REAGENTS

RANDOX SDLDL CHOLESTEROL (SDLDL-C) – SIZE MATTERS:
THE TRUE WEIGHT OF RISK IN LIPID PROFILING

RANDOX

Randox sdLDL Cholesterol (sdLDL-C) – Size Matters: The True Wight of Risk in Lipid Profiling

1. BACKGROUND

Cardiovascular Disease (CVD) is recognised as a leading cause of death, with approximately 17.7million people dying each year from CVDs, an estimated 31% of all deaths worldwide.

Furthermore, 80% of all CVD deaths are due to heart attacks and strokes (9).

There is a global commitment to reduce the probability of premature CVD deaths by 25% by 2025; a target set by the United Nations member states (7).

Globally, the mortality rate for CVDs has dramatically declined over the past 20 years, however, in low and middle-income regions, the number of lives lost to CVD is increasing (7).

The global distribution of CVD is complex and defined by national and regional characteristics as much as by global disease trends. Even with the differences between regions, CVD remains a dominant cause of death, even in those who are under the age of 40. This highlights the growing need for the assessment of CVD risk to include methods that account for uncertainty and heterogeneity.

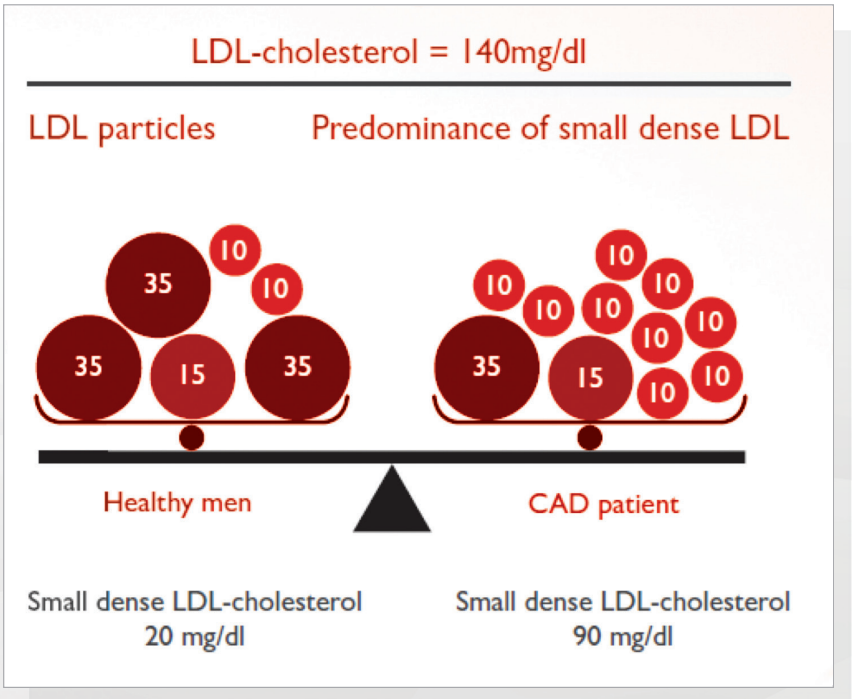
2. CLINICAL SIGNIFICANCE

LDL Cholesterol (LDL-C) is a low density lipoprotein involved in cholesterol and triglycerides transfer from the liver to peripheral tissues. LDL-C consists of two parts: the bigger part with phenotypic pattern A is light and almost rich in cholesterol (LBLDL or Large Buoyant LDL) and the smaller part with more special weight and phenotypic pattern B (sdLDL-C) composed of less cholesterol. The two types of LDL-C vary in size through genetic determination and dietary lipid intake. All LDLs transport triglycerides and cholesterol to the tissues but their atherogenesis varies according to size. sdLDL-C is therefore a subtype of LDL-C, and these smaller particles can more readily permeate the inner arterial wall and are more susceptible to oxidation (5).

Research has shown that individuals with a predominance of sdLDL Cholesterol have a **3-fold increased risk of myocardial infarction (MI)** (1). Elevated levels of sdLDL-C are caused by a sedentary lifestyle, a diet high in saturated fat, insulin resistance, pre-diabetes and genetic disposition. Measurement of sdLDL-C allows the clinician to get a more comprehensive picture of lipid risk factors and tailor treatment accordingly. In addition, the high prevalence of sdLDL-C is mainly observed in individuals with familial hyperlipidaemia, non-insulin dependent diabetes mellitus, and central obesity and insulin resistance syndromes (5).

