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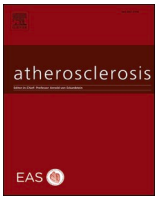

Review article

Non-HDL-cholesterol in dyslipidemia: Review of the state-of-the-art literature and outlook

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ABSTRACT

Dyslipidemia refers to unhealthy changes in blood lipid composition and is a risk factor for atherosclerotic cardiovascular diseases (ASCVD). Usually, low-density lipoprotein-cholesterol (LDL-C) is the primary goal for dyslipidemia management. However, non-high-density lipoprotein cholesterol (non-HDL-C) has gained attention as an alternative, reliable goal. It encompasses all plasma lipoproteins like LDL, triglyceride-rich lipoproteins (TRL), TRL-remnants, and lipoprotein a [Lp(a)] except high-density lipoproteins (HDL). In addition to LDL-C, several other constituents of non-HDL-C have been reported to be atherogenic, aiding the pathophysiology of atherosclerosis. They are acknowledged as contributors to residual ASCVD risk that exists in patients on statin therapy with controlled LDL-C levels. Therefore, non-HDL-C is now considered an independent risk factor or predictor for CVD. The popularity of non-HDL-C is attributed to its ease of estimation and non-dependency on fasting status. It is also better at predicting ASCVD risk in patients on statin therapy, and/or in those with obesity, diabetes, and metabolic disorders. In addition, large follow-up studies have reported that individuals with higher baseline non-HDL-C at a younger age (<45 years) were more prone to adverse CVD events at an older age, suggesting a predictive ability of non-HDL-C over the long term. Consequently, non-HDL-C is recommended as a secondary goal for dyslipidemia management by most international guidelines. Intriguingly, geographical patterns in recent epidemiological studies showed remarkably high non-HDL-C attributable mortality in high-risk countries. This review highlights the independent role of non-HDL-C in ASCVD pathogenesis and prognosis. In addition, the need for a country-specific approach to dyslipidemia management at the community/population level is discussed. Overall, non-HDL-C can become a co-primary or primary goal in dyslipidemia management.

1. Introduction

Dyslipidemia is characterized by the altered composition of lipids in the blood [1]. Clinical assessments of blood lipids such as total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG) are routinely

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performed for the diagnosis and/or prognosis of cardiovascular diseases (CVD) [1]. Serum lipoproteins differ based on their composition, size, and associated apolipoproteins that govern the density and metabolic fate of these particles [2] (Fig. 1). In addition to LDL and HDL, the other major lipoproteins in the blood are triglyceride-rich lipoproteins (TRLs). The TRLs represent liver-generated very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and gut-derived chylomicrons (CM). Chylomicrons are present only in the immediate post-prandial state as they are rapidly metabolized to form CM remnants. The CM-remnants and VLDL metabolic-derivatives (VLDL-remnants) are called TRL-remnants or remnant lipoproteins (RLPs). All lipoproteins have a hydrophobic core carrying varying amounts of TG and cholesterol-esters enclosed in a membranous monolayer. The lipoproteins are associated with one or more specific apolipoproteins, which are characteristic of each lipoprotein particle. Hepatic-derived lipoproteins LDL, VLDL, IDL, and VLDL-remnants each carry one ApoB100, while gut-derived CM and CM-remnants carry one ApoB48, a truncated version of ApoB100 [2,3]. Lipoprotein (a), another liver-generated lipoprotein whose levels are mostly genetically determined, comprises apolipoprotein (a) as the major structural protein in addition to ApoB100 [4]. On the other hand, the major apolipoproteins associated with HDL are Apo AI-II [2] (Fig. 1).

VLDL and other LDL-derived lipoproteins carry cholesterol from hepatocytes to the peripheral system and are the major players in atherosclerotic plaque formation. On the other hand, HDL is involved in reverse cholesterol transport from peripheral tissues back to the liver for further metabolism, thereby reducing peripheral and circulating cholesterol. Serum lipoproteins are dominated by LDL particles and therefore LDL-C serves as the key marker for the assessment of CVD risk and the focus of lipid-lowering treatment. However, a significant ASCVD risk called “residual risk” remains in patients on lipid-lowering therapy even upon achieving the recommended levels of LDL-C. The existence of residual ASCVD risk has shone the spotlight on the atherogenic potential of serum lipids other than LDL-C [1,5]. Non-high-density lipoprotein cholesterol (non-HDL-C) is a composite measure of cholesterol present in diverse types of lipoproteins - LDL, TRL, TRL remnants, and Lp(a) - excluding HDL. It is calculated simply by deducting the HDL-C values from TC in the conventional lipid panel and denotes the serum cholesterol of all ApoB-carrying lipoproteins [2,6,7]. The total cholesterol content of TRL remnants is called remnant cholesterol (RC), which is alternatively defined as the sum of all serum cholesterol minus HDL-C and LDL-C. Recent studies have unraveled the role of RC as a causal factor of CVD and have also highlighted its potential for predicting adverse CV events independent of LDL-C [2,8–10]. Significantly, non-HDL-C represents RC as well as cholesterol present in all ApoB100-carrying lipoproteins, such as LDL and Lp(a). Epidemiological studies and clinical trials have underscored the importance of non-HDL-C in predicting future ASCVD risk better than LDL-C. Most importantly, non-HDL-C is a better risk predictor in the subset of patients with metabolic disorders, type 2 diabetes, and obesity displaying atherogenic dyslipidemia. Even though these patients display the recommended levels of LDL-C, they are reported to be at significantly higher risk of ASCVD due to elevated levels of the non-LDL component of non-HDL-C [6,7].

Non-HDL-C was first endorsed as a secondary target for ASCVD risk assessment in the guidelines of the National Cholesterol Education Program/Adult Treatment Panel III [ATP III] in 2001 [11]. Most countries recognize non-HDL-C as an independent factor for CVD risk and recommend it as an important treatment goal for dyslipidemia management. Non-HDL-C and ApoB100 levels are recommended as secondary targets for ASCVD in major worldwide guidelines and consensus statements [12–14]. It is especially important to lower the residual CVD risk in patients with optimal LDL-C lowering therapy, but elevated serum TG [15]. Apolipoprotein B100 is a robust, reliable, and inclusive marker for measuring all atherogenic particles and estimating CVD risk [16]. Non-HDL-C values are reported to correlate strongly with ApoB100, providing similar information in most circumstances, and therefore each could be accepted as a clinical surrogate for the other [17–19]. Data from UK Biobank analysis suggest that the inclusion of LDL-C and non-HDL-C in routine lipid panels can capture most of the variability (92%) in ApoB100 values and that ApoB100 measurement does not add any further predictive value to ASCVD risk [18,19]. Testing

