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The Importance of LDL Particle Number in Predicting Risk of Cardiovascular Events

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The Importance of LDL Particle Number in Predicting Risk of Cardiovascular Events

Abstract

Background: Cardiovascular events are the leading cause of death in the United States. Providers use various risk factors as a guide to monitor and treat patient's cardiovascular risk. Low-density lipoprotein cholesterol (LDL-C) has been used as a way to measure cholesterol, a known major risk factor of cardiovascular disease. This systematic review examines the importance of using LDL particle number in predicting future cardiovascular events compared to total LDL cholesterol, LDL-C.

Methods: An exhaustive search of available medical literature was conducted using Medline-OVID, Web of Science, CINAHL and EBMR Multifile databases. The following keywords were utilized as search terms: LDL particle number, LDL cholesterol, cardiovascular disease and nuclear magnetic resonance. Study quality was assessed using the GRADE system.

Results: This search resulted in 51 articles. After unrelated articles were excluded, two cohort studies and one case-control study met criteria and were included in the review. The studies looked at LDL particle number and LDL-C with primary outcomes being cardiovascular events and coronary artery disease. Overall, when looking at LDL particle number compared to total LDL cholesterol, LDL particle number was more predictive of a future cardiovascular event. The quality of both the cohort studies were low and the case-control study was very low.

Conclusion: This systematic review demonstrated that LDL particle number is more predictive of future cardiovascular events when compared to LDL-C. The standard lipid panel continues to be a critical quantitative test to evaluate cholesterol, a major cardiovascular risk factor, but the implementation of looking at particle number as well should be performed and is an important aspect to further reduce risk of cardiovascular events and patient important outcomes.

Keywords: LDL particle number, LDL cholesterol, Cardiovascular disease, Nuclear Magnetic Resonance

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The Importance of LDL Particle Number in Predicting Risk of Cardiovascular Events

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Biography

[Redacted for Privacy]

Abstract

Background: Cardiovascular events are the leading cause of death in the United States. Providers use various risk factors as a guide to monitor and treat patient's cardiovascular risk. Low-density lipoprotein cholesterol (LDL-C) has been used as a way to measure cholesterol, a known major risk factor of cardiovascular disease. This systematic review examines the importance of using LDL particle number in predicting future cardiovascular events compared to total LDL cholesterol, LDL-C.

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Results: This search resulted in 51 articles. After unrelated articles were excluded, two cohort studies and one case-control study met criteria and were included in the review. The studies looked at LDL particle number and LDL-C with primary outcomes being cardiovascular events and coronary artery disease. Overall, when looking at LDL particle number compared to total LDL cholesterol, LDL particle number was more predictive of a future cardiovascular event. The quality of both the cohort studies were low and the case-control study was very low.

Conclusion: This systematic review demonstrated that LDL particle number is more predictive of future cardiovascular events when compared to LDL-C. The standard lipid panel continues to be a critical quantitative test to evaluate cholesterol, a major cardiovascular risk factor, but the implementation of looking at particle number as well should be performed and is an important aspect to further reduce risk of cardiovascular events and patient important outcomes.

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Table I: Characteristics of Reviewed Studies

Table II: Summary of Findings

List of Abbreviations

ApoB.....	ApolipoproteinB
CAD.....	Coronary Artery Disease
CV.....	Cardiovascular
CVD.....	Cardiovascular Disease
GRADE.....	Grading of Recommendation, Assessment, Development and Evaluation
IDL.....	Intermediate-density Lipoprotein
IMT.....	Intima-media Thickness
LDL-C.....	Low-density Lipoprotein Cholesterol
LDL-P.....	Low-density Lipoprotein Particle
NMR.....	Nuclear Magnetic Resonance
VLDL.....	Very Low-density lipoprotein

The Importance of LDL Particle Number in Predicting Risk of Cardiovascular Events

BACKGROUND

“In every year since 1900 except 1918, cardiovascular disease (CVD) accounted for more deaths than any other major cause of death in the United States.”¹

Cardiovascular (CV) risk factors that contribute to this death rate include age, gender, family history, smoking, diet, lack of exercise, stress, obesity, diabetes mellitus and hyperlipidemia. For decades measuring low-density lipoprotein cholesterol (LDL cholesterol or LDL-C), in conjunction with other associated risk factors, has been the quantitative test used to identify, evaluate and manage patients with hyperlipidemia and therefore risk for coronary artery disease (CAD).