The below diagrams demonstrate the difference between LDL-C, and sdLDL cholesterol. From this, it can be seen that even if LDL-C levels are the same, sdLDL cholesterol levels can differ. Therefore it is important to assess the quality of LDL-C to assess the level of risk of Coronary Heart Disease (CHD) in patients.

Figure 1 – Predominance of sdLDL-C particles in comparison to LDL-C particles



The numerical difference in size and density is demonstrated in the below table:

Lipoproteins	Large LDL-C	sdLDL-C
Diameter (nm)	25.5 – 28.0	22.0 – 25.5
Density (g/cm^3)	1.019 – 1.044	1.044 – 1.063

Figure 2 – The Atherogenic mechanism of sdLDL-C

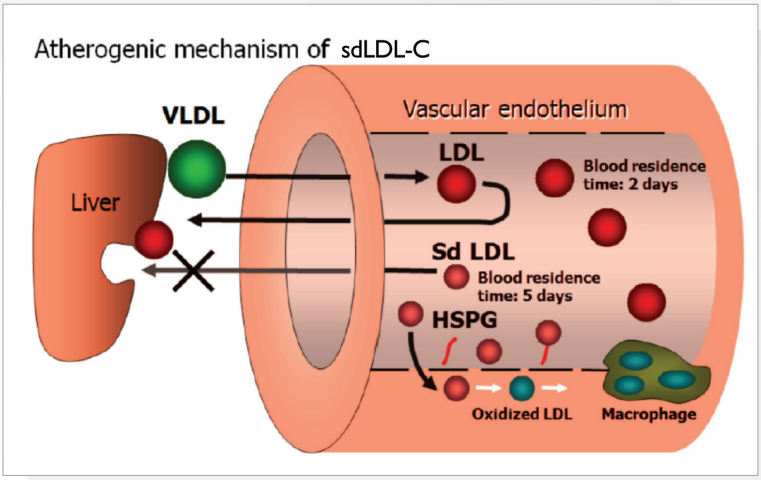


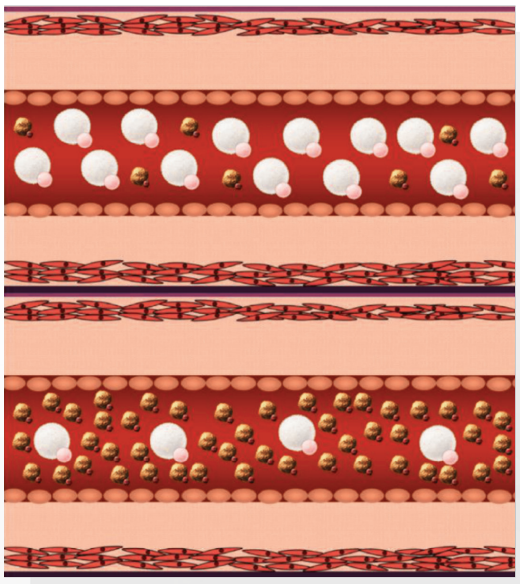
Figure 2 outlines the atherogenic mechanism of sdLDL-C. From this we can see:

1. sdLDL-C has a lower affinity to the hepatic LDL-C receptor, thus circulates in blood longer than larger LDL-C.
2. sdLDL-C has a stronger affinity to vessel wall heparin sulphate proteoglycans (HSPGs), which means that sdLDL-C can more readily permeate the arterial wall.
3. sdLDL-C is also liable to oxidation from its physicochemical properties which leads to foam cell formation.

Similar to Figure 2, Figure 3 illustrates the difference between two patients, both with identical LDL-C levels, however, as sdLDL-C particles carry less cholesterol than LDL-C particles, for the same amount of LDL-C the patient with predominantly sdLDL-C particles may require nearly 70% more LDL-C particles to carry the same amount of cholesterol as the patient with dominantly LDL-C particles.

A LARGE NUMBER OF PATIENTS WITH CVD DON'T HAVE ELEVATED LDL-C (SACHDEVA ET AL., 2009)

