct causal relationship between apoB-containing lipoproteins and ASCVD, independent of cholesterol levels, with each 1 mmol/L reduction in apoB-containing lipoproteins associated with approximately 54% lower coronary heart disease risk [5].

These results suggest that ApoB is an important contributor to residual cardiovascular risk and can help identify patients who remain at risk. Therefore, several up-to-date guidelines consider apoB as a secondary treatment target. Especially in patients with diabetes, obesity, or hypertriglyceridemia [36].

LDL-C and apoB dissociation are common in insulin resistance, obesity, and hypertriglyceridemia. In these patients, LDL particles contain less cholesterol but remain numerically elevated. Therefore, apoB-based risk assessment can improve the identification of patients who may benefit from further lipid-lowering therapy regardless of meeting LDL-C desired goals. As a result, apoB has gained increasing recommendation as an adjunct or alternative therapeutic target in preventive strategies [37].

Multiple limitations were identified for ApoB-targeted strategies. Key limitations were that most randomized outcome trials have used LDL-C rather than apoB as the treatment target, limiting direct evidence for apoB-guided therapeutic strategies [1, 2, 6]. Persistent cardiovascular events despite intensive therapy were noted in PCSK9 inhibitor outcome trials [7-9].

Lipoprotein(a)

Lipoprotein(a) is an inherited lipoprotein made up of an LDL-like particle bound to apolipoprotein(a) [16]. This elevated Lp(a) is associated with an increased risk of ASCVD, regardless of LDL-C. Elevated levels of Lp(a) are associated with a higher risk of myocardial infarction, stroke, and aortic stenosis, with Lp(a) above 50 mg/dL associated with approximately a 2-fold increased risk of myocardial infarction and stroke [38]. Multiple mechanisms to promote atherosclerosis were identified, including the Lp(a) LDL-like core, which causes intimal retention, a prothrombotic state due to plasminogen activation inhibition, and the direct promotion of vascular inflammation and calcification [16, 38]. Levels of Lp(a) are minimally affected when treated with statins [16].

As a result, Lp(a) represents an important factor in the residual risk of ASCVD even in patients who have reached the desired levels of LDL-cholesterol.

The recent developments in antisense oligonucleotide and small interfering RNA therapies, including pelacarsen and olpasiran, have shown markedly reduced levels of Lp(a), with pelacarsen reducing Lp(a) by approximately 80% and olpasiran by greater than 90% in phase 2 trials [39, 40]. However, ongoing clinical trials' outcomes are needed to clarify whether reducing Lp(a) levels decreases the number of cardiovascular events.

Given the lifelong stability of Lp(a) levels, and as it is minimally affected by lifestyle or statin therapy, a single lifetime measurement may be adequate to screen for high-risk individuals. Incorporating Lp(a) assessment into routine cardiovascular risk evaluation may improve detection of residual inherited risk that can be missed by standard lipid testing [41].

Several limitations of therapeutic strategies were identified. Firstly, no definitive evidence that lowering Lp(a) reduces cardiovascular events is currently available. Secondly, as discussed, antisense oligonucleotide and siRNA therapies markedly reduce Lp(a) levels [39, 40]. However, ongoing outcome trials are required to confirm clinical benefit. Also, treatment with a PCSK9 inhibitor results in only a modest reduction in Lp(a), of approximately 20-25%. It remains unclear whether this degree of reduction contributes significantly to observed event reductions [7, 8, 39].

HDL dysfunction as a contributor to residual cardiovascular risk

Many pharmacological strategies aim to decrease cardiovascular risks and events by increasing HDL-C. However, these strategies failed to reduce cardiovascular events. Niacin raised HDL-C by 25% in the AIM-HIGH trial with no cardiovascular benefit [31]. Torcetrapib, a CETP inhibitor, raised HDL-C by 72% in the ILLUMINATE trial but increased cardiovascular mortality [42]. Dalcetrapib raised HDL-C by 30% in dal-OUTCOMES without cardiovascular benefit [43]. Emerging data suggest that HDL function is more important than HDL-C concentration. Cholesterol efflux capacity, which reflects HDL-mediated cholesterol removal from macrophages, has been shown to predict cardiovascular outcomes, regardless of HDL-C concentrations, with each 1-standard-deviation increase in efflux capacity associated with approximately a 67% lower risk of cardiovascular events, independent of HDL-C. When impaired, macrophages within the arterial wall accumulate excess cholesterol, accelerating foam cell formation, sustaining local inflammation, and promoting plaque growth and instability [44]. Therefore, impaired HDL function may play a role in the residual cardiovascular risk despite optimal LDL-C lowering, demonstrating the need for qualitative assessment of lipoproteins [44].

