



TITLE: LDL Particle Number as Assessed by NMR Spectroscopy

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A Technology Assessment

INTRODUCTION

The California Technology Assessment forum is asked to assess the evidence for the use of low density lipoprotein particle number (LDL-P) as an adjunct to low density lipoprotein cholesterol (LDL-C) for prediction of coronary heart disease (CHD) risk in individuals with CHD or at high risk for CHD. This topic is being reviewed now because a consensus statement released by the American College of Cardiology and the American Diabetes Association suggests that measuring LDL particle number may be a more accurate way to evaluate cardiometabolic risk.

BACKGROUND

Coronary artery disease (CAD) is the number one cause of death in men and women. Many risk factors increase an individual's risk for CHD, including family history of premature CHD, smoking, hypertension, diabetes and hyperlipidemia. Many of these risk factors may cluster, and since each may be associated with an increase in CHD risk, the concept of global cardiometabolic risk (CMR) has been developed. Patients with global CMR often have central obesity, insulin resistance, dyslipoproteinemia and hypertension, all of which put them at increased CHD risk.

Hyperlipidemia is a long established risk factor for CHD. Many epidemiologic studies have established that hyperlipidemia, specifically elevated levels of LDL-cholesterol, is a risk factor for CHD. A risk factor is anything that increases a person's chance of getting disease. As with any risk factor, if hyperlipidemia is a risk factor for CHD, does changing the level of LDL-cholesterol change the risk for CHD?

Multiple studies of drug treatment of hyperlipidemia mostly with the statins have shown that treatment of hyperlipidemia reduces subsequent CHD risk among individuals with CHD and in individuals at high risk for CHD¹⁻⁶. For individuals at lower risk for CHD, e.g. for primary prevention, there is some evidence although the benefit is less clear in women.



Even with adequate LDL cholesterol lowering, many patients on statin therapy may have significant residual CVD risk. It is not clear whether lipoprotein parameters other than LDL or non-HDL cholesterol provide additional clinically significant information regarding CVD risk. Some patients experience CHD events despite reassuring cholesterol levels. Many patients with CHD, diabetes or CMR have normal levels of LDL cholesterol but increased levels of small dense LDL-P. It has been suggested that assessment that *includes* these other lipoproteins might be more useful than assessments limited to LDL alone.

LDL-C is measured indirectly and LDL cholesterol level is typically calculated using the Friedewald equation (total cholesterol minus HDL minus triglycerides/5=LDL) but this measure can underestimate LDL level as triglycerides increase. Cholesterol is carried within LDL particles. The standard way to measure LDL cholesterol has been to measure LDL cholesterol content. Since the amount of cholesterol in each particle may vary, measuring LDL cholesterol may not reflect actual particle number.

LDL particle number

Cholesterol is carried within LDL particles. The cholesterol content of LDL varies between individuals because of differences in particle size and lipid composition. Small dense LDL has long been known to be associated with an increased CHD risk. However, it is possible that the association between small LDL and CVD may reflect an increased number of LDL particles in patients with small LDL. Newer information suggests that it is LDL particle number that is important- if LDL is small and dense, then particle number is greater. Therefore, some individuals with normal LDL-cholesterol can still have an elevated number of LDL particles. It is not clear whether or not LDL particle size measurements add value to measurement of LDL particle number.

Among individuals with diabetes and at high risk for CVD, LDL particle number can be heterogeneous. Among 2,235 diabetics, all of whom had LDL-C levels at <100 mg/dl, there was a lot of variability in LDL-P levels. Among patients with an LDL-C cholesterol between 70 and 99 mg/dl, only 26% had a low LDL-P level (defined as <20th percentile of an ethnically diverse reference population). Even among individuals with very low LDL-C (<70 mg/dl), 10% had LDL-P



levels greater than the 50th percentile⁷. It has been suggested that this heterogeneity of LDL-P levels may be responsible for the varying levels of CHD risk in this population.