Coronary artery disease is apparent when effects of atherosclerosis are measurable. Atherosclerosis occurs when cholesterol and fat build up in the artery walls creating plaque. LDL-C is a measure of the total cholesterol content in the LDL particles (LDL-P); however, it does not adequately quantify how many particles of LDL an individual actually has. The LDL cholesterol content varies from person to person and frequently their LDL-C level is discordant to their LDL-P level.² This is in part why LDL particle number can vary greatly between two individuals even if they had the same amount of low-density lipoprotein cholesterol content.

Despite the decreasing trend of average LDL-C from 108mg/dL to 103mg/dL, from 2000 to 2006 there still continues to be cardiovascular related events in individuals with low levels of LDL-C.³ In a recent large cohort study³ that analyzed 136 905

patients hospitalized for CAD, 48 093 of these patients had no history of CAD, diabetes or other atherosclerotic vascular disease and of those patients 41.5% had LDL-C below goal (<100mg/dL). Based upon the data from this study, it is evident that normal LDL cholesterol levels can underestimate the true cardiovascular risk of a patient.

Low-density lipoprotein particle number can be measured a few different ways. The molecular structure of an LDL particle contains many phospholipids and proteins but each LDL, very low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL) particles have a single protein called apolipoproteinB (apoB) on the surface of their respective particles.^{4,5} LDL particles comprises >90% of the apolipoproteinB which is why apoB is often used interchangeably to estimate the quantity of LDL particles a person has. However, nuclear magnetic resonance spectroscopy can provide a direct measurement of the number of LDL particles.⁵ This is done by measuring the amplitudes of the signals that are emitted by each lipoprotein; which then, provides a plasma concentration of LDL, VLDL, and IDL individually.⁶

In evaluating healthy adults in the general population free of cardiovascular disease, does LDL particle number serve as a better predictor of cardiovascular event outcomes compared to the standard LDL cholesterol levels? Clinicians monitor and treat patients according to their LDL-C levels to decrease their cardiovascular risk, but in using LDL-C are we under representing and not adequately treating the individuals that may have normal or low levels of LDL-C but continue to experience a cardiovascular event?

METHODS

An exhaustive literature search was conducted using Medline-OVID, Web of Science, CINAHL and EBMR Multifile databases. The following keywords were utilized as search terms: LDL particle number, LDL cholesterol, cardiovascular disease and nuclear magnetic resonance. The search was limited to humans and English language publications. The literature search was supplemented by reviewing reference lists from relevant articles and a search for ongoing clinical trials via the NIH website was performed as well. Eligibility Criteria included healthy adults free of cardiovascular disease or a previous event, cardiovascular risk assessment comparing LDL particle number with total LDL cholesterol and cardiovascular event as the primary outcome. Studies were excluded if they did not have CVD event as the primary outcome, if the study was published more than 10 years ago or if the study examined a specific population.

RESULTS

The literature searches yielded 51 articles that were then reviewed for further consideration in the research question of interest. After initial screening for relevant articles there were three articles that met eligibility criteria. These articles consisted of two cohort studies^{4,7} and one case-control study.⁸ See Table I.

The Framingham Offspring Study

The Framingham Heart Study began in 1948 as a prospective study to look at cardiovascular disease of men and women from Framingham, Massachusetts. The participants of The Framingham Offspring study,⁴ a large community-based cohort study which began in 1971, are from the fourth examination cycle from 1987-1991. These

individuals were eligible to participate if they were the offspring or their spouses of the parents who were enrolled in The Framingham Heart Study.⁹ Participants were excluded from the present study if they were younger than 30 or older than 74 years old, had established cardiovascular disease at baseline, lacked follow up data, had serum triglycerides were >400mg/dL or had missing data on lipid variable or other covariate. This resulted in 3066 individuals, of which 53% were female.⁴

