Nonfasting LDL-C as a Predictor of Cardiovascular Event Risk

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Abstract
Cardiovascular health is often assessed through predictive tools that rely upon measured lipid values. It has long been held that lipids were most accurately measured with the patient in the fasting state; however, mounting evidence has suggested that nonfasting lipid measurements are not significantly different from fasting. This systematic review examined the cardiovascular disease predictive value of nonfasting lipid levels, specifically LDL-C, compared to fasting lipid measurements.

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Nonfasting LDL-C as a Predictor of Cardiovascular Event Risk

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A Clinical Graduate Project Submitted to the Faculty of the
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For the Masters of Science Degree, August 13, 2016

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Abstract

Background: Cardiovascular health is often assessed through predictive tools that rely upon measured lipid values. It has long been held that lipids were most accurately measured with the patient in the fasting state; however, mounting evidence has suggested that nonfasting lipid measurements are not significantly different from fasting. This systematic review examined the cardiovascular disease predictive value of nonfasting lipid levels, specifically LDL-C, compared to fasting lipid measurements.

Methods: An exhaustive literature search was conducted using the following search engines: MEDLINE-Ovid, Web of Science, and CINAHL. The following keywords were used: fasting, nonfasting, cholesterol, lipids, and cardiovascular. Eligible studies were assessed for quality of evidence using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).

Results: Three studies met inclusion criteria. Two were prospective cohort studies and one was a combined cross-sectional and prospective cohort study. Two of the studies agreed that nonfasting lipid values were of similar prognostic value with regards to cardiovascular events. The third article concluded that nonfasting LDL-C was not of predictive value and should not be used.

Conclusion: Nonfasting LDL-C levels, when elevated, correlated with an increase in cardiovascular events and have similar predictive power to fasting measurements. Total cholesterol and HDL-C levels do not deviate significantly between fasting and nonfasting states and it is reasonable to use these values to calculate 10-year cardiovascular disease risk. Thus requiring the patient to fast prior to phlebotomy for lipid measurement is an unnecessary practice.
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Table I: GRADE Quality Assessment

List of Abbreviations
CVD  Cardiovascular Disease
TC   Total Cholesterol
LDL – C Low Density Lipoprotein – C
HDL – C High Density Lipoprotein – C
HRT  Hormone Replacement Therapy
ATP-IV Adult Treatment Panel - IV
HR   Hazard Ratio
Nonfasting LDL-C as a Predictor of Cardiovascular Event Risk

BACKGROUND

Lipid measurement is a cornerstone of cardiovascular event prediction. Two widely used cardiovascular disease prediction models, the Framingham Heart Study and the Cardiovascular Risk Assessment (10-year, ACC/AHA 2013) are both dependent upon measured total cholesterol and HDL-C levels. Adult Treatment Panel IV (ATP-IV) guidelines for statin therapy center in part around calculated LDL-C measurements. In its current published form the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (ATP-IV) stipulates that lipid measurement be done with the patient in the fasting state. This is a generally accepted practice by the larger body of medicine. It is thought that this practice exists because LDL-C is commonly calculated using the Friedewald equation, which relies upon fasting triglycerides. Nonfasting triglyceride measurements have been shown to be as much as 15-30% higher than their fasting counterparts. This would have serious implications for the calculation of LDL-C. However, it has been demonstrated that with correction factors it is possible to calculate an accurate LDL-C level from a nonfasting triglyceride measurement. Furthermore it has been proven numerous times that traditional Friedewald calculated LDL-C values do not vary significantly between fasting and nonfasting states. Likewise total cholesterol (TC) and HDL-C levels have not been shown to vary significantly between fasting and nonfasting states. This raises the question of why patients are being required to fast prior to having their lipid levels measured. Fasting places a steep burden upon the patient and it is foreseeable that the fasting requirement might be a barrier to care for some patients.

