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The Importance of Non High Density Lipoprotein Cholesterol in Dyslipidaemia Management

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Abstract

Dyslipidaemia is a major contributor to cardiovascular disease which has assumed epidemic proportions worldwide. The traditional approach to the management of dyslipidaemia focusses mainly on LDL cholesterol. However, recent evidence suggests that non HDL-C is an important marker of cardiovascular risk and might play a more important role than LDL cholesterol in the causation of cardiovascular disease. Non HDL cholesterol includes all ApoB containing lipoproteins and can be tested more reliably and conveniently with the available laboratory assays. Inspite of the evidence, the role of non HDL cholesterol in atherosclerosis is underrecognised and this lipid parameter is often undertreated. This review highlights the importance of non HDL cholesterol in dyslipidaemia management, both in diabetics and otherwise.

Keywords: Dyslipidaemia; Non HDL cholesterol; Cardiovascular disease; Triglycerides; Diabetes

Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide with an estimated 17.3 million deaths from CVDs in 2008, representing 30% of all global deaths [1]. Recent estimates state that CVD accounts for more than 25% of the total deaths in India. Studies also show that the prevalence has increased two-fold in rural areas (2.06% in the 1970s to 4.14% in the 1990s) and has increased nine-fold in urban areas (1.04% in the early 1960s to 9.45% in the mid 1990s) [2].

The main cause of CVD development is atherosclerosis and as cholesterol is one of the key components of atherosclerotic plaques, hyperlipidaemia is an important risk factor for the same [3]. The traditional lipid profile, including a fasting plasma measurement of total cholesterol (TC), HDL cholesterol (HDL-C), triglycerides (TG) and LDL cholesterol (LDL-C) has been recognized as the standard by which coronary heart disease (CHD) risk assessment and on-treatment management decisions are made. Among these, LDL-C has been identified as the primary therapeutic target for lipid management to reduce the future risk of coronary events. Despite the use of LDL cholesterol-targeted therapy with statins and other lipid-altering agents, many patients still suffer coronary events [4]. Residual risk for such events has been attributed, at least in part, to persistently elevated atherogenic particle concentration which has given rise to the debate as to whether non-HDL-C and/or apolipoprotein B (apoB) should supplant LDL-C [5-8].

What is Non HDL Cholesterol?

Non HDL-C is calculated by subtracting HDL-C from TC and therefore includes not only LDL-C but also cholesterol contained in all other apoB containing potentially atherogenic lipoproteins in blood, including cholesterol in lipoprotein (a) {Lp(a)}, intermediate density lipoprotein (IDL), very low density lipoprotein (VLDL-C) and cholesterol-enriched remnant lipoproteins. Experimental evidence supports a more important role for apolipoprotein B (apoB) and apoB-containing lipoproteins than for LDL-C content in mediating atherogenesis. Lipoproteins containing apoB must first enter the arterial wall and undergo oxidative modification before they can contribute to atherogenesis. This modification affects the structure of the apoB molecule or the phospholipid membrane of these lipoproteins, yielding ligands for the scavenger receptors of macrophages in the arterial wall [9]. Subsequently, cholesterol accumulation and crystallization in macrophage cytoplasm leads to the formation of foam cells and progression to atherosclerotic plaque [10]. Interestingly, measured apoB and non HDL-C have been found to be highly correlated in a number of studies [11,12]. Since neither TC nor HDL-C is significantly affected by food intake, non HDL-C can be measured not only in the fasting state but also in the post-prandial state. Since the normal VLDL-C should be below 30 mg/dl (on the basis of a normal TG being below 150 mg/dl and VLDL-C = TG / 5), the therapeutic goals for non HDL-C were set 30 mg/dl higher than for LDL-C in the Adult Treatment Panel (ATP) III guidelines [13]. Indian diabetics have atherogenic dyslipidemia typically characterized by high triglycerides (TG), VLDL-C, sd-LDL-C and Apo B levels with low HDL- C levels [14]. This high TG resulting in higher VLDL particles leads to high non HDL and Apo B levels. Considering the higher incidence of CVD in Indians, it has been suggested that the treatment has to be more aggressive and should begin at a lower threshold than is recommended for Western populations. [15].

