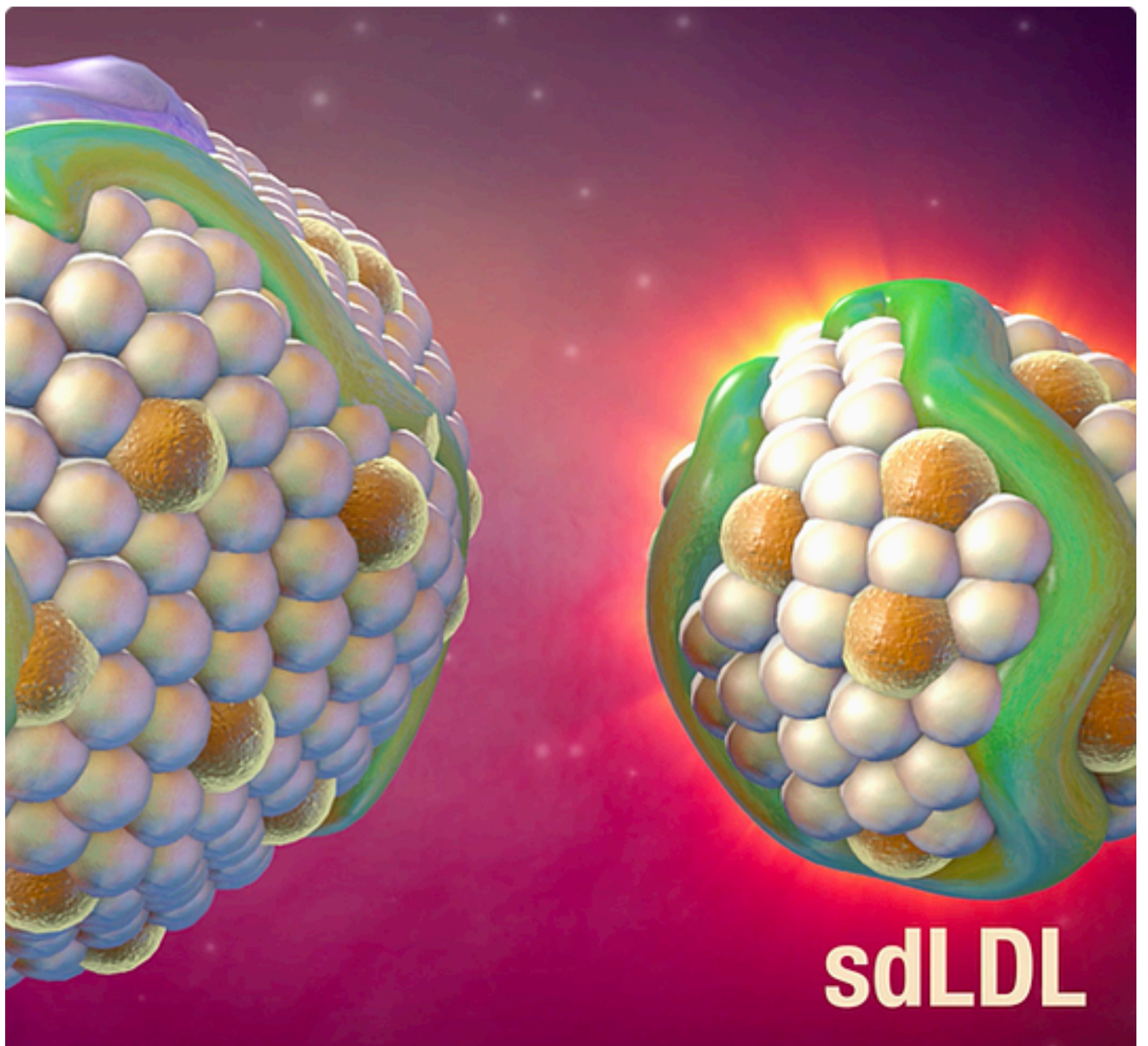


Small-dense LDL



Analytical Performance

Evaluation of a new homogenous method for detection of small dense LDL cholesterol: Comparison with the LDL cholesterol profile obtained by density gradient ultracentrifugation

Albers, J, et al. Clinical Chemica Acta, 2011.

