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Usefulness of Low-Density Lipoprotein Particle Size Measurement in Cardiovascular Disease Prevention

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Summary

Background: Cardiovascular disease is largely explained by the traditional risk factors, but there are several novel risk factors that have been shown to predict cardiovascular morbidity. The measurement of low-density lipoprotein particle size (LDLPS) is a novel cardiovascular risk factor, yet it is unknown whether this measurement provides additional information that may influence the subsequent medical treatment of patients.

Hypothesis: The measurement of LDLPS provides additional information that may influence preventive treatment for cardiovascular disease.

Methods: In an observational study of 82 patients referred to a tertiary care preventive cardiology clinic, LDLPS was dichotomized as either small or large and was determined by either the NMR LipoProfile test, the Vertical Auto Profile (VAP™) cholesterol test, or gradient gel electrophoresis. Lipid profiles were obtained and Framingham risk scores were calculated. Patients were stratified by Adult Treatment Panel guidelines as being at low, intermediate, or high risk.

Results: The study included 56 men and 26 women with a mean age of 54 ± 11 years. In the entire cohort of 82 patients, only 31 (38%) were at non-high-density lipoprotein (HDL) goal, only 21 (26%) were at goals for both non-HDL and HDL, and only 18 (22%) were at goal for non-HDL, HDL, and triglycerides. When considering each of the risk factor strata, 19 of 43 (44%) low-risk patients were at non-HDL goal and 12 of these also had a small LDLPS. Only 8 of 18 (44%) intermediate-risk patients were at non-HDL goal and 7 of these (88%) had small LDLPS. Finally, only four high-risk patients were at non-HDL goal and three of these (75%) had small LDLPS.

Conclusions: Knowing the LDLPS could alter subsequent therapeutic recommendations for most patients who have reached target lipid values.

Key words: lipids, risk factors, cardiovascular disease, screening

Introduction

Cardiovascular (CV) disease is largely explained by traditional risk factors.[1] Since the majority of patients who suffer CV events have at least one risk factor,[2] focusing treatment on these proven causes seems appropriate. In principle, the degree of therapeutic aggressiveness is best guided chiefly by an individual's overall CV risk.[3] However, many patients are at intermediate risk and/or have one or more borderline risk factor(s)[4] whereby the appropriate intensity of medical treatment remains uncertain. Moreover, hundreds of novel risk factors have been described,[5] many of which may be independently associated with CV risk. Unfortunately, the optimal intensity of medical treatment for any single individual and the role of assessing novel risk factors during CV prevention remain unclear.

Patients with a Framingham risk score between 6 and 19% (intermediate risk) may benefit from novel risk factor testing in order to better characterize their individual CV risk and thereby the appropriate intensity of medical treatment.[4] We have previously reported the usefulness of determining carotid intima-media thickness[6] and C-reactive protein[7] in such patients. Both measurements led to changes in clinical management in the majority of patients tested when established clinical guidelines were followed. However, it remains to be determined whether such an algorithm would actually yield superior outcomes. In the present investigation, we report our observations of the clinical usefulness of measuring another novel independent CV risk factor, low-density lipoprotein particle size (LDLPS).

Materials and Methods

This study was approved by the Institutional Review Board of the University of Michigan. We retrospectively collected

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clinical/demographic data and laboratory results of all patients who had LDLPS determined for clinical reasons during their initial visit to our outpatient preventive cardiology clinic. The LDLPS was determined by either the NMR LipoProfile test (LipoScience, Inc, Raleigh N.C., USA),[8] the Vertical Auto Profile (VAP™) cholesterol test (Atherotech, Birmingham, Ala., USA),[9] or gradient gel electrophoresis (Berkeley Heart Lab, Burlingame, Calif., USA).[10] The LDLPS for each patient was dichotomized to small or large based upon the criteria provided by each laboratory. When an intermediate phenotype was reported (e.g., pattern A/B by VAP), LDLPS was categorized as small (i.e., small size category includes all patients without a large "normal" LDLPS).

To determine the clinical usefulness of measuring LDLPS, we calculated the percentage of patients in each CV risk category in whom knowing LDLPS might influence subsequent therapy and/or mandate more aggressive treatment beyond that recommended by standard lipids and clinical guidelines. For LDLPS to be deemed useful, patients would need to have a small LDLPS, yet have their traditional lipid profiles meet present-day guidelines. For example, if a patient had a small LDLPS, yet non-high-density lipoprotein cholesterol (HDL-C) was not at goal, guidelines would already mandate more aggressive treatment and knowing the LDLPS would not add incremental information to mandate additional therapy. However, if standard lipid values met goals and a patient had a small LDLPS, then additional treatment may be warranted based solely upon the findings of LDLPS measurement and the test would be deemed clinically useful. The percentage of patients who achieved goal non-HDL-C for each CV risk category, yet had a small LDLPS, was calculated as the primary outcome. Cardiovascular risk strata and their goal non-HDL-C values were defined per Adult Treatment Panel (ATP) III Cholesterol Guidelines:[11] low risk (< 2 risk factors, goal non-HDL-C < 190 mg/dl), intermediate risk (≥ 2 risk factors, goal non-HDL-C < 160 mg/dl), and high risk (CHD or any risk equivalent, goal non-HDL-C < 130 mg/dl).