Reliability of LDL-C Measurements

The LDL-C concentration is the primary lipid marker of CHD risk and the target of lipid-altering therapy. It is most often reported as a calculated value using the Friedewald equation, in which the

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concentration of LDL-C equals that of TC minus HDL-C minus VLDL cholesterol (VLDL-C). This equation is based upon the assumption that the concentration of VLDL-C equals the plasma triglyceride concentration divided by five. The Friedewald equation has several limitations. Importantly, there are limitations in the accuracy that require multiple fasting samples to be tested prior to initiation or modification of therapy and recommends against reporting a calculated LDL-C in patients who are nonfasting, have triglycerides greater than 400 mg/dL, or have type III hyperlipoproteinaemia. The equation is also inaccurate once the triglycerides are above 200 mg/dL or at low LDL-C concentrations. An analysis of data from the National Health and Nutrition Examination Survey (NHANES) and the American Heart Association comparing population data from 1994 to 2002 versus those of 2003 to 2010 shows that there has been a progressive increase in the incidence of hypertriglyceridaemia making LDL-C based CV risk assessment faulty [16]. Moreover, at lower LDL-C concentrations near the cutoff of 100 mg/dL, there is an error of plus or minus 15 mg/dL, indicating the "true" LDL cholesterol is somewhere between 85 and 115 mg/dL [17]. This presents a major opportunity for misclassification of patients in terms of risk assessment and management. Thus, calculated LDL provides only marginal reflection of true LDL cholesterol concentration.

Homogeneous or "direct" LDL-C assays were designed to circumvent these issues and some cllinical laboratories routinely utilize direct LDL-C assays for this purpose. However recent studies clearly indicate that these methods, like lower calculated LDL-C, are unable to meet the National Cholesterol Education Program (NCEP) total error goal of <12% for LDL-C and are particularly unsuitable for use in a dyslipidaemic population [18].

Interestingly, a study examining the correlation between 145 pairs of Friedewald-calculated and directly measured LDL-C found that one-third of the measurements had a >15 mg/dl difference and one-fourth had a >20 mg/dl difference [19].

Non HDL-C and Measures of Atherosclerosis Severity

The Pathobiological Determinants of Atherosclerosis in Youth Study (PDAY) examined serum lipids and lipoproteins obtained during autopsy within 72 hours of death in 715 cases of accidental death, homicide or suicide in subjects aged 15–34 years to determine whether the measurement of ApoA1 and B, lipoprotein(a), and sizes of lipoproteins improved the ability to predict the extent of fatty streaks in the thoracic and abdominal aorta, and in the right coronary artery more than the lipid measurements of HDL-C and non-HDL-C. Non-HDL-C was positively associated with extent of fatty streaks in all 3 arteries (P=0.0001) and with extent of raised lesions in the abdominal aorta (P=0.0465) and the right coronary artery (P=0.0103). ApoB was significantly, although not as strongly, associated with fatty streaks in all 3 arteries (thoracic aorta, P = 0.0016; abdominal aorta, P = 0.4671; coronary artery, P = 0.9994) but not with raised lesions (thoracic aorta, P = 0.0961; abdominal aorta, P = 0.0027; coronary artery, P = 0.0114). HDL-C was inversely associated with fatty streaks in all 3 arteries (thoracic aorta, P=0.0019; abdominal aorta, P=0.0013; coronary artery, P=0.0308) and with raised lesions in the thoracic aorta (P=0.0189) and the right coronary artery (P=0.0186). ApoA1 was inversely associated with fatty streaks in the thoracic (P=0.0464) and abdominal (P=0.0384) aortas and with raised lesions only in the thoracic aorta (P=0.0011). In this study, none of the apolipoprotein measurements were as strongly or consistently correlated with the extent of lesions as was the measurement of HDL-C or non-HDL-C. Beyond the basic model that included sex, age, race, smoking status, hypertension, HDL-C and non-HDL-C, the addition of ApoA1 and ApoB measurements added only an average 1.3% explanatory ability to the model, whereas the lipid measures of HDL-C plus non-HDL-C added an average 2.5% [20]. In a Finnish study, non HDL-C measured between the ages of 12 and 18 years strongly predicted carotid intimal medial thickness (CIMT) measured 21 years later [regression coefficient of 12 (95% CI of 2-22), P = 0.009] [21].