Parameters	Chylomicrons	VLDL	IDL	LDL	Lp(a)	HDL
Size (nm)	~75-1000	30-80	25-35	18- 25	~30	5-12
Density (g/ml)	<0.95	0.950- 1.006	1.006- 1.019	1.019- 1.063	1.055- 1.085	1.063- 1.210
TG Content (%)	~85-90	~50-65	~20-30	~5-10	~5	~5-10
Cholesterol Ester Content (%)	~3-5	~10-15	~30-35	~35-48	~35-40	~12-30
Major Apo-proteins	Apo B-48	Apo B-100	Apo B-100	Apo B-100	Apo (a); Apo B-100	Apo A I-II

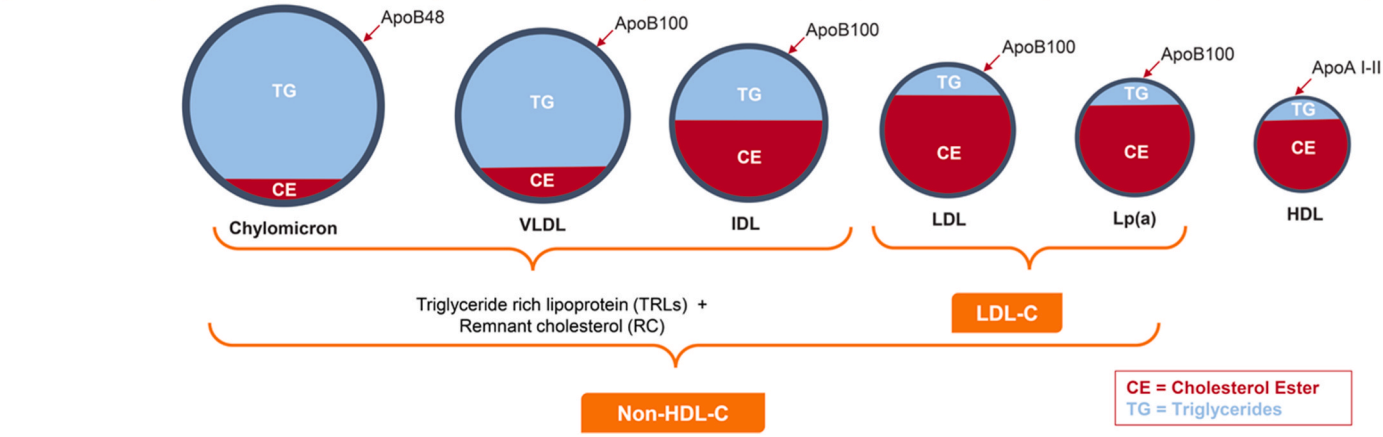

Fig. 1. Overview and key characteristics of the lipid particles.
(Upper panel) The table describes the key physical characteristics of the blood lipid particles. (Lower panel) Diagrammatic representation of blood lipid particles showing the respective distribution of cholesterol (CE) and triglyceride (TG) content in addition to associated apolipoprotein particles.

for ApoB100 is more expensive than a conventional lipid panel with an average four-times longer mean reporting time. On the other hand, non-HDL-C is simply calculated from the values reported in the routine lipid panel, making it easier to estimate or report [19]. Therefore, non-HDL-C has gained widespread application and is increasingly accepted as a clinically relevant biomarker as well as an important treatment goal. In routine clinical care, the consensus is to augment LDL-C with non-HDL-C as a treatment goal and prognostic marker [12,19]. The utility of targeting ApoB100 beyond non-HDL-C for CVD risk reduction has not been unequivocally proven to be superior [20]. Here we present a narrative review of the recent literature on the emergence of non-HDL-C as a significant biomarker, in addition to its pathophysiology in CVD, methods of estimation, clinical context, and its potential for estimating residual CVD risk in dyslipidemia patients.

2. Pathophysiological mechanisms of non-HDL-C

The pathophysiology of atherosclerosis is not very well understood. It has been extensively reviewed in the literature, with a particular focus on the mechanisms related to the primary target LDL-C [21]. Evidence suggests that besides LDL-C, other lipoproteins partaking in non-HDL-C can independently contribute to the atherogenic mechanisms during atherosclerotic lesion initiation and progression stages [9].

Atherosclerotic plaque formation is a complex event that is initiated with the transcytosis of ApoB-positive lipoproteins smaller than <70 nm, including LDL, Lp(a), TRLs, and TRL remnants, into the arterial wall [21,22]. These lipoproteins are selectively retained in intima through specific interactions of ApoB (B100/B48) to extracellular matrix components such as proteoglycans. The entrapped lipoproteins trigger metabolic and immuno-inflammatory responses beckoning monocytes to the site of lesion initiation and promoting its differentiation into macrophages. The LDL trapped in the atrial wall undergoes oxidative modifications resulting in oxidized LDL (OxLDL) - an omnipotent chemokine - before being phagocytosed by macrophages. Alternately, the TRLs and TRL remnants can be phagocytosed without any enzymatic alterations (Fig. 2) [9,21,23]. Remnants are reportedly as atherogenic as LDL, and being enriched in ApoCIII and ApoE apolipoproteins, possess pro-inflammatory as well as pro-coagulatory properties. Each particle of TRL/TRL remnant is known to carry significantly more cholesterol as compared to LDL. Notably, other than the cholesterol of TRL/TRL remnants, the TG component also aids in atherosclerosis pathogenesis through its immunomodulatory properties post-hydrolysis [2,24,25].

The entrapped lipoproteins are phagocytosed by the macrophages in a bid to clear the lipid infiltration but rather lead to the formation of the characteristic foam cells (macrophages laden with lipids) and their death. This is followed by smooth muscle cell proliferation, vascular fibrosis, necrosis, and tissue damage, developing the lesion into unstable plaques. Disruption of such plaques can cause thrombus formation leading to life-threatening CVD events [21,22]. Although several less-understood genetic and epigenetic factors enhance susceptibility to ASCVD, targeting elevated serum cholesterol is considered a straightforward and easily modifiable element for reducing adverse CV events [22] (Fig. 2).