There are limitations to using medications that raise HDL-C, as increasing HDL-C levels has not been successful in reducing cardiovascular events, limiting HDL-C's usefulness as a treatment target. Although HDL cholesterol efflux capacity is associated with cardiovascular outcomes, there are currently no approved therapies that specifically improve HDL function, limiting its use in clinical practice [44].

Metabolic dysfunction and thrombotic susceptibility

Metabolic dysfunction, including Type 2 diabetes mellitus, obesity, and insulin resistance, contributes to ongoing cardiovascular risk by increasing the production of apoB-containing lipoproteins. These will enhance inflammatory signals, endothelial dysfunction, and prothrombotic states [45]. Insulin resistance also decreases endothelial synthesis of nitric oxide, increases a hypercoagulable state, and increases vascular inflammation, all factors that contribute to an environment favoring plaque progression and a higher probability of acute thrombotic events [45].

Moreover, blood clot formation and plaque instability play a major role in causing clinical events. Imaging studies suggest that high-risk plaque features and a tendency toward thrombosis can persist even with intensive lipid-lowering therapy, with approximately 20-25% of statin-treated patients retaining high-risk plaque features on imaging despite LDL-C control, which may explain why some patients continue to have recurrent events [46].

GLP-1 receptor agonists and SGLT2 inhibitors have been recognized as important contributors in the reduction of residual cardiovascular risk in patients with metabolic dysfunction. One of the largest meta-analyses to date, encompassing 21 RCTs and 99,599 patients, showed that GLP-1 RAs decreased all-cause death by 12% (IRR 0.88; 95% CI 0.84-0.92), cardiovascular death by 13% (IRR 0.87; 95% CI 0.81-0.92), and MACE by 13% (IRR 0.87; 95% CI 0.83-0.91), with an NNT of only 66 for MACE prevention over a mean follow-up of 2.4 years [47]. Importantly, in most participants, these benefits were observed in the context of statin therapy, thus addressing precisely the residual risk that persists after LDL-C optimization. The cardiovascular benefits of these agents go far beyond glycemic control and operate through mechanisms that intersect directly with the residual risk pathways discussed in this review. GLP-1 RAs reduce hsCRP and IL-6 levels, enhance endothelial function by increasing nitric oxide production, downregulate the secretion of inflammatory cytokines from monocytes and macrophages, thereby decreasing the proliferation of smooth muscle cells and inhibiting the activity of matrix metalloproteinases - potentially stabilizing atherosclerotic plaques [48]. The cardioprotective effects of SGLT2 inhibitors are mediated by beneficial hemodynamic effects, including natriuresis and reduced plasma volume without sympathetic activation, decreased vascular oxidative stress and inflammation, improved renal function, and metabolic effects, including increased ketone body utilization [49]. These pleiotropic mechanisms make both drug classes agents that simultaneously target the inflammatory, metabolic, and hemodynamic contributors to residual risk. Furthermore, emerging data suggest that a combination of both classes yields additive cardiovascular and kidney benefits. A meta-analysis of 3 trials showed that GLP-1 RAs reduced MACE by 21% (HR 0.79; 95% CI 0.71-0.87), with consistent effects regardless of whether patients were on an SGLT2 inhibitor at baseline [50].

Imaging and residual cardiovascular risk

Cardiovascular imaging can determine the residual cardiovascular risk even after achieving the desired LDL range. The calcium coronary score measures calcium buildup in the coronary arteries and helps determine the severity of atherosclerosis. It was shown that people with high calcium scores remain at a high risk of having cardiovascular diseases, even if they are treated with high-intensity statins, with a CAC score above 300 associated with approximately a 3-fold higher cardiovascular event rate despite statin therapy, suggesting that advanced plaque continues to drive risk that isn't explained by circulating biomarkers [51]. Other studies, such as intravascular ultrasound and optical coherence tomography, can reveal additional plaque characteristics, including lipid-rich cores, thin protective caps, and vessel wall enlargement, which can persist even after LDL reduction. These features are highly linked to plaque rupture and clot formation. These structural features indicate underlying plaque vulnerability, in which a thin fibrous cap overlying a lipid-rich necrotic core is susceptible to mechanical stress, rupture, and subsequent thrombus formation, which directly precipitates acute coronary syndromes [51, 52]. CTCA is another modality that has demonstrated that noncalcified and high-risk plaques are associated with future cardiovascular events, with high-risk plaque features on CTCA associated with approximately a 5-fold increased risk of future cardiovascular events, even among patients taking statins [52].