The Framingham Offspring Study looked at various measurements of cholesterol including LDL-C, high-density lipoprotein cholesterol (HDL-C), LDL-P, very low-density lipoprotein particle (VLDL-P), and their associations with CVD and the prediction of cardiovascular risk. The primary outcome of this study was the first incident of a cardiovascular event defined as “recognized or unrecognized MI, angina pectoris, coronary insufficiency, coronary heart disease death, stroke, transient ischemic attack, intermittent claudication or congestive heart failure.”⁴

Participants provided 12-hour fasting blood specimens during the original study period which were evaluated at that time for their plasma lipid concentrations including total cholesterol, triglycerides and HDL-C. The Friedewald formula was used to calculate their LDL-C concentrations. Their blood was also banked at that time on plasma samples which were later retrieved in 1995 to be analyzed by NMR spectroscopy for their LDL particle number. The status of the participants and the actual lipoprotein analysis by NMR was blinded to all investigators.⁴

Throughout the follow-up period, from baseline examination to December 31, 2005, patients were under longitudinal surveillance with recurrent examinations during the Framingham Heart Study and also were required to update their health history

biennially.^{4,9} Over a median of 14.8 years, there were 431 participants that experienced their first CVD event. These events were determined by expert investigators who reviewed hospital and physician medical records. Significantly lower CVD event rates (59 per 1000 person-years) were associated with patients that had low LDL-P levels (<25th percentile) compared to those with equally low levels of LDL-C (81 per 1000 person-years). When assessing for prediction of future CVD events, LDL-P for both men and women with HR 95% CI 1.28 (1.17-1.39) was proven to be the superior indicator compared to LDL-C with HR 95% CI 1.11 (1.01-1.22).⁴

Multi-Ethnic Study of Atherosclerosis (MESA)

The Multi-Ethnic Study of Atherosclerosis (MESA)⁷ is a community based cohort study initiated by the National Heart, Lung and Blood Institute looking at subclinical cardiovascular disease. There were 6814 participants between the ages of 45-85 years old, free of self-reported cardiovascular disease from 4 diverse ethnicities: white, African American, Hispanic and Chinese American from 6 different centers across the US. Participants were excluded if they did not provide informed consent, triglycerides >400mg/dL or if they had missing lipid, NMR or covariate information. This resulted in 5598 individuals (39% white, 25% African American, 23% Hispanic and 13% Chinese) a mean age of 62 years old and with 51% of the participants being women.

The purpose of this study was to look at the concordant and discordant levels of LDL-C and LDL-P in the prediction of cardiovascular events with primary outcome being incident CVD events defined as MI, coronary heart disease death, angina, stroke death or other atherosclerotic or CVD death. This study was also supplemented by a cross-sectional study looking at LDL-C and LDL-P with carotid intima media thickness

(IMT), a measure of subclinical atherosclerosis and predictor of cardiovascular disease. Data was collected, except for incident events, during the first MESA study between 2000-2002 and participants were followed for a mean of 5.5 years.⁷

The MESA study showed that both LDL particle number and LDL-C were associated with future CVD events but particle number appears to be more predictive than LDL-C with hazards ratios of 1.32 (95% CI 1.19-1.47) and 1.20 (95% CI 1.08-1.34), respectively. The correlation between LDL-C and LDL-P was relatively high with $r=0.75$ but the relationship was frequently discordant. The study measured discordance as being $\geq 12\%$, which allowed half the study sample to be concordant. With regards to the patients that had a discordant LDL-C and LDL-P, it was the LDL-P that tracked closer with future cardiovascular events than LDL-C.⁷

The EPIC-Norfolk Prospective Population Study

The European Prospective Investigation of Cancer (EPIC)-Norfolk study⁸ is a case-control study that was performed within the prospective EPIC-Norfolk study comprising 25 663 patients who were residents of Norfolk, United Kingdom. The original study design was to look at the relationship between diet and cancer. The participants were healthy men and women between the ages of 45 and 79 years old who had been recruited by mail and filled out an extensive survey between the years of 1993 and 1997. During that time participants were to be examined by their general practitioner and non-fasting blood samples were drawn. Participants were excluded from the study if they had a history of a myocardial infarction or stroke at the baseline visit. The purpose of the nested case-control study was to examine LDL particles and their size by NMR

measured against LDL-C and each of their associations predicting future coronary artery disease.