3. Non-HDL-C as a residual risk factor in CVD

Residual CVD risk or the risk of CVD occurrence even with good LDL-C control is a critical concern in dyslipidemia management [26]. Large clinical studies on statin-treated patients have demonstrated a direct correlation between the lowering of LDL-C levels and reduction in CVD risk. It is reported that every 1 mmol/L (40 mg/dL) reduction in serum LDL-C lowers the relative risk of ASCVD by 22% [27,28]. However, even after achieving the recommended levels of LDL-C, many patients still experience major adverse cardiovascular events (MACE) [29–31]. For example, a meta-analysis of data from 14 randomized trials showed that even though LDL-C was lowered, the 5-year risk of MACE was 14% *vs.* 18% in the statin-treated and placebo group, respectively [29]. Another study examining the data from 62,154 patients on statin therapy, with

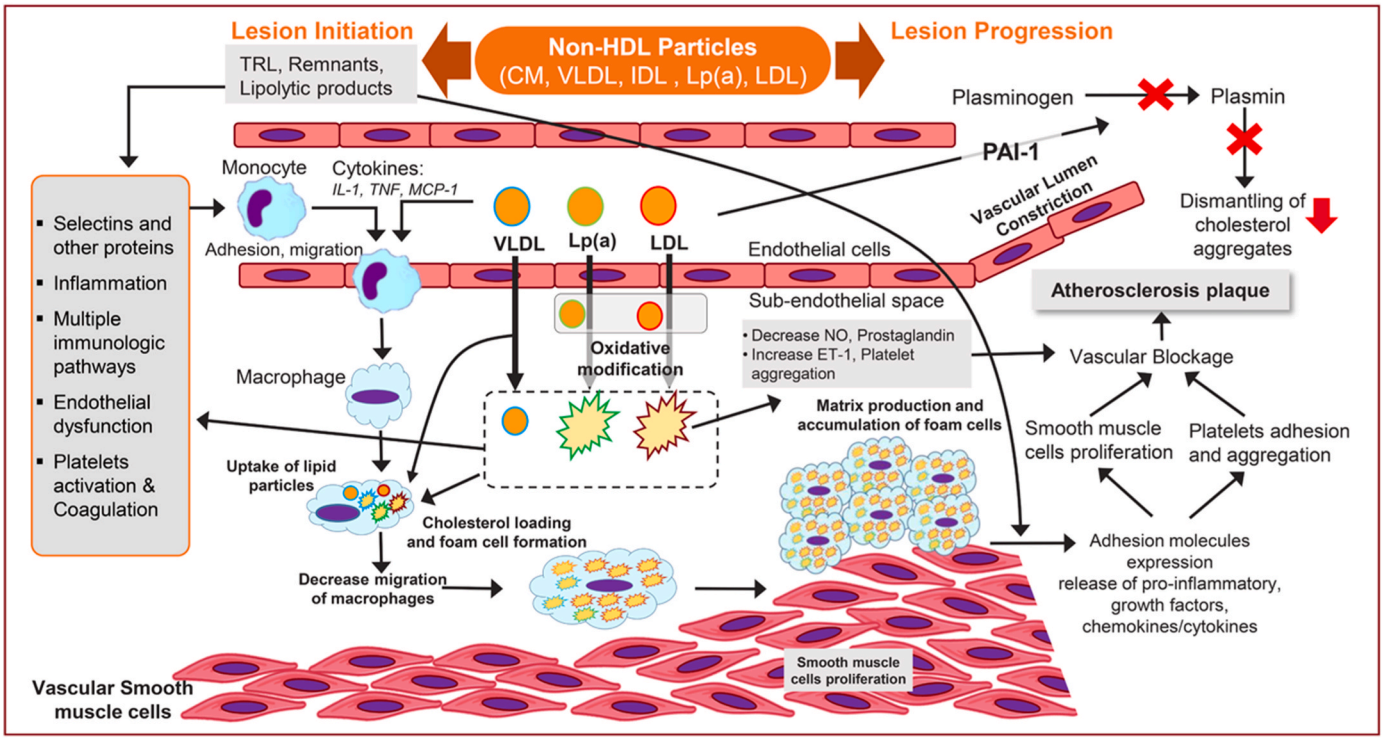

Fig. 2. Overview of non-HDL-C pathogenesis.
All lipoproteins partaking in non-HDL-C independently contribute to the initiation and progression stage, resulting in the growth of atherosclerotic plaques, arterial occlusion, plaque rupture, and consequent cardiovascular diseases.

controlled LDL-C (<2.6 mmol/L) but elevated non-HDL-C (>3.4 mmol/L), reported a 32% higher risk of CV events [HR1.32 (95% CI: 1.17–1.50)] [31]. Similar trends were replicated in other clinical studies and registries across locations. In a Japanese subset of the CHART-2 study (Chronic Heart Failure Analysis and Registry in the Tohoku District-2), non-HDL-C levels at baseline predicted higher odds of MI recurrence (p for trend = 0.009), based on non-HDL-C levels between three patient groups (G1 = ≤100 mg/dL, G2 = 100–129 mg/dL, G3 = ≥130 mg/dL) [32]. In another large study based on 13,000+ statin-treated patients, the association of non-HDL-C showed HR of 1.18 (95% CI: 1.02–1.36) and 1.78 (95% CI: 1.35–2.34) for all-cause mortality and MI, respectively [26]. The evidence strongly points towards the independent role of non-HDL-C as a risk factor for ASCVD.

Studies in the last decade have improved our understanding of the atherogenicity of TRLs, their metabolic intermediates (TRL remnants), and their constituent remnant cholesterol (RC) as they are associated with ASCVD risk independent of LDL-C [2,8,33]. In a 33-month longitudinal study of coronary artery disease (CAD) patients on lipid-lowering therapy (LDL-C <100 mg/dL), RC was found to be an independent predictor of CVD risk as compared to non-HDL-C or ApoB [34]. Similarly, a sub-analysis of the JUPITER trial showed an independent and dose-response reduction of ASCVD risk linked to decreased VLDL-C (p = 0.002) and VLDL-particles numbers (p = 0.006), which remained unchanged even after adjusting LDL-C levels [35]. Furthermore, in CAD patients, each unit increase in VLDL-C (mmol/L) was reported to increase the risk of MACE (HR 1.19, 95% CI: 1.04–1.37), major adverse limb events (MALE) (HR 1.30, 95% CI: 1.03–1.65), and MI (HR 1.31, 95% CI: 1.07–1.59) [36]. All this put together reiterates that besides LDL-C, other contributors to non-HDL-C are independent drivers of CVD risk. As noted earlier, the pathophysiological relevance of components such as TRLs and TRL remnants (in addition to LDL) in atherogenesis provides a mechanistic explanation for potentially modifiable and controllable residual risk (Fig. 2).

Non-HDL-C (≥190 mg/dL) and ApoB100 were highlighted in the AHA/ACC guidelines (2018) as additional risk factors for ASCVD and a major determinant of the therapy decision to include a PCSK-9 inhibitor in the treatment regimen [13]. Although ApoB100 appears to be better at predicting CVD risk, its widespread application in the clinical setting is currently debated [19,20,37]. The consensus-based guidance from EAS and EFLM recommends non-HDL-C as the secondary treatment target because of the lack of significant health-economic benefits from pharmacological interventions aimed at reducing ApoB100 at very low LDL-C levels [12]. Considering the relevance and usefulness of non-HDL-C, recent ESC guidelines for CVD prevention (2020) also use non-HDL-C as input in the Systematic Coronary Risk Estimation 2 (SCORE-2) algorithm for assessing disease risk [38]. The Residual Risk Reduction Initiative (R3i), a globally active, multidisciplinary non-profit organization, has also emphasized targeting non-HDL-C when making treatment decisions. It recommends adding fibrate, niacin, omega-3 fatty acids, or ezetimibe to the standard statin regimen to further lower non-HDL-C and residual CV risk in patients with atherogenic dyslipidemia (www.r3i.org/) [39,40].