For the above reasons, incorporating imaging into clinical risk assessment may help identify patients with a high residual cardiovascular risk. Benefits may arise from more intensive or targeted preventive therapy alongside a traditional biomarker-based approach to preventing ASCVD [52].

Clinical implications and future perspectives

Recognizing residual cardiovascular risk makes clear that lowering LDL alone does not fully address cardiovascular risk and underscores the need for a more comprehensive approach to ASCVD prevention. Assessment of apoB, remnant cholesterol, inflammatory markers, and Lp(a) may help identify patients at increased risk even with standard therapy, with approximately 70% of cardiovascular events remaining unaddressed by LDL-C lowering alone even after achieving LDL-C below 70 mg/dL [12]. The developing intervention strategies

are focusing on treating patients based on their specific profile and phenotype. The focus will be on identifying which residual risk factors, such as inflammation, apoB burden, lipoprotein(a), or metabolic disease, are most important for that individual and then targeting those pathways specifically [18, 53]. The major residual risk pathways and their corresponding therapeutic strategies are summarized in **Table 1**.

Discussion

LDL-C at target, risk remains: a clinical alarm call

One of the great successes of modern cardiology has been the ability to reduce LDL-C to previously unachievable levels. However, anyone who has taken care of patients in a secondary prevention clinic knows the disappointment of watching a patient suffer a second myocardial infarction with an LDL-C of 55 mg/dL on maximal therapy. This is not an isolated finding. This pattern has been confirmed repeatedly in many trials, including FOURIER and ODYSSEY OUTCOMES, where a significant proportion of patients still experienced events even at the lowest achieved LDL-C levels [7, 8]. The lesson here is that plaque already accumulated, inflamed, and calcified over decades does not simply go away when LDL-C is brought under control [18, 51]. Therefore, telling a patient their LDL-C is "at goal" while other factors, including inflammatory burden, apoB, and Lp(a), remain unaddressed, is an incomplete assessment of their true cardiovascular risk.

Inflammation: the underlying driver of plaque instability

For much of the history of cardiovascular medicine, inflammation was recognized as a component of atherosclerosis but was rarely treated as a therapeutic target. That changed with the CANTOS trial [23], which demonstrated that blocking interleukin-1β reduced cardiovascular events without affecting lipids, establishing that inflammation is not merely a marker of atherosclerosis but an active driver of plaque vulnerability and rupture. This concept came closer to practice with the colchicine trials, COLCOT and LoDoCo2, which showed a meaningful reduction in events with a cheap, widely available drug [24, 25]. In the authors' view, when a patient has achieved their LDL-C target but still has a persistently elevated hs-CRP, their residual inflammatory risk has not been adequately addressed. The hs-CRP test is inexpensive and widely available. If hs-CRP remains elevated, further reduction in cardiovascular risk can be achieved by lifestyle modification, low-dose colchicine, or intensified risk factor management.

Lipoprotein(a): the inherited risk we keep ignoring

Lipoprotein(a) is possibly the most under-evaluated source of residual cardiovascular risk in clinical practice today. It is inherited, not responsive to statins, and associated with significant risk of myocardial infarction, stroke, and aortic stenosis [38]. But in most patients with cardiovascular disease, it is still not measured. RNA-based therapies, including pelacarsen and olpasiran, have shown Lp(a) reductions of 80-90% in phase 2 trials [39, 40], and outcome data are eagerly awaited. Until then, the 2026 ACC/AHA Dyslipidemia Guideline now carries a Class I recommendation for universal Lp(a) measurement at least once in all adults - the first time a US guideline has made this recommendation universally [54]. We support this recommendation, as it is a single-lifetime test, inexpensive, and may fundamentally change the approach to assessing a patient's residual risk.

