ARIC Manuscript Proposal #3957

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1.a. Full Title: Association of high-density lipoprotein parameters and risk of heart failure: a multi-cohort analysis

b. Abbreviated Title (Length 26 characters): HDL parameters and HF risk

2. Writing Group:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __KVP___ **[please confirm with your initials electronically or in writing]**

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3. Timeline: 12/2021 – 06/2022

4. Rationale:

Epidemiological studies have consistently demonstrated an inverse association between high-density lipoprotein cholesterol (HDL-C) and incident atherosclerotic cardiovascular disease (ASCVD), establishing HDL-C as a component of multiple ASCVD risk prediction tools (1; 2). However, pharmacological therapies aimed at increasing HDL-C have failed to show reduction in risk of adverse cardiovascular events (3-7). These observations have led to the hypothesis that HDL-C measurement alone does not capture the functional properties of HDL particles, which may be more proximate mediators of ASCVD risk. Consistently, recent studies have shown that HDL particle concentration (HDL-P) is inversely associated with adverse cardiovascular events independent of HDL-C level (8). Moreover, our group recently reported the distinct associations of HDL-P and other advanced lipoprotein composite measures with risk of atherosclerotic cardiovascular outcomes, independent of HDL-C (9).

While HDL-P appears to be a robust, independent predictor of ASCVD, it is less established whether HDL-P and other advanced lipoprotein phenotypes are associated with risk of incident heart failure (HF), specifically HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF). The equipoise to examine this question stems from studies demonstrating that low HDL-P portends a worse prognosis among patients with HF. In a small cohort study of approximately 150 patients, investigators showed that lower HDL-P is associated with greater risk of mortality among patients acutely hospitalized for HF (10). Furthermore, in a large-scale database analysis, investigators demonstrated that low HDL-P is independently associated with greater risk of adverse cardiovascular events and death in patients with chronic HF (HFrEF more than HFpEF) (11). These data suggest HDL-P may play a mechanistic role in the natural history of HF. Addressing this knowledge gap may refine current HF risk prediction tools and examine HDL-P as a potential therapeutic target for HF, which is particularly relevant given the dearth of available therapies for HFpEF.

We propose to perform an individual participant pooled cohort analysis to examine the relationship between NMR-derived advanced lipoproteins and risk of incident HF and its subtypes. Our group has previously performed a multi-cohort analysis including participants from the Atherosclerosis Risk in Communities Study (ARIC), Dallas Heart Study (DHS), Multi-Ethnic Study of Atherosclerosis (MESA), and Prevention of Renal and Vascular End-stag Disease (PREVEND) (9). We plan to utilize this established cohort for this proposed analysis examining HF outcomes.

5. Main Hypothesis/Study Questions:

1. HDL-P will be inversely associated with risk of HF independent of other traditional risk factors and interval incidence of myocardial infarction.
2. HDL-P will be more strongly associated with risk of HFrEF vs HFpEF.
3. HDL-C will be inversely associated with risk of HF events.

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: Pooled multi-cohort analysis including participants from ARIC, DHS, MESA, and PREVEND.

Participants from ARIC, DHS, MESA, and PREVEND with available HDL-P data and free of established HF will be included.

Inclusion criteria:

ARIC: ARIC began in 1987 and enrolled 15,792 White and Black adults 45 to 64 years of age across four US communities. Participants underwent serial examinations including carotid plaque assessment based on carotid ultrasound performed during ARIC visit 3 (1993 to 1995) and visit 4 (1996 to 1998). The ARIC Carotid MRI substudy was designed to oversample participants with known carotid plaque from ARIC visits 3 and 4 and participants underwent advanced lipoprotein analysis with nuclear magnetic resonance (NMR) spectroscopy. The proposed study will include participants enrolled in the ARIC Carotid MRI substudy (Year 18: 2004 to 2005, n = 2066) (12; 13). Participants included in the proposed study must have available data for advanced lipoprotein analysis (n = 1595).

