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Working Group on Future Research Opportunities in the ARIC Study

Meeting Summary July 1, 2008

TABLE OF CONTENTS

- [Purpose](#)
 - [Background](#)
 - [Draft Plan](#)
 - [NHLBI Heart Failure Research Profile](#)
 - [ARIC Investigators' Presentations](#)
 - [Panel Discussions](#)
 - [Recommendations and Priorities](#)
 - [Working Group Members, NHLBI Staff, and ARIC Investigators](#)
-

Purpose of the Working Group

The Working Group was charged with identifying future research opportunities in the Atherosclerosis Risk in Communities (ARIC) Study, based on scientific knowledge of the field and an understanding of the research resource that ARIC has created.

Background of ARIC Study

The study was initiated in 1985 with two components: a community-based surveillance and a prospective cohort. The community surveillance has been monitoring trends in the incidence of coronary heart disease (CHD) (1987-) and heart failure (2005-) in four communities. The cohort study has been examining the etiology and natural history of cardiovascular disease (CVD) in approximately 16,000 participants aged 45-64 years at baseline from the same communities under surveillance. The participants received four clinical exams over 9 years. Since 1998, the participants have been followed only through annual telephone interview except for a small proportion of participants enrolled in an ancillary study. As of 2007, about 13,000 cohort members were still alive.

Draft Plan for Future Research in ARIC Study

To maximize the scientific potential in the ARIC study, the Project Office is considering the possibility of another clinical exam on the full cohort of remaining participants. The rationale for the exam was discussed. The ARIC study is a valuable resource for CVD and heart failure research because of its large cohort size, biracial and community-based study population, and prevalent CVD events and their risk factors.

Potential major aims for the newly proposed clinical exam, which would focus on heart failure, include: 1) Characterize phenotype and staging of heart failure, by race and gender; 2) Identify risk markers, triggers, and modifiers in the initiation and progression of heart failure (stages A to D), by race and gender; and 3)

Identify factors related to outcomes of heart failure, by race and gender. Other possible topic areas include diastolic dysfunction, subclinical cardiovascular disease, physical functioning, renal function, atrial fibrillation, and cognitive function.

[Back to Table of Contents](#)

NHLBI Heart Failure Research Profile

Dr. Bild, Deputy Director of the DPPS, provided an overview of the NHLBI heart failure research supported by two of the extramural divisions. The Division of Cardiovascular Disease (DCVD) funded several large studies, including the Specialized Centers of Clinically Oriented Research (SCCOR), Clinical Heart Failure Network, Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT), Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), and the Surgical Treatment for Ischemic Heart Failure (STICH) Trial. The studies funded by the Division of Prevention and Population Sciences (DPPS) were reviewed, including the HF ACTION, Olmsted County Study, and nine other large NHLBI cohort studies that are closest in scope to ARIC.

NHLBI supports a broad spectrum of research in heart failure. The coordination of multiple research efforts, however, is a challenge. There is also great opportunity in supporting complementary research programs.

[Back to Table of Contents](#)

ARIC Investigators' Presentations

The ARIC study has accumulated extensive data on CVD risk factors and subclinical measures for the cohort beginning from middle age. Incident CVD-related events were collected through clinical exams and annual contact before 1998, but since then have been identified only through telephone interviews, with systematic chart-review confirmation of coronary and stroke events and since 2005 of heart failure events. Self-reported data may not be complete and reliable, especially for conditions such as hypertension, diabetes, and renal function. The study has stored biological specimens; one million SNPs and numerous candidate genes are available for future research endeavors. A total of 79 ancillary studies have been funded, mainly by the National Institute of Health (NIH). Some major contributions of the ARIC study include: identification of carotid IMT as a subclinical marker of atherosclerosis, identification of traditional and novel risk markers and genetic variants for CHD, and development of prediction equations for CHD and stroke in apparently healthy individuals.