The Nuclear Magnetic Resonance LipoProfile test used with an automated nuclear magnetic resonance (NMR) spectrometer, measures lipoprotein particles to quantify LDL particle number, HDL cholesterol and triglycerides in serum and plasma using NMR spectroscopy. NMR is a measurement of LDL particle number, and measures the diameter and lipid concentration of LDL. NMR measurement of LDL P is not proposed to replace conventional LDL testing, but rather to be used as an adjunct to conventional lipid testing. Proposed candidates for LDL-P measurement are high risk individuals whose LDL cholesterol levels are near goal, including individuals with CHD or CHD risk equivalents or diabetes with LDL <100 mg/dl and individuals with CMR with LDL <130 mg/dl.

The potential goal of using LDL-P would be to determine whether or not it adds additional prognostic value to conventionally measured lipoproteins, and whether treating elevated LDL-P affects clinical outcomes. Thus, the following questions are relevant: 1) Is elevated LDL particle number associated with CHD risk? 2) Does LDL particle number add prognostic value to measurement of LDL-C? 3) Does treatment of elevated LDL-particle number change clinical outcomes?

TECHNOLOGY ASSESSMENT (TA)

TA Criterion 1: The technology must have final approval from the appropriate government regulatory bodies

The NMR Profiler and NMR LipoProfile[®] Test received FDA 510(k) clearance on July 23, 2008.

Indications for Use:

“The NMR LipoProfile[®]-2 test, used with the NMR Profiler, an automated NMR spectrometer, measures lipoprotein particles to quantify LDL particle number (LDL-P), HDL cholesterol (HDL-C),



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and triglycerides in serum and plasma using nuclear magnetic resonance (NMR) spectroscopy. LDL-P and these NMR-derived concentrations of triglycerides and HDL-C are used in conjunction

with other lipid measurements and clinical evaluation to aid in the management of lipoprotein disorders associated with cardiovascular disease. The test is performed and provided as a service by Liposcience Laboratory.”

TA criterion 1 is met.

TA Criterion 2: The scientific evidence must permit conclusion concerning the effectiveness of the technology regarding health outcomes.

Search Methods: We searched Medline, the Cochrane clinical trials database, Cochrane reviews, database and the Database of Abstracts of Reviews of Effects (DARE) using the search terms of cardiovascular disease or heart disease or coronary disease or carotid artery diseases cross referenced with hyperlipidemia, lipoproteins, LDL and LDL-P or LDL-Num or particle. In addition, we searched the bibliographies of the identified articles and other reviews to identify primary data sources and search strategies to ensure a complete review of the relevant literature. The abstracts of citations were reviewed for relevance and all potentially relevant articles were reviewed in full. Studies were included if they included the use of LDL-P in predicting cardiovascular disease.

Studies were excluded if they only focused on non-clinical outcomes such as lipid levels or other metabolic parameters. We identified relevant published articles: we identified eight observational studies- five were nested case-control studies and three were cross sectional studies. The outcomes evaluated included MI, CHD mortality angina, change in coronary artery lumen diameter, carotid artery intimal thickness and coronary artery calcification. No studies that addressed whether treatment of LDL-P affected cardiovascular outcomes were identified.

Inclusion criteria:

Study had to assess a clinical outcome or an intermediate outcome

Study had to measure LDL- P

Study had to independently assess LDL-P as a predictor of CHD risk or assess the impact of treatment of LDL-P on clinical outcomes
 Included only humans
 Published in English as a peer reviewed article

