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Cholesterol Insights and Controversies from the UK Biobank Study::

Three Take-home Messages for the Busy Clinician

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The UK Biobank is a large prospective study that was recently established to examine genetic and lifestyle risk factors for a variety of chronic diseases affecting middle aged and older individuals living in the UK.[1] Between 2006 and 2010, >9 million individuals aged 40–69 years who were registered in the UK National Health Service and lived within 25 miles of one of the 22 assessment centers in England, Wales, and Scotland, were invited to enter the UK Biobank study. A total of 5.5% (approximately 500,000) volunteers consented and were enrolled into the UK Biobank study after answering baseline questionnaires, completing physical examinations, and providing baseline blood and other specimens.[1] Participants are followed prospectively for incident events through linkage to the electronic health care record. While population-based, the UK Biobank study is not representative of the general UK population, as it enrolled healthier volunteers who were older, more likely to be women, white (95%), and have higher socioeconomic status, and less likely to have prevalent cardiovascular disease (CVD) or cardiovascular risk factors (e.g. lower rates of smoking, lower body mass index [BMI]) compared with the general UK population of the same age. Indeed, age-adjusted all-cause mortality rates over 6 year follow up in the UK Biobank are about half those seen in the general UK population.[1]

In the current study conducted among the UK Biobank study population,[2] Welsh et al examined the associations of standard lipids (total, LDL, HDL, non-HDL cholesterol) and compared them with apolipoproteins (apo) B and A in relation to incident cardiovascular

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disease. In the primary prevention subset of the UK Biobank (i.e. those with no self reported prior CVD and not taking statin therapy), the authors found the expected associations of higher atherosclerotic CVD (ASCVD) risk with higher baseline levels of LDL cholesterol, non-HDL cholesterol, or apoB, which were mostly comparable in magnitude to each other, and similar to the associations with ASCVD risk that prior studies had found. Furthermore, the results confirm results from prior studies in the US such as the Framingham study,[3] the Women's Health Study,[4] or the international individual participant-level meta-analysis results from the Emerging Risk Factor Collaboration,[5] all of which did not show substantial improvement in risk prediction with apoB or apoA compared with standard lipids for overall CVD risk prediction.

The study by Welsh et al in this issue of *Circulation*[2] also provides several important insights. First, should clinicians measure apoB, if overall risk prediction is similar for apoB compared with the standard lipids, in particular total and HDL cholesterol? Clinically useful biomarkers are ones that change patient management through more accurate classification of risk. From a clinical standpoint, the clinician who is seeing a patient in the office wants to know "What is the chance that *my* patient will develop ASCVD in the future?" Ideally, clinicians desire an assessment of the patient's chance of developing ASCVD that matches the observed outcome for that patient during follow-up. In order to assess whether two tests are clinically equivalent, they should be examined in the subgroup of patients in whom the test results disagree. Since apoB and LDL cholesterol (or non-HDL cholesterol) are highly correlated, the two tests will agree in most individuals. However, when the tests disagree in the information they provide, which test is more precise?[6] This "discordance" analysis is in line with precision approaches that evaluate biomarker results for each individual, instead of relying on the overall population results that are mostly driven by the majority of individuals in whom the two tests agree, and not by the smaller proportion of patients in whom the tests disagree.

In this regard, the current UK Biobank study adds to our understanding, as the authors also provide those results. For a majority of patients, measurement of traditional lipids should suffice. Among the subset of 63,520 UK Biobank participants who were "discordant" (>10% absolute percentile difference with respect to apoB and LDL cholesterol), only apoB was associated with increased CVD risk (adjusted hazard ratio per SD, 1.23 [1.12–1.35], $p<0.001$) while no increased CVD risk was noted for directly measured LDL cholesterol (adjusted hazard ratio [HR] 1.00, [0.91–1.10], $p=0.97$) or for calculated LDL cholesterol (adjusted HR 1.00, [0.91 – 1.09], $p=0.94$). Likewise, among these "discordant" individuals, non-HDL cholesterol was also not associated with increased CVD risk (adjusted HR 1.08 [0.98–1.18], $p=0.11$), although, discordance was not defined between non-HDL cholesterol and apoB but rather, between LDL cholesterol and apoB. This discordant subset of participants represented ~15% of the UK Biobank study population, which is a relatively healthier population compared with the general UK population. In other study populations, the proportion of individuals with discordant apoB and LDL cholesterol test results has been noted to be at least one quarter of the general population, with greater prevalence noted among populations enriched with cardiometabolic risk factors such as obesity, metabolic syndrome, and diabetes.

