PC Reviewed: 3/12/13   **Status: <u>A</u>**   **Priority: <u>2</u>**
SC Reviewed: _____   **Status:** _____   **Priority:** ____

1.a.   **Full Title**: **Cardiovascular Risk Factor Control in Diabetes Pooling Project**

b. Abbreviated Title (Length 26 characters): **CV Risk Factor Control in DM**

2. Writing Group:

Writing group members: Nathan D. Wong, PhD (Chair/Corresponding Author), Christopher Patao, BS (UC Irvine), Shaista Malik, MD, PhD (UC Irvine), Alain Bertoni, MD, MPH (MESA), Aaron Folsom, MD (MESA and ARIC), Elizabeth Selvin (ARIC), Aldolfo Correa, MD (JACKSON), Herman Taylor, MD (JACKSON), Shemesh Kachroo, MD (Bristol-Myers Squibb), and Uchenna Iloeje, MD, MPH (Bristol-Myers Squibb).

Bristol-Myers Squibb will be providing a contract to the University of California, Irvine (Dr Wong) to perform the analysis / manuscript preparation. Bristol-Myers Squibb will not have access to the data.

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

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3. **Timeline**:

February 27, 2013 – Approval from MESA P&P obtained (attached)

March 2013 – Obtain approvals from ARIC and JACKSON P&P's and complete required data distribution agreements (DDAs) and obtain study data

May-June 2013 – Complete required data management to merge relevant variables from all datasets

July-September 2013 – Draft analyses

October-December 2013 – Complete analyses and draft manuscript

January-February 2013 – Finalize manuscript

4. **Rationale**: Current CVD risk factor control is suboptimal in those with diabetes and there are no prospective data from large observational trials on the degree of risk reduction expected from composite control of risk factors. This study will show the extent to which CHD event risk in a pooled longitudinal study of US adults from the MESA, ARIC, and JACKSON heart studies with diagnosed diabetes is lower according to extent of control of individual and composite CHD risk factors. Importantly, we will examine whether CHD event risk is substantially lower if there is composite control of multiple CHD risk factors, namely HbA1c, blood pressure, and LDL-cholesterol. We will also examine whether further reductions in risk are observed from additional control of other factors such as HDL-C, weight, and inflammation (c-reactive protein).

5. **Main Hypothesis/Study Questions**:

Primary Hypothesis:

Among those with *diagnosed* diabetes, those who are simultaneously controlled for HbA1c, LDL-cholesterol, and blood pressure will have rates of CHD and CVD that are significantly lower than those controlled for individual factors or not at control, or those with undiagnosed diabetes.

Secondary Hypotheses:

1) Those at control at earliest (baseline or Exam 2-3 in the case of MESA) for individual measures of HbA1c, LDL-cholesterol, and blood pressure will have lower rates of CHD and CVD than those not at control for these individual measures.

2) Those who additionally are at non-obese levels of body mass index (<30 kg/m2) and who are at lower levels of triglycerides, HDL-C, and C-reactive protein will have even lower rates of CHD and CVD.

3) The risk reduction observed from composite risk factor control will be similar across major ethnic groups represented.
4) Those developing incident CHD during the follow-up will have improved control of CVD risk factors following their event compared to before their event.

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 Population and Inclusion Criteria:

We will include approximately 2,500 persons with *diagnosed* diabetes defined according to a self-reported physician diagnosis or being on hypoglycemic therapy for diabetes from the following three NIH population-based prospective studies:

1) Multiethnic Study of Atherosclerosis (Exam 2-3 "baseline" in 2004-2006)
2) Jackson Heart Study (Baseline examinations in 2002)
3) Atherosclerosis Risk in Communities Study (Baseline examinations in 1987-1989)

Each of these cohorts have measured levels of fasting glucose, HbA1c, lipids (including total and LDL-cholesterol, HDL-cholesterol and triglycerides), blood pressure, smoking information, and C-reactive protein and follow-up for subsequent CVD events (coronary heart disease, heart failure, and stroke) through 2011.

Data Variables (from baseline and available follow-up examinations):

1. Physician told of diabetes (yes/no)
2. Currently taking insulin or other hypoglycemic therapy for diabetes (yes/no)
3. Fasting glucose (mg/dl)
4. HbA1c (%)
5. LDL-C (mg/dl)
6. HDL-C (mg/dl)
7. Triglycerides (mg/dl)
8. C-reactive protein (mg/L), high sensitivity
9. Systolic and diastolic blood pressure (mmHg)
10. Cigarette smoking (past, current, never)
11. Family history of coronary heart disease or stroke
12. Body mass index
13. Waist circumference
14. Physical activity (number of times per week moderate intensity exercise 30 minutes or greater per time, or number of minutes per week moderate intensity or

greater exercise). An appropriate metric to provide consistent information between the different studies (MESA, ARIC, and JACKSON) will be developed.