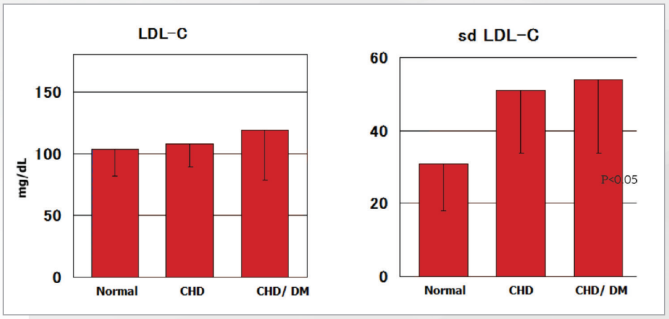
Figure 3



3. SDLDL CHOLESTEROL AND IT'S APPLICATION TO DIABETES

Figure 4 demonstrates a high prevalence of sdLDL-C particles in patients with type 2 diabetes mellitus (T2DM). It was found that not only the prevalence of sdLDL-C, but also the concentration was substantially increased in patients with T2DM. However, previous studies stated that the presence of diabetes did not affect sdLDL-C levels in Coronary Heart Disease (CHD patients). Therefore, these results suggest that sdLDL cholesterol is a powerful predictor of CHD for diabetic and nondiabetic populations.

Figure 4 (Hirano et al., 2004)



4. THE CURRENT NICE GUIDELINES ON THE LIPID PANEL

The current UK National Institute for Health and Care Excellence (NICE) (2014) guidelines which assesses the 'full lipid profile' includes:

- Total Cholesterol
- HDL Cholesterol
- Non-HDL Cholesterol
- Triglycerides
- Risk factors (including age, diet, smoking, QRISK, co-morbidities to view risk and management of risk)

With sdLDL cholesterol being an important marker for cardiovascular risk assessment, it should be considered by NICE for inclusion in the routine lipid profile guidelines to accurately assess the risk of CVD in individuals with a normal level of LDL-C. This will allow action to be taken by clinicians and patients, ultimately lowering the number of deaths caused by CVD and myocardial infarction.

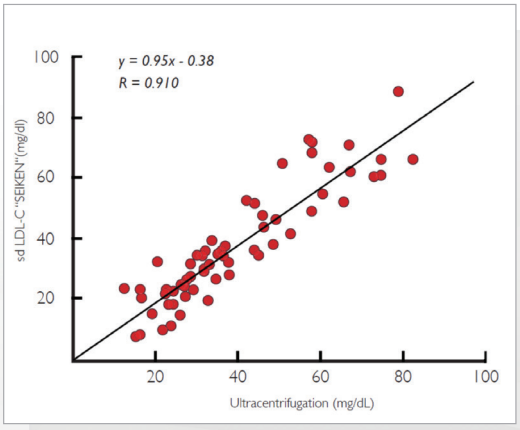
5. RANDOX SDLDL-C ASSAY

DENKA SEIKEN METHOD

The Randox sdLDL-C assay utilises the quantitative "Denka Seiken" method which produces results in as little as ten minutes, facilitating faster patient diagnosis and treatment plan implementation. Previously, ultracentrifugation and electrophoresis based methods were options for the measurement of sdLDL cholesterol, which are both laborious and time consuming (Hirano, 2005).

Studies have highlighted that the use of this quantitative method is more informative in assessment, comparison and measurement of the effective parameters in obesity (Najmafshar at al., 2012). The method consists of two main reaction steps which are based on the presence of surfactants and enzymes that selectively react with a certain group of lipoproteins. Figure 5 demonstrates the correlation of ultracentrifugation and the Denka Seiken method, highlighting that the Randox automated sdLDL-C assay correlates well with the gold standard method (Leary, 2006). For this study, 64 samples were taken from healthy people, coronary artery disease (CAD) and Diabetic patients.

Figure 5 - Correlation of Ultracentrifugation & Denka Seiken Methods (Leary, 2006)



6. OTHER BENEFITS OF THE RANDOX ASSAY INCLUDE:

- Direct, automated test – the Randox sdLDL-C assay is specifically designed for use on automated analysers making the test more convenient and efficient
- Liquid ready-to-use reagents – for convenience and ease-of-use
- Applications are available for a wide range of automated biochemistry analysers – detailing instrument-specific settings for the convenient use of Randox sdLDL-C on a variety of systems
- sdLDL-C controls and calibrator available
- Randox sdLDL is a niche product, meaning that we are one of the only manufacturers of this test in an automated format.

7. CONCLUSION

Cardiovascular disease (CVD) is a leading cause of death worldwide, with 7 million people living with CVD in the UK. In addition, there is a global commitment to reduce the probability of premature CVD deaths by 25% by 2025. Although there is a declining number of CVD deaths over the past 20 years, the number of lives lost to CVDs in low and middle income countries is still increasing.

For these reasons, it is necessary to review the traditional lipid panel outlined in the NICE guidelines to include sdLDL cholesterol. This will enable clinician's to gain a more comprehensive view of a patient's CVD risk, allowing them to take the appropriate measures ito prevent CVD deaths.

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