Next, for each CV risk strata, we determined the percentage of patients who had a small LDLPS yet achieved progressively more stringent standard lipid profile target goals. The number of patients who met both their non-HDL-C goal and had an HDL-C > 40 mg/dl, yet had a small LDLPS was calculated. Finally, the percentage of patients who met all standard lipid profile goals (CV risk strata non-HDL-C target, HDL > 40 mg/dl, plus triglycerides (TG) < 200 mg/dl) yet had a small LDLPS was calculated.

Data were analyzed using Statistical Package for Social Sciences 12.0 for windows (SPSS Inc., Chicago, Ill., USA). Descriptive statistics are presented as mean ± standard deviation (SD).

Results

Tables I and II provide the demographic/clinical data and the medication regimens of our study population, respectively (n = 82). Upon initial visit to our clinic, 68% of patients were taking at least one lipid-lowering medication. Table III demonstrates the results of the standard lipid and the LDLPS profiles. The most common abnormality was elevated TG (mean = 446 ± 688 mg/dl), which accounts for the high prevalence of a small LDLPS (78%).

Table IV illustrates the chief results of our study. Upon referral to our clinic, most patients were not at non-HDL-C goal (range 19–44%). Fewer patients had all lipid parameters at goal for their individual CV risk (range 10–30%). Among all

TABLE I Clinical characteristics of the patients (n = 82)

Age (years)	54 ± 11
Male / female	56 / 26
Number of current smokers	5
Number of patients with diabetes mellitus	9
Systolic blood pressure (mmHg)	124 ± 20
Diastolic blood pressure (mmHg)	78 ± 11
Heart rate (beats/min^{-1})	70 ± 14
Body weight (kg)	89 ± 19
Body mass index (kg·m^{-2})	30.0 ± 5.4
Framingham risk score	8.2 ± 5.8

Values represent mean ± standard deviation.

TABLE II Medication profile (n = 82)

Medication class	Number of patients (%)
ACE inhibitor	24 (29)
Aspirin	40 (49)
Beta blocker	19 (23)
Lipid-lowering drug(s)	56 (68)
Statin	26
Fibrate	17
Niacin	8
Bile acid resin	1
Ezetimibe	4

Abbreviation: ACE = angiotensin-converting enzyme.

TABLE III Lipid results (n = 82)

Total cholesterol (mg·dl^{-1})	253 ± 101
High-density lipoprotein cholesterol (mg·dl^{-1})	50 ± 27
Non-high density lipoprotein cholesterol (mg·dl^{-1})	202 ± 98
Low-density lipoprotein cholesterol (mg·dl^{-1})	145 ± 93
Triglycerides (mg·dl^{-1})	446 ± 688

Low-density lipoprotein particle size	Large n (%)	Small n (%)
All subjects (n = 82)	18 (22)	64 (78)
Low risk (n = 43)	14 (33)	29 (67)
Intermediate risk (n = 18)	2 (11)	16 (89)
High risk (n = 21)	2 (10)	19 (90)

Values represent mean ± standard deviation.

TABLE IV Main study results

Risk factor stratum	Number of patients at non-HDL goal		Number of patients at non-HDL and HDL (>40 mg·dl^{-1}) goals (%)		Number of patients at non-HDL, HDL (>40 mg.dl^{-1}), and TG (<200 mg.dl^{-1}) goals (%)	
	At above goal, yet with a small LDLPS		At above goal, yet with a small LDLPS (%)		At above goal, yet with a small LDLPS (%)	
	n	%	n	%	n	%
Low (n = 43)	19	(44)	15	(35)	13	(30)
	12	(63)	9	(60)	7	(54)
Intermediate (n = 18)	8	(44)	4	(22)	3	(17)
	7	(88)	3	(75)	2	(67)
High (n = 21)	4	(19)	2	(10)	2	(10)
	3	(75)	2	(100)	2	(100)
Total cohort (n = 82)	31	(39)	21	(26)	18	(22)
	22	(71)	14	(67)	11	(61)

Abbreviations: HDL = high-density lipoprotein, TG = triglycerides, LDLPS = low-density lipoprotein particle size.

levels of risk, the majority of patients who had achieved their non-HDL-C goal (range 63–75%) and/or all predefined standard lipid goals (range 54–100%) still had a small LDLPS. It was surprising that when patients with TG values that were within goals and even with values < 100 mg/dl^{-1}, traditionally believed to be associated with a very low likelihood of having a small LDL pattern, were analyzed, patients across all risk categories still had a small LDL pattern (Table V). The clinical usefulness of LDLPS determination tended to an increase in direct relation to the overall CV risk.