4. Estimation of non-HDL-C: Pros and cons

Non-HDL-C measurement does not require additional tests, other than a routinely performed lipid profile as per clinical practice. It encompasses all the cholesterol circulating in the blood that is not from HDL, including cholesterol derived from CMs and CM remnants. It can be estimated based on the simple formula [41]:

$$Non\ HDL\ Cholesterol = Total\ Cholesterol\ (TC) - HDL\ Cholesterol$$

Non-HDL-C is usually measured in mg/dL and can be converted to mmol/L when multiplied by a factor of 0.0259 [42].

The non-HDL-C threshold is recommended to be < 30 mg/dL (0.8 mmol/L) higher than the desired LDL-C threshold by most of the international guidelines [30,41,43]. The concept of adding 30 mg/dL to the LDL-C is rooted in a 5:1 weight-ratio of TG: cholesterol in regular VLDL particles. Since the target level of TG in fasting status is < 150 mg/dl, the normal VLDL-C levels can be estimated to be < 30 mg/dl [29]. However, this way of estimating the non-HDL-C threshold is debatable because it does not consider cholesterol from TRL remnants. Also, experts are often concerned about the risk of underestimating non-HDL-C and the need to lower non-HDL-C goals by 5–10 mg/dL to match risk estimates with LDL-C goals [29,43]. Hence, future studies will be needed to form a consensus on non-HDL-C thresholds and treatment goals.

Notably, the values of calculated non-HDL-C depend on the direct analytical measurement of two variables, TC and HDL-C. Therefore, these measurements are prone to error and over/underestimation. As per a previous study, most methods used for direct HDL-C assays did not meet the National Cholesterol Education Program's (NCEP) performance goal. The total error in non-HDL-C estimations ranged from 28.2% to 36.3%, while the mean bias between the reference methods and assays ranged from 8.8% to 28.6% [44]. In a detailed study on the errors and biases of widely used HDL-C measurement methods (Denka Seiken, Kyowa Medex, Sekisui Medical, Roche, Serotec, Wako, UMA, and Sysmex methods), the data suggested that most of the HDL-C measurement methods exceeded the total error goal of ≤13% and recommended mean bias of ≤5% in the sample from a non-diseased group [45]. However, TC estimation methods are considered precise and reliable and pose no apparent additional bias or error to non-HDL-C estimation. Thus, the precise and bias-free estimation methods of HDL-C, and non-HDL-C remain an unmet need. Given the current food consumption patterns, many people stay in the post-prandial phase for up to 16 h a day. Because of this, more lipid specialists consider that dyslipidemia and atherosclerosis are mostly post-prandial phenomena [12]. Non-HDL-C values are shown to be more stable than LDL-C during fasting and less prone to post-prandial fluctuations in non-fasting states [42,46]. These results indicate that non-HDL-C is a more realistic prognostic marker as compared to LDL-C for CVD risk [14,46]. Furthermore, the utility of non-HDL-C is thought to be greater in subjects such as youngsters or in cases of physiological constraints that make it difficult to not eat before lipid screening [47].

Thus, while non-HDL-C has emerged as a potential target for assessing residual CVD risk in individuals with controlled LDL-C levels, it is not without limitations and drawbacks. For instance, analytical mistakes and biased HDL-C measurements can affect the estimation of non-HDL-C. Moreover, the current treatment threshold of non-HDL-C - set at 30 mg/dL higher than the LDL-C target-is debated and requires adjustment. Non-HDL-C reported at very high baseline TG levels or when VLDL particles are relatively cholesterol deficient in hypertriglyceridemia (TG > 150–200 mg/dL may be subject to additional bias [43,44,48]. Thus, there is a need for larger systematic studies to reproduce these findings, identify more precise estimation methods, and set more specific and scientifically validated non-HDL-C goals.

5. Non-HDL-C as prognostic target and treatment goal

A meta-analysis of long-term follow-up studies found that patients with higher non-HDL-C levels at baseline had a higher risk of CVD-related mortality (1.24, 95%CI: 1.05–1.46, p = 0.011). Additionally, it reported a higher risk of overall death (RR 1.13, 95%CI: 1.06–1.21, p= 0.001) with every 10 mg/dL increase in non-HDL-C [49]. Non-HDL-C levels were also significantly associated with an increased risk of all CVD events in mild-to-moderate hypercholesterolemia (TC: 220–270 mg/dL) patients on statin treatment, but no history of CVD. As compared to individuals in the first tertile (2.6–4.6 mmol/L), the HR for CVD risk for patients in the third tertile (5.0–6.1 mmol/L) was 2.75 (95% CI: 1.37–5.53) in diabetics and 1.94 (95% Cl: 1.02–3.71) in non-diabetics. Irrespective of their diabetes status, patients displayed an incremental HR of 1.02 (95% CI: 1.01–1.04) per one-SD increment of non-HDL-C

Table 1
Cardiovascular risk estimation by non-HDL-C level in various patient segments with comorbidities or statin therapy.