15. Dietary habits (following a diabetic diet, cholesterol-lowering diet). An appropriate metric to provide consistent information between the different studies (MESA, ARIC, and JACKSON) will be developed.
16. Cardiovascular disease (coronary heart disease, stroke, or heart failure) at baseline
17. Occurrence (and date of first occurrence) of coronary heart disease (angina, myocardial infarction, or CHD death)
18. Occurrence (and date of first occurrence) of cardiovascular disease (CHD above, stroke, or heart failure)

Power Analysis

From our recent analysis of CHD event rates among persons with DM in the MESA study (16), an overall 1.5% annual CHD event rate was obtained, which can be projected to 15% over a mean 10-year follow-up we can conservatively estimate combining MESA, JACKSON, and ARIC studies (MESA will have follow-up from 2004-2006, JACKSON from 2002, and ARIC from 1987-1989).   If we project 20% of subjects are at goal for HbA1c, blood pressure, and lipids and these persons have a minimum one-third reduction in CHD events (based on references 14 and 15), 2223 subjects with diabetes would be needed for our study (1778 not at control vs. 445 at control) to show this reduction in risk with 90% power at alpha=0.05.

Statistical Methods

1. We will initially define diagnosed diabetes according to a self-reported physician diagnosis of diabetes or being on hypoglycemic therapy. Persons included will be free of known CVD (myocardial infarction or known revascularization, angina, stroke, heart failure, or peripheral arterial disease) as determined by questionnaire at their designated baseline.
2. We will define "control" for A1c as <7%, blood pressure as <130/80 mmHg (target in use during most of the study duration), LDL-C as <100 mg/dl, and BMI as <30 kg/m^2 regardless of the use of therapy   Also, we will define low HDL-C as <40 in males and <50 in females and normal C-reactive protein as <1 mg/L. HbA1c will be further categorized as <6.5%, 6.5-<7%, 7-<8%, 8-<10%, and >=10%.   BP categories will also be defined be further stratified by JNC7 categories as: <120/80 (normal), 120-139 / 80-89 (pre-HTN), 140-159 / 90-99 (Stage I HTN), and 160+/100+ (Stage II HTN) regardless of the use of therapy.   LDL-C categories will be further stratified as <100 mg/dl, 100-129 mg/dl, 130-159 mg/dl, and 160+ mg/dl regardless of the use of therapy.
3. We will initially examine incident CHD and CVD rates per 1000 person years overall and according to whether each of the above factors are controlled/not-

controlled.   Additionally, we will examine rates according to the number of above factors that are controlled and whether or not there is composite control for A1c, BP, BMI, LDL-C (based on being at the above goals for all four of these measures).

4. We will determine using Cox Proportional Hazards Regression whether those controlled/not controlled for the above factors are at lower risks (and to what extent) for future CHD and CVD events, adjusting for age, gender, ethnicity, sociodemographic factors, and other CVD risk factors.

5. Similar analyses will be done for HbA1c, blood pressure, and LDL-C according to the further categorization noted above.

6. Another Cox Regression model will examine all the risk factors together (A1c, BP, BMI, LDL-C, HDL-C, and C-reactive protein) to determine which are most strongly related to CHD and CVD risk.   Dietary patterns and exercise habits will be included to the extent that they can be standardized between the different studies.

7. We will stratify analyses (where sample sizes permit) according to gender and ethnicity (Hispanics, African-Americans, Asians, and Whites), as well as global 10-year CVD risk level (<10% low, 10-20% intermediate, and >20% high) to determine whether the benefit of multiple risk factor control is similar between genders, ethnicities, risk level and level of obesity stratified by BMI (<30 vs. >=30 kg/m^2) or waist circumference (at cutpoints of 88cm for women and 102 cm for men).

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)?**

ARIC MS proposal #1024 – Glycemic control and CHD risk in persons with and without diabetes
ARIC MS proposal #1067 – Glycemic control and Risk of Ischemic Stroke

These proposals only examine glycemic control; our paper looks at comprehensive risk factor control and long-term total and individual CVD outcomes. The first author of the above two proposals, Elizabeth Selvin, MD is a co-author on our proposed paper and approves our submission.

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/

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.