The purpose of this systematic review was to determine if LDL-C measurements, when gathered in the nonfasting state, have the same power for predicting cardiovascular events as their fasting counterparts.
METHODS
An exhaustive literature search was conducted using the following search engines: MEDLINE-Ovid, Web of Science, and CINAHL. The following keywords were used: fasting, nonfasting, cholesterol, lipids, and cardiovascular. References of all eligible studies were also reviewed for relevant articles. Inclusion criteria specified that studies evaluate nonfasting and fasting lipid measurement with regards to cardiovascular disease, events, or mortality. Exclusion criteria eliminated studies of non-human subjects, studies not published in English, and dated systematic reviews. Eligible studies were assessed for quality of evidence using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).10

RESULTS
A total of 153 articles were identified in the initial search. After review for eligibility criteria, three studies were selected: two were prospective cohort studies7,8 and one was a combined cross-sectional and prospective cohort study.4

Doran et al
This was a prospective cohort study7 designed to assess the predictive power of fasting and nonfasting lipid measurements in regards to all cause mortality and cardiovascular mortality. The sample population was derived from participants of NHANES-III; as such they were adults over the age of 18 living within the United States. Primary outcome of interest was all cause mortality, with the secondary outcome of cardiovascular mortality (including ischemic heart disease, heart failure, essential hypertensive heart disease, and atherosclerosis). Both outcomes were obtained using death records. Inclusion criteria included age over 18 years, resident of the United States, and available fasting time. Fasting was defined as time since last meal greater than 8 hours as reported by the patient at the time of sample acquisition. Exclusion criteria included missing HDL-C, TC, or triglycerides or patients whose triglycerides exceeded 400 mg/dL. The initial data set totaled 20,024 adults, after exclusion criteria were
applied the data set totaled 16,161, of which 10,023 were fasting and 6138 were nonfasting. Follow-up was 14.0 (±0.22) years; in that time there were 3788 total deaths and 1454 cardiovascular deaths.  

Patient data was examined both as an unmatched cohort and as a paired (matched) cohort that was derived using propensity score matching. Fasting status and specific cardiovascular risk factors were accounted for in the nonparsimonious multivariable logistic regression model that was used by the study to generate the matched cohort. Thus the patients studied were homogenous with regard to all cause mortality and cardiovascular death. Propensity score matching paired 4299 individuals from the fasting and nonfasting cohorts. Both cohorts were further divided into cut points of <4 hours versus ≥4 hours, <8 hours versus ≥8 hours, and <12 hours versus ≥12 hours. Thus it was possible to evaluate whether the amount of time since the last meal had influence over LDL-C. Both the primary and secondary outcomes were separately evaluated with regards to diabetic status. SAS v9.3 and SAS macro (GMATCH) were used for statistical analysis. Kaplan-Meier curves were generated for both fasting and nonfasting cohorts. Hosmer-Lemeshow C statistics were generated for both the fasting and nonfasting cohorts. Finally Cox proportional hazards models were generated to separate confounders from outcomes in regards to LDL-C and fasting status; 3 tertiles were generated by placing individuals into LDL-C levels of <100 (referent), ≥100-130, and ≥130mg/dL. This was done for both cohorts.  

In regards to cardiovascular mortality, the study found fasting and nonfasting LDL-C measurements equally useful when determining cardiovascular risk status. In the unmatched cohort there was an increased risk of cardiovascular mortality with increasing LDL-C: tertile 1, Hazard Ratio (HR) 1 (reference); tertile 2, HR 1.82 (95% CI, 1.38-2.39); and tertile 3, HR 2.94 (95% CI, 2.20-3.93). Fasting and nonfasting groups had similar C statistics for predicting cardiovascular mortality: fasting C statistic 0.62 (95% CI, 0.59-0.64) versus nonfasting C statistic 0.62 (95% CI, 0.60-0.64), P=0.80. This suggests that both measurements are somewhat useful in predicting future cardiovascular mortality. When the study analyzed the cut points it concluded that fasting and nonfasting LDL-C values had similar prognostic utility.
fasting versus nonfasting in nondiabetics versus diabetics were found to be similar, suggesting that fasting status and diabetes have little interaction in regards to predicting cardiovascular mortality. Finally, sensitivity analysis was performed on individuals with triglycerides over 400 mg/dL, which demonstrated similar prognostic value between fasting and nonfasting LDL-C levels.  