Apolipoprotein B: a superior marker of atherogenic risk

ApoB measures one thing that LDL-C cannot: the true number of atherogenic particles circulating in the blood. In patients with metabolic dysfunction, obesity, or insulin resistance, cardiovascular risk is usually underestimated by LDL-C. In these patients, LDL-C particles are smaller and cholesterol-depleted, yet numerically elevated, and apoB provides a better reflection of the atherogenic burden [34, 35]. In clinical practice, LDL-C and apoB do not always tell the same story. When they diverge, apoB is the more accurate reflection of the patient's true cardiovascular risk. Both the 2019 ESC/EAS guidelines and their 2025 Focused Update recognize apoB as an important secondary treatment target, particularly in metabolic high-risk populations such as those with diabetes, obesity, or elevated triglycerides [36, 55]. Most recently, the 2026 ACC/AHA Dyslipidemia

Guideline formally endorses apoB measurement as a tool to assess residual ASCVD risk and guide further treatment decisions in high-risk patients who have already met their LDL-C and non-HDL-C targets [54]. We believe that apoB measurement needs to be incorporated more routinely in lipid assessment, especially in patients with metabolic dysfunction where LDL-C alone can be misleading.

HDL cholesterol: quantity versus quality

The history of HDL-targeted therapy is largely a story of unsuccessful attempts. In the AIM-HIGH trial, niacin increased HDL-C by 25% but failed to reduce cardiovascular events [31]. Torcetrapib, a CETP inhibitor, increased HDL-C by 72% in the ILLUMINATE trial but was actually associated with increased cardiovascular mortality [42]. Dalcetrapib increased HDL-C by 30% in dal-OUTCOMES without cardiovascular benefit [43]. Together, these trials taught us that raising HDL-C is not the same as improving HDL function. We believe that the failure of these agents was not a failure of the HDL hypothesis, but rather a failure to target the right metric. HDL-C concentration tells us how much cholesterol is being carried, not how effectively it removes cholesterol from the arterial wall. It is that difference between quantity and quality that these trials missed. Until therapies that specifically target cholesterol efflux capacity are developed and validated, HDL-C should not be a treatment target in and of itself. The focus should shift from raising the number to improving the function.

GLP-1 receptor agonists and SGLT2 inhibitors: cardiovascular drugs in metabolic clothing

One of the most significant shifts in cardiovascular medicine over the past decade has been the realization that GLP-1 receptor agonists and SGLT2 inhibitors are not only glucose-lowering drugs but cardiovascular drugs that happen to lower glucose. Their benefit on MACE, heart failure hospitalization, and progression of kidney disease has been consistently demonstrated across multiple large trials, on top of background statin therapy, in patients who had already achieved reasonable LDL-C control [47, 50]. What makes these agents particularly relevant to this discussion is that they address the metabolic, inflammatory, and hemodynamic dimensions of residual risk that statins do not touch [48, 49]. We believe that any high-risk patient with metabolic dysfunction, irrespective of diabetes status, deserves a serious discussion about these agents as part of their cardiovascular prevention strategy, rather than as an afterthought once glycemic targets are addressed.

Precision prevention: matching therapy to the biology of residual risk

The collective evidence reviewed in this paper supports a fundamental change in our approach to cardiovascular prevention. We favor a phenotype-driven strategy that systematically identifies and individually targets each patient's dominant residual risk pathway. A patient with high apoB and metabolic dysfunction needs a different intervention than a patient with high hs-CRP and normal apoB, or high Lp(a) and no metabolic disease. Measuring apoB, hs-CRP, and Lp(a) in addition to standard lipid panels is relatively inexpensive and provides substantially more information regarding residual risk [54, 55]. Coronary imaging, where available, provides an additional layer of individualization by identifying patients with high-risk plaque features who deserve more aggressive intervention irrespective of their biomarker profile [51, 52]. GLP-1 receptor agonists and SGLT2 inhibitors address the metabolic and hemodynamic components of residual risk not covered by statins and have emerged as evidence-based tools to be considered in a comprehensive cardiovascular prevention strategy for high-risk patients with metabolic dysfunction [47, 49, 50]. The newly released 2026 ACC/AHA Dyslipidemia Guideline formally recommends universal Lp(a) screening and apoB measurement in high-risk patients, providing a practical guide for applying this broad approach in clinical practice [54]. We believe the future of cardiovascular prevention is not to find a single drug that addresses all residual risk, but rather to develop individualized therapeutic strategies that address the specific biological drivers of risk in each patient.