In cross-sectional analyses in adults, non HDL-C has been found to correlate with coronary calcification in non-diabetic and diabetic cohorts [22,23]. In the first of these studies, in diabetic participants, plasma levels of non-HDL cholesterol had stronger coronary calcification association (regression coefficient of 1.28, 95% CI of 0.99 – 1.67) than LDL cholesterol (regression coefficient of 1.13, 95% CI of 1.13). In the other study, in a multivariate model controlling for age, gender, race, cigarette smoking, hypertension, family history of coronary artery disease and obesity, there was a significant increase in the prevalence of coronary calcification with increasing values of each lipid variable of LDL-C, TG and non HDL-C. However, in a multivariate model simultaneously controlling for increasing quartiles of the remaining lipid variables, only the association of Non-HDL-C with coronary calcification remained statistically significant (p=0.002). A relationship between coronary artery disease and non HDL-C was demonstrated in a multivariate logistic regression analysis of data from the Cholesterol Lowering Atherosclerosis Study, a randomized placebo-controlled trial of colestipol with niacin therapy in men previously treated with coronary artery bypass grafting (CABG). In this analysis, non HDL-C was the best predictor of overall change in the extent of coronary disease among men who were not using lipid lowering drugs [24]. Non HDL-C has been found to correlate with CIMT in pre-dialysis patients with chronic kidney disease (regression coefficient of – 0.079, P < 0.05) [25].

Deventer HE et al undertook a study to evaluate the accuracy of cardiovascular disease (CVD) risk score classification by direct LDL cholesterol (dLDL-C), calculated LDL cholesterol (cLDL-C), and non-HDL cholesterol (non-HDL-C) compared to classification by reference measurement procedures (RMPs). They examined 175 individuals, including 138 with CVD or conditions that may affect LDL-C measurement. For participants with triglycerides <2.26 mmol/L (<200 mg/dL), the overall misclassification rate for the CVD risk score ranged from 5% to 17% for cLDL-C methods and 8% to 26% for dLDL-C methods when compared to the RMP. For participants with triglycerides ≥2.26 mmol/L (≥200 mg/dL) and<4.52 mmol/L (<400 mg/dL), dLDL-C methods, in general, performed better than cLDL-C methods. Non-HDL-C methods showed better correspondence to the RMP for CVD risk score than either dLDL-C or cLDL-C methods at all levels of hypertriglyceridaemia [26].

Non HDL-C, LDL-C and Cardiovascular Events and Mortality

Over the past decade or so, a number of primary and secondary prevention trials have shown non HDL-C to be a better marker of CV risk than LDL-C in both genders, individuals with and without diabetes and in groups of different ethnic origin.

In Emerging Risk Factors Collaboration study, individual records were collected from 302,430 people without initial vascular disease from 68 long-term prospective studies, (mostly in Europe and North America). Total follow up duration was 2.79 million person-years. The patient were divided in three tertiles of serum triglycerides, HDL-C and non-HDL-C levels. The rates of CHD per 1000 person-years in the

bottom and top thirds of baseline lipid distributions, respectively, were 2.6 and 6.2 with triglyceride, 6.4 and 2.4 with HDL-C, and 2.3 and 6.7 with non-HDL-C. Adjusted HRs for CHD were 0.99 (95% CI, 0.94-1.05) with triglyceride, 0.78 (95% CI, 0.74-0.82) with HDL-C, and 1.50 (95% CI, 1.39-1.61) with non-HDLC. Hazard ratios for ischemic stroke were 1.02 (95% CI, 0.94-1.11) with triglyceride, 0.93 (95% CI, 0.84-1.02) with HDL-C, and 1.12 (95% CI, 1.04-1.20) with non-HDL-C. In this study, non HDL-C was as good as directly measured LDL-C, both for prediction of CAD events as well as for strokes [27].

Sniderman et al. [28] carried out a meta-analysis including three large studies that were not part of the Emerging Risk Factors Collaboration meta-analysis. They reviewed 12 independent epidemiological studies, including 233,455 subjects and 22,950 cardiovascular events, and examined published risk estimates, converted them to standardized risk ratios, and analyzed them, employing quantitative meta-analysis using a random effects model. For each standard deviation increase, the relative risk (RR) ratio and 95% CI for LDL-C was 1.25 (1.18–1.33), non-HDL-C 1.34 (1.24–1.44) and ApoB 1.43 (1.35–1.51).