Nonetheless, disagreement is post-hoc information. Hence, the question remains as to which patients should also undergo apoB testing beyond the standard lipid profile? The recently published 2018 AHA/ACC Multisociety guideline on the management of blood cholesterol also lists elevated apoB levels (if measured) as a "risk- enhancing factor."[7] Presence of one or more risk enhancing factors (including apoB) can tip the balance towards earlier initiation of statin therapy in intermediate-risk adults after calculation of 10-year ASCVD risk using Pooled Cohort risk equations. We can also take guidance from a recent consensus statement from the European Atherosclerosis Society and the European Federation of Clinical Chemistry and Laboratory Medicine,[8] which recommended that when the LDL cholesterol goal is achieved, then apoB and non-HDL cholesterol are preferred as secondary treatment targets in patients with triglycerides >175 mg/dL, obesity, metabolic syndrome, or diabetes. The first take-home message from the UK Biobank study therefore is that for most "healthy" individuals, lipid related ASCVD risk can be assessed from standard lipid profile; but that there is a smaller subset of individuals for whom apoB testing will further refine ASCVD risk assessment.

A second important take-home message from the current UK Biobank study is that nonfasting lipids are adequate for assessing lipid-related CVD risk. The current study was conducted using nonfasting blood samples, nearly doubling the total number of participants from prior studies that examined nonfasting lipids. Importantly, risk associations with CVD in the UK Biobank were similar to those previously noted from other studies using fasting or nonfasting lipids. The results are consistent with a recent individual-level analysis from the ASCOT-LLA study that compared nonfasting and fasting lipids and apolipoproteins measured among the same participants 4 weeks apart, and found similar associations with ASCVD risk for fasting or nonfasting tests.[9] Hence, for the busy clinician, the second take-home message is that fasting is not necessary when assessing lipid-related ASCVD risk as also noted in the 2018 AHA/ACC Multisociety guideline on the management of blood cholesterol.[7]

Third, should clinicians measure direct LDL cholesterol instead of relying on the calculated LDL cholesterol? Here, the UK Biobank study provides a large study assessing directly measured LDL cholesterol (using a direct homogeneous Beckman assay). Most prior epidemiological studies used the Friedewald equation to calculate LDL cholesterol, and ultracentrifugation or precipitation methods to measure HDL. The current UK Biobank study used direct homogenous assays to measure direct LDL cholesterol, direct HDL cholesterol, total cholesterol and apoB. These assays do not require ultracentrifugation or precipitation. While apoB assays are standardized, there is significant variability in direct LDL cholesterol or HDL cholesterol assays that are in clinical use.[8] The third take-home message from the UK Biobank is that direct measurement of LDL cholesterol does not provide additional CVD risk information beyond calculated LDL cholesterol or calculated non-HDL cholesterol.

In sum, the current study by Welsh et al from the UK Biobank confirms prior findings albeit with a larger sample size, that among healthier populations with lower prevalence of cardiovascular risk factors, standard lipid testing, in particular calculating non-HDL cholesterol, is clinically useful. It also reminds us that for patients with multiple

cardiometabolic risk factors, apoB testing captures ASCVD risk information that may not be captured by LDL cholesterol nor by non-HDL cholesterol. Finally, forget fasting prior to ordering that lipid test in the next primary prevention patient you see for ASCVD risk assessment.

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