ARIC Manuscript Proposal # 3095

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1.a. Full Title: Use of secondary lipid targets in high and very high-risk individuals with on-target low-density lipoprotein cholesterol: The Atherosclerosis Risk in Communities (ARIC) study

b. Abbreviated Title (Length 26 characters): Secondary apoB and non-HDL-C targets

2. Writing Group:

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3. Timeline:
We aim to submit this abstract to the American Society for Preventive Cardiology 2018, for which we are aiming to submit an abstract to the ARIC publications committee within the next 3 months, and the subsequent manuscript within the following 6 months.

4. Rationale:
Low-density lipoprotein-cholesterol (LDL-C) currently is the cornerstone for guiding strategies to reduce cardiovascular risk, and directs guideline-recommended decisions regarding lipid-lowering therapy. Recent major guidelines, including the National Lipid Association (NLA)[1] and European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) Dyslipidemia Guidelines[2] supported LDL-C targets for very-high and high-risk patients, such as <70 and <100 mg/dL, respectively.

However, residual cardiovascular risk has been shown to remain significantly elevated after adequate attainment of LDL-C targets, which can be explained by underestimation of non-LDL-C cholesterol-related risk. For instance, the concentration of cholesterol in other key atherogenic lipoproteins, such as very low-density lipoprotein (VLDL-C),[3] is particularly elevated among individuals at high cardiovascular risk (i.e. diabetics or those with elevated triglyceride levels),[4, 5] and is not included in calculated LDL-C levels. On the other hand, apolipoprotein B (apoB) and non-high-density lipoprotein cholesterol (non-HDL-C), are more comprehensive measures of atherogenic lipoproteins and cholesterol since they include non-LDL lipoprotein particles. As such, both have been shown to be better associated with CVD outcomes compared to LDL-C.[6-9]

The advantages of apoB and non-HDL-C over LDL-C in terms of risk prediction and patient management are especially relevant in the presence of inter-parameter discordance, such as when LDL-C levels are low or below target levels but non-HDL-C or apoB are above target. These scenarios may particularly reflect elevated levels of atherogenic lipoprotein particles other than LDL that are accounted in non-HDL-C and apoB. Since significant discordance between LDL-C levels vs. non-HDL-C and apoB levels has been previously described,[10-12] using these parameters as secondary targets in the management of very high- and high-risk patients, where risk reduction should be maximized, may help lower residual risk.

Additionally, inaccuracy of LDL-C estimation using the Friedewald equation (LDLf-C) can contribute to observed residual risk. We have previously shown significant inaccuracy of the Friedewald equation, mostly characterized by underestimation at low LDL-C levels,[13, 14] which may contribute to residual risk by further decreasing LDL-C predictive power. However, we noticed that such inaccuracy improves dramatically after using a novel estimation method.[13] Similar to the Friedewald equation, our novel method (LDLn-C)[15] is derived from the standard lipid profile. Conversely, it uses adjustable triglyceride to very low-density lipoprotein-cholesterol (TG:VLDL-C) ratios rather than the fixed ratio of 5 used in the Friedewald equation.[15] Its accuracy has been externally validated[16] and many national labs have endorsed its use in their lab reports. We hypothesize that using the novel method of LDL-C estimation may reduce the

proportion of discordance between LDL-C and other parameters such as apoB and non-HDL-C, thus decreasing the utility of these secondary targets in residual risk management.

Finally, it has been shown that many patients who attained both LDL-C and non-HDL-C targets did not achieve correspondingly low population-equivalent apoB.[17] We hypothesize that the currently recommended apoB secondary targets in guidelines may be set too high. If apoB were to be implemented as a secondary target, using population-equivalent targets would help identify a greater proportion of individuals that may benefit from intensification of lipid-lowering therapy.

5. Main Hypothesis/Study Questions:

Aims:
1) To identify the proportion of very high- and high-risk adults with LDL-C below guideline target levels and discordantly high non-HDL-C or apoB (above guideline target levels). Additionally, we will identify the proportion of these individuals meeting dual targets (LDL-C and non-HDL-C below guideline cutpoints) and discordantly high apoB (above guideline cutpoints).

2) To determine the increased predictive risk of ASCVD and mortality in very high- and high-risk individuals with LDL-C levels below guideline target levels but discordantly high non-HDL-C or apoB levels (above guideline cutpoints) compared to those with concordantly low levels. Additionally, we will determine increased risk of ASCVD and mortality for those individuals who meet dual targets (LDL-C and non-HDL-C below guideline cutpoints) but discordantly high apoB (above guideline cutpoints) compared to those with concordantly low levels.

3) To determine the increased risk of ASCVD and mortality in very high- and high-risk individuals with LDL-C levels below guideline target levels but discordantly high non-HDL-C or apoB levels (above percentile-equivalents) compared to those with concordantly low levels. Additionally, we will determine increased risk of ASCVD and mortality for those individuals who meet dual targets (LDL-C and non-HDL-C below guideline cutpoints) but discordantly high apoB (above percentile-equivalents) compared to those with concordantly low levels.