In the matched cohort there was an increased risk of cardiovascular mortality with increasing LDL-C: tertile 1, HR 1 (reference); tertile 2, HR 1.68 (95% CI, 1.13-2.51); tertile 3, HR 3.04 (95% CI, 2.00-4.62). Evaluation of fasting status and cardiovascular mortality yielded $P_{\text{interaction}} = 0.34$, conferring no association between fasting status and predictive power of LDL-C with regards to cardiovascular mortality. Fasting and nonfasting groups had identical C statistics for predicting cardiovascular mortality: fasting C statistic 0.62 (95% CI, 0.60-0.66) versus nonfasting C statistic 0.62 (95% CI, 0.60-0.66), $P=0.96$.  

Study limitations as described by the authors included the use of data from a pre-existing source, and that the fasting and nonfasting data were collected from different individuals, not from the same source. Finally patient diet was unknown.  

**Langsted et al**  
This was a combined cross-sectional and prospective cohort study designed to evaluate the predictive power of fasting versus nonfasting lipid, lipoproteins, and apolipoproteins in relation to cardiovascular risk in the setting of normal food intake. Fasting was defined for both studies as >8 hours since last meal, and both populations were further divided into 1 hour intervals between the last meal and the blood draw (0-1 hour up to >8 hours).  

The cross-sectional study population was pulled from the Copenhagen General Population Study and contained 33,391 individuals, 795 of whom were fasting. The population was further divided into 5-year age groups from 20 to ≥80 years old. Exclusion criteria for the cross-sectional study included statistical outliers for the study variables (±3 SD from the mean).
The prospective cohort study population was pulled from the Copenhagen City Heart Study and contained 9319 individuals, all of whom were nonfasting. Primary study outcomes were ischemic cardiovascular event (fatal or nonfatal, ischemic stroke or the study’s conclusion in July 2007). This information was collected from hospital records and government death records. Follow up was 14 years and all participants were nonfasting. In that time there were 1166 cardiovascular events. Exclusion criteria for the prospective cohort study stipulated that the participants must have been free of ischemic CVD at baseline. The study used tertiles (lower tertile, middle tertile, and higher tertile) to analyzed total cholesterol, non-HDL cholesterol, LDL-C, apolipoprotein A1, apolipoprotein B, triglycerides, total cholesterol/HDL-C, and apolipoprotein B/apolipoprotein a1.4

Statistical analysis was performed using STATA v9.2. In the cross-sectional study testing adjustment was performed using general linear models to account for age, sex and other covariates that might influence cholesterol. Comparisons were done using the Bonferroni method. In the prospective-cohort study Cox proportional-hazards regression models were generated. Hazard ratios were generated using two models, model 1 adjusted for age, blood pressure, smoking, use of lipid-lowering drugs, and use of HRT; Model 2 did not adjust for these. Both were adjust for regression dilution bias.4

In the cross-sectional study it was found that cholesterol levels changed minimally after food intake, and nonfasting lipid measurements did predict increased risk of cardiovascular events when elevated. It was also concluded that nonfasting triglycerides might be as efficacious as fasting triglycerides for predicting cardiovascular events. The prospective cohort study demonstrated that elevated nonfasting lipid levels were associated with increased rates of cardiovascular events. Hazard ratios for nonfasting LDL-C were: lower tertile model 1 and model 2 HR 1 (reference). Middle tertile model 1 HR 1.4 (95% CI, 0.9-2.1) and model 2 HR 1.6 (95% CI, 1.0-2.4), P<0.001. Higher tertile model 1 HR 2.1 (95% CI, 1.4-3.1) and model 2 HR 2.2 (95% CI, 1.5-3.5), P<0.001. Finally the study evaluated the use of nonfasting triglycerides to calculate LDL-C using the Friedewald equation was still appropriate if adjustment was made for hemodilution.4
Study limitations as described by the authors were that serial fasting lipid measurements were not performed, that there was a relatively small number of participants who were fasting in the cross-sectional study, that there was a lack of information relating to what the participants had eaten, that the participants self-reported time since last meal, that the cross-sectional study participants and the prospective cohort participants were drawn from studies that were conducted a decade apart from each other, finally the study was comprised of mostly white, Danish individuals.  

