LDL Cholesterol as a Predictor of Mortality, and Beyond:

To Fast or Not to Fast, That is the Question?

Running title: *Eckel et al.; Non-Fasting or Fasting LDL Cholesterol & Mortality*

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The ‘necessity’ of a fasting lipid panel for assessment of atherosclerotic cardiovascular disease (ASCVD) risk has been assumed now for decades. The rationale for this position has been the estimation of levels of low density lipoprotein cholesterol (LDL-C), a major risk factor for ASCVD, by correcting for non-fasting changes in plasma triglycerides using the so-called Friedewald equation developed during the 1960s at the then National Heart Institute. Because LDL-C determination by ultracentrifugation is time consuming and expensive and direct LDL-C measurements have proven no more accurate than the Friedewald equation, the calculation of LDL-C has remained more than adequate, and was recently endorsed by the 2013 ACC/AHA Risk Assessment Work Group and utilized in the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Disease Risk in Adults. The equation estimates LDL-C after measuring total cholesterol, high density cholesterol (HDL-C) and triglycerides (TG), and then subtracting from the total cholesterol concentration the HDL-C plus very low density lipoprotein cholesterol (VLDL-C) which is estimated by TG/5. This formula is not used when plasma TG >400 mg/dL because in this metabolic setting VLDL particles contain relatively less cholesterol and VLDL-C contribution is therefore overestimated and the calculated LDL-C is falsely low.

The scientific rationale for addressing the importance of fasting vs. non-fasting is that food consumption results in variable increases in plasma TG. Here the effect is not only that of dietary fat but also carbohydrate. Carbohydrate intake increases VLDL TG secretion within 30-90 minutes after ingestion whereas fat intake in normotriglyceridemic people increases plasma TG via chylomicron assembly and secretion from the small intestine over an interval up to 8 hours. Moreover, even without eating fasting triglycerides are subject to substantial biological variability, e.g. up to 30%.
This ‘necessity’ of fasting to estimate LDL-C risk for all cause mortality and CVD mortality has now been challenged by Doran et al in this issue of Circulation\textsuperscript{5}. Their report provides convincing evidence over a long interval of 14 years in middle-aged USA men and women that non-fasting vs. fasting LDL-C values provide equal predictability for all cause mortality and CVD mortality (ASCVD + congestive heart failure). Of course congestive heart failure (CHF) has other etiologies than coronary heart disease and it would have been instructive if analyses excluding subjects with CHF would have been included in the manuscript. To accomplish this the authors used propensity score matching to accrue fasting and non-fasting cohorts of 4299 individuals each with similar baseline characteristics from 20,024 NHANES-III (1988-1994) participants. Important to note is that these were two different populations, a necessary limitation in this type of epidemiological inquiry. In these cohorts smoking was identified in >50\% of both groups reflecting the historic nature of these data, and in part the relatively high number of deaths.

The definition of fasting vs. non-fasting placed at 8 hours was somewhat arbitrary, but defended by the authors as a definition used in previous analyses. For patients with normal fasting triglycerides, i.e. <150 mg/dL, this may be acceptable but is less so in patients with fasting hypertriglyceridemia. Although subjects included in these cohorts had fasting TG <400 mg/dL, wherein fasting chylomicronemia should be absent, in patients with moderate fasting hypertriglyceridemia, e.g. 150-400 mg/dL, postprandial TG excursion may not return to pre-meal levels by up to 12 hours\textsuperscript{6,7}. This concern, however, was in part addressed by also examining the impact of the calculated LDL-C on all cause mortality and CVD mortality by variable intervals of fasting, i.e. from <4 vs. > 4 hours and <12 vs. >12 hours, and finding similar predictability. In addition, even in the unmatched cohort the C-statistics of TG levels in fasting vs. non-fasting
groups were essentially equal for predicting the relationship between LDL-C and all-cause and CVD mortality.

The practical application of these analyses is substantial including convenience for patients, and in particular for those with diabetes on pharmaceuticals that can cause hypoglycemia including insulin, sulfonylureas and glinides. Moreover, for years there has been substantial support for the concept that the fed state is a better predictor of ASCVD than the fasted condition 8. This effect may be a consequence of triglycerides themselves or more cholesterol-enriched chylomicron remnants that are downstream of TG-rich lipoprotein metabolism by lipoprotein lipase 9. Of interest, upon examining the 2nd tertile of LDL-C in the two cohorts, in whom the fasting and non-fasting levels of LDL-C were almost identical, ~100-130 mg/dL, the hazard ratio for all cause mortality for fasting was 1.61 (1.25-2.08, 95%CI) and highly significant (p<0.001) whereas the ratio was 1.21 (0.92-1.60) with a p=0.17 for the non-fasting group. If anything this trend would suggest the opposite i.e. that in this tertile the fasting level may be more revealing. An extension of this consideration is the perceived importance of fasting levels of TG and their relationship to ASCVD. Despite substantial evidence to support this claim, at present there is no convincing evidence from clinical trials that lowering TG independent of lowering LDL-C reduces ASCVD events and/or all cause mortality or death from CVD 10.

The fasting vs. non-fasting TG level, however, raises an important inquiry about additional analyses that may prove useful from the same NHANES-III data set. What about non-HDL-C or even apo B; would fasting and non-fasting values be equally predictive of either all cause and/or CVD mortality? What about other outcomes? Everyone is concerned about death as the ultimate sequel but would fasting vs. non-fasting LDL-C impact other CVD events
differentially such as acute coronary syndromes with or without acute myocardial infarction, congestive heart failure, transient ischemic attacks or cerebrovascular accidents? In the general population living in Copenhagen, Nordesgaard et al demonstrated the relationship between non-fasting TG and myocardial infarction and death in men and women over intervals up to 31 years (11,12); however, comparisons between fasting and non-fasting TG or LDL-C were not made. When fasting and non-fasting status was compared in healthy women in the Women’s Health Study, only non-fasting TG levels showed independent effects on incident CVD events over an average interval of 11.4 years (13). The level of calculated LDL-C as a confounder apparently failed to influence this non-fasting TG effect.

So where does that leave us? The 2013 ACC/AHA Cholesterol Guideline (3) does in fact claim that a fasting lipid panel is preferred and should be implemented in a manner consistent with previous lipid recommendations in the Third Report of the National Cholesterol Education Program (14), i.e. after a 12 hour fast. Of course this recommendation was based on only coronary heart disease events, not all cause or CVD mortality. According to the 2013 AC/AHA Cholesterol Guideline, when a non-fasting lipid panel reveals a non-HDL-C ≥220 mg/dL, a genetic form of hypercholesterolemia is likely and/or a secondary etiology present that requires further evaluation. A fasting lipid panel is strongly encouraged here. Even if a non-fasting sample is obtained the newly developed risk estimator utilizes total cholesterol and HDL-C to approximate the 10 year risk for a CVD event (http://tools.cardiosource.org/ASCVD-Risk-Estimator/) and should be equally as applicable as a fasting value. Other consideration is patients with more severe hypertriglyceridemia who may be at risk for acute pancreatitis, a potentially life-threatening event. In fact in this NHANES-III population 2.2% had non-fasting TG >400 mg/dL, and some of these participants may have had TG levels >1000 mg/dL.
At this time the practicality of non-fasting favors this approach and it may be time to make a change. However, in anticipation of more frequent updates of the 2013 ACC/AHA Cholesterol Guideline, perhaps new evidence will accumulate to consider that an 8 or 12 hour fast is no longer needed to assess the relationship between plasma lipids and all cause and/or CVD mortality, but also ASCVD risk. Until then, let the 12 hour fast recommendation remain.

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**References:**


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