ARIC Manuscript Proposal #2055

1.a.   Full Title: Assessing cardiovascular risk in diabetics using traditional indicators of target organ damage and serum biomarkers: the ARIC study

  b. Abbreviated Title (Length 26 characters): **target organ damage and cardiovascular events.**

2.   Writing Group:
        Writing group members: Mauro Gori, Deepak Gupta, Natalie Bello, Brian Claggett, Amil Shah, Hicham Skali; Aaron Folsom; Christie M Ballantyne; Brad C Astor; Barbara Klein, Kunihiro Matsushita; David Aguilar, Orly Vardeny; Hanyu Ni; Elizabeth Selvin, Scott D. Solomon….. <mark>OTHERS WELCOME</mark>

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

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   3.   Timeline:
Analysis will begin once this manuscript proposal is approved. Anticipate manuscript completion in approximately the following 12 months.

   4.   Rationale:

Cardiovascular disease (CVD) is the most common cause of death among persons with diabetes, and the presence of multiple organ damage further impacts on the prognosis of these individuals.[1,2,3,4,5,6,7,8,9,10]

Among persons with diabetes, there is heterogeneity in the risk of CVD such that accurate risk assessment depends on a variety of individual patient characteristics, like number of concomitant risk factors, duration of diabetes, presence of coronary heart disease (CHD), overall atherosclerotic burden, presence of proteinuria.[11,12,13,14] Consequently, measuring target organ damage may be an attractive approach to improving risk prediction of cardiovascular outcome in diabetics. As the great vessels, kidneys, eyes, and heart are commonly affected by diabetes, several markers of diabetic involvement of these organ systems already exist. The ankle brachial index (ABI) can be used as a measure of atherosclerosis in peripheral vessels, while another validated index of generalized atherosclerosis is the B-mode ultrasound detected carotid intima media thickness (CIMT). Nephropathy can be assessed by estimated glomerular filtration rate and urine albumin/creatinine ratio (UACR), while retinopathy can be detected by retinal photography. The ECG can demonstrate abnormalities as manifestations of diabetic induced cardiac damage. All of these measures of target organ damage are commonly used in population-based studies because they are relatively inexpensive, noninvasive, and easy to assess. Importantly, each one of these measures of target organ damage has been strongly associated with cardiovascular events.[15,16,17,18,19,20,21,22,23,24,25,26,27,28,29] Other potentially useful measures of target organ damage in diabetics include serum biomarkers such as NTproBNP, hsTnT, hsCRP. NTproBNP and hsTnT have been used to improve the accuracy in the diagnosis of subclinical left ventricular dysfunction, while hsCRP have been related to inflammation and atherogenesis. Importantly, these serum biomarkers have also been found to be markers of adverse CV outcome both in the general population and in persons with diabetes. [30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47]

Among subjects with diabetes few population-based studies have compared the differential predictive value of several measures of target organ damage,[48,49,50] let along taking into account the serum biomarkers.[51] The ARIC Study, a population-based cohort study of middle age men and women, is the ideal setting to select diabetic persons without prevalent CVD and prospectively investigate several noninvasive measures of target organ damage and combinations of these measures in relation to incident CVD outcome. *Specifically, we propose to evaluate the association of established tests of target organ damage (ABI, CIMT, retinopathy, nephropathy, ECG) and of serum biomarkers (NTproBNP, hsTnT, hsCRP) on the primary outcome of fatal or nonfatal CV events in persons with diabetes. Additionally, we will evaluate whether the association between established markers of target organ damage and CV risk is modified by serum biomarkers.*

5. Main Hypothesis/Study Questions:
Among diabetic ARIC participants without prevalent CVD at visit 4 the aims of the study are:
1) To describe the prevalence, clinical characteristics, and correlations of specific measures of target organ damage.
2) To describe the event rates for the primary outcome (see definition of outcome variables) according to types of target organ damage.

3) To compare the differential risk of the primary outcome associated with specific measures of target organ damage (traditional markers and serum biomarkers). We will test for independent associations of specific markers of target organ damage with the risk of the primary and secondary outcomes (see definition of outcome variables) in univariate and multivariate adjusted models (adjusting for baseline age, sex, race, center, smoking status, pack of cigarettes/year, body mass index, waist-hip ratio, systolic blood pressure, hypertensive medication use, diabetic medication use, lipid lowering medication, aspirin use, education, total/HDL cholesterol, triglycerides, family history of CHD).

4) To describe effect modification on the primary outcome by serum biomarkers on traditional measures of target organ damage.

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 methodological limitations or challenges if present).

Study design/population:

Cohort analysis of diabetic participants without history of cardiovascular disease at visit 4. The study population will be comprised of persons with diabetes with available data regarding ECG, ABI, CIMT, eGFR, UACR, hsTnT, NTproBNP, hsCRP at visit 4, as well as retinal photography, CIMT, ABI from visit 3, or ABI from visit 1. We anticipate an estimate of 1500 persons with diabetes with these characteristics.