Conclusion

LDL-C-lowering therapies remain the central approach for reducing ASCVD risk. However, they do not fully address residual cardiovascular risk, as some patients continue to experience significant cardiovascular events despite

statin therapy even after achieving desired LDL-C levels. Additional residual factors contribute to ongoing cardiovascular risk, including persistent inflammation, apoB-containing lipoprotein burden, remnant cholesterol, lipoprotein(a), metabolic dysfunction, and thrombotic mechanisms. ApoB offers a more holistic approach to understanding lipid-related residual risk and may enable more accurate cardiovascular risk assessment than LDL-C alone. GLP-1 receptor agonists and SGLT2 inhibitors address the metabolic and hemodynamic components of residual risk not covered by statins and have emerged as evidence-based tools to be considered in a comprehensive cardiovascular prevention strategy for high-risk patients with metabolic dysfunction [47, 49, 50]. The newly released 2026 ACC/AHA Dyslipidemia Guideline formally recommends universal Lp(a) screening and apoB measurement in high-risk patients, providing a practical guide for applying this broad approach in clinical practice [54]. Addressing these pathways represents a critical next step toward more effective risk assessment and personalized, tailored prevention strategies.

Acknowledgements

Artificial intelligence tools, specifically ChatGPT-4o, were used solely to assist with language editing, grammar correction, and clarity improvement of this manuscript. The authors are solely responsible for the scientific content, data interpretation, and integrity of the work presented.

Disclosure of conflict of interest

None.

Abbreviations

ApoB, apolipoprotein B; non-HDL-C, non-high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TRLs, triglyceride-rich lipoproteins; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; IL-1β, interleukin-1 beta; Lp(a), lipoprotein(a); siRNA, small interfering RNA; PCSK9, proprotein convertase subtilisin/kexin type 9; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2, sodium-glucose cotransporter-2.

Address correspondence to: Dr. Mohammed Taha, Department of Internal Medicine, Baptist Health-UAMS Internal Medicine Residency Program, 3116 N Hills BLVD, Apt 10322, North Little Rock, AR 72116, USA. Tel: 2162624460; E-mail: mohammed94nabeeltaha@gmail.com

References

[1] Silverman MG, Ference BA, Im K, Wiviott SD, Giugliano RP, Grundy SM, Braunwald E and Sabatine MS. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. JAMA 2016; 316: 1289-1297.

[2] Cholesterol Treatment Trialists' (CTT) Collaboration, Fulcher J, O'Connell R, Voysey M, Emberson J, Blackwell L, Mihaylova B, Simes J, Collins R, Kirby A, Colhoun H, Braunwald E, La Rosa J, Pedersen TR, Tonkin A, Davis B, Sleight P, Franzosi MG, Baigent C and Keech A. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. Lancet 2015; 385: 1397-1405.

[3] Libby P. Inflammation in atherosclerosis. Nature 2002; 420: 868-874.

[4] Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 2005; 352: 1685-1695.

[5] Ference BA, Yoo W, Alesh I, Mahajan N, Mirowska KK, Mewada A, Kahn J, Afonso L, Williams KA Sr and Flack JM. Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: a Mendelian randomization analysis. J Am Coll Cardiol 2012; 60: 2631-2639.

[6] Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E and Califf RM; IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015; 372: 2387-2397.

[7] Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS and Pedersen TR; FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017; 376: 1713-1722.

[8] Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, Jukema JW, Lecorps

G, Mahaffey KW, Moryusef A, Pordy R, Quintero K, Roe MT, Sasiela WJ, Tamby JF, Tricoci P, White HD and Zeiher AM; ODYSSEY OUTCOMES Committees and Investigators. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 2018; 379: 2097-2107.

[9] Hoogeveen RC and Ballantyne CM. Residual cardiovascular risk at low LDL cholesterol levels: remnants, lipoprotein(a), and inflammation. Circulation 2020; 141: 884-886.

[10] Bangalore S, Fayyad R, Laskey R, DeMicco DA, Messerli FH and Waters DD. Body-weight fluctuations and outcomes in coronary disease. N Engl J Med 2017; 376: 1332-1340.

[11] Cholesterol Treatment Trialists' (CTT) Collaboration; Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, Barnes EH, Voysey M, Gray A, Collins R and Baigent C. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 2012; 380: 581-590.

[12] Libby P and Everett BM. Novel antiatherosclerotic therapies. Arterioscler Thromb Vasc Biol 2019; 39: 538-545.

[13] Soehnlein O and Libby P. Targeting inflammation in atherosclerosis - from experimental insights to the clinic. Nat Rev Drug Discov 2021; 20: 589-610.