Discussion

Our findings demonstrate the potential clinical usefulness of measuring LDLPS at all levels of CV risk. Knowing the LDLPS could alter subsequent therapeutic recommendations in most patients who have reached non-HDL-C goals or even met sequentially more stringent target standard lipid values. In general, this therapy would involve adding either niacin or a fibrate to the medical regimen, which otherwise may not have been considered. Prior to this analysis, it would have been reasonable to hypothesize that the intensity of lifestyle changes and medication usage normally required to achieve non-HDL-C goals would assure success in increasing LDLPS in a high percentage of patients. If that were the case, standard lipid measurements would eliminate most of the clinical benefit of determining LDLPS. However, these findings show that simply targeting therapeutic aggressiveness in order to achieve ATP III guidelines for non-HDL-C[11] (or even HDL-C > 40 mg/dl and triglycerides < 200 mg/dl) does not assure that patients are successfully treated specifically to increase their LDLPS. Despite being at goal, 61–71% patients still had small LDLPS. Even when controlled for TG level, many subjects still had small LDL size (Table V). Therefore, even in patients perceived to be at lipid goals, LDLPS measurement is clinically beneficial and could lead to more intensive subsequent therapy in most patients tested.

TABLE V Identification of patients' risk stratification based on triglyceride level

Risk factor stratum	Triglycerides < 100 mg·dl^{-1}		Triglycerides < 150 mg·dl^{-1}	
	Pattern B (%)		Pattern B (%)	
Low	11	(73)	19	(63)
	6	(55)	10	(53)
Intermediate	3	(20)	5	(17)
	2	(67)	1	(20)
High	1	(1)	6	(20)
	1	(100)	1	(17)
Total Cohort	15	—	30	—
	9	(60)	12	(40)

Small LDLPS has been shown in some[12–14] but not all[15] studies to predict CV mortality independently. Enhanced atherosclerosis could occur by a variety of mechanisms.[16] In several studies, once other lipid values were accounted for,[17, 18] or once apoB (atherogenic particle number) was lowered to goal,[12] LDLPS did not convey independent risk information. More recent observations suggest that the simple classification of small versus large size is not as beneficial as quantifying the severity of small LDLPS distribution.[13, 14] In addition, atherogenic particle number may be at least as important.[19] Whether a small LDLPS phenotype conveys excess CV risk once lipids are aggressively treated (i.e., non-HDL-C, HDL-C, and TG are at goal) has never been demonstrated. It is possible that lower-

ing non-HDL to < 100 mg/dl (i.e., apoB < 80 mg/dl) would eliminate any risk associated with a small LDLPS. In theory, in such patients, a small LDLPS may be common because of reductions in the available cholesterol content for lipoproteins, thus making apoB (or particle number) a superior risk predictor. However, the focus of this observational study was not to validate the prognostic importance of LDLPS, but to investigate the theoretical clinical usefulness of knowing this laboratory information during CV disease prevention treatment.

Study Limitations

This study is limited by a potential selection bias of referral to our tertiary care preventive cardiology and lipid management clinic, as well as by the small number of patients. The high overall percentage of patients with a small LDLPS, due to the prevalence of hypertriglyceridemia, may also account for some of our findings. Nevertheless, due to the overwhelming prevalence of obesity and the metabolic syndrome,[20] we feel these findings have significant external validity. In addition, most patients still had a small LDLPS even when TG were treated to goal. We used three different methods that may not always agree to quantify LDLPS. However, our purpose was not to assess the validity of each technique, but rather to investigate in routine practice the impact of assessing LDL pattern, regardless of the methodology utilized. A final limitation is that few high-risk patients were at standard lipid goals compared with lower-risk patients; this may limit the strength of our findings in this portion of our cohort. However, the percentages of patients reaching non-HDL-C goal at each level of CV risk are similar to population-wide observations.[21]

Conclusions

Measurement of LDLPS may provide important clinical information at all levels of CV risk. Targeting treatments to achieve standard lipid goals does not assure that such therapy will increase LDLPS. Further studies are required to determine whether modulating therapy (such as adding niacin) based upon LDLPS determination actually improves clinical outcomes.

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