Definition of Diabetes

Participants will be classified as having a history of diabetes at visit 4 if they report a physician diagnosis of diabetes or medications for diabetes at visit 4 or previous visits. Undiagnosed diabetes will be defined as a fasting glucose $\geq$126 mg/dl or non-fasting glucose $\geq$200 mg/d at visit 4 or previous visits.

Exclusions:

We will exclude ethnicity other than black or white, missing data on target organ damage tests, or missing covariates of interest. Participants with prevalent CVD at visit 4 will be excluded.

Definition of Prevalent CVD

CHD: defined as self-reported myocardial infarction (MI) before visit 1, or silent MI (diagnosed by ECG Q waves), validated MI event, or revascularization procedure between visit 1 and 4.

HF: defined as either participants reported medication use for heart failure or Gothenberg score=3 [52,53] or missing HF status, or incident HF hospitalization (based upon ICD-9 codes 428.xx) prior to visit 4.

Stroke: defined as self-reported stroke before visit 1 or incident stroke between visit 1 and visit 4.

Exposure variables:

Traditional indicators of target organ damage

1) Retinopathy (visit 3)

Retinopathy will be defined as present if any characteristic lesion as defined by the Early Treatment Diabetic Retinopathy Study severity scale was present (microaneurysms, hemorrhages, cotton wool spots, intraretinal microvascular abnormalities, hard exudates, and new retinal vessels).[54]

2) Major ECG abnormalities (visit 4)

ECG abnormalities will be defined as present if any major criteria are met.

Major electrocardiographic abnormalities will be defined according to the Minnesota coding system [50,55,56] as:

Ventricular conduction defect codes:

7-1 (left bundle branch block),

7-2 (right bundle branch block),

7-4 (IV block of indeterminate type with QRS >120 ms);

Left ventricular hypertrophy codes:

3-1, 3-3

4-1 to 4-3

5-l to 5-3

Isolated major ST-T wave abnormalities (ST-T) codes:

4-1, 4-2

5-1, 5-2 without (3-1, 3-3, l-l to l-3);

Atria1 fibrillation code:

8-3

3) Nephropathy (visit 4)

Nephropathy will be defined as present based on eGFR < 60 ml/min per 1.73 m^2, and/or UACR $\geq$30 mg/g.[57] eGFR will be calculated using the recently validated combined creatinine–cystatin C equation, that has been shown to perform better than equations based on either of these markers alone for chronic kidney disease detection.[58,59] Since it has been demonstrated that there is risk gradient within normal range of UACR, we will also evaluate the risk associated with a threshold of 10 mg/g as a sensitivity analysis.[60]

4) ABI (visit 4)

Peripheral arterial disease will be defined as present based on an ABI value < 0.9. Since ABI has been collected at visit 4 in a sample of the total population, for those patients with missing data on this parameter we will carry forward the last available measure from prior visits (visit 1 and 3). For those subjects in whom ABI data is not available at visit 4 or from prior visits, we will assign these participants as negative for PAD. We recognize that this may lead to misclassification bias, but this approach is conservative and would tend to mitigate any association we may find between PAD and incident CVD.

5) Carotid IMT (visit 3 and 4)

CIMT will be defined as the mean of IMT measurements at six sites of the carotid arteries using B-mode ultrasound,[61] with a cut off value for detection of target organ damage of $\geq$1 mm.[62] Since CIMT has been collected in half of the population at visit 4 and the other half at visit 3, for those patients with missing

data on this parameter at visit 4 we will carry forward the last available measure from visit 3.

Serum biomarkers
HsTnT, NTproBNP, hsCRP (visit 4)
Biomarkers will be evaluated as both continuous and categorical variables. For continuous models, undetectable levels of hsTnT will be assigned a value of half the lower limit of detection. For the categorical analysis, NTproBNP will be divided into quartiles, hsCRP values will be dichotomized using the cut point of high risk proposed by the American Heart Association recommendations,[63] while cTnT levels will be separated based on the manufacturer proposed 99th percentile decision limit for the Roche assay.[37,64]

For each serum biomarker, target organ damage will be defined as present if:
   1) *hsTnT ≥ 0.014 $\mu g/L$.*
   2) *NT proBNP in the highest quartile.*
   3) *hsCRP is >3mg/L.* [46]

Outcome variables**:**
Primary outcome
- Composite of fatal and non fatal CV events (defined as CHD, HF and stroke events).[65]
Secondary outcomes
- All cause mortality.
- CV death (CHD, HF, stroke).
- Incident heart failure hospitalization based on diagnosis codes from hospital discharges (ICD-9 code 428.XX). [52]
- Total incident CHD events (fatal CHD, definite or probable MI, or coronary revascularization) ascertained per ARIC study procedures.[66]
- Total incident stroke events (validated stroke death, definite or probable non fatal stroke) ascertained per ARIC study procedures.[67]

Incident CV events will be defined as new events occurring subsequent to the fourth examination through December 31, 2008.