4) To determine if increased risk of ASCVD and mortality in very high- and high-risk individuals by using secondary targets, non-HDL-C and apoB (both guideline cutpoints and percentile-equivalent) is reduced when using LDL-C estimated by our novel method compared to Friedewald equation.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Study design: The present study will have two components: 1) cross-sectional and 2) prospective.

In the cross-sectional analysis, we will determine the proportion of adults at high- and very high-cardiovascular risk (defined below) with LDL-C and non-HDL-C levels below guideline-recommended cutpoint (<100 mg/dL and <130 mg/dL, respectively) and discordantly high apoB levels above guideline-recommended cutpoints (90 mg/dL as per NLA and 100 mg/dL as per ESC), where intensifying therapy may have implications for residual risk reduction. For this analysis, we will include individuals from ARIC who had apoB measures from the 4th visit.

In the prospective analysis, we will assess the actual risk of hard outcomes (cardiovascular diseases and mortality) of attaining dual targets (non-HDL-C and/or apoB over LDL-C) compared to those who did not. For this analysis, the baseline population will also be individuals from ARIC who had apoB measures from 4th visit who were followed-up until December 31, 2012 (or most recent follow-up available). We will use a time-fixed analysis approach.

Exposures: The exposure of interest will be the LDL-C, estimated using the Friedewald equation (calculated as TC minus HDL-C minus triglycerides/5 at triglycerides <400 mg/dl) and our novel method (using an adjustable TG:VLDL-C ratio). Non-HDL-C will be calculated as TC minus HDL-C. ApoB will be obtained from visit 4, and percentile-equivalent will be obtained using cross-sectional data from National Health and Nutrition Examination Survey (NHANES) 2011-2012. LDL-C, non-HDL-C and apoB will be included in the analysis as time-fixes covariates.

We created the very high- and high-risk categories using the NLA and ESC/EAS guidelines. Description of each category as well as the targets to be used is in **Table 1** below:

Table 1. Very high- and high-risk individuals

	High Risk	**Very High Risk**

National Lipid Association	• ≥3 major ASCVD risk factors
	• Diabetes mellitus (type 1 or 2) and:
	• 0-1 other major ASCVD risk factors, and
	• No evidence of end-organ damage
	• Chronic kidney disease stage 3B or 4 (eGFR 15 to <45 mL/min/1.73m^2)
	• LDL-C of ≥190 mg/dL
	• High risk using quantitative risk score (we will use Pooled Cohort Risk Equations ≥15%)
	• LDL-C target: <100 mg/dL
	• **Secondary Targets:**
	  ○ Non-HDL-C: <130 mg/dL
	  ○ apoB: <90mg/dL
		• ASCVD
		• Diabetes mellitus (type 1 or 2) and:
		• ≥2 other major ASCVD risk factors, or
		• Evidence of end-organ damage
		• LDL-C target: <70 mg/dL
		• **Secondary Targets:**
		  ○ Non-HDL-C: <100 mg/dL
		  ○ apoB: <80mg/dL

European Society	• LDL-C of ≥190 mg/dL	• ASCVD

of Cardiology	• Severe hypertension (SBP>180 or DBP>110 mmHg)
	• Moderate CKD (eGFR 30-59 mL/min/1.73m^2)
	• Calculated SCORE ≥5% and <10% for 10 year risk of fatal CVD.
	• LDL-C target: <70 mg/dL
	• **Secondary Targets:**
	  ○ Non-HDL-C: <130 mg/dL
	  ○ apoB: <100mg/dL
		• Diabetes mellitus (type 1 or 2) with target organ damage or major risk factor
		• Severe CKD (eGFR <30 mL/min/1.73m^2)
		• Calculated SCORE ≥10% for 10 year risk of fatal CVD.
		• LDL-C target: <70 mg/dL
		• **Secondary Targets:**
		  ○ Non-HDL-C: <100 mg/dL
		  ○ apoB: <80mg/dL

Of note, major ASCVD risk factors include:

a. Age (Male ≥45 yo, Female ≥55 yo)
b. Family history of early CHD defined as <55 years old (male first-degree relative) or <65 years old (female first-degree relative).
c. Current cigarette smoking
d. Hypertension (BP ≥140/90 mm Hg or the use of BP medications)
e. Low HDL-C (male <40 mg/dL, female <50 mg/dL)

End-organ damage will be indicated by increased albumin-to-creatinine ratio (≥30mg/g), CKD (eGFR<60 mL/min/1.73m^2) or retinopathy.