[14] Nordestgaard BG. Triglyceride-rich lipoproteins and atherosclerotic cardiovascular disease: new insights from epidemiology, genetics, and biology. Circ Res 2016; 118: 547-563.

[15] Sehayek D, Cole J, Björnson E, Wilkins JT, Mortensen MB, Dufresne L, Pencina KM, Pencina MJ, Thanassoulis G, and Sniderman AD. ApoB, LDL-C, and non-HDL-C as markers of cardiovascular risk: a systematic discordance analysis. J Clin Lipidol 2025; 19: 844-859.

[16] Tsimikas S. A test in context: lipoprotein(a). J Am Coll Cardiol 2017; 69: 692-711.

[17] Tabas I and Bornfeldt KE. Macrophage phenotype and function in different stages of atherosclerosis. Circ Res 2016; 118: 653-667.

[18] Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, Hegele RA, Krauss RM, Raal FJ, Schunkert H, Watts GF, Borén J, Fazio S, Horton JD, Masana L, Nicholls SJ, Nordestgaard BG, van de Sluis B, Taskinen MR, Tokgözoglu L, Landmesser U, Laufs U, Wiklund O, Stock JK, Chapman MJ and Catapano AL. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J 2017; 38: 2459-2472.

[19] Ridker PM. Inflammation, C-reactive protein, and cardiovascular disease: moving past the marker versus mediator debate. Circ Res 2014; 114: 594-595.

[20] Ridker PM, Rifai N, Rose L, Buring JE and Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med 2002; 347: 1557-1565.

[21] Ridker PM. Residual inflammatory risk. Eur Heart J 2017; 38: 3295-3297.

[22] Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT and Glynn RJ; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008; 359: 2195-2207.

[23] Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, Kastelein JJP, Cornel JH, Pais P, Pella D, Genest J, Cifkova R, Lorenzatti A, Forster T, Kobalava Z, Vida-Simiti L, Flather M, Shimokawa H, Ogawa H, Dellborg M, Rossi PRF, Troquay RPT, Libby P and Glynn RJ; CANTOS Trial Group. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 2017; 377: 1119-1131.

[24] Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, Pinto FJ, Ibrahim R, Gamra H, Kiwan GS, Berry C, López-Sendón J, Ostadal P, Koenig W, Angoulvant D, Grégoire JC, Lavoie MA, Dubé MP, Rhainds D, Provencher M, Blondeau L, Orfanos A, L'Allier PL, Guertin MC and Roubille F. Efficacy and safety of low-dose colchicine after myocardial infarction. N Engl J Med 2019; 381: 2497-2505.

[25] Nidorf SM, Fiolet ATL, Mosterd A, Eikelboom JW, Schut A, Opstal TSJ, The SHK, Xu XF, Ireland MA, Lenderink T, Latchem D, Hoogslag P, Jerzewski A, Nierop P, Whelan A, Hendriks R, Swart H, Schaap J, Kuijper AFM, van Hessen MWJ, Saklani P, Tan I, Thompson AG, Morton A, Judkins C, Bax WA, Dirksen M, Alings M, Hankey GJ, Budgeon CA, Tijssen JGP, Cornel JH and Thompson PL; LoDoCo2 Trial Investigators. Colchicine in patients with chronic coronary disease. N Engl J Med 2020; 383: 1838-1847.

[26] Ridker PM, Everett BM, Pradhan A, MacFadyen JG, Solomon DH, Zaharris E, Mam V, Hasan A, Rosenberg Y, Iturriaga E, Gupta M, Tsigoulis M, Verma S, Clearfield M, Libby P, Goldhaber SZ, Seagle R, Ofori C, Saklayen M, Butman S, Singh N, Le May M, Bertrand O, Johnston J, Paynter NP and Glynn RJ; CIRT Investigators. Low-dose methotrexate for the prevention of