DHS: Participants began enrollment in DHS between July 2000 and September 2002. The first visit of DHS included an in-home visit and interview that included 6,101 participants. Adults aged 30 to 65 years underwent another in-home visit (second) with blood and urine sampling (n = 3,557). The third DHS visit involved participants traveling to the University of Texas Southwestern Medical Center where imaging was performed (n = 2,971) (14). Participants with NMR spectroscopy data for advanced lipoprotein analysis will be included in the proposed study (n = 2535).

MESA: MESA enrolled 6,814 participants without established cardiovascular disease across 6 sites from 2000 to 2002. Participants with available laboratory testing data including assessment of advanced lipoproteins will be included (n = 6632).

PREVEND: PREVEND enrolled 8,592 participants aged 28 to 75 years between 1997 to 1998 from Groningen, the Netherlands during the initial screening program and outpatient visit. The proposed study included participants who completed the second screening program with outcome data and NMR-based advanced lipoprotein data available (n = 5022).

Exclusion criteria:

Participants with a history of HF or niacin use will be excluded from the proposed study.

Outcomes of interest:

Incident HF event: The primary outcome of interest for the proposed study is incident HF. Across all cohorts, established criteria were used to define HF based on standardized definitions incorporating signs and symptoms of HF.

ARIC: HF events were identified based on retrospective surveillance of hospitalizations across each of the four US communities in which ARIC participants were enrolled. HF cases were identified based on ICD 9 and 10 diagnosis codes associated with HF and adjudicated by the ARIC study committee based on review of medical records including signs and symptoms of HF.

DHS: HF events were identified through two mechanisms. First, the DHS Data Coordinating Center contacted study participants annually by telephone and participants completed a detailed survey regarding HF events. Second, hospitalization data from the Dallas-Fort Worth Hospital Council Data Initiative database were tracked every 3 months. This database includes hospitalization data from 70 of 72 hospitals in the surrounding area.

MESA: Trained personnel contacted study participants every 9 to 12 months to obtain information regarding hospitalizations. A panel of physicians adjudicated HF events. Based on review of medical records, probable or definite HF events were included. Probable HF events included HF diagnosed by a physician and medical treatment. Definite HF events included probable HF criteria plus X-ray findings of pulmonary congestion, imaging findings with reduced LVEF or diastolic dysfunction.

PREVEND: Medical records from the two main hospitals in the region of Groningen were reviewed. A committee of seven HF experts reviewed hospitalization and office records and adjudicated all incident HF events based on signs, symptoms, and objective findings.

HF subtypes - HFpEF and HFrEF: Key secondary outcomes included HF subtypes which were defined similarly across cohorts using standardized categories of left ventricular ejection fraction. HF events with LVEF ≥50% were classified as HFpEF. Participants with incident HF and LVEF <50% were classified as having HFrEF.

ARIC (15): LVEF data were obtained from inpatient diagnostics tests or studies before and within 6 months of the hospitalization for HF.

DHS (16): HF subtypes were based on LVEF cutoffs or documentation of “depressed or low” or “preserved or normal” LVEF.

MESA (17): LVEF data at the time of HF hospitalization from echocardiograms or imaging studies were used to classify HF subtype events.

PREVEND (18): LVEF data at the time of HF diagnosis were available in >98% of HF events and used to define HF subtypes.

Key analytic variables:

- NMR lipoprotein analysis data:
  - HDL-P
  - HDL particle size
  - Ratio of HDL Cholesterol/HDL Particle
  - Ratio of HDL Particle size/HDL Particle
  - LDL-P
- All other clinical variables:
  - HDL cholesterol
  - Total cholesterol
  - Triglycerides
  - LDL cholesterol
  - Non-HDL cholesterol
  - Lipoprotein(a) concentration
  - HS-CRP
  - physical activity (all survey questions related to dose, intensity, and frequency to allow met-min/week calculation if not already calculated)
  - Alcohol intake (grams/week by self-report survey responses)
  - Age
  - Sex
  - Race/ethnicity
  - Education
  - Hypertension (systolic and diastolic blood pressure, hx HTN, blood pressure medication use)
  - Diabetes (hx DM, glucose lowering medications, glucose, HbA1c)
  - Smoking (never, former, current, pack-years)
  - Statin use
  - Use of other lipid lowering medications
  - BMI
  - Waist circumference

Statistical analysis plan:

Our group has previously performed a pooled cohort analysis incorporating data from ARIC, DHS, MESA, and PREVEND for ASCVD outcomes (9). The proposed study will examine incident HF outcomes using a similar pooled cohort and updated event datafiles. Participant-level data from each of the four cohorts will be merged. Standardized categories across the 4 cohorts will be used to harmonize data that may be reported differently across cohorts.