SCORE calculator will be obtained from ESC/EAS guidelines.[2]

Outcomes: The primary outcome will be atherosclerotic cardiovascular disease (ASCVD) events, defined as incident coronary heart disease (CHD), fatal CHD, and stroke occurring after Baseline Visit through December 31, 2012 (or most recent follow-up available). Incident ASCVD will be defined as definite or probable nonfatal myocardial infarction or fatal CHD, definite or probable stroke (defined as sudden or rapid onset of neurological symptoms that lasted for 24 hours or led to death in the absence of another cause). As secondary outcomes, we will include total mortality occurring after baseline visit through December 31, 2012 (or most recent follow-up available).

Exclusions: We will exclude individuals with missing data for standard lipid profile at baseline. We will exclude participants who were non-black or non-white, as well as blacks from MN and MD sites due to small numbers.

Covariates: Other covariates that will be further included in models are: age, sex, race, education, physical activity (Baecke questionnaire), BMI (in kg/m^2), mean blood pressure, diabetes mellitus (defined as fasting plasma glucose ≥126 mg/dl, or self-reported physician diagnosis of diabetes or use of diabetes medications), smoking status, **use of lipid-lowering medication and hsCRP (time-varying covariates).**

Main Analyses: As mentioned before, the present study will have two components: cross-sectional and prospective.

Cross-sectional analysis: Among very high- and high-risk individuals, we will identify those who attained LDL-C target (using both LDLf-C and LDLn-C, separately), and will estimate the following proportions:

1. Individuals with non-HDL-C below target
2. Individuals with apoB below target
3. Individuals with both non-HDL-C and apoB below targets
4. Individuals with apoB below percentile-equivalent target (obtained from NHANES)
5. Individuals with both non-HDL-C below target and apoB below percentile-equivalent target (obtained from NHANES)

*We will reproduce the analyses as shown above separately for NLA and ESC/EAS recommended targets.

*Along with the analyses above, we will also calculate the proportion of individuals within 5mg/dL of the secondary target (non-HDL-C or apoB) to address within-assay coefficient of variation.

Prospective analysis: Using baseline information from very high- and high-risk individuals described above, we will construct Cox proportional hazards models to estimate hazard ratios (95% confidence intervals) for each outcome (primary and secondary) using the following models:

a. Model 1: adjusted by age, sex and race/center
b. Model 2: Model 1 + smoking status + education + physical activity +BMI+ mean blood pressure + diabetes
c. Model 3: Model 2 + log triglycerides + HDL-C
d. Model 4: Model 3 + use of lipid-lowering medication
e. Model 5: Model 4 + hsCRP

We will run these models comparing individuals meeting LDL-C and secondary targets (reference group) compared to those who only met LDL-C, and non-HDL-C. For instance, we will perform the following analyses for high-risk individuals using ESC targets (following Table 1):

a) LDL-C<100 mg/dL AND non-HDL-C<130 mg/dl **(reference)**
b) LDL-C<100 mg/dL AND non-HDL-C≥130 mg/dl

a) LDL-C<100 mg/dL AND apoB<90 mg/dl **(reference)**
b) LDL-C<100 mg/dL AND apoB≥90 mg/dl

a) [LDL-C<100 mg/dL AND non-HDL-C<130 mg/dl] AND apoB<90 mg/dL **(reference)**
b) [LDL-C<100 mg/dL AND non-HDL-C<130 mg/dl] AND apoB≥90 mg/dL

a) LDL-C<100 mg/dL AND apoB<80 mg/dl **(reference)**
b) LDL-C<100 mg/dL AND apoB≥80 mg/dl (percentile-equivalent from NHANES)

a) [LDL-C<100 mg/dL AND non-HDL-C<130 mg/dl] AND apoB<80 mg/dL **(reference)**
b) [LDL-C<100 mg/dL AND non-HDL-C<130 mg/dl] AND apoB≥80 mg/dL (percentile-equivalent from NHANES)

*For primary analysis, LDL-C will be estimated by Friedewald equation. In a secondary analysis, LDL-C will be estimated using our novel method.

Limitations:

- There is the likelihood for some residual confounding by other risk factors not included in these models.
- Interim initiation of lipid lowering medication likely will modify the association between lipid discordance and ASCVD events.
- We will not have serial apoB measurements over the follow-up time.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes __X__ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? ____ Yes ____ No
(This file ICTDER03 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ____ Yes __X__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ____ Yes ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

___X___ Yes _____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

Similar ARIC Manuscripts:

2753 (Quispe) The clinical impact of TC/HDL-C discordance with LDL-C, non-HDL-C and apoB: The Atherosclerosis Risk in Communities (ARIC) Study

Notes: this proposal looked at discordance between TC/HDL-C vs. LDL-C and non-HDL-C using median cutpoints in the overall population. ApoB discordance was not assessed. The baseline population for this proposal was ARIC 1st visit, whereas for the current proposal we will use ARIC 4th (where apoB data is available).

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ___ Yes __x__ No

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* __)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

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