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ORIGINAL ARTICLE

Non-HDL-C is a Better Predictor for the Severity of Coronary Atherosclerosis Compared with LDL-C

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Background Recent guidelines recommended both low-density lipoprotein cholesterol (LDL-C) and non–high-density lipoprotein cholesterol (non-HDL-C) are the primary target of lipid modulating therapy. However, which lipid measure is most closely related to the severity of coronary atherosclerosis has not yet been assessed.

Methods We studied 1757 consecutive subjects undergoing coronary angiography who were not receiving any lipid-lowering therapy. Low-density lipoprotein cholesterol was measured directly, and non-HDL-C was calculated. The severity of coronary stenosis was determined using the Gensini Score (GS) system.

Results In the overall population, LDL-C and non-HDL-C were all dramatically increased according to the quartiles of GS ($p<0.001$, both). In patients with coronary atherosclerosis (n=1097), non-HDL-C ($r=0.138$, $p<0.001$) was more closely related to GS than LDL-C ($r=0.113$, $p<0.001$) tested by Spearman correlation analysis. Multivariate logistic regression analysis suggested that non-HDL-C (OR=1.326, 95% CI 1.165-1.508, $p<0.001$) was slightly superior to LDL-C (OR=1.286, 95% CI 1.130-1.463, $p<0.001$) in predicting high GS after adjusting for potential confounders. Among patients with LDL-C less than the median, discordant non-HDL-C could not provide extra value in predicting high GS (OR=0.759, 95% CI 0.480-1.201). However, among patients with LDL-C greater than or equal to the median, the cardiovascular risk was overestimated for patients with discordant non-HDL-C (OR=0.458, 95% CI 0.285-0.736).

Conclusions Our data support the use of non-HDL-C ahead of LDL-C in predicting the severity of coronary atherosclerosis, especially among patients with LDL-C greater than or equal to the median.

Keywords Coronary atherosclerosis • Non-HDL-C • LDL-C • Gensini score

Introduction

Guidelines for the detection and treatment of high cholesterol, such as the US National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines [1], the 2011 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines[2], and the Chinese guidelines for the management of dyslipidaemia [3], recommend using low-density lipoprotein (LDL) cholesterol (LDL-C) as the primary marker to guide lipid

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management. However, recently, guidelines from Europe [4] and Canada[5], as well as the US consensus statements/recommendations[6] continue to endorse LDL-C as the primary lipid measure before and after treatment but acknowledge that non-high density lipoprotein cholesterol (non-HDL-C) could be recommended for individuals with hypertriglyceridaemia or cardiometabolic abnormalities. Moreover, recommendations from the International Atherosclerosis Society Expert Dyslipidemia Panel[7] and the National Lipid Association[8] recommend non-HDL-C also as a primary target of therapy.

Among these most commonly used metrics evaluating cardiovascular risk, the LDL-C measures the mass of cholesterol within LDL particles, and the non-HDL-C indicates the mass of cholesterol within all the apolipoprotein B (apoB) particles including LDL and very low-density lipoprotein (VLDL). However, whether LDL-C or non-HDL-C is the better marker reflecting the atherogenic risk remains controversial. The meta-analysis among patients treated with statins showed that on-treatment levels of non–HDL-C was superior to LDL-C in relation to the risk of future major cardiovascular events[9], whereas a large participant-level analysis showed non-HDL-C was superior to LDL-C or total cholesterol (TC)[10]. Despite these controversial data, which lipid measures can most accurately evaluate the severity of coronary atherosclerosis has not yet been investigated. Moreover, most studies were conducted among patients already on statin treatment. Thus, the lipid measures may be intensively influenced and the predictive value may be deeply modified by the therapy.

Therefore, in the current study, we sought to investigate the most closely related lipid marker to the severity of coronary atherosclerosis assessed by Gensini Score (GS) system in a cohort of patients who did not receive lipid-lowering therapy.

Materials and Methods

Study Design and Population

The study complied with the Declaration of Helsinki and was approved by the hospital's ethical review board (FuWai Hospital & National Center for Cardiovascular Diseases, Beijing, China). Each participant provided written, informed consent before enrollment.

In a group of subjects scheduled for coronary angiography because of angina-like chest pain and/or positive treadmill exercise test or clinically suspected coronary artery disease (CAD) in our department, we selected 1757 consecutive individuals who were not treated with lipid-lowering drugs. Inclusion criteria were as follows: (1) having no treatment history of statins and/or other lipid-lowering drugs at least three months before entering the study; (2) having detailed clinical, laboratory data and well-documented traditional cardiovascular risk factors; (3) underwent coronary angiography. Exclusion criteria were subjects with previous revascularisation, psychiatric disorder, the existence of any infectious or systematic inflammatory disease, acute coronary syndrome, serious heart failure or arrhythmia, significant haematologic disorders, thyroid dysfunction, severe liver dysfunction and/or renal insufficiency and malignant tumours.

Hypertension was defined as repeated blood pressure measurements≥140/90 mmHg (at least two times in different environments) or currently taking anti-hypertensive drugs. Diabetes mellitus (DM) was defined as a fasting serum glucose level≥7.0mmol/L in multiple determinations, and/or the current use of medication for diabetes. Dyslipidaemia was defined by medical history or the use of lipid-modulating medications in order to reduce lipids or fasting TC≥5.18 mmol/L or triglyceride (TG) ≥1.7 mmol/L.

Biochemical and Clinical Analyses

Fasting blood samples were collected in pre-cooled EDTA tubes at baseline from each patient. After centrifugation at 3000 rpm for 15 min at 4^0C, all fresh plasma aliquots were measured in our hospital immediately.

In the current study, the lipid concentrations were measured with the automatic biochemistry analyser (Hitachi 7150, Tokyo, Japan). In detail, TC was tested by CHOD-PAP method (Cholesterol kit, BioSino Bio-technology & Science Inc. China) with a coefficient of variation of less than 3%. The TG level was detected by GPO-PAP method (Triglyceride kit, BioSino Bio-technology & Science Inc. China) with a coefficient of variation of less than 4%. The LDL-C concentration was analysed by selective solubilisation method (Low density lipid cholesterol test kit, Kyowa Medex, Tokyo). Using this method, the coefficient of variation was less than 5%. Similarly, the HDL-C concentration was also determined by a homogeneous method (Determiner L HDL, Kyowa Medex, Tokyo) with a coefficient of variation of <5%. The total imprecision of all the related methods was less than 10%. The non-HDL-C level was calculated as TC minus HDL-C.

Severity of Coronary Atherosclerosis

The severity of coronary atherosclerosis was quantified by GS system[11]. The GS was computed by assigning a severity score to each coronary stenosis according to the degree of luminal narrowing and the importance of location, which was defined as 1 point for stenosis of 1–25%, 2 points for 26–50%, 4 points for 51–75%, 8 points for 76–90%, 16 points for 91–99% and 32 points for total occlusion. The score is then multiplied by a factor that represents the importance of the lesion's position. That is 5 for the left main coronary artery, 2.5 for the proximal left anterior descending or proximal left circumflex artery, 1.5 for the mid-region, 1 for the distal left anterior descending or mid-distal region of the left circumflex artery, and 0.5 for small vascular branches. In patients who have undergone revascularisation, the angiographic severity was measured before the procedures.

Statistical Analysis

Statistical analyses were performed with the SPSS program (version 19.0, SPSS, Chicago, Illinois, USA). First, we