Covariates
Variables of interest will include age, sex, race, center, smoking status, pack of cigarettes/year, body mass index, waist-hip ratio, systolic blood pressure, hypertensive medication use, diabetic medication use, lipid lowering medication, aspirin use, education, triglycerides, total/HDL cholesterol (all detected at visit 4), family history of CHD (per protocol detected only at visit 2).

Statistical Analysis
All non-normally distributed variables will be natural logarithmically transformed, as needed.

First, we will describe characteristics of the diabetic population without prevalent CVD at visit 4 according to the presence of each traditional indicator of target organ damage and of serum biomarkers (continuous variables will be expressed as mean ± SD or median (IQR) and compared with a t-test or Wilcoxon rank-sum test as appropriate, while categorical variables will be presented as counts and percentages and compared using a Fisher exact test).

Second, we will calculate incident event rates, overall and within each category of target organ damage and sub-clinical dysfunction, expressed as events per person-time.

Third we will evaluate risk associated with target organ damage using Cox proportional hazards regression. We will construct four sets of models:
Model 1 will be unadjusted; model 2 will adjust for age, sex, race, center, smoking status, pack of cigarettes/year, body mass index, waist-hip ratio, systolic blood pressure, hypertensive medication use, diabetic medication use, lipid lowering medication, aspirin use, education, total/HDL cholesterol, triglycerides, family history of CHD; model 3a will be further adjusted for traditional indicators of target organ damage and for biomarkers considered as dichotomous variables (considering the following cut off: hsTnT $\geq$ 0.014 μg/L, NT proBNP in the highest quartile, hsCRP >3mg/L); model 3b will feature the same predictors as 3a, but with biomarkers considered as continuous variables.
We will assess the discriminatory ability of each model using a C-statistic. For models 1 and 2, the univariate effect of each key predictor (indicators of target organ damage and biomarkers) will be assessed by considering the addition of only new marker at a time. The associated hazard ratio and resulting C-statistic will be reported for each predictor. Models 3a and 3b will be used to assess the effects of all key predictors, controlling for all others. The hazard ratio for each predictor in these fully adjusted models will be reported.

Fourth we will investigate potential effect modification by novel serum biomarkers on the relationship between each traditional measure of target organ damage and the risk of CV death or nonfatal CHD or HF.

Two-sided *P* values of <0.05 will be considered statistically significant. All analyses will be performed using STATA 12.

Limitations:
The study will be restricted to Caucasians and African Americans; thus the results cannot be generalized to other races. Additionally, the retinal examinations and laboratory analyses of cardiac biomarkers were obtained at different study visits (3 and 4), separated by a period of approximately 3 years. The same holds true for a part of ABI and CIMT data.
We will not be able to rule out the possibility of residual confounding.
The results cannot be generalized to younger population.
CHF events will be defined from hospitalization or death records (both self-reported events and detected by surveillance of community hospital discharges or by surveying

death certificates from state vital statistics). Self-report may result in underreporting of hospitalization, and milder CHF cases that did not require hospitalization won't be included. The latter may limit the applicability of our results to a wider spectrum of CHF cases not requiring inpatient treatment. Additionally, data derived from death certificates may have limited accuracy and it is possible that some CHF events may have been misclassified.

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 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 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)?
#546: Subclinical markers and incident CHD in diabetes mellitus; Duncan BS
#606: C-reactive protein and incident coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) Study. Am Heart J. 2002 Aug;144(2):233-8. Folsom AR
#781: Subclinical atherosclerosis measures and incident CVD in diabetics; Diabetes Care. 2003 Oct;26(10):2777-84. Folsom AR
#855: Retinopathy and risk of congestive heart failure. JAMA 2005;293:63-9. Wong TY
#1123: Albuminuria and Kidney Function as Predictors of Cardiovascular Events and Mortality; Am J Epidemiol. 2008 May 15;167(10):1226-34. Astor B

#1564: Correlation of high sensitivity troponin-T (hs-cTnT) and amino terminal pro-brain natriuretic peptide (NT-proBNP) with renal function parameters; and association with mortality and adverse cardiovascular events. Circulation 2011;123:1367-76. Saunders J

#1596: Hyperglycemia and risk of subsequent elevation of NT-proBNP and hs-cTnT; J Am Coll Cardiol. 2012 Jan 31;59(5):484-9. Rubin J

#1757: The association of high sensitivity troponin with heart failure, mortality and recurrent coronary heart disease (CHD) in individuals with prevalent CHD. Nambi V

#1759: Associations of traditional cardiovascular risk factors and high-sensitivity cardiac troponin T. Rubin J

#1808: The utility high sensitivity cardiac troponin T in the prediction of heart failure risk. Nambi V

#1811: Association of high sensitive troponin T (hs-cTnT),N- Terminal pro- brain natriuretic peptide (NT-proBNP) and high sensitivity C- reactive protein (hs-CRP) with cause- specific mortality: ARIC study. Oluleye OW

#2031: Interaction of Kidney Disease Measures with Diabetes and Hypertension on Cardiovascular Disease: the Atherosclerosis Risk in Communities (ARIC) Study. Alexander N

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 (2008.10, 2006.16)
     ___   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/

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.

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