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Utility of high density lipoprotein particle concentration in predicting future major adverse cardiovascular events among patients undergoing angiography

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ABSTRACT

Background: HDL-C is recognized to be inversely associated with cardiovascular (CV) risk. However, attenuation of the association of HDL-C with CV risk may occur after adjustment for other lipoprotein parameters and in various disease states, especially in the setting of acute coronary syndrome (ACS). Recently, the number of HDL particles (HDL-P) has been suggested to improve CV risk prediction.

Methods and results: Patients ($n = 2999$) in the Intermountain Heart Collaborative Study who underwent angiography and had lipoprotein particle measurements determined by nuclear magnetic resonance (NMR) spectroscopy were studied. Multivariable Cox hazard regression was utilized to evaluate the association of HDL-C, HDL-P, and HDL-P subclasses with future major adverse CV events (MACE: death, myocardial infarction, heart failure, and stroke). Patients averaged 64 ± 12 years, 66% male, 26% diabetic, and 42% ACS. At angiography, 65% of patients were diagnosed with coronary artery disease (CAD). HDL-C and HDL-P averaged 41 ± 13 mg/dL and 28 ± 8 μmol/L, respectively. HDL-P (HR = 0.903, $p = 0.001$), but not HDL-C (HR = 0.947, $p = 0.102$) was significantly associated with MACE. In a model that included all HDL-P subclasses, both small (HR = 0.862, $p < 0.0001$) and medium (HR = 0.922, $p = 0.020$) were associated with CV risk, but not large HDL-P (HR = 1.0042, $p = 0.185$). Small HDL-P continued to be associated with all of the individual components of MACE, but not stroke.

Conclusion: In this study of patients undergoing angiography, HDL-P was a strong, independent predictor of future MACE, with the smaller HDL-P accounting for this association.

1. Introduction

Plasma concentrations of high density lipoprotein cholesterol (HDL-C) are recognized to be inversely associated with cardiovascular (CV) risk. However, attenuation of the association of HDL-C with CV risk may occur after adjustment for other lipoprotein parameters [1,2], in various disease states [2], and after treatment [2,3]. These parameters include triglycerides, diabetes, and statin use. Therefore, other measurements of HDL, such as HDL size and HDL particle numbers (HDL-P) [1] are now being explored for their association with CV risk. HDL size is the weighted average of the HDL subclasses and HDL-P is the mix of different sized particles that differ in lipid and protein content, with protective and nonprotective components not reflected by HDL-C.

The Multi-Ethnic Study of Atherosclerosis (MESA) [1], Heart Protection Study (HPS) [4], and Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) [3], important epidemiological and clinical studies, demonstrated that nuclear magnetic resonance (NMR)-measured HDL-P was a stronger, more independent predictor of CV risk than HDL-C. In HPS and JUPITER, investigators evaluated the relationship of HDL-C and HDL-P with CV risk in subjects randomized to statin or placebo. Both studies showed a significant, strong, inverse association between HDL-P concentrations and CV risk. However, HDL-C was not associated with CV risk after adjustment by other lipoprotein parameters in statin-treated patients. Therefore, NMR-measured HDL-P may provide a more accurate and reliable biomarker for future CV events than HDL-C.

The objective of this study was to evaluate and compare the predictive abilities of HDL-C, HDL-P, and HDL-P subclasses for CV risk among patients undergoing angiography for coronary artery disease (CAD) determination.

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2. Materials and methods

2.1. Study population

The study patients (09/2000–09/2006) were drawn from the cardiac catheterization registry of the Intermountain Heart Collaborative Study, a cohort of patients that underwent coronary angiography at the LDS Hospital (Salt Lake City, Utah) [4–6]. Patients ($n = 2998$ consecutive patients) were included if they were ≥18 years of age, underwent angiography for CAD determination, had at least 5 years follow-up, received a lipid panel as part of their clinical care and had NMR lipoprotein particle measurements. At the time of angiography, patients who provided informed consent had blood samples taken using Becton-Dickinson vacutainer with potassium EDTA as the anticoagulant. This study was performed in accordance with the Declaration of Helsinki and was approved by the Intermountain Urban Central Region Institutional Review Board. The plasma was separated from the cellular material within 4 h of collection and promptly stored at −70 °C for future testing. This registry is fairly homogenous, with Caucasians comprising approximately 90% of the patients.

2.2. NMR spectroscopy

NMR spectra were acquired using EDTA plasma samples on the NMR Profiler platform at LipoScience (now LabCorp, Raleigh, NC), a CLIA and CAP approved laboratory. HDL parameters (concentrations of total, small, medium and large HDL-P) were quantified by *NMR LipoProfile®* analysis using the LP3 algorithm as previously described [7,8]. Small, medium, and large HDL-P subclasses have estimated diameter ranges of 7.3–8.2 nm, 8.2–9.4 nm, and −9.4 to 14 nm, respectively.

2.3. Other laboratory testing

As part of the patient's clinical care, lipid panel and if applicable, troponin I was measured by the Intermountain Healthcare Central Hematology Laboratory (CLIA and CAP approved). Total cholesterol (enzymatic), HDL-C (colorimetric) and triglycerides (glycerol phosphate oxidase) were quantified using the ABBOTT Architect Methodologies. LDL-C was calculated if triglycerides were <400 mg/dL otherwise were measured directly using a liquid selective detergent. Troponin also used the ABBOTT Architect by Chemiluminescent Microparticle Immunoassay.