In order to establish endpoints, the United Kingdom Office of National Statistics tagged the participants for death certification with a National Health Service number. This number was also used for any hospital admissions as well. Follow up for the study was from their baseline visit until January 2003, an average of 6 years, with primary outcome as being diagnosed with CAD, defined by either hospital admission or death having CAD as the underlying cause.⁸

The case participants were 1,003 individuals who had experienced a fatal or non-fatal CAD incident. The control participants, those who did not have a CAD event, were matched to the cases with a 2:1 ratio based on age (within 5 years), gender and enrollment time (within 3 months). There were 121 cases that could not be matched and those were matched with a 1:1 ratio which resulted in a total of 1,885 controls.⁸

The authors did report that the study had some limitations. They mentioned that the study population was relatively elderly and also that CAD events in the study were ascertained through death certificate and hospital admission data which may lead to both under ascertainment and misclassification of the cases. Additionally, that study reported that LDL-C levels in this study were generally much higher than the US population with a mean LDL-C value corresponding to the 80th percentile of the Framingham subjects of similar age and gender.⁸

The EPIC-Norfolk study determined that when comparing the 4th quartiles, that LDL-P had a closer association with coronary artery disease with odds ratio of 2.00 (95% CI 1.58 to 2.59) compared to LDL-C with odds ratio of 1.73 (95% CI 1.37 to 2.18).

However, once LDL-C and LDL-P were adjusted for HDL-C and triglycerides, LDL-P with OR 1.37 (95% CI 1.04 to 1.83) did not appear to be any more valuable in predicting future cardiovascular events than LDL cholesterol with OR 1.55 (95% CI 1.22 to 1.96).⁸

DISCUSSION

Although clinicians today are primarily using LDL-C levels as a tool to help detect, manage and treat patients at risk for cardiovascular disease, is there a better predictor of CVD in LDL particle concentration? This systematic review reveals that LDL-P does seem to be a better predictor of future cardiovascular events than LDL cholesterol content. Overall LDL-P had higher hazard ratios and odds ratio in all 3 studies^{4,7,8} studies that were reviewed, as can be seen in Table II. However, the EPIC-Norfolk study⁸ did indicate that when adjusted for HDL-C and triglycerides, LDL-P added no additional predictive value.

The Framingham Offspring Study⁴ does not have any serious limitations to its methodology; therefore, this study was not downgraded and remains at a low level of quality of evidence (see Table I). This study revealed that the LDL particle number and the LDL cholesterol content varied greatly among many of the individuals in the study. There were participants that had low LDL-C together with low LDL-P and there were others that had high LDL-C and high LDL-P, but the participants that are of most concern especially to a clinician are those patients that have low LDL-C and high LDL particles. This study uncovered that when looking at cardiovascular events, they followed more accurately with LDL-P than it did with LDL-C. Clinically, these are the patients that should be monitored more closely, they are asymptomatic and are going undetected and untreated but yet their risk of a CV event is greater.

The MESA study⁷ is an ethnically diverse study that showed a widespread variation of the LDL cholesterol content among the participants and that this content does not always appear to correlate with LDL particle number. The study shows that when disagreement occurs between LDL-C and LDL-P both CVD events and the cross-sectional study looking at carotid IMT, (when LDL-P > LDL-C the IMT value was 1012 μm (95% CI 975-1049) and when LDL-P < LDL-C the IMT value was 886 μm (95% CI 841-932)), track clinically and subclinically with particle number more than LDL-C. The study did not appear to have any limitations or imprecision issues and was not downgraded therefore receiving a low quality of evidence (see Table I).