The investigation of heart failure events occurring before and after 2005 was discussed. Incident heart failure cases are identified by retrospective medical chart review. Significant efforts are made to differentiate decompensated heart failure from chronic stable heart failure. Criteria used in ARIC for heart failure classification were reviewed, including Framingham Heart Study, Boston, NHANES, and Gothenburg criteria. As acknowledged by the investigators, it is extremely difficult to fully characterize and capture heart failure cases based on hospital data alone due to missing key information, the shifts in the management of these patients to the outpatient setting for care, and inconsistent diagnostic criteria used in medical practice and epidemiology.

The cohort retention rate remains high (90%). Information on heart failure has been self-reported by the participants through the annual telephone interview. The Gothenburg questionnaire was included in the baseline survey and current interview questionnaire. Another exam could identify individuals with asymptomatic heart failure and clinical cases managed in outpatient settings, which would provide opportunities to study the roles of behavioral, genomic and medical care factors in a full range of heart failure phenotypes and their associated outcomes. Another exam would also provide opportunities to develop and calibrate simple tools to study heart failure in the broader community-based setting, including an assessment of its magnitude, risk factors, and long-term outcomes. The ARIC participants are enthusiastic about the additional and novel scientific information that would be obtained from another participant exam.

ARIC has genotyped the entire cohort for genome-wide association study (GWAS) markers through multiple funding sources, and the study has become a key component of multiple national and international GWAS consortia. Future research plans include GWAS of target heart, lung, and blood phenotypes, follow-up of GWAS to identify candidate functional mutations, medical re-sequencing, study of gene-environment interactions, and whole genome and transcriptome sequencing. Another clinical exam is needed to update phenotype information, obtain novel aging phenotypes, update informed consent from participants, and study functional genomics.

A grant proposal will be submitted to the NIH in the fall of 2008 for a large ancillary study on risk factors associated with dementia and cognitive impairment in the ARIC cohort. The study rationale and preliminary data were presented. The plan is to bring the full cohort back for a brief clinical exam to identify persons with impaired cognitive function, and then perform brain MRI on the cases with impaired function and a control group without the abnormality. If this study is funded, the efforts can be leveraged with the contract study to enhance efficiency.

[Back to Table of Contents](#)

Panel Discussions

Heart Failure Diagnosis and Screening

The Working Group acknowledged that the diagnosis and classification of heart failure has been an ongoing challenge to clinical and epidemiological researchers working in the field. Heart failure symptoms are not specific and often are not concordant with the state of ventricular function. Also, patients move across heart failure classes due to exacerbation and re-compensation. Heart failure is of mixed etiologies in most hospitalized patients, even with preserved systolic function or diastolic heart failure, due to their associated co-morbidities. Although systolic heart failure appears to be a model of chronic progressive pump failure, it is unclear if diastolic heart failure is also a progressive disorder. Research efforts could focus on one or both of two main entities: preclinical heart failure (stages A and B) vs. heart failure with clear clinical de-compensation. Three target groups of interest for heart failure prevention research include: 1) those without heart failure but with risk factors (stage A), for whom there is a need to follow and identify precursors (biomarkers and genetic markers), and 2) those with structural change (stage B) who move in and out of symptomatic status and as a result are difficult to identify. 3) those with heart failure with preserved systolic function

ARIC has captured heart failure cases through community surveillance and follow-up of the original cohort, and is a great source for studying the utility of various diagnostic criteria and screening for symptomatic or asymptomatic heart failure with left ventricular dysfunction. Because the study has done considerable and high quality work on heart failure classification, using all major sets of criteria and all components of these sets, ARIC can provide information on which elements of diagnostic criteria are most useful in the classification of heart failure and components of this clinical syndrome. With a gold standard (detailed phenotyping by imaging and biomarkers) for comparison, ARIC may develop new approaches to define heart failure for epidemiologic studies and genetic research.

