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Comparison of cardiovascular disease risk associated with 3 lipid measures in Japanese adults

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BACKGROUND: To assess dyslipidemia, measurement of low-density lipoprotein cholesterol via either Friedewald equation (LDL-F) or direct assay (LDL-D), and non–high-density lipoprotein cholesterol (non–HDL-C) are recommended with some guidelines showing preference to direct over calculated measurements. However, direct comparisons of their respective associations with cardiovascular disease (CVD) risk are currently unavailable.

OBJECTIVE: In this study, we evaluated the clinical effectiveness of LDL-F and non–HDL-C vs LDL-D and their associations with CVD.

METHODS: This retrospective cohort study comprised apparently healthy Japanese individuals who underwent an annual health check-up between 2005 and 2007 and completed a 5-year follow-up visit. The incidence of CVD, including coronary and cerebrovascular diseases, during a 5-year follow-up period was evaluated using multivariate logistic regression.

RESULTS: At baseline, 26,739 participants (mean age, 47 years; 49.0% men) were enrolled, and 292 (1.09%) incidents of CVD were identified at follow-up. Baseline LDL-F, LDL-D, and non–HDL-C were all significantly associated with CVD, although the effect appeared higher for LDL-F, particularly for coronary heart disease. Increased risks of CVD were observed for high LDL-F (≥130 mg/dL), despite being categorized into the lower LDL category based on LDL-D (odds ratio [OR], 1.85; 95% confidence interval [CI], 1.19–2.87) and non-HDL-C (OR, 1.75; 95% CI, 1.22–2.52). Without high LDL-F, no CVD associations were found for high LDL-D ($P = .62$) or non-HDL-C ($P = .93$).

CONCLUSION: Despite growing availability of direct assays and increasing evidence of non-HDL-C utility, the Friedewald equation may offer better clinical utility for CVD prevention, especially in the screening of apparently healthy individuals.

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Background

The association between dyslipidemia and cardiovascular disease (CVD) has been established in numerous previous studies. In particular, low-density lipoprotein cholesterol (LDL-C) has been strongly associated with the risk of CVD events, including coronary heart disease (CHD).[1,2] As such, the third report of the National Cholesterol Education Program (NCEP) Adult Treatment Panel recommends using LDL-C as a primary target for intervention.[3] Aggressive screening and monitoring of lipid profiles and initiating lipid-lowering therapies when appropriate targets are exceeded remain an essential element of both preventive primary care and cardiovascular medicine practice. Historically, LDL-C measurements have relied on calculation via the Friedewald equation (LDL-F),[4] estimating LDL-C value from total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C); numerous previous large cohort studies determining CVD risk were established based on this LDL-C calculation method.[1,2] However, recent technology using a fully automated homogeneous direct assay to precisely measure LDL-C (LDL-D) have been developed, and is increasingly available in hospitals, clinics, and preventative health centers.[5–7] More recently, non-HDL-C appears to be another potent predictor of CVD, also employing a calculation method that consists of simple subtraction of HDL-C from TC, and representing a summation of apolipoprotein B (apoB)-containing lipoproteins, such as LDL-C and very low-density lipoprotein cholesterol (VLDL-C).[8,9]

Although NCEP guidelines state that direct assays should continue to be developed, they continue to recommend use of LDL-F as a primary target for prevention of CVD in the clinical setting, and non-HDL-C as a secondary target when TG values exceed 200 mg/dL, given a robust relationship with CVD risk factors in previous studies.[3,10] In contrast, in its latest guidelines, the European Society for Cardiology and European Atherosclerosis Society comment that LDL-D should be used whenever available, citing that LDL-F, requiring 3 variables in its calculation, including TG, which is affected by fasting status, may allow methodological errors to accumulate.[11]

Nonetheless, as both NCEP and European Society for Cardiology/European Atherosclerosis Society guidelines state, the vast majority of previous trials are based on LDL-F.[3,11] In addition, numerous epidemiologic studies insist that non-HDL-C is superior to LDL-C in terms of relevance to CVD risk.[12–16] However, because of the scarcity of robust comparisons of outcomes between these lipid measurement methods, there is little direct evidence available to confirm that LDL-D provides equivalent utility as a CVD risk factor compared with either LDL-F or non-HDL-C.[17,18] Despite prior studies claiming that LDL-D provides clinical validity comparable to LDL-F, the majority of these studies merely evaluated correlations or focused on methodological differences.[19–21] The value of direct methods (LDL-D) compared with conventional calculations (LDL-F and non-HDL-C) in a general screening population, and the impact on clinical decision-making for risk stratification in the primary care setting, is still undetermined.

In this study, using data from a large cohort of apparently healthy Japanese adults, we examined CVD risk with respect to 3 lipid measures (direct LDL-C assay vs Friedewald equation and non-HDL-C) and assessed the clinical implications associated with potential misclassification of these lipid-measurement methods on risk stratification for disease prevention.

Methods

Study participants and study site

This retrospective cohort study included participants older than 19 years of age who underwent routine health screening physicals at the Center for Preventive Medicine at St. Luke's International Hospital in Tokyo, Japan, between 2005 and 2007. The purpose of this government-mandated health check-up program is to foster health consciousness and promote early detection of chronic diseases and their risk factors.[22,23] Clients at the study site are referred from approximately 30 companies and local governmental organizations in Tokyo. Employees and their dependents accounted for approximately 80% of participants in this study, with the remaining 20% were self-referred individuals from the community. Patients with a 5-year follow-up health screening physical were included in the study.

Between 2005 and 2007, the Center for Preventive Medicine had 128,832 adult visits representing 68,802 unique participants. Among them, 28,389 individuals completed a 5-year follow-up visit and their electronic medical records were accessed. We excluded 225 individuals whose TG value exceeded 400 mg/dL because previous studies have shown that the Friedewald equation becomes increasingly unreliable above this level.[4] We also excluded 73 and 129 individuals with a self-reported baseline history of acute myocardial infarction and ischemic stroke, respectively. Finally, 1219 individuals taking a lipid-lowering medication and 4 individuals whose baseline lipid profile could not be obtained were also excluded resulting in a total of 26,739 individuals included in this study. The incidence of self-reported CVD over this period was subsequently examined, with data extraction implemented with a structured form performed by 2 investigators. This study was approved by the Institutional Review Board of St. Luke's International Hospital.

Measurement of lipid and other risk factors

As part of the baseline examination, blood samples were obtained and the following variables were analyzed using the JCA-BM2250 automatic analyzer (JEOL Co., Tokyo, Japan.): TC and TG were measured with Pure Auto S CHO-N and Pure Auto S TG-N (Sekisui Medical Co., Tokyo,