atherosclerotic events. N Engl J Med 2019; 380: 752-762.
[27] Nordestgaard BG and Varbo A. Triglycerides and cardiovascular disease. Lancet 2014; 384: 626-635.
[28] Varbo A, Benn M, Tybjærg-Hansen A, Jørgensen AB, Frikke-Schmidt R and Nordestgaard BG. Remnant cholesterol as a causal risk factor for ischemic heart disease. J Am Coll Cardiol 2013; 61: 427-436.
[29] Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, Doyle RT Jr, Juliano RA, Jiao L, Granowitz C, Tardif JC and Ballantyne CM; REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med 2019; 380: 11-22.
[30] Nicholls SJ, Lincoff AM, Garcia M, Bash D, Ballantyne CM, Barter PJ, Davidson MH, Kastelein JJP, Koenig W, McGuire DK, Mozaffarian D, Ridker PM, Ray KK, Katona BG, Himmelmann A, Loss LE, Rensfeldt M, Lundström T, Agrawal R, Menon V, Wolski K and Nissen SE. Effect of high-dose omega-3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk: the STRENGTH randomized clinical trial. JAMA 2020; 324: 2268-2280.
[31] AIM-HIGH Investigators, Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, Koprowicz K, McBride R, Teo K and Weintraub W. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med 2011; 365: 2255-2267.
[32] Duran EK, Aday AW, Cook NR, Buring JE, Ridker PM and Pradhan AD. Triglyceride-rich lipoprotein cholesterol, small dense LDL cholesterol, and incident cardiovascular disease. J Am Coll Cardiol 2020; 75: 2122-2135.
[33] Johannesen CDL, Mortensen MB, Nordestgaard BG and Langsted A. Discordance analyses comparing LDL cholesterol, non-HDL cholesterol, and apolipoprotein B for cardiovascular risk estimation. Atherosclerosis 2025; 403: 119139.
[34] Wilkins JT, Li RC, Sniderman A, Chan C and Lloyd-Jones DM. Discordance between apolipoprotein B and LDL-cholesterol in young adults predicts coronary artery calcification: the CARDIA study. J Am Coll Cardiol 2016; 67: 193-201.
[35] Sniderman AD, Williams K, Contois JH, Monroe HM, McQueen MJ, de Graaf J and Furberg CD. A meta-analysis of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B as markers of cardiovascular risk. Circ Cardiovasc Qual Outcomes 2011; 4: 337-345.
[36] Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen MR, Tokgozoglu L and Wiklund O; ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020; 41: 111-188.
[37] Sniderman AD, Thanassoulis G, Glavinovic T, Navar AM, Pencina M, Catapano A and Ference BA. Apolipoprotein B particles and cardiovascular disease: a narrative review. JAMA Cardiol 2019; 4: 1287-1295.
[38] Kamstrup PR, Tybjærg-Hansen A and Nordestgaard BG. Elevated lipoprotein(a) and risk of aortic valve stenosis in the general population. J Am Coll Cardiol 2014; 63: 470-477.
[39] O'Donoghue ML, Fazio S, Giugliano RP, Stroes ESG, Kanevsky E, Gouni-Berthold I, Im K, Lira Pineda A, Wasserman SM, Češka R, Ezhov MV, Jukema JW, Jensen HK, Tokgözoğlu SL, Mach F, Huber K, Sever PS, Keech AC, Pedersen TR and Sabatine MS. Lipoprotein(a), PCSK9 inhibition, and cardiovascular risk. Circulation 2019; 139: 1483-1492.
[40] Kronenberg F, Mora S, Stroes ESG, Ference BA, Arsenault BJ, Berglund L, Dweck MR, Koschinsky M, Lambert G, Mach F, McNeal CJ, Moriarty PM, Natarajan P, Nordestgaard BG, Parhofer KG, Virani SS, von Eckardstein A, Watts GF, Stock JK, Ray KK, Tokgözöğlu LS and Catapano AL. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement. Eur Heart J 2022; 43: 3925-3946.
[41] Wilson DP, Jacobson TA, Jones PH, Koschinsky ML, McNeal CJ, Nordestgaard BG and Orringer CE. Use of lipoprotein(a) in clinical practice: a biomarker whose time has come. A scientific statement from the National Lipid Association. J Clin Lipidol 2019; 13: 374-392.
[42] Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ, Komajda M, Lopez-Sendon J, Mosca L, Tardif JC, Waters DD, Shear CL, Revkin JH, Buhr KA, Fisher MR, Tall AR and Brewer B; ILLUMINATE Investigators. Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med 2007; 357: 2109-2122.
[43] Schwartz GG, Olsson AG, Abt M, Ballantyne CM, Barter PJ, Brumm J, Chaitman BR, Holme IM, Kallend D, Leiter LA, Leitersdorf E, McMurray JJ, Mundl H, Nicholls SJ, Shah PK, Tardif JC and Wright RS; dal-OUTCOMES Investigators. Effects of dalcetrapib in patients with a recent acute coronary syndrome. N Engl J Med 2012; 367: 2089-2099.