The panel recommended that in addition to echocardiogram assessing systolic function, there should be a detailed "diastology" echo including tissue Doppler. In addition with new advances in echo technology, 2-D speckle tracking echocardiography could be used to measure left ventricular myocardial strain and strain rate. An echo core lab would be needed to standardize the imaging procedure and the echo measurements. The study could consider the measure of left atrial volume index because it is easy to calculate from the 2-D echo image and it reflects the severity and chronicity of heart disease, as HbA1c is for chronic diabetes control. This could also be obtained from previous echocardiograms to study its association with clinical events. In terms of biomarkers, the results from the Framingham Heart Study and Olmstead County study did not support the value of brain natriuretic peptide (BNP) in screening, but these studies may be underpowered. Screening for heart failure and /or its precursors in the elderly may need some imaging modality, and the ARIC study has many advantages in characterizing asymptomatic participants and clarifying this issue.

Having only one detailed assessment of ventricular structure and function is a limitation for studying disease progression, but should have significant value in describing the burden of asymptomatic and symptomatic patients, defining staging of heart failure in a community-based population, and establishing a baseline for follow-up. The study could go back to 1987 baseline data and use genetic and biomarker analyses to advance our present understanding of the progression of heart failure.

It would be useful to obtain more proximate measures for diastolic dysfunction because we do not have a good understanding of this condition, and therefore cannot effectively manage diastolic dysfunction as well as we do systolic dysfunction. Renal function decline, diabetes, and vascular stiffness have all been associated with diastolic dysfunction, but efforts should be made to understand the interactions of these and other conditions in relation to measures of diastolic dysfunction. There may be a need to pool data from several large cohort studies to obtain enough patients with mild dysfunction to better describe the phenotype of preclinical diastolic dysfunction and develop strategies for prevention and treatment.

The ARIC study could use electronic medical records to find out in real time whether participants are hospitalized with de-compensated heart failure and phenotype them during that hospitalization -- that is, to do a more active and prospective surveillance. This would also set the stage for carrying out studies for the triggers, or precipitating factors, of acute heart failure that is described in the following section. In the Framingham Heart Study, study staff visits the participants with acute stroke in the hospital to collect data. Although this would be very valuable, it would require considerable effort and expense.

Etiology and Prevention of Heart Failure

Determining heart failure etiology is important, but assigning etiology can be very problematic. There is a need to carefully assess medical history, including drugs and cardiotoxicity, to integrate with functional history. Family history is also important, but its reliability is poor. It would be helpful to obtain a structural etiology as well, which is a further rationale for a repeated exam and re-phenotyping the remaining cohort. The study could better define etiologies of heart failure and if possible, collect detailed information on catheterization and nuclear medicine for complete phenotyping of these participants.

Although it is known that hypertension and CAD account for two-thirds of heart failure cases, most patients with these conditions do not develop heart failure; therefore, it is important to know what characteristics determine different rates of progression of this clinical syndrome and to understand mechanisms behind the differences. ARIC has the opportunity to understand triggers of clinical heart failure and how stage A and B patients respond to environmental exposures or drugs. Currently there is not enough evidence for treating asymptomatic patients with left ventricular dysfunction but without a history of MI. Information obtained from this research can inform physicians how to more effectively manage these potentially high risk patients, for example, those with a borderline low ejection fraction.

The panel emphasized the importance of identifying triggers and precipitating factors for decompensated heart failure. The possibility of identifying triggers and precipitating factors through "warm" (active pursuit) surveillance, even at a selected set of hospitals, was discussed. ARIC could collect additional data from those hospitalized, for example, with heart failure and other acute potential contributory causes including infection, arrhythmias, physical activity, dietary indiscretion, stress, and medical non-compliance. Use of a case-crossover design to explore these associations could be adopted with the use of both in-person interviews and review of hospital charts. ARIC may also consider collecting metabolic triggers such as changes in renal function and troponin leaks below the threshold for acute MI.