2.4. Other risk factors, demographic information, and clinical assessments

In addition to age and gender, patient information collected included diabetes status (fasting blood glucose > 125 mg/dL, clinical diagnosis of diabetes mellitus, or anti-diabetic medication use), hypertension (systolic blood pressure ≥ 140 mm Hg, diastolic ≥90 mm Hg, or antihypertensive medication use), hyperlipidemia (total cholesterol ≥200 mg/dL, LDL cholesterol ≥130 mg/dL, or cholesterol-lowering medication use), renal failure (clinical diagnosis or GFR <15 mL/min), and heart failure (HF) (clinical diagnosis or physician-reported). Family history was patient-reported if a first-order relative had suffered cardiovascular death, myocardial infarction (MI), or coronary revascularization before age 65 years. Smoking included active smokers or those with a > 10 pack-year history. Clinical presentation included stable angina (stable exertional symptoms only), unstable angina (progressive symptoms or symptoms at rest), or acute MI (troponin I level > 0.4 ng/mL or a discharge diagnosis of an MI). Discharge medications (i.e., statin, other lipid lowering medications, ace-inhibitors [ACEI], aspirin, angiotensin receptor blocker [ARB], beta-blocker, clopidogrel, diuretic) were also available.

Significant CAD was defined as the presence of one or more ≥ 70% obstructive lesions by coronary angiography. Assessment of CAD was made by review of angiograms by the patient's cardiologist. On the basis of angiographic evaluation, patients were determined to have single-, double-, or triple-vessel disease in each major vessel counted, with the left main counting as two vessels. Assessment of CAD was performed blinded to results of blood testing.

2.5. Patient follow-up and event assessment

Average length of follow-up was 7.0 ± 2.8 years (median: 7.9 years). All patients are followed electronically using Intermountain Healthcare's Enterprise Data Warehouse (EDW). The EDW uses standardized schemas to combine clinical and administrative data from nearly all facilities and clinical offices in the Intermountain Healthcare system. Each patient is tracked throughout the Intermountain Healthcare system using a unique patient index ID. Therefore, a patient's healthcare information from primary care physicians, cardiology consultations, hospitalizations, and other facility visits can be tracked and queried.

Major adverse cardiovascular events (MACE) were defined as the composite of death, MI, HF hospitalization, and stroke. MI was defined as a hospitalization where a patient had a troponin I level ≥ 0.4 ng/mL with an acute coronary syndrome diagnosis or a discharge diagnosis of an MI (ICD-9 code 410; ICD-10 codes: I21.x, I22.x, I23.x). Heart failure hospitalization was determined by a discharge diagnosis of HF or discharge diagnosis codes (ICD-9 codes: 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.0; ICD-10: I50.x). Stroke was determined by ICD-9 codes (433.1 and 434.1) and ICD-10 codes (I60.x, I61.x, I62.x, I63.x, I64.x). Deaths were determined by hospital records, Utah State Health Department records (death certificates), and the Social Security Administration death master file. Access to cause of death is only available for residents of the state of Utah ($n = 2818$). Cardiac death ($n = 2849$) was defined using ICD-9 (391.0–392.0, 393–398.99, 402–404.93, 410–429.9 and 779.85) and ICD-10 codes (I01.0–I02.0, I05.0–I09.9, I11.0–I13.9, I20.0–I28.9, I30.0–I52.8, I97.0–I97.191, I98.0 and I98.1, P29.81, Q20.0–Q24.9, R00.0–R01.2, T80.0xxA, T81.718A, T81.72xA, T82.817A, T82.818A). Patients not listed as deceased in any registry were considered as alive.

2.6. Statistical analysis

Variables are summarized as mean ± standard deviation for continuous variables and frequencies for discrete variables. The chi-square statistic and student's *t*-test were utilized to compare baseline characteristics among those who did and did not experience follow-up MACE. The Pearson correlation coefficient was utilized to evaluate the correlations of HDL-C and HDL-P. Multivariable Cox hazard regression was utilized to determine the association of HDL-C, HDL-P, and HDL-P subclasses with MACE, its individual components (death, MI, stroke, and HF hospitalization), and cardiovascular death. Covariables included in the multivariable models were age, sex, diabetes, hypertension, hyperlipidemia, smoking, HF, renal failure, prior MI, prior stroke, significant CAD, presentation (reason for angiography), statin use at discharge, antiplatelet use at discharge, digoxin use at discharge, ACEI use at discharge, heparin use prior to or during angiography, LDL-C, and triglycerides. Triglycerides were non-normally distributed and therefore log-transformed with the normality of the transformation verified prior to inclusion in the models. All other lipoproteins were normally distributed. HDL-C, HDL-P, and HDL-P subclasses were included in models with each other to examine if correlations were masking associations. Hazard ratios (HR) are presented as per standard deviation (SD) increment. A *p*-value of ≤0.05 was designated nominally significant.

3. Results

Of the 2999 patients evaluated, a total of 1211 (40.4%) had a MACE event. Table 1 displays the baseline characteristics of the population