Study overview

- > EDTA plasma samples were measured by the density gradient ultracentrifugation (DGUC) method as well as directly measuring small dense LDL-C with homogenous method from Denka, Tokyo, Japan
- > In a 4-month period, samples referred to the laboratory to be analyzed by DGUC were stored frozen <4 weeks
- > n = 840

Study objective

Evaluate the specificity of homogeneous method quantifying sdLDL-C in comparison to LDL-C profile from DGUC

Key study points

- > The mean lipoprotein cholesterol distributions of the 840 samples in this study approximated the mean lipoprotein cholesterol distribution previously observed in other cohorts
- > Evaluation of the samples with the new method quantifying sdLDL-C indicates that it primarily identifies lipoproteins in the dense LDL fractions
- > No sdLDL-C was identified in fractions corresponding to VLDL, IDL, buoyant LDL and HDL – but variation was observed, where sdLDL was found in one fraction, but was expected as sdLDL represents a spectrum of lipoprotein particles that vary in size, density, and composition
- > The authors concluded that new homogenous method has an excellent precision, appears to be fairly specific for measuring cholesterol in small, dense LDL particles, and that can be implemented on a chemistry autoanalyzer which facilitate rapid measurement of a large number of samples in routine laboratories.

Risk for Coronary Heart Disease

Small Dense Low-Density Lipoprotein-Cholesterol is the Most Atherogenic Lipoprotein Parameter in the Prospective Framingham Offspring Study

Ikezaki, H, et al. Journal of the American Heart Association, 2021.

Study overview

- > Measured directly LDL-C, sdLDL-C, LDL-TG, RLP-C, TRL-C and lipoprotein(a)
- > Subjects were from cycle 6 of the Framingham Offspring Study, which is a prospective observational study of risk factors for ASCVD, which originates from the Framingham Heart Study cohort and their spouses.
- > n = 3,094

Study objective

Investigate elevated levels of direct low-density lipoprotein cholesterol (LDL-C), small dense LDL-C (sdLDL-C), low-density lipoprotein (LDL) triglycerides, triglycerides, triglyceride-rich lipoprotein cholesterol, remnant lipoprotein particle cholesterol, and lipoprotein(a) to assess which biomarker has strongest association with ASCVD risk.

Key study points

- > Among these advanced lipid biomarkers, only sdLDL-C, direct LDL-C, and lipoprotein(a) remained significant in multivariate analysis and net classification adjusted for standard risk factors (age, sex, hypertension, diabetes mellitus, smoking, total cholesterol, and HDL-C)
- > The incremental value in the prediction of ASCVD risk, above and beyond the Pooled Cohort Equation (PCE), was shown for many specialized lipoprotein parameters when assessed individually, but no parameter added significant information once sdLDL-C (HR 1.42, $p < 0.0001$) was in the model
- > Data demonstrated that sdLDL-C provides additional information about ASCVD risk, even after controlling for all standard risk factors including HDL-C, total cholesterol, and cholesterol lowering medication, in univariate, multivariate, and discordance analysis, in addition to the PCE. It was concluded that sdLDL-C is the most atherogenic lipoprotein parameter and is worth measuring in subjects at increased ASCVD risk

Small Dense Low-Density Lipoprotein-Cholesterol Concentrations Predict Risk for Coronary Heart Disease

The Atherosclerosis Risk in Communities (ARIC) Study

Hoogeveen, RC, et al. Atherosclerosis, Thrombosis, and Vascular Biology, 2014.

Study overview

- > Measured directly small dense low-density lipoprotein cholesterol concentration in plasma with a homogeneous assay method (sd-LDL-EX "Seiken") shown to be in good agreement with ultra-centrifugal method
- > Individuals that participated in ARIC study visit 4 were followed up for 11 years
- > n = 11,419

Study objective

Investigate the relationship between small dense LDL-cholesterol and risk for incident coronary heart disease in a prospective study among ARIC study participants.