The panel discussed the need to have a study focusing on taking heart failure genomics as a starting point. Those genetically at risk may be selected and then followed prospectively. ARIC would be a set-up for this potential "next big study." However, such a study would need to have a well-defined phenotype in order to conduct the best genetic investigations, and so far this does not exist for heart failure. Efforts are needed to explore the data to determine which measurements are of value to best phenotype heart failure. Another exam in the ARIC study could help improve the phenotype by looking at outcomes and identifying biomarkers that predict them. The ARIC study has enough DNA to do full-genome sequencing in most participants. Another exam would collect new material to replenish DNA supply, save more serum and plasma, and store material to study the transcriptome. ARIC is an excellent resource for heart failure genetic research, and the study is encouraged to collect data that will allow pooling with other cohorts to improve power for such research.

It would be worthwhile to compare ARIC and the Cardiovascular Health Study (CHS) results in heart failure, since the etiology of heart failure at the same age may differ by birth cohort. For example, there may be differences in earlier life exposures and treatments, such as vaccinations, blood pressure control, and use of statins between CHS and ARIC cohort participants. A younger population would have been exposed to anti-hypertensives and statins much longer at the same age than that in CHS. Therefore, heart failure etiologies and patterns of cardiac dysfunction in ARIC may differ from those in CHS. The results from ARIC and CHS could be compared to assess the impact of factors differing between birth cohorts on heart failure etiology.

ARIC includes a large proportion of African Americans, which is one of its major strengths for heart failure research. Thirteen years have passed since the last clinical exam, and it is important to determine changes in predisposing factors in the interim, including blood pressure, lifestyle, dietary intake, psychosocial, and behavioral factors. Currently, technological advances allow web-based food frequency questionnaires to be done by phone to assess dietary intakes. It is important to re-measure physical activity (objectively if possible), which is important in regulating autonomic tone. A good physical activity measure with actigraphy and maybe a 6-minute walk would be much better than a physical activity questionnaire. Obtaining fitness measures would also be of interest for a baseline before onset of sarcopenia and frailty. The study may consider including measures of arterial stiffness and the treadmill test to look for hyper-reactive blood pressure response to exercise.

The ARIC study also has opportunities to understand more about the prevalence of atrial fibrillation and its association with heart failure development. For example, the study can examine predisposing factors and prognostic implications of heart failure preceding atrial fibrillation or the converse situation. The panel recommended the report from the recent NHLBI Working Group on atrial fibrillation regarding the value of inception cohorts and high-risk groups for primary prevention.

Outcomes Research in Heart Failure

It is important to collect and adjust for quality of care and patient compliance measures in studying factors associated with clinical outcomes in population based studies. For example, how well are the participants getting integrated care for the spectrum of geriatric syndromes? ARIC should take advantage of merges with Medicare, as has been done in the CHS. The study could also link data with pharmacy databases for more accurate data on medication use and timing, or to ramp up data collection during periods of illness. Although it will be difficult to obtain all of the desired time-sensitive detail necessary to address this, the study could obtain information by thinking creatively and ramping up active surveillance.

Diastolic heart failure, as well as diastolic ventricular dysfunction without flagrant heart failure, are often not identifiable from discharge codes, so the study needs to carefully review medical records for these events. For example, the study could review records of people hospitalized for other causes such as pneumonia to determine if diastolic heart failure is in the clinical pathway as a contributor of cause of death.

ARIC may find ways to involve the physician community to obtain data on heart failure management and to see if clinicians agree with ARIC diagnoses for their patients. Additionally, the study may follow up participants with significant results to determine if the results reporting changes physicians' management on heart failure. For example, what happens to participants with a systolic blood pressure of 140-160? How are they being treated? Are they avoiding events? Does participation in ARIC benefit them?

The panel also suggested that the study obtain information on care-seeking behavior in the setting of acute heart failure