HDL-P concentration will be analyzed primarily as increasing quartiles and continuously. Baseline clinical characteristics will be compared across quartiles of HDL-P. Hazard ratios will be reported for each quartile referenced to quartile 1 or per 1 standard deviation increase in HDL-P concentration. The associations will be adjusted for the following potential confounders: age, sex, race/ethnicity, education, hypertension, diabetes, smoking, statin use, use of other lipid lowering medications, traditional lipid measurements (HDL-C, LDL-C, triglyceride) and BMI. Additional adjustments will be made for waist circumference, physical activity, alcohol intake, hs-CRP, lipoprotein(a) concentration, and interval myocardial infarction.

We will use a 2-stage analysis approach – 1) participant-level pooled analysis, and; 2) cohort-specific analyses. First, pooling across studies will be done by the random-effects inverse variance method. Cox proportional hazard models will be used with HDL-P as the primary exposure and HF events (HFpEF and HFrEF) as detailed above as the outcome.

Additional exposure variables include HDL-C, HDL-size, the ratios HDL-C/HDL-P and HDL size/HDL-P. For hypothesis/question #3, we will evaluate the association of very high levels of HDL-C (defined as >60 mg/dl, 70mg/dl, and 80mg/dl in men; >80mg/dl and 90 mg/dl in women) with the same outcomes. We will assess for non-linearity between each exposure and our outcomes of interest. For exposures with non-linear relationships with the outcomes, restricted cubic spline plots will be computed. We will perform analyses examining all available outcome data and censoring at 10 years to ensure comparable follow-up across cohorts. For HF subtype analysis, we will censor for death and the other HF subtype. Second, estimates of association will be calculated separately within each study.

We will use interaction terms to explore whether any association with HF (HFpEF and HFrEF) events differ according to the covariates in the models. Sensitivity analyses will impute missing values on covariates using the expectation maximization method (single imputation) for each cohort separately. We will analyze heterogeneity across the included studies using Cochran’s Q test and the I2 statistic. All statistical analyses will be performed using SAS.

Anticipated potential limitations: The HF subtype analyses may be limited by missing data on LVEF at the time of incident HF diagnosis. HF events missing LVEF data will be included in the overall HF analyses and excluded from HF subtype analyses.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __X__ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The file ICTDER 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 current derived consent file ICTDER05 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/aricproposals/dtSearch.html

___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)?

Relation of cholesterol and lipoprotein parameters with carotid artery plaque characteristics: the Atherosclerosis Risk in Communities (ARIC) carotid MRI study.
Virani SS, Catellier DJ, Pompeii LA, Nambi V, Hoogeveen RC, Wasserman BA, Coresh J, Mosley TH, Otvos JD, Sharrett AR, Boerwinkle E, Ballantyne CM.
Atherosclerosis. 2011 Dec;219(2):596-602. doi: 10.1016/j.atherosclerosis.2011.08.001

Singh K, Chandra A, Sperry T, Joshi PH, Khera A, Virani SS, Ballantyne CM, Otvos JD, Dullaart RPF, Gruppen EG, Connelly MA, Ayers CR, Rohatgi A.
Associations Between High-Density Lipoprotein Particles and Ischemic Events by Vascular Domain, Sex, and Ethnicity: A Pooled Cohort Analysis. Circulation. 2020 Aug 18;142(7):657-669. doi: 10.1161/CIRCULATIONAHA.120.045713. Epub 2020 Jun 18. PMID: 32804568; PMCID: PMC7425196.