Search Results

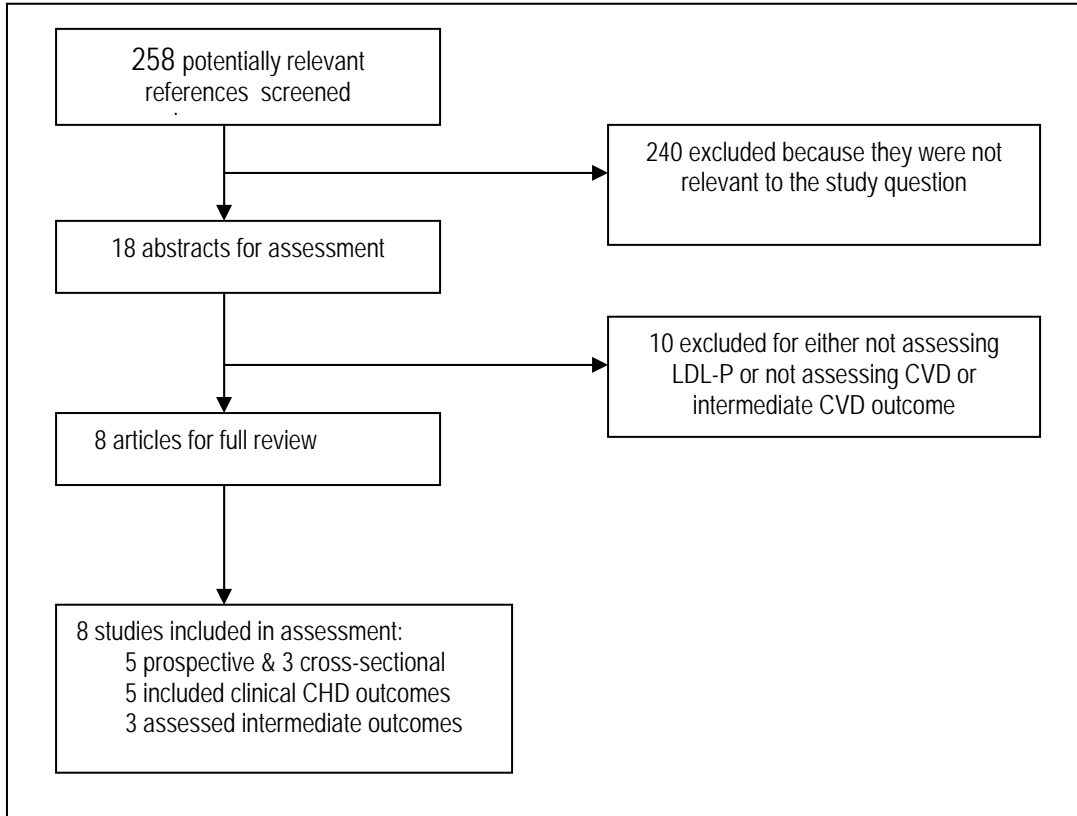


Figure 1. Study Selection

Table 1: Prospective Studies (nested case control) Assessing LDL-particle Size as a Predictor of CHD Risk

STUDY	N	Length of follow-up	Predictor	Outcome	Results
Women's Health Study ⁸	260 women	3 year	LDL particle concentration	MI Stroke or CHD death	LDL particle concentration RR for CV events 4.17 (1.96, 8.87) for highest vs. lowest quartile LDL-C 2.06 (1.03, 4.12) RR for CV events Adjusting for other risk factors (e.g. lipids, CRP, other risk factors) tended to attenuate the association Magnitude of predictive value of LDL particle concentration was not substantially different from total to HDL ratio
Cardiovascular Health Study ⁹	683 women	2-6 years (average length not stated)	LDL particle number	MI or angina	OR 3.54 for MI and angina by quartiles of LDL particles (4 th compared with first) OR 2.58 for MI and angina by quartiles of LDL-C (4 th compared with first)
VA-HIT ¹⁰	364 men	5.1 year	LDL particle number LDL particle size	Nonfatal MI or CHD death	LDL-P was a significant predictor of CHD events OR 1.28 (1.12, 1.47) per 1 SD increment in each lipid lipoprotein variable HDL-P was also a predictor OR (0.71 (0.61, 0.81) LDL-C 1.08 (0.95, 1.23) not a predictor
PLAC-I ¹¹	241 (24% women)	3 year	LDL particle number LDL particle size	Angiographic lumen diameter	Those with higher LDL particle number had bigger decrease in minimum lumen diameter ($r=-0.13$; $P,0.01$) LDL particle number (adjusted for age, sex and race and baseline lumen diameter and lipids
EPIC ¹²	2888 (37% women)	6 year	LDL particle number LDL particle size	Fatal or nonfatal CHD event	OR for 4 th quartile compared with first for CAD Univariate LDL-P OR 2.0 (1.58 to 2.59) Non-HDL C 2.14 (1.69 to 2.69) LDL-C 1.73 (1.37 to 2.18) LDL-P independently related to CAD after adjusting for FRS and after adjusting for LDL-C Multivariate adjusting for FRS LDL-P 1.34 (1.03, 1.73) 4 th quartile compared with first LDL 1.24 (0.97-1.58) LDL- P value abolished after correcting for TGs and HDL-C