Mora et al

This was a prospective cohort study designed to evaluate the predictive power of fasting versus nonfasting lipid and apolipoprotein measurements in relation to cardiovascular disease. The study sample was derived from participants in the Women’s Health Study (a randomized, double-blinded, placebo controlled clinical trial of low-dose aspirin and vitamin E as primary prevention for CVD and cancer) and totaled 26 330 acceptable participants, 19 983 were fasting and 6347 were nonfasting; all were female. The primary outcome of interest was cardiovascular events including nonfatal myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, nonfatal stroke, or cardiovascular death. Potential participants were eliminated if the time since last meal was missing from their initial intake questionnaire. Fasting was defined as ≥8 hours since last meal at the time of blood draw. The study population was further subdivided into groups based on 2-hour time intervals between meals from <2 hours up to ≥16 hours. Homogeneity was compared and it was found that the nonfasting women were slightly younger with marginally fewer incidences of hypertension but higher incidences of diabetes. STATA v8.2 was used to compare the fasting and nonfasting groups, with Student t tests, Kruskal-Wallis, and χ2 tests generated to evaluate means, medians, and categorical variables. Hazard ratios (HR) were calculated using Cox proportional hazard regression models.
Median follow up was 11.4 years, with participants submitting questionnaires every 6 or 12 months. In that time 754 of the 19,983 fasting women and 207 of the 6,347 nonfasting women experienced a first CVD event.  

The study found that while fasting versus nonfasting lipid measurements were similar (nonfasting results were ~1%-5% lower), the predictive value of fasting total cholesterol and LDL-C cholesterol was greater than that of nonfasting values. Triglycerides were ~15% higher in the nonfasting group. Fasting total cholesterol HR 1.22 (95% CI, 1.14-1.30) P<0.001 and LDL-C HR 1.21 (95% CI, 1.13-1.29), P<0.001. Nonfasting total cholesterol HR 1.07 (95% CI, 0.93-1.21) P=0.35 and LDL-C HR 1.00 (95% CI, 0.87-1.15), P=1.0. Interaction between fasting versus nonfasting LDL-C with regards to CVD event prediction was calculated at: P_{interaction} =0.03. The study also evaluated the predictive value of apolipoprotein B-100 levels in fasting versus nonfasting states, and the results were similar to that of LDL-C. The study evaluated fasting versus nonfasting associations between HDL-C, apolipoprotein A-1, and total/HDL-C and CVD events and found that these measurements were of equal predictive strength between both groups. Of note, fasting and nonfasting triglycerides were associated with increased CVD event after adjustment for total cholesterol and HDL-C. Lastly the study evaluated the influence on postmenopausal hormones, with the results resembling those in the larger data set.  

Study limitations as described by the authors included the time since last meal being self reported, the fact that fasting and nonfasting measurements were not taken from the same individuals, the results not being corrected for potential regression dilution bias, and that the data set contained only females, many of whom were white and healthy.  

**DISCUSSION**

The fasting requirement placed upon patients is a potentially disruptive practice; moreover patients are liable to forget or be noncompliant with the fasting order. It is also a requirement that deviates from the homeostatic state – one in which the patient is at most several hours from their last meal and has not been fasting. This systematic review sought to
understand the necessity of fasting by determining the ability of nonfasting LDL-C to predict cardiovascular events.

The Doran et al study\textsuperscript{7} specifically looked at the influence of fasting versus nonfasting on LDL-C with regards to predicting all cause mortality and cardiovascular events and found that for both nonfasting was of similar prognostic value. In the matched cohort both fasting and nonfasting C statistics were 0.62 (95% CI, 0.60-0.66), P=0.96. This suggests that either measurement has a positive predictive value. In the unmatched cohort there was a similar finding regarding C statistic. Furthermore, both the unmatched and matched cohorts demonstrated through hazard ratios an increasing risk of cardiovascular mortality with increasing LDL-C, regardless of fasting status. Lastly the $P_{interaction} = 0.34$ signals that there is little interaction between fasting status and cardiovascular risk prediction ability.