The Lipid Research Clinics Program Follow-Up study showed that the use of non HDL-C concentrations may be of value in CHD risk prediction even in populations in which the plasma triglycerides are <200 mg/dl. It was a primary prevention study of 4462 subjects aged 40–64 years, whose mean baseline plasma triglycerides were 153 mg/dl in men and 117 mg/dl in women. The participants were followed for an average of 19 years. Non-HDL-C was found to be a stronger predictor of all-cause mortality and CV mortality than LDL-C (χ^2-test for non-HDL-C 24.3 vs 5.0 for LDL-C) [29].

The European Prospective Investigation into Cancer and Nutrition-Norfolk Prospective Population Study followed 21,448 participants, aged 45–79 years, without diabetes or CHD, for 11 years. The mean plasma triglyceride levels in subjects without and with CHD were 150 and 159 mg/dl, respectively, in men and 115 and 150 mg/dl, respectively, in women. A total of 2086 participants developed clinical CHD during follow-up. After adjustment for age, smoking, waist circumference, physical activity, systolic blood pressure and hormone replacement therapy for women, increasing levels of non-HDL-C were a better predictor of risk for future CHD (HR: 2.39; 95% CI: 1.91–2.99) than LDL-C, triglycerides and total cholesterol:HDL-C ratio. Among individuals with LDL-C <100 mg/dl, those with non-HDL-C >130 mg/dl had a HR for future CHD of 1.84 (95% CI: 1.12–3.04), a finding that confirms that increased risk is associated with elevated non-HDL-C, even in those with low LDL-C concentrations [30].

The Bypass Angioplasty Revascularization Investigation (BARI) examined baseline lipid levels in 1514 patients (73% men; mean age: 61 years). All of the patients had multivessel coronary artery disease. The study followed patients for a mean of 5 years, examining outcomes of death or non-fatal myocardial infarction, using univariate and multivariate time-dependent proportional hazard methods. While LDL-C and HDL-C did not predict events at follow-up, non HDL-C was a strong and independent predictor of non-fatal myocardial infarction (RR: 1.049; 95% CI: 1.006–1.093) and angina pectoris (RR: 1.049; 95% CI: 1.004–1.096; p<0.05 for both, but not mortality) [31].

Liu et al. [32] analyzed data from the Framingham Heart Study (2,693 men, 3,101 women) to determine if non HDL-C is a more useful predictor of CHD risk than LDL-C. As continuous variables in separate multivariate adjusted models, non-HDL cholesterol and LDL cholesterol were significantly (p <0.05) and similarly associated with an increased incidence of CHD (non-HDL cholesterol: RR 1.008, 95% CI 1.007 to 1.010; LDL cholesterol: RR 1.008, 95% CI 1.006 to 1.010). For those with TG levels ≥200 mg/dl, non-HDL cholesterol (RR 1.006) was a significant (p <0.05) predictor of CHD risk, whereas LDL cholesterol (RR 1.004) and VLDL cholesterol (RR 1.003) were not, in separate models.

Non HDL-C in Patients with Diabetes

Non HDL-C measurement is particularly important in diabetes as it makes no assumption about the relationship between VLDL cholesterol and triglycerides which can be altered in patients with diabetes leading to falsely low LDL values as calculated by the Friedewald formula, especially in conjunction with elevated triglyceride levels.

Liu et al. [33] compared the diagnostic value of non-HDL-C as a prognostic factor of acute coronary events and myocardial infarction among healthy subjects and diabetics. Within diabetes categories, risk was assessed based on lipid levels (in mg/dl): non-HDL <130 and LDL<100 (group 1); non-HDL <130 and LDL ≥100 (group 2); non-HDL ≥130 and LDL <100 (group 3); and non-HDL ≥130 and LDL ≥100 (group 4). Group 1 within those without diabetes was the overall reference group. In a multivariate model, CHD risk in those with diabetes did not increase with increasing LDL, whereas it did increase with increasing non-HDL: RR (95% confidence interval) for group 1: 5.7 (2.0 –16.8); group 2: 5.7 (1.6 –20.7); group 3: 7.2 (2.6 –19.8); and group 4: 7.1 (3.7–13.6).