Table 2: Cross Sectional Studies Assessing the Association Between LDL-P and CVD Outcomes

Study	N	Predictor	Outcome	Results
MESA ¹³	5538 (53% women)	LDL particle concentration LDL particle number	Carotid intimal media thickness	LDL-P was related in a linear regression model to IMT. 40.2 micron (4.1) change in intimal medial thickness in micrometers per 1 SD LDL C 37.4 (4.1) change in IMT (SE) per micrometer per 1 SD.
Framingham ¹⁴	2993	LDL particle number	Metabolic Syndrome CVD	Increased LDL particle number predicted metabolic syndrome Among individuals with metabolic syndrome, LDL particle number was not associated with a greater CVD event rate
Healthy Women Study ¹⁵	286	LDL particle number	Coronary artery calcification score	Increased LDL particle number associated with higher coronary artery calcification score (OR 1.44: 95% C.I. 1.04, 1.99) per 1 SD increase

LDL-P as a predictor of CHD

A total of eight studies assessed LDL particle number as a predictor of CHD risk. Five of the eight were nested case-control studies within either a cohort or a clinical trial. The remaining three were cross sectional studies. Study size ranged from 241 to 5538 individuals.

The five nested case control studies are described in Table 1. Length of follow-up ranged from two to six years. Four of the nested case control studies included clinical outcomes such as MI, angina, CHD death, and stroke. The other study assessed the intermediate outcome of angiographic lumen diameter.



The largest case-control study was conducted within the EPIC- (European Prospective Investigation into Cancer and Nutrition) - Norfolk study. The EPIC-Norfolk Study is a prospective population study of 25,663 men and women aged 65-79 residing in Norfolk which is part of a ten country study. Cases were selected based on having fatal or non-fatal CHD during average six year follow up. Controls (two per case) were matched on gender and time of enrollment. LDL-P was more closely associated with CAD than was LDL-C. (Odds Ratio (OR) 2.14; 95% C.I. 1.58, 2.59). It was associated with CAD after adjusting for LDL-C and Framingham Risk Score. However, after adjusting for HDL-C and triglycerides, the value of LDL-P was abolished.¹²

The Women's Health Study was another nested case control study of 260 women which assessed the relationship between LDL particle size and CHD events. LDL particle concentration was a predictor of CHD (RR 4.17; 95% C.I. 1.96, 8.87 for highest vs. lowest quartile). However, the predictive value of LDL-P was similar to that of the total cholesterol to HDL ratio.⁸

In the Cardiovascular Health study, another nested control study, there were 434 cases with MI and angina and 349 healthy controls. Participants were followed from two to six years. LDL particle number was a significant predictor of CHD events (OR 3.54 for 4th quartile compared with 1st quartile of LDL particles). LDL cholesterol was also related to CHD risk (OR 2.58 for fourth quartile compared with 1st quartile). After correcting for triglycerides and HDL-C, LDL-P remained a significant predictor of MI and angina.

The VA-HIT study was a nested case control study of 364 men with nonfatal MI or cardiac death and 6978 controls. Participants were followed for an average of 5.1 years. Participants in the VA-HIT study were treated with gemfibrozole, which in addition to its effects on HDL lowers the number of LDL particles. LDL-P was a significant predictor of CHD events both at baseline (OR 1.20: 95% C.I. 1.05, 1.37) and on trial (OR 1.28 (1.12, 1.47), whereas LDL-C was not a predictor of CHD in this study. It is possible that gemfibrozole mediated some of its positive effects on CHD risk by reducing LDL particle number.