[44] Khera AV, Cuchel M, de la Llera-Moya M, Rodrigues A, Burke MF, Jafri K, French BC, Phillips JA, Mucksavage ML, Wilensky RL, Mohler ER, Rothblat GH and Rader DJ. Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. N Engl J Med 2011; 364: 127-135.

[45] Bornfeldt KE and Tabas I. Insulin resistance, hyperglycemia, and atherosclerosis. Cell Metab 2011; 14: 575-585.

[46] Budoff MJ, Young R, Burke G, Jeffrey Carr J, Detrano RC, Folsom AR, Kronmal R, Lima JAC, Liu KJ, McClelland RL, Michos E, Post WS, Shea S, Watson KE and Wong ND. Ten-year association of coronary artery calcium with atherosclerotic cardiovascular disease (ASCVD) events: the multi-ethnic study of atherosclerosis (MESA). Eur Heart J 2018; 39: 2401-2408.

[47] Galli M, Benenati S, Laudani C, Simeone B, Sarto G, Ortega-Paz L, Rocco E, Bernardi M, Spadafora L, D'Amario D, Greco E, Frati G, Federici M, Mehran R, Crea F, Angiolillo DJ and Sciarretta S. Cardiovascular effects and tolerability of GLP-1 receptor agonists: a systematic review and meta-analysis of 99,599 patients. J Am Coll Cardiol 2025; 86: 1805-1819.

[48] Nauck MA, Tuttle KR, Tschöp MH and Blüher M. Glucagon-like receptor agonists and next-generation incretin-based medications: metabolic, cardiovascular, and renal benefits. Lancet 2026; 407: 892-908.

[49] Xu J, Hirai T, Koya D and Kitada M. Effects of SGLT2 inhibitors on atherosclerosis: lessons from cardiovascular clinical outcomes in type 2 diabetic patients and basic researches. J Clin Med 2021; 11: 137.

[50] Neuen BL, Fletcher RA, Heath L, Perkovic A, Vaduganathan M, Badve SV, Tuttle KR, Pratley R, Gerstein HC, Perkovic V and Heerspink HJL. Cardiovascular, kidney and safety outcomes with GLP-1 receptor agonists alone and in combination with SGLT2 inhibitors in type 2 diabetes: a systematic review and meta-analysis. Circulation 2024; 150: 1781-1790.

[51] Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, Mehran R, McPherson J, Farhat N, Marso SP, Parise H, Templin B, White R, Zhang Z and Serruys PW; PROSPECT Investigators. A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011; 364: 226-235.

[52] Motoyama S, Ito H, Sarai M, Kondo T, Kawai H, Nagahara Y, Harigaya H, Kan S, Anno H, Takahashi H, Naruse H, Ishii J, Hecht H, Shaw LJ, Ozaki Y and Narula J. Plaque characterization by coronary computed tomography angiography and the likelihood of acute coronary events in mid-term follow-up. J Am Coll Cardiol 2015; 66: 337-346.

[53] Ridker PM. Residual inflammatory risk: addressing the obverse side of the atherosclerosis prevention coin. Eur Heart J 2016; 37: 1720-1722.

[54] Blumenthal RS, Morris PB, Gaudino M, Johnson HM, Anderson TS, Bittner VA, Blankstein R, Brewer LC, Cho L, de Ferranti SD, Gianos E, Gluckman TJ, Gradney KF, Isiadinso I, Lloyd-Jones DM, Marrs JC, Martin SS, McLain KH, Mehta LS, Mora S, Mulugeta WM, Natarajan P, Navar AM, Orringer CE, Polonsky TS, Reynolds HR, Saseen JJ, Shapiro MD, Soffer DE, Tynes SA, Villavaso CD, Virani SS and Wilkins JT. 2026 ACC/AHA/AACVPR/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of dyslipidemia: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol 2026; 87: 2624-2757.

[55] Mach F, Koskinas KC, Roeters van Lennep JE, Tokgözoğlu L, Badimon L, Baigent C, Benn M, Binder CJ, Catapano AL, De Backer GG, Delgado V, Fabin N, Ference BA, Graham IM, Landmesser U, Laufs U, Mihaylova B, Nordestgaard BG, Richter DJ and Sabatine MS; ESC/EAS Scientific Document Group. 2025 focused update of the 2019 ESC/EAS guidelines for the management of dyslipidaemias. Atherosclerosis 2025; 409: 120479.