This prognostic value was also supported by Langsted et al\textsuperscript{4} who sought to identify what influence fasting versus nonfasting had upon lipid levels and whether nonfasting lipid measurement could predict cardiovascular events. Regarding fasting status and lipid levels it was found that there was minimal change in lipid levels with increasing time since last meal. Nonfasting lipid measurements were found to predict cardiovascular events with hazard ratios for the higher tertile models reaching HR 2.1 (95% CI, 1.4-3.1) and HR 2.2 (95% CI, 1.5-3.5), $P<0.001$ for models 1 and 2.

However, Mora et al\textsuperscript{8} demonstrated different results. They evaluated the cardiovascular event predictive power of fasting versus nonfasting lipids in women and found that nonfasting measurements predicted a lower risk of cardiovascular event. The fasting LDL-C hazard ratio was 1.21 (95% CI, 1.13-1.29), $P<0.001$ while the nonfasting LDL-C hazard ratio was 1.00 (95% CI, 0.87-1.15), $P=1.0$, suggesting that a nonfasting LDL-C level is not useful in predicting cardiovascular events. Furthermore, $P_{interaction} = 0.03$ between nonfasting LDL-C and cardiovascular events is statistically significant, voiding the hypothesis that nonfasting LDL-C measurements can be used to predict cardiovascular events.

In regards to the question posed by this systematic review both the Doran et al and Langsted et al\textsuperscript{4,7} studies agreed that nonfasting lipid values were of predictive value with
regards to cardiovascular events. The Doran et al study\textsuperscript{7} was particularly clear, because of strong methodology, in demonstrating that nonfasting LDL-C values were of similar prognostic value to fasting LDL-C values. The study went on to suggest that guidelines be updated or modified to reflect this reality as doing so might improve patient outcomes. The Langsted et al article\textsuperscript{4} was limited in its presentation of data and the lack of a fasting comparison group in the prospective cohort study limits the usefulness of the conclusion put forth, that nonfasting LDL-C values are of prognostic value. Conversely, Mora et al\textsuperscript{8} concluded that LDL-C was not of predictive value and should not be used. This is of interest because it deviates from the findings of the other two studies. Of the three the Doran et al is most clear in its support of the use of nonfasting lipid measurement as an acceptable practice.\textsuperscript{7}

All three studies\textsuperscript{4,7,8} were assessed with GRADE. Given that they were observational type studies they each began with a quality appraisal of low. Doran et al\textsuperscript{7} was found to be of sufficient quality to keep its initial appraisal. Langsted et al\textsuperscript{4} was downgraded to very low quality due to indirectness, specifically due to a lack of head-to-head comparison between fasting and nonfasting lipid measurements in the prospective cohort study and because the sample population was limited to whites of Danish descent. Mora et al\textsuperscript{8} was downgraded to very low quality due to indirectness, specifically because the study was limited primarily to white, otherwise healthy, professional women. Further research into this topic should center on the use of blind comparison between fasting and nonfasting LDL-C levels that uses serial lipid and triglyceride measurements of the same patients.

**CONCLUSION**

Nonfasting lipid measurement produces useable values from both an all-cause mortality and cardiovascular event prediction standpoint. Nonfasting LDL-C levels, when elevated, correlated with an increase in cardiovascular events and have similar predictive power to fasting measurements. Because TC and HDL-C levels do not deviate significantly between fasting and nonfasting states it is reasonable to use these values to calculate 10-year
cardiovascular disease risk. Thus requiring the patient to fast before phlebotomy for lipid measurement is an unnecessary practice.
References


http://dx.doi.org/10.1016/j.jacc.2013.11.002.


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<sup>a</sup> Population limited to whites of Danish decent. Prospective Cohort only examined nonfasting participants.

<sup>b</sup> Population limited to mostly white, otherwise healthy, professional women.