The PLAC I study was also a nested case control study. In it, 241 participants were followed for an average of three years and the intermediate outcome assessed was angiographic lumen diameter. Elevated LDL particle number and levels of small HDL were the strongest predictor of CAD progression.

In the MESA¹³ and the Framingham¹⁴ and Healthy women¹⁵ studies, the association between LDL-P and CVD was assessed by cross sectional analyses. In the MESA study, LDL particle subclasses were assessed as a predictor of intimal media thickness, an intermediate outcome. Total LDL particle concentration was significantly associated with a 40.2 micrometer change in intimal medial thickness per one standard deviation. LDL-C was significantly associated with a 37.4 micrometer change in IMT per one standard deviation.

In the Framingham study, also cross-sectional, LDL-P was assessed as a predictor of the metabolic syndrome, as assessed by the presence or absence of 0- 5 traits (blood pressure, HDL, waist circumference, triglycerides, fasting glucose). Then among individuals with metabolic syndrome, LDL-P was assessed as a predictor of CVD. Although individuals with elevated LDL-P were more likely to have the metabolic syndrome, among individuals with metabolic syndrome, LDL-P was not associated with an increased CVD event rate.

In the Healthy Women Study, LDL-P was assessed as a predictor of coronary artery calcification score, a noninvasive index of coronary artery disease. Higher levels of LDL-P were associated with an increased coronary artery calcification (CAC) score, with an odds ratio of 1.44 (1.04-1.99) per 1 standard deviation increase in LDL-P.¹⁵

In summary, several prospective observational studies and case control studies have shown that elevated LDL-P is a predictor of CHD risk.



Does LDL particle number add additional prognostic value to LDL-C?

Several of the prospective and cross sectional studies above⁸⁻¹³ show that LDL particle number is a predictor of CHD risk and that it may be a better discriminator of CHD risk than LDL alone. However, its effect is sometimes attenuated when correcting for other lipid variables.

Among individuals with the metabolic syndrome, one of the main groups in which its use is suggested, LDL-P did not predict CHD risk. In addition, it is not currently known whether its ability to predict CVD is consistent across ages, ethnicities and other factors that affect lipid metabolism.

Does treatment of elevated LDL particle number affect clinical outcomes?

No articles were identified which assessed whether treating an elevated lipid particle number with either drugs or non-pharmacologic treatment reduces CHD risk.

Level of Evidence 3

TA Criteria is met for LDL-P as a predictor of CHD events

TA Criteria 2 is not met for whether treatment of elevated LDL-P affects clinical outcomes

TA Criteria 3: The technology must improve net health outcomes

For a diagnostic test, ideally there should be evidence that use of the test would result in improved medical management in a way that would benefit the patient. Therefore, once LDL-P elevation has been identified, there should be evidence that identification of elevated LDL-P leads to a reduction in CHD outcomes compared with not identifying an elevated LDL-P.

There are currently no studies that have addressed whether or not treating elevated LDL-P affects clinical outcomes.



LDL-P has been proposed for use in identifying individuals at elevated CHD risk, even if their LDL-cholesterol levels are normal. However, since it is already recommended that these high risk individuals be treated to more aggressive LDL-C goals, that any other cardiac risk factors be treated and that aspirin be considered, it is not clear what else should be done. No studies have evaluated what else will be done after identifying an elevated LDL particle number.

It has been suggested that in patients with an LDL-C level at goal and an elevated LDL-particle level that either higher doses of medication or combination therapy can be utilized to decrease levels of LDL-P. Conversely, those who are at LDL-P targets and have an acceptable level of LDL-P could be managed without more intensive regimens. Although these guidelines may have intuitive appeal, there is currently no evidence that this strategy will improve clinical outcomes.

TA Criterion 3 is not met.