The EPIC-Norfolk study⁸ showed that LDL-P was in fact a superior predictor of coronary artery disease but after adjusting for HDL-C and triglycerides, LDL-P no longer added any additional value in this prediction. However, there were a number of limitations to this study. One such limitation being that LDL cholesterol levels in the study population were much higher than the general US population. In fact, the LDL-C values in EPIC-Norfolk were equivalent to the 80th percentile of Framingham patients. Another potential limitation to this study was that the blood samples taken were non-fasting. Non-fasting blood can have an impact on a person's triglyceride levels,¹⁰ which could have inaccurately contributed to the assessment of LDL-P when they adjusted for HDL-C and triglycerides. Lastly, the authors also mentioned that the study population was relatively elderly but being that the majority of patients that experience cardiovascular events are more elderly in nature, the study was not downgraded for this age limitation. One positive design to the study was the examination of the serum blood samples by NMR, were ran in random order to avoid any systemic bias. Overall, the

study was downgraded one level due to the LDL-C levels being significantly elevated compared to the general population and for the potential inaccuracy with using non-fasting blood specimen, which resulted in the study being given a very low quality of evidence (see Table I).

In order to gather a patient's particle number it needs to be done by NMR and at the current time of this systematic review there are only a small number of medical labs that have the ability to perform this analysis. Additionally, the cost of the test at this time seems to be more expensive than having a standard lipid panel performed. Both cost and accessibility to a lab are important for both clinicians and patients when choosing to examine cholesterol for particle number. The results of this systematic review prove to clinicians that there is a better tool to predict cardiovascular events in their patients. The need for earlier cardiovascular risk detection, intervention and management in both low and high-risk patients needs to be addressed.

CONCLUSION

LDL particle number proves to be a better predictor of future cardiovascular events when compared to LDL-C. Although the overall level of evidence is low, the results from the Framingham Offspring Study, the Multi-Ethnic Study of Atherosclerosis and the EPIC-Norfolk study all provide support indicating that the use of LDL-P is beneficial to predict future cardiovascular events. However, future research is needed to continue to increase the quality of evidence and to possibly add further indications for the use of LDL-P in clinical settings.

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Table I. Characteristics of Reviewed Studies

Quality Assessment							
Study	Design	Downgrade Criteria					Quality
		Limitations	Indirectness	Imprecision	Inconsistency	Publication bias likely	
Cardiovascular Event							
The Framingham Offspring Study ⁴	Cohort	No Serious limitations	No serious indirectness	No Serious imprecision	No serious inconsistencies	Possible ^a bias likely	Low
The MESA Study ⁷	Cohort	No serious limitations	No serious indirectness	No serious imprecision	No serious inconsistencies	Possible ^b bias likely	Low
The EPIC-Norfolk Study ⁸	Case-Control	Serious ^c limitations	No serious indirectness	No serious imprecision	No serious inconsistencies	No bias likely	Very Low

^a Dr. Cromwell is a consultant for or has served on the bureau for Abbott, AstraZeneca, Isis, LipoScience, Kos, Merck, Merck-Schering, Reliant, and Schering-Plough, in addition to receiving research grant or funding from Merck, Kos and Pfizer. Dr. Otvos is an employee and stockholder of LipoScience. Study was not downgraded due to objective measures of cholesterol content and particles.

^bNMR lipoprotein particle analyses were donated by LipoScience, Inc. Drs. Otvos and Shalaurova are employees of LipoScience, Inc. Dr. Otvos is also a shareholder of LipoScience, serves as Chief Scientific Officer, and is a member of its Board of Directors. Study was not downgraded due to objective measures of cholesterol content and particles.

^c Downgraded for LDL cholesterol levels were significantly higher than the general US population and for potential inaccuracy in using non-fasting blood specimens.

Table II. Summary of Findings

<i>Study</i>	<i>Participants</i>	<i>Participants with incident CVD event at follow-up</i>	<i>Length of Follow-Up</i>	<i>CVD event rate (95% CI)</i>	<i>p-value</i>
The Framingham Offspring Study ⁴	3066 (1440 men 1626 women)	n=431	14.8 years (median)	LDL-P HR 1.28 (1.18-1.40)	<0.0001
				LDL-C HR 1.11 (1.01-1.22)	0.03
The MESA Study ⁷	5598 2855 (51% women)	n=319	5.5 years (mean)	LDL-P HR 1.32 (1.19-1.47)	<0.0001
				LDL-C HR 1.20 (1.08-1.34)	0.0009
The EPIC-Norfolk Study ⁸	2888 (1003 cases, 1885 matching controls)	n=1003	6 years (mean)	LDL-P OR 1.78 (1.34-2.37)	<0.0001
				LDL-C OR 1.22 (0.92-1.61)	0.3