Non-HDL-C threshold [mg/dL]	Underlying conditions or adjustments	Patient segments	Risk estimate HR (95% CI range)	Outcome measures against which risk estimation was performed	Additional remarks	Sources
Non-HDL-C <130 mg/dL	Crude, not adjusted for comorbidities or LDL targets	Control patients	**1.48 (1.18–1.85)**	Unadjusted-pooled estimates of CVD events	Unadjusted estimates, as well as post-multivariable adjustments estimates (age, gender, BMI, smoking), offered similar predictive values of non-HDL-C for CVD events. Similarly, other predictors were ApoB/ApoA-I ratio, ApoB, and LDL-C/HDL-C ratio.	[93]
			1.27 (1.14–1.41)	Adjusted-pooled estimates of CVD events		
		Statin treated patients	**1.12 (1.05–1.20)**	Unadjusted-pooled estimates of CVD events	For unadjusted estimates, HDL-C and TC showed the strongest association, while after multivariable adjustment (age, gender, BMI, smoking variables) only HDL-C showed an association with CVD events.	
			1.35 (1.10–1.65)	Adjusted-pooled estimates of CVD events		
	Patients with established ASCVD (AIM-HIGH Trial)	Simvastatin + ezetimibe treated patients with High TG (150–400 mg/dl), low HDL-C, and LDL-C adjusted (<180 mg/dl)	**1.31, (1.13–1.52)** #	CV event rate	The non-HDL-C association was significant only in the control (LLT + Placebo) group but not in the treatment (LLT + ERN) group. Baseline and in-trial HDL-C levels were not significantly associated with CV events in either treatment group.	[94]
	Patients with stable ASCVD (AIM-HIGH Trial)	Statin (simvastatin) treated patients with controlled LDL-C (40–80 mg/dL); HDL-C < 32 mg/dL; TG > 200 mg/dL	1.20 (0.85–1.69) ns	Adjusted – composite CVD events	Baseline non-HDL-C did not show a significant association with primary endpoint (composite of CV mortality, nonfatal MI, ischemic stroke, hospitalization for acute coronary syndrome, or symptom-driven coronary or cerebrovascular revascularization) in the entire population or patients with low HDL-C<32 mg/dl, LDL-C, and high TG > 200 mg/dL. A similar lack of significant association was observed in statin and ERN-treated groups.	[95]
Non-HDL-C 130–160 mg/dL	Copenhagen General Population	Statin-treated patients (LDL-C: <89 mg/dL)	**1.18 (1.02–1.36)**	Adjusted - All-cause mortality	In a multivariable adjusted model (for age, sex, smoking status, pack-years, systolic blood pressure, any diagnosis of ASCVD, cancer, or chronic obstructive pulmonary disease at baseline) non-HDL-C and ApoB (but not LDL-C) linked with increased risk of all-cause mortality and MI.	[51]
			1.78 (1.35–2.34)	Adjusted - Myocardial infarction		
	Patients with a history of confirmed acute MI (IDEAL Trial)	Atorvastatin or Simvastatin treated patients	1.236 (0.834–1.832)[ns]	Incidence of HF events	Higher baseline non-HDL-C (≥135) level associated with HF events compared to the lowest non-HDL-C quartile but did not reach a significant level ($p = 0.2182$).	[96]
Non-HDL-C > 160 mg/dL	Ischemic stroke patients (VISP trial)	–	1.28 (0.99–1.64)	Adjusted-Stroke/CHD/vascular death events	Non-HDL-C did not show any significant association with primary or secondary outcome events in any quintile even after age and sex adjustment.	[97]
	Aging patients with a history of CVD (NIPPON DATA 90)	–	**2.46 (1.29–4.71)**†	Adjusted - Mortality by CHD	After adjustment of CV risk factors (age, sex, hypertension, diabetes, history of CVD, smoking, alcohol intake, BMI) the association remained significant (p trend = 0.010). No association between non-HDL-C levels and mortality by stroke (p trend = 0.052) was observed.	[98]
	General population - a meta-analysis	–	**1.79 (1.68–1.91)**	Relative risk for CHD	Subgroup analysis suggests that the risk of CHD is more pronounced among men (HR 1.98, 1.70–2.30) than women (HR 1.63, 1.35–1.96).	[99]
	Type 2 diabetes patients (FIELD Trial)	Aged 50-to 75 years, no requiring LLT at study entry. TC (3.0–6.5 mmol/l) triacylglycerol (1.0–5.0 mmol/l)	**1.59 (1.35–1.87)** #	Unadjusted-CVD event rate	Patients in the highest non-HDL-C quartile (>4.40 mmol/l) associated with high CVD event rate as compared to the lowest quartile, even after adjustment for age, history of MI/coronary artery bypass grafting, smoking, insulin use, HbA1c level, and country. The same trends were seen in patients without any adjustment.	[100]
			1.65 (1.40–1.95) #	Adjusted-CVD event rate		
	Patients without a history of CVD (CARE Trial)	Absence of symptomatic CHF. Left ventricular ejection fractions ≥25%. Fasting glucose ≤220 TC < 240 mg/dl	**1.76 (1.05–2.54)**	Incidence of cerebrovascular events (CVE) risk after MI	After adjustment of age- and gender, the higher baseline non-HDL-C quartile (non-HDL-C≥185) showed a higher risk of CVE as compared to the lower quartile range. In both genders and irrespective of diabetes and metabolic syndrome, an increase in log	[101]

(*continued on next page*)

Table 1 (*continued*)

Non-HDL-C threshold [mg/dL]	Underlying conditions or adjustments	Patient segments	Risk estimate HR (95% CI range)	Outcome measures against which risk estimation was performed	Additional remarks	Sources
	Mild or moderately hypercholesterolemic patients with no history of CVD (CHD or stroke) (MEGA Study)	Non-diabetic patients. Statin-treated patients (Pravastatin)	**2.75 (1.37–5.53)†**	Occurrence of all CVD events	HR of first CVE with higher non-HDL-C quartiles showed a linear relationship. Patients in higher non-HDL-C tertile (Diabetic patients 5.0–6.1 mmol/l; non-diabetic patients 5.1–5.9 mmol/l) associated with a greater incidence of all CVD events than lowest non-HDL-C tertile	[71]
		Diabetic patients. Statin-treated patients (Pravastatin)	**1.94 (1.02–3.71)††**		In higher tertile, non-HDL-C is also significantly linked with individual CVD events such as CHD and CHD plus stroke.	
	Statin-treated patients with a history of CAD (JELIS study) and hypercholesterolemia (TC ≥ 250 mg/dL)	Patients with no EPA treatment, who achieved LDL-C goal but did not achieve non-HDL-C goal	**2.31 (1.06–4.65)††**	Occurrence of coronary artery disease (CAD)	Patients who did not achieve non-HDL-C level (but achieved LDL-C level) showed higher CVD risk than those who achieved the non-HDL-C goal or achieved both. Patients who did not achieve both goals showed higher CVD risks than those who achieved either of the goals. The same trends were also seen in patients treated with EPA.	[75]
		Patients with no-EPA treatment, who did not achieve LDL-C goal, but achieved non-HDL-C goal	1.90 (0.80–4.01)^{ns}			

p-values: # (<0.001), † (0.001–0.01), †† (≤0.05), ns= > 0.05 (statistically non-significant).
Note: References for data in this table are provided in the Supplementary files.
CVE: cardiovascular events; CVD: cardiovascular disease; MI: myocardial infarction; HF: heart failure; CHD: coronary heart disease; CAD: coronary artery disease; MCVE: major cardiovascular events; ASCVD: atherosclerotic cardiovascular disease; LLT: lipid-lowering treatment; ERN: extended-release niacin; EPA: eicosapentaenoic acid; TC: total cholesterol; HR: hazard ratio; AIM-HIGH: Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes) trial; IDEAL: Incremental Decrease in Endpoints Through Aggressive Lipid Lowering Trial; VISP: Vitamin Intervention for Stroke Prevention; NIPPON DATA 90: The National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged; JELIS: Japan EPA Lipid Intervention Study; FIELD: Fenofibrate Intervention and Event Lowering in Diabetes; CARE: Cholesterol and Recurrent Events.