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

11.b. If yes, is the proposal

X A. primarily the result of an ancillary study (list number* _Carotid MRI Study_)

___ 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 https://sites.cscc.unc.edu/aric/approved-ancillary-studies

12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PubMed Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

Proposed Table 1-5. Baseline characteristics in the overall cohort and stratified by sex-specific quartiles of HDL-C, HDL-P, HDL-size, HDL-C/HDL-P, HDL-size/HDL-P

	Overall	Q1	Q2	Q3	Q4	P value
Age						
Female						
Black						
Body mass index						
Waist circumference						
Systolic BP						
Diastolic BP						
Smoking status						
Comorbidities						
Hypertension						
Diabetes						
History of MI						
History of stroke						
Fasting glucose						
Triglycerides						
Hs-CRP						
Total cholesterol						
LDL-C						
HDL parameters						
HDL-C						
HDL-P						
HDL-size						
HDL-C/HDL-P						
HDL-size/HDL-P						
Study cohort						
ARIC						
DHS						
MESA						

PREVEND						

Proposed Table 6. Cumulative incidence of HF events overall and stratified by sex-specific quartiles of HDL-C, HDL-P, HDL-size, HDL-C/HDL-P, HDL-size/HDL-P

Overall median (IQR follow-up): XXX

	Overall HF	HFpEF	HFrEF
Overall			
Cohort-specific			
ARIC			
DHS			
MESA			
PREVEND			
Sex-specific			
Women			
Men			
Sex-specific quartiles of HDL-C			
Q1			
Q2			
Q3			
Q4			
Sex-specific quartiles of HDL-P			
Q1			
Q2			
Q3			
Q4			
Sex-specific quartiles of HDL-size			
Q1			
Q2			
Q3			
Q4			
Sex-specific quartiles of HDL-C/HDL-P			
Q1			
Q2			

Q3			
Q4			
Sex-specific quartiles of HDL-size/HDL-P			
Q1			
Q2			
Q3			
Q4			

Proposed Table 7. Categorical association of sex-specific quartiles of HDL parameters and risk of overall HF, HFpEF, and HFrEF

	Model 1		Model 2		Model 3	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Overall HF						
HDL-C: Q4 vs. Q1						
HDL-P: Q4 vs. Q1						
HDL-size: Q4 vs. Q1						
HDL-C/HDL-P: Q4 vs. Q1						
HDL-size/HDL-P						
HFpEF						
HDL-C: Q4 vs. Q1						
HDL-P: Q4 vs. Q1						
HDL-size: Q4 vs. Q1						
HDL-C/HDL-P: Q4 vs. Q1						
HDL-size/HDL-P						
HFrEF						
HDL-C: Q4 vs. Q1						
HDL-P: Q4 vs. Q1						
HDL-size: Q4 vs. Q1						
HDL-C/HDL-P: Q4 vs. Q1						
HDL-size/HDL-P						

Model 1 – age, race, hypertension, diabetes, smoking, LDL-C, triglycerides, lipid lowering medications, BMI, hs-CRP

Model 2 – model 1 covariates plus HDL-P or HDL-C

Model 3 – model 2 covariates plus interval myocardial infarction

Proposed Table 8. Interaction between HDL parameter and sex for risk of HF events

	Overall HF	HFpEF	HFrEF
Sex * HDL parameter			
HDL-C			
HDL-P			
HDL-size			
HDL-C/HDL-P			
HDL-size/HDL-P			
Model – age, sex, race, hypertension, diabetes, smoking, LDL-C, triglycerides, lipid lowering medications, BMI, hs-CRP, HDL-P or HDL-C, interval myocardial infarction + primary exposure variable (either HDL-C, HDL-P, HDL-size, HDL-C/HDL-P, or HDL-size/HDL-P).			

Proposed Figure 1. Spline analysis examining continuous association of HDL parameters (HDL-C, HDL-P, HDL-size, HDL-C/HDL-P, HDL-size/HDL-P) and risk of overall HF, HFpEF, and HFrEF

	Overall HF	HFpEF	HFrEF
Overall			
Model – age, sex, race, hypertension, diabetes, smoking, LDL-C, triglycerides, lipid lowering medications, BMI, hs-CRP, HDL-P or HDL-C, interval myocardial infarction + primary exposure variable (either HDL-C, HDL-P, HDL-size, HDL-C/HDL-P, or HDL-size/HDL-P).			

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