Chaoyang Li et al. analyzed data from 1,122 adults aged ≥ 20 years with diagnosed diabetes who participated in the Third National Health and Nutrition Examination Survey (NHANES) linked mortality study. Those subjects with higher serum non HDL-C levels had a higher risk of death from total CVD: the RRs were 1.34 (95% CI: 0.75-2.39) and 2.25 (95% CI:1.30-3.91) for non HDL-C concentrations of 130-189 mg/dL and 190-403 mg/dL, respectively (p=0.003). In subgroup analyses, significant linear trends were identified for the risk of death from ischemic heart disease: the RRs were 1.59 (95% CI: 0.76-3.32) and 2.50 (95% CI: 1.28-4.89) (p=0.006 for linear trend), and stroke: the RRs were 3.37 (95% CI: 0.95-11.90) and 5.81 (95% CI: 1.96-17.25) (p=0.001 for linear trend). The authors concluded that, higher serum non-HDL-C concentrations were significantly associated with increased risk of death from CVD in diabetic patients [34].

Using data collected during Strong Heart Study, Lu et al. [35] evaluated the ability of non–HDL-C and individual lipoprotein indicators to predict CVD in 2,108 diabetic patients. Although lipoprotein parameters were all significant predictors of CVD risk in men and women with diabetes (except HDL cholesterol in women), non-HDL cholesterol seemed to be the stronger predictor (except for total/HDL cholesterol ratio in men), with an HR of 2.23 (95% CI 1.41–3.43) in men and an HR of 1.80 (1.32– 2.46) in women.

Jiang et al. [36] prospectively followed 746 diabetic men in the Health Professionals' Follow-up Study who were aged 46–81 years and free of CVD or cancer at the time of drawing blood and ascertained 103 incident CVD cases during 6 years of follow-up. After adjustment for age, BMI, and other lifestyle risk factors, the multivariate relative risk of CVD (the highest versus the lowest quartile) was 2.34 (95% CI 1.26–4.32) for non-HDL cholesterol, 2.31 (1.23– 4.35) for apoB, and 1.74 (0.99 –3.06) for LDL cholesterol. Comparisons of nested models indicated that non-HDL cholesterol, but not apoB, added significantly to the prediction of CVD risk beyond LDL cholesterol.

Elisson et al. [37] conducted an observational study of patients with type 2 diabetes from the Swedish National Diabetes Register.

Baseline LDL cholesterol, non-HDL cholesterol, ratio of non-HDL to HDL cholesterol (non-HDL:HDL), and ratio of TG to HDL cholesterol (TG:HDL) was measured in 18,673 patients aged 30–70 years followed for a mean of 4.8 years. Hazard ratios (HRs) for CHD per 1-SD increment in lipid measures were 1.23 with non-HDL:HDL, 1.20 with non-HDL cholesterol, 1.17 with LDL cholesterol, and 1.15 with TG: HDL (all $p < 0.001$ when adjusted for clinical characteristics and nonlipid risk factors). The best global model fit was found with non-HDL:HDL. HRs for CHD were 0.52, 0.62, and 0.66 with the lowest deciles of non-HDL:HDL, non-HDL cholesterol, and LDL cholesterol ≤ 1.8 mmol/L (all $p < 0.001$). Mean TG:HDL was considerably lower in patients within the lowest tertile of non-HDL:HDL, 0.82 ± 0.47, than in those within the lowest tertile of LDL cholesterol (<2.5 mmol/L), 1.49 ± 1.03.

Non HDL-C, LDL-C and Lipid Lowering Therapy

Interestingly there is no prospective randomized controlled trial evidence showing that a therapeutic approach targeting non HDL-C would be superior to that targeting LDL-C although available evidence points to the same. Lack of quality evidence is due to less frequent reporting of non HDL-C data, exclusion of hypertriglyceridaemic patients from trials, and use of statins resulting in lowering of both thereby making it impossible to attribute cardiovascular outcomes to one or the other.