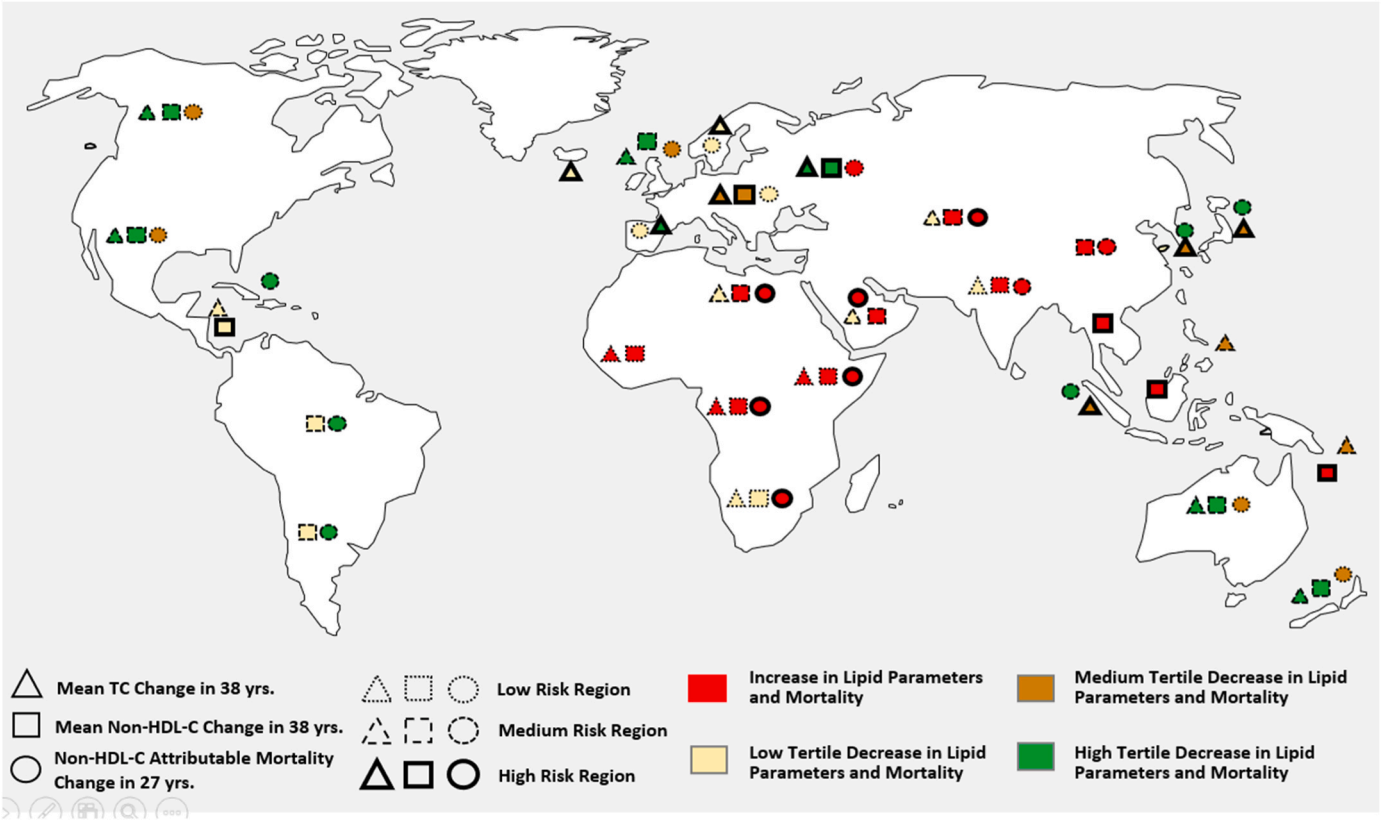

Fig. 3. Trends of change in select lipid parameters between 1980 and 2018 across geographies.
An analysis of change in select lipid parameters across geographies reveals a distinct zone of high-risk countries where mean lipid parameters have increased over the past >30 years and have high non-HDL-C-attributable mortality, especially in EMEA/Central Asia regions. (re-analyzed and modified from NCD-RisC, 2020; please refer to the Supplementary Tables 3a and 3b for details of the analysis) [62].

[50]. A similar trend was seen in a Chinese study that demonstrated a positive correlation of non-HDL-C with MI (Odds Ratio 1.371, 95% CI: 1.103–1.704, $p = 0.004$), but not LDL-C [51]. A sub-analysis of a consortium database with 524,444 individuals from 44 cohorts found that 30-year CVD event rates were three to four times higher in patients in the highest non-HDL-C category (57 mmol/L) than among those in the lowest category (26 mmol/L) [7]. The greatest impacts were reported in people under 45 years old, with an HR of 43 (95% CI: 30–61) in women and an HR of 46 (95% CI: 33–65) in males. However, this association of non-HDL-C with CVD was attenuated in older patients (aged ≥60 years) but was still detectable and statistically significant. These results reflect the harmful effects of long-term exposure to high non-HDL-C. In other words, higher baseline non-HDL-C levels in early life (aged <45 years) seem to be persistent and predictive of CVD events in later life [7]. The expanding body of data points to non-HDL-C as a possible independent CVD risk factor.

Statins are the first-line lipid-lowering drugs that largely reduce LDL-C levels but only have a moderate effect on TRLs. As mentioned earlier, in statin-treated individuals, a substantial residual risk of CVD exists even with maximum tolerated doses of statins (Table 1). Research has shown that add-on therapies to statin that target other constituents of non-HDL-C reduce residual CV risk in patients even on maximum statin dosage when compared to placebo [52–55]. Intriguingly raising the dose of statins or its combination with other lipid-lowering drugs like ezetimibe is still associated with considerable residual risks of MACE [29].

The hazard ratio (HR) for all-cause mortality and MI in patients with non-HDL-C above the median and LDL-C below the median was reported to be 1.18 and 1.78, respectively, based on the data from statin-treated patients with a median follow-up of 8-years [26]. Interestingly, participants displaying LDL-C levels above the median, but non-HDL-C and ApoB below the median were not associated with a higher risk of all-cause mortality [26]. Similarly, the Japan EPA Lipid Intervention Study (JELIS) highlighted the importance of non-HDL-C, rather than LDL-C, as a treatment goal for the primary prevention of CAD [56]. Particularly, the patient subgroup with LDL-C in the desired range but not meeting non-HDL-C goals was at higher risk of CAD [HR 2.31 (95% CI: 1.06–4.65, $p = 0.04$)] as compared to the other subgroup with non-HDL-C in target range without achieving LDL-C goals [HR of 1.9 (95% CI: 0.80–4.01, $p = 0.13$)] [56].

