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EDITORIAL

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 United Kingdom.[1] Between 2006 and 2010, >9 million individuals 40 to 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% (≈500 000) volunteers consented and were enrolled in the UK Biobank study after answering baseline questionnaires, completing physical examinations, and providing baseline blood and other specimens.[1] Participants are followed up prospectively for incident events through linkage to the electronic health care record. Although population based, the UK Biobank study is not representative of the general UK population in that it enrolled healthier volunteers who were older and were more likely to be women and white (95%), more likely to have a higher socioeconomic status, and less likely to have prevalent cardiovascular disease (CVD) or cardiovascular risk factors (eg, lower rates of smoking, lower body mass index) compared with the general UK population of the same age. Indeed, age-adjusted all-cause mortality rates over the 6-year follow-up in the UK Biobank are about half those seen in the general UK population.[1]

In the present study conducted among the UK Biobank study population, Welsh et al[2] examined the associations of standard lipids (total, low-density lipoprotein [LDL], high-density lipoprotein [HDL], non-HDL cholesterol) and compared them with apolipoprotein (apo) B and A in relation to incident CVD. In the primary prevention subset of the UK Biobank (ie, those with no self reported previous 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 apo B, which were mostly comparable in magnitude to each other and similar to the associations with ASCVD risk that previous studies had found. Furthermore, the results confirm results from previous studies in the United States such as the Framingham study,[3] the Women's Health Study,[4] and 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 apo B or apo A compared with standard lipids for overall CVD risk prediction.

The study by Welsh et al[2] in this issue of *Circulation* also provides several important insights. First, should clinicians measure apo B if overall risk prediction is similar for apo B 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

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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. To assess whether 2 tests are clinically equivalent, they should be examined in the subgroup of patients in whom the test results disagree. Because apo B and LDL cholesterol (or non-HDL cholesterol) are highly correlated, the 2 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 driven mostly by the majority of individuals in whom the 2 tests agree, not by the smaller proportion of patients in whom the tests disagree.

In this regard, the current UK Biobank study adds to our understanding, because 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 apo B and LDL cholesterol), only apo B was associated with increased CVD risk (adjusted hazard ratio per SD, 1.23 [95% CI, 1.12–1.35]; $P<0.001$), whereas no increased CVD risk was noted for directly measured LDL cholesterol (adjusted hazard ratio, 1.00 [95% CI, 0.91–1.10]; $P=0.97$) or for calculated LDL cholesterol (adjusted hazard ratio, 1.00 [95% CI, 0.91 – 1.09]; $P=0.94$). Likewise, among these discordant individuals, non-HDL cholesterol also was not associated with increased CVD risk (adjusted hazard ratio, 1.08 [95% CI, 0.98–1.18]; $P=0.11$), although discordance was not defined between non-HDL cholesterol and apo B but rather between LDL cholesterol and apo B. 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 apo B 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 mellitus.

Nonetheless, disagreement is post hoc information. Hence, the question remains as to which patients should also undergo apo B testing beyond the standard lipid profile. The recently published 2018 American Heart Association/American College of Cardiology multisociety guideline on the management of blood cholesterol also lists elevated apo B levels (if measured) as a "risk-enhancing factor."[7] Presence of ≥1 risk-enhancing factors (including apo B) can tip the balance toward earlier initiation of statin therapy in intermediate-risk adults after calculation of 10-year ASCVD risk with the 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 apo B and non-HDL cholesterol are preferred as secondary treatment targets in patients with triglycerides >175 mg/dL, obesity, metabolic syndrome, or diabetes mellitus. 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 there is a smaller subset of individuals for whom apo B 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 present study was conducted with nonfasting blood samples, nearly doubling the total number of participants from previous studies that examined nonfasting lipids. 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 (Anglo-Scandinavian Cardiac Outcomes Trial) 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 American Heart Association/American College of Cardiology 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 previous epidemiological studies used the Friedewald equation to calculate LDL cholesterol and ultracentrifugation or precipitation methods to measure HDL. The present UK Biobank study used direct homogeneous assays to measure direct LDL cholesterol, direct HDL cholesterol, total cholesterol, and apo B. These assays do not require ultracentrifugation or precipitation. Although apo B assays are standardized, there is significant variability in the direct LDL cholesterol or HDL cholesterol assays 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 study by Welsh et al from the UK Biobank confirms previous 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, apo B testing captures ASCVD risk information that may not be captured by LDL cholesterol or by non-HDL cholesterol. Finally, we can forget fasting before ordering the lipid test in the next primary prevention patient we see for ASCVD risk assessment.

ARTICLE INFORMATION

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REFERENCES

1. Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, Collins R, Allen NE. Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. *Am J Epidemiol*. 2017;186:1026–1034. doi: 10.1093/aje/kwx246
2. Welsh C, Celis-Morales CA, Brown R, Mackay DF, Lewsey J, Mark PB, Gray SR, Ferguson LD, Anderson JJ, Lyall DM, et al. Comparison of conventional lipoprotein tests and apolipoproteins in the prediction of cardiovascular disease: data from UK Biobank. *Circulation*. 2019;140:542–552. doi: 10.1161/CIRCULATIONAHA.119.041149
3. Ingelsson E, Schaefer EJ, Contois JH, McNamara JR, Sullivan L, Keyes MJ, Pencina MJ, Schoonmaker C, Wilson PW, D'Agostino RB, et al. Clinical utility of different lipid measures for prediction of coronary heart disease in men and women. *JAMA*. 2007;298:776–785. doi: 10.1001/jama.298.7.776
4. Mora S, Otvos JD, Rifai N, Rosenson RS, Buring JE, Ridker PM. Lipoprotein particle profiles by nuclear magnetic resonance compared with standard lipids and apolipoproteins in predicting incident cardiovascular disease in women. *Circulation*. 2009;119:931–939. doi: 10.1161/CIRCULATIONAHA.108.816181.
5. Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, Thompson A, Wood AM, Lewington S, Sattar N, Packard CJ, et al; Emerging Risk Factors Collaboration. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA*. 2009;302:1993–2000. doi: 10.1001/jama.2009.1619
6. Glasziou P, Irwig L, Deeks JJ. When should a new test become the current reference standard? *Ann Intern Med*. 2008;149:816–822. doi: 10.7326/0003-4819-149-11-200812020-00009
7. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139:e1082–e1143. doi: 10.1161/CIR.0000000000000625
8. Langlois MR, Chapman MJ, Cobbaert C, Mora S, Remaley AT, Ros E, Watts GF, Borén J, Baum H, Bruckert E, et al; European Atherosclerosis Society (EAS) and the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) Joint Consensus Initiative. Quantifying atherogenic lipoproteins: current and future challenges in the era of personalized medicine and very low concentrations of LDL cholesterol: a consensus statement from EAS and EFLM. *Clin Chem*. 2018;64:1006–1033. doi: 10.1373/clinchem.2018.287037
9. Mora S, Chang CL, Moorthy MV, Sever PS. Association of nonfasting vs fasting lipid levels with risk of major coronary events in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm. *JAMA Intern Med*. 2019. doi: 10.1001/jamainternmed.2019.0392