A meta-analysis of 14 statin trials, seven fibrate trials, seven trials of niacin monotherapy or combination therapy, one study of ileal bypass, one of a diet high in polyunsaturated fatty acids and one of bile acid-binding therapy, showed a strong one-to-one relationship between the percentage of non HDL-C lowering and CHD risk reduction For statins, each 1% decrease in non–HDL-C resulted in an estimated 4.5-year CHD relative risk of 0.99 (95% Bayesian confidence interval: 0.98 to 1.00). The fibrate model did not differ from the statin model (Bayes factor K = 0.49) with no evidence of heterogeneity. The niacin model was moderately different from the statin model (K = 7.43), with heterogeneity among the trials (Q = 11.8, 5 df; p = 0.038). The only niacin monotherapy trial (n = 3,908) had a 1:1 relationship between non–HDL-C and risk reduction. No consistent relationships were apparent for the 5 small trials of niacin in combination. The 95% confidence intervals for the single trials of diet, bile acid sequestrants, and surgery also included the 1:1 relationship [38].

Boekholdt et al. performed a meta-analysis of randomized controlled statin trials in which lipids and apolipoproteins were determined in all study participants at baseline and at 1-year follow-up [31]. They identified eight trials published between 1994 and 2008, contacted the investigators and evaluated individual patient data of 62,154 patients. HR and corresponding 95% CI for risk of major cardiovascular events were adjusted for established risk factors by one standard deviation increase in LDL-C, non-HDL-C and ApoB. Among 38,153 statin-treated subjects, the adjusted HR and 95% CI per one standard deviation were 1.13 (1.10–1.17) for LDL-C, 1.16 (1.12–1.19) for non-HDL-C and 1.14 (1.11–1.18) for ApoB. These HRs were significantly higher for non-HDL-C than LDL-C ($p = 0.002$) and ApoB ($p = 0.02$). Thus, among these statin-treated patients, on-treatment levels of all three measures were associated with increased risk of cardiovascular events, but the association slightly favoured non-HDL-C [39].

A study examined the association of mean absolute ApoB reduction with RR of CHD (nonfatal myocardial infarction and CHD death), stroke (nonfatal and fatal) or CVD (CHD, stroke and coronary revascularization), and compared its ability to predict CVD events with non-HDL-C. This Bayesian random effects meta-analysis included 25 studies (n = 131,134): twelve on statin, four on fibrate, five on niacin, two on simvastatin/ezetimibe, one on ileal bypass surgery and one on aggressive versus standard LDL-C and blood pressure targets. Each 10 mg/dl decrease in ApoB was associated with a 10% reduction in CHD, no decrease in stroke and a 6% decrease in major CVD risk. Non-HDL-C decrease modestly outperformed ApoB for prediction of CHD (Bayes factor: 1.45) and CVD (Bayes factor: 2.07) risk decrease [40].

However, there are studies as well which show non-superiority of non HDL-C over LDL-C in patients receiving treatment. In JUPITER, on-treatment concentrations of non–HDL-C and apoB were comparable with LDL-C in the prediction of residual risk [41]. The Heart Protection Study was a randomized controlled trial that enrolled 20,536 men and women, aged 40–80 years, with a history of CHD, cerebrovascular disease or other occlusive disease of non-coronary arteries, or Type 1 or 2 diabetes mellitus. The study also included men aged ≥ 65 years undergoing treatment for arterial hypertension. Subjects were randomly assigned to receive 40 mg simvastatin daily, matching placebo and antioxidant vitamins, or placebo. Major occlusive events were found to be equally strongly associated with lipids and atherogenic particle measures. Adjusted HR per one additional standard deviation higher with 95% CI were 1.25 (1.16–1.34) for LDL-C, 1.23 (1.15–1.33) for non-HDL-C, 1.25 (1.16–1.35) for ApoB and 1.25 (1.16–1.35) for LDL particle number (LDL-P). The authors concluded that in this population with a 2% average coronary event rate per year, lipids and Apolipoprotein, and LDL-P had similar predictive values for incident major occlusive vascular events [42].

Conclusions

Non HDL-C scores over LDL-C on the basis of available evidence besides having a number of other advantages like inclusion of all apolipoprotein B-containing lipoproteins, no additional cost of testing, valid postprandial measurement, assessment holding good in patients with TG>400 mg/dl or diabetes and lowering with the available medications and lifestyle modification. Presently, non HDL-C as a treatment target is under-recognised and under-treated. Given the mounting evidence in favour of Non-HDL-C, laboratories should be encouraged to routinely report this and clinicians should consider it to guide treatment decisions.

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