Studies examining the effect of drugs targeting non-HDL-C constituents other than LDL-C have reported encouraging results. A pre-specified analysis of the FOURIER trial (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) reported lowering of Lp(a) concentration using PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors led to enhanced reduction of CVD risk in patients with higher baseline Lp(a) levels as compared to others with median-level or lower Lp(a) [4]. Similarly, clinical trials with fibrates have revealed that lowering TG levels in serum is associated with CV risk reduction in subsets of patients with elevated TG or atherogenic dyslipidemia at baseline, i.e., elevated RC [57–59]. The addition of fenofibrate to the statin regimen resulted in an incremental reduction in non-HDL-C and ApoB levels regardless of baseline TG level in a post-hoc analysis of the Simvastatin plus Fenofibrate for Combined Hyperlipidemia (SAFARI) study [60]. It has been hypothesized that the risk reduction upon fibrate treatment is directly proportional to the lowering of non-HDL-C levels. The amount of CVD risk reduction is the same as per unit change in non-HDL-C levels [27]. This perhaps could be a reason that PROMINENT, a trial for selective PPARα modulator, failed to produce gains in CVD protection. Although the reduction in TG levels upon treatment was substantial, the change in non-HDL-C levels was negligible [61]. Supporting the hypothesis of non-HDL-C as a biomarker for risk reduction, the Reduction of Cardiovascular Events with EPA-Interventional Trial (REDUCE-IT) study found that administration of omega-3 fatty acid (EPA) reduced adverse CV events by 25% in patients with a history of ASCVD and type 2 diabetes correlated with the reduction in non-HDL-C levels even though it was partially independent to the reduction in TG levels [55]. Collectively, the growing evidence suggests the need to elevate the status of non-HDL-C from a secondary to a co-primary goal in the management of dyslipidemia and CVD risks.

A thorough examination of the FDA/EMA labels for most authorized pharmaceuticals reveals that changes in non-HDL-C levels were used as secondary outcome measures in the relevant pivotal studies. (Supplementary Table 1). Additionally, most of these approved drugs also underwent phase-4 or extended phase-3 trials to evaluate non-HDL-C reduction as an additional primary treatment goal. A few clinical trials for the approved lipid-lowering therapies have also evaluated non-HDL-C as a primary outcome measure, (Supplementary Table 1). For example, trials of a recently approved drug, Inclisiran, reported the lowering of TC, LDL-C, and non-HDL-C as the primary outcome (Supplementary Table 2).

All of this suggests an improvement in the perceived importance of non-HDL-C as a therapy target by clinical professionals and industry partners.

6. Outlook and utilization of non-HDL-C in developed and emerging economies

Large population-based studies and meta-analyses have shown interesting patterns in the way lipid profiles change over time. Non-HDL-C levels have dropped sharply in high-income countries, especially in North-West Europe, North America, and Australasia. They have, on the other hand, increased in low- and middle-income nations, particularly in East and Southeast Asia [62]. This trend was initially observed in a pooled analysis of the NCD-RisC research, which included 2.3 million patients from 12 countries (https://ncdrisc.org/index.html). It was then seen yet again using data from 102.6 million people from 200 different nations [62,63]. Additionally, based on risk categories defined by baseline lipid parameters, there is an increasing trend in mean non-HDL-C levels in low-risk countries and greater non-HDL-C attributable mortality in high-risk countries (Fig. 3). There are some regions where the average levels of lipid parameters have been going up over time. These locations need lipid management programs to improve the health of the community. The above results show how relevant non-HDL-C is and how important it is to treat all aspects of dyslipidemia at the community/population level in a way that is specific to each country.

There are minor differences in the guidelines for ASCVD or dyslipidemia management from developed countries such as US/EU as compared to those from major emerging world areas. The ESC/EAS 2019 recommendations endorse non-HDL-C targets of 130 mg/dL, 100 mg/dL, and 85 mg/dL for moderate-risk, high-risk, and extremely high-risk individuals, respectively [27]. In the US, the goals for patients with moderate to high risk and very high risk are 130 mg/dL and 100 mg/dL, respectively [13,64]. The risk-based non-HDL-C goals recommended by the Russian National Atherosclerosis Society (RNAS), Lipid Association of India (LAI), and Brazilian Cardiology Society (SBC) are similar to EAS/ECS 2019 guidelines [65–67]. In contrast, Chinese guidelines recommend higher treatment goals for non-HDL-C as 160 mg/dL and 130 mg/dL for low-risk, and moderate to high-risk patients, respectively [68].

NICE guidelines (UK), National Lipid Association (US), and the International Atherosclerosis Society have emphasized non-HDL-C as the primary treatment goal, particularly in patients with dyslipidemia at high risk. The consensus clinical recommendations for lipid disorder management from the Middle East endorses using non-HDL-C, in addition to LDL-C, as a primary treatment target [69–71]. Similarly, the Chinese guidelines recommend using non-HDL-C as a co-primary goal for people with high TG (200–500 mg/dL) and conditions like diabetes, metabolic syndrome, or obesity [72]. As noted above, Non-HDL-C has been consistently recommended as a co-primary treatment goal by international guidelines, particularly for high-risk dyslipidemia patients.

Many non-HDL-C generated scores and ratios have been explored in

various scientific research, in addition to the direct use of non-HDL-C as a risk factor and treatment goal for dyslipidemia. The non-HDL-C/HDL ratio, for example, is a linear representation of TC/HDL-C. The TC/HDL-C ratio (or non-HDL-C/HDL-C ratio) was added to the Framingham equation to increase risk prediction and is more potent than other ratios, especially in women [73]. Furthermore, in individuals with serum TGs above 300 mg/dL (3.36 mmol/L), when LDL-C estimation using Friedewald's formula is unreliable and invalid, the TC/HDL-C ratio is recommended [73]. A recent report found a higher prognostic value of the non-HDL-C/TC ratio for predicting adverse cardiac events. The non-HDL-C/TC ratio was highly concordant with Gensini's Score which measures the severity of coronary artery lesions and clinical outcomes [74]. However, additional systematic studies and a longer length of follow-up are required to validate this measure. Another non-HDL-C-based risk score that is not widely used is the non-HDL-C/ApoB100 ratio. However, larger validation studies are needed before these scores can be used as a reliable indicator of dyslipidemia and CVD risk. Notwithstanding the lack of any universal recommendations in clinical practice, non-HDL-C-based ratios may be used at the discretion of the physician in certain instances or patient segments. Overall, in clinical settings, non-HDL-C works efficiently in estimating the future CVD risk and assessing the effectiveness of ongoing lipid-lowering therapies.