TA Criterion 4: The technology must be as beneficial as any of the established alternatives

Identification of individuals at high CHD risk

Several studies have shown that LDL-P is a predictor of CHD risk and that it may even be a stronger predictor than LDL-cholesterol. However, the proposed use of LDL-P is for high risk individuals at or near LDL-C goal. Therefore, the individuals in whom LDL-P is proposed to be measured are individuals who already have their LDL-C measured.

Therefore, if LDL-P is to be useful as an adjunct to LDL-C measurement, then the results should lead to a change in management other than that which would be recommended based on LDL-C alone.

There are well established guidelines for the treatment of hyperlipidemia based on LDL-C levels and overall risk of CHD¹⁶. Decisions about the level of LDL-C at which to treat are based on an



individual's ten year risk of CHD as assessed by the Framingham risk score. Thus, an individual at high CHD risk will be treated to a goal LDL of <100 mg/dl, with an optional goal of <70 mg/dl.

Although it has been suggested that intensifying treatment in individuals with an elevated LDL-P but with LDL-C at goal, may be beneficial, this has not been compared to the current standard of treating LDL-C alone. Ideally, trials would address the impact of lowering LDL-C vs. lowering LDL-C and LDL-P and the impact on clinical outcomes.

TA Criterion 4 is not met

TA Criterion 5: The improvement must be attainable outside the investigational settings.

Whether the use of LDL-P in addition to LDL-C results in a reduction in CHD events has not been demonstrated in the investigational setting and therefore it cannot be considered attainable outside this setting.

TA Criterion 5 is not met.

SUMMARY

In summary, LDL-P as an adjunct to LDL-C is being evaluated for use in patients with CHD or CHD equivalents or CMS who have already achieved LDL-C goals. Although LDL-P is associated with CHD risk, and may be a more discriminatory risk factor than LDL-C alone, there is currently no evidence that treatment of elevated LDL-particle number changes clinical outcomes.

RECOMMENDATION

Measurement of LDL-P does not meet CTAF criteria 2-5 for efficacy and improvement in health outcomes as an adjunct to LDL-C for individuals with CHD or CHD equivalents or CMS who have already achieved LDL-C goals

October 15, 2008

This is the first review for this topic

The California Technology Assessment Forum panel voted to accept this recommendation.



RECOMMENDATIONS OF OTHERS

Blue Cross and Blue Shield Association (BCBSA)

The BCBSA Technology Evaluation Center has not conducted an assessment of this technology

Centers for Medicare and Medicaid Services (CMS)

CMS appears to be silent on the use of this technology.

California Chapter of the American College of Cardiology (CA ACC)

A representative of the CA ACC attended the meeting and noted support for the use of this technology.

US Preventive Services Task Force (USPSTF)

The Screening for lipid disorders in adults: U.S. Preventive Services Task Force recommendation statement published in June 2008 does not specifically mention the use of this technology.

National Heart Lung and Blood Institute (NHLBI)

The Adult Treatment Panel III (ATP III) published in 2001 does not mention the use of this technology. An update of this guideline, ATP IV, is currently in process. Release of ATP IV is expected in 2009

American College of Cardiology and American Diabetes Association Consensus Report on Lipoprotein Management in Patients with Cardiometabolic Risk;

The consensus report recently issued by the ACC and ADA recommends that for patients with CMR on statin therapy, therapy can be guided with measurements of another lipoprotein apoB in addition to LDL and non-HDL cholesterol measurements. The use of LDL-P in managing patients with dyslipoproteinemia is not addressed.



ABBREVIATIONS USED N THIS REPORT

LDL-P	Low density lipoprotein particle number
LDL-C	Low density lipoprotein Cholesterol
CHD	Coronary heart disease
CAD	Coronary artery disease
CMR	Cardiometabolic risk
CVD	Cardiovascular disease
MI	Myocardial infarction
NMR	Nuclear Magnetic Resonance
DARE	Databases of Abstracts of Reviews of Effects
EPIC	European Prospective Investigation into Cancer and Nutrition
OR	Odds ratio
CAC	Coronary artery calcification

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