Key study points

- > Elevated sdLDL-C levels were associated with increased risk of incident CHD in a multivariable model – HR 1.51 for the highest versus the lowest quartile
- > Even in individuals considered to be at low risk cardiovascular based on their LDL-C levels, elevated sdLDL-C predicted risk for incident CHD – HR 1.61
- > The cumulative incidence curves for risk of CHD illustrated the direct relation between sdLDL-C levels and CHD risk, whereas similar relation was not found for large buoyant LDL-C, suggesting that the sdLDL subfraction is a major contributor to the risk for incident CHD that is associated with LDL-C

New Automated Assay of Small Dense Low-Density Lipoprotein Cholesterol Identifies Risk of Coronary Heart Disease

The Multi-Ethnic Study of Atherosclerosis

Tsai, M., et al. Arterioscler Thromb Vasc Biol., 2014.

Study overview

- > Measured small dense low-density lipoprotein (sdLDL) cholesterol with new automated assay, sd-LDL-C "Seiken", Denka, Tokyo, Japan
- > In individuals from the Multi-Ethnic Study of Atherosclerosis (MESA) both the NMR and

direct measure of sdLDL-C

- > First study to look at sdLDL-C in multi-ethnic prospective study for an 8.5 year period
- > n = 4,387, normoglycemic and non-diabetic

Study objective

Evaluated sdLDL measured from a new assay and its risk factor when compared to LDL-C or small dense LDL particle levels derived from nuclear magnetic resonance spectroscopy

Key study points

- > Elevated sdLDL-C levels identified risk for CHD that would remain undetected when using standard lipid tests
- > After adjusting for age, race, sex, blood pressure, hypertension medication use, HDL-C, TG – top quartile sdLDL-C associated higher risk of CHD – hazard ratio, 2.41
- > sdLDL-C indicated greater risk association when compared to the corresponding fourth quartile of LDL-C – hazard ratio, 1.75
- > NMR derived sdLDL concentrations did not convey a significant risk of CHD

Treatment

Effects of Maximal Doses of Atorvastatin Versus Rosuvastatin on Small Dense Low-Density Lipoprotein Cholesterol Levels

Ai, M, et al. American Journal of Cardiology, 2008.

Study overview

- > Post hoc sub analysis of STELLAR samples (Statin Therapies for Elevated Lipid Levels Compared Across Doses to Rosuvastatin) which was an open label study comparing rosuvastatin with atorvastatin over a 6-week period on direct LDL-C and small dense LDL-C
- > Using serum samples directly measured LDL-C and small dense LDL-C from Denka, Tokyo, Japan
- > n = 271

Study objective

Primary objective was to evaluate the impact of atorvastatin, 80 mg/day, to rosuvastatin, 40 mg/day on changes to direct LDL-C and small dense LDL-C

Key study points

- >The two statins significantly affected all biomarkers, and only HDL cholesterol increased significantly with rosuvastatin
- >Rosuvastatin treatment had greater decrease than atorvastatin in direct LDL-C and sdLDL-C, and others
- >First time intensive statin therapy with atorvastatin and rosuvastatin reduces sdLDL-C as much as calculated LDL-C or direct LDL-C on a percentage basis

The Effects of Statin and Fibrate on Lowering Small Dense LDL-Cholesterol in Hyperlipidemic Patients with Type 2 Diabetes

Tokuno, A, et al. Journal of Atherosclerosis and Thrombosis, 2007.

Study overview

- >Evaluate the effects of therapeutic agents, statin and fibrate, on sdLDL-C in type 2 diabetes patients with hypercholesterolemia and hypertriglyceridemia
- >Quantified sdLDL-C level by using automated assay sd-LDL-C "Seiken", Denka, Tokyo, Japan rather than measuring the LDL size
- > n = 72

Study objective

Evaluate the effects of treatment in patients with statin and fibrate to investigate the mechanism on whether either can reduce LDL-C subspecies, specifically sdLDL-C

Key study points

- >Low dose of pitavastatin decreased LDL-C by 25%, as well as sdLDL-C at comparable levels, which was significantly correlated to the reduction in LDL-C induced by pitavastatin
- >Low dose fenofibrate significantly reduced TG and increased HDL-C, and it also decreased sdLDL-C but not lb-LDL
- >Both statin and fenofibrate are effective in reducing sdLDL-C. Though it is still unknown which has greater capability in sdLDL-C reduction due to the difference in baseline sdLDL-C and hyperlipidemia phenotype between the two treated groups, substantial reduction is expected when administered to the patients