7. Conclusion

Non-HDL-C has been recognized as a valuable screening parameter due to its simplicity, independence from the non-fasting state, and superior prognostic value. It is a more precise gauge of atherogenic risk than any other individual lipoprotein constituent. This may be especially important for people with metabolic disorders, obesity, and type 2 diabetes whose LDL-C levels are under control. It is also highly beneficial in determining the residual CVD risk in individuals who have had optimum statin treatment and have LDL-C levels within the therapeutic range (Fig. 4). It is essential to note, however, that patients with similarly elevated levels of non-HDL-C can exhibit varying dyslipidemia profiles. Also, the estimation bias of non-HDL-C in individuals with extremely high baseline levels of TG (>200 mg/dL) should be noted. Therefore, it is crucial to recognize the distinct roles of individual lipoproteins in the pathogenesis of atherosclerosis. In determining the subsequent lipid-lowering therapy for patients, a primary evaluation of non-HDL-C parameters that are abnormal must be followed by an evaluation of individual lipid-risk factors, their baseline measurements, conditions for non-HDL-C testing, and all the prescription drugs in use.

The geographical distribution of mean non-HDL-C levels and their association with mortality underscores the need for country-specific cholesterol management guidelines that emphasize non-HDL-C as a primary treatment aim (Fig. 4). Such research implies that non-HDL-C is gaining popularity among experts. Interestingly, the current choice of determining non-HDL-C threshold (i.e., 30 mg/dL higher than recommended LDL-C values) is widely debated, warranting the need for further goal optimization studies. This review highlights the need for using non-HDL-C as a preferable independent assessment marker or as a co-primary target for dyslipidemia management.

Non-HDL-C is an important residual risk factor for CVD particularly the high-risk and statin-treated patients with LDL-C within the target range. It is also a reliable predictor of future CVD risk in the younger population (<45 years). Non-HDL-C, a composite of all atherogenic lipoproteins, has been recognized as an alternate treatment goal by major international guidelines from both high-income and low-middle-income economies. An analysis of change in select lipid parameters across geographies reveals a distinct zone of high-risk countries where mean lipid parameters have increased over the past >30 years and have high non-HDL-C-attributable mortality. This review emphasizes non-HDL-C as an important treatment goal in dyslipidemia management and the necessity of a country-specific approach for community health.

Author contributions

Vikrama Raja: conceptualized the requirements and scope of the review, conducted the literature review, conceptualized and prepared the figures and tables. Ramesh Pandey: conceptualized the requirements and scope of the review, conducted the literature review, wrote the first draft, conceptualized and prepared. Yogeyaa S Chibber: conceptualized the requirements and scope of the review, conceptualized and prepared the figures and tables. Jean-Pascal Berrou: conceptualized the

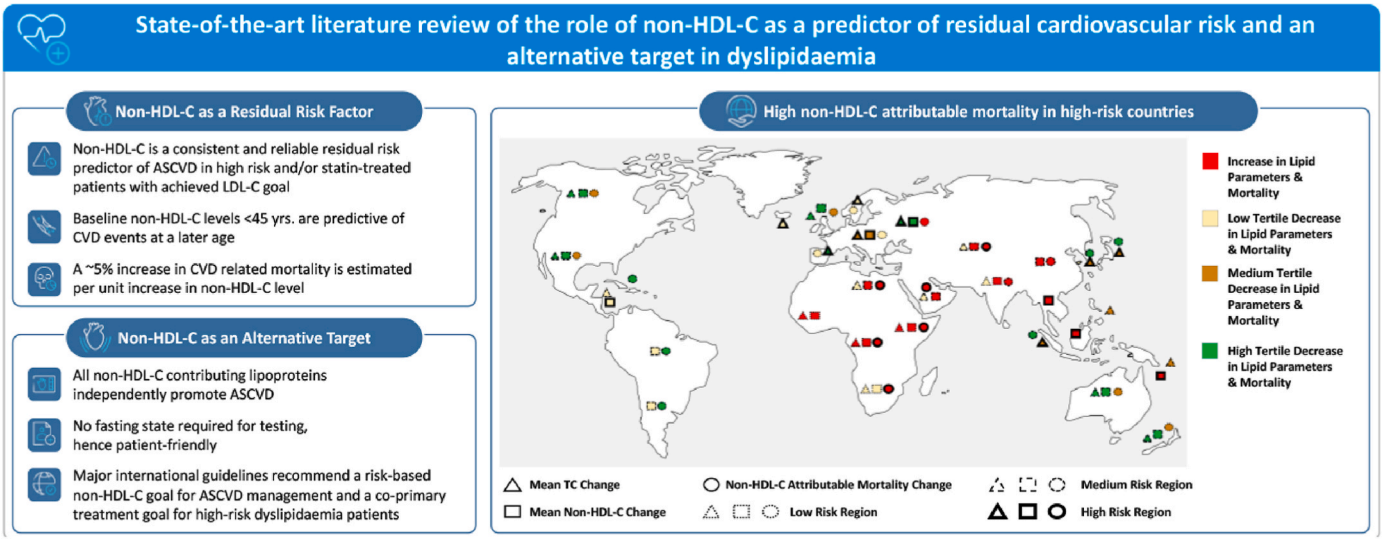

Fig. 4. The role of non-HDL-C as a predictor of residual cardiovascular risk and an alternative target in dyslipidemia.
Non-HDL-C is an important residual risk factor for CVD particularly the high-risk and statin-treated patients with LDL-C within the target range. It is also a reliable predictor of future CVD risk in the younger population (<45 years). Non-HDL-C, a composite of all atherogenic lipoproteins, has been recognized as an alternate treatment goal by major international guidelines from both high-income and low-middle-income economies. An analysis of change in select lipid parameters across geographies reveals a distinct zone of high-risk countries where mean lipid parameters have increased over the past >30 years and have high non-HDL-C-attributable mortality. This review emphasizes non-HDL-C as an important treatment goal in dyslipidemia management and the necessity of a country-specific approach for community health.

requirements and scope of the review, conceptualized and prepared the figures and tables, compiled and finalized the manuscript for submission. Michel Farnier: conceptualized the requirements and scope of the review, conceptualized and prepared the figures and tables, compiled and finalized the manuscript for submission, reviewed the draft and provided expert opinions. Carlos Aguiar: conceptualized the requirements and scope of the review, reviewed the draft and provided expert opinions. Nasreen Alsayed: conceptualized the requirements and scope of the review, reviewed the draft and provided expert opinions. Hussein El Badawi: conceptualized the requirements and scope of the review, reviewed the draft and provided expert opinions. Marat Ezhov: conceptualized the requirements and scope of the review, reviewed the draft and provided expert opinions. Michel P. Hermans: conceptualized the requirements and scope of the review, reviewed the draft and provided expert opinions. Kausik Ray: conceptualized the requirements and scope of the review, reviewed the draft and provided expert opinions. Lale Tokgözoglu: conceptualized the requirements and scope of the review, reviewed the draft and provided expert opinions. Alberto Zambon: conceptualized the requirements and scope of the review, reviewed the draft and provided expert opinions.

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Declaration of interest

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All the other authors declare no known competing financial interests or personal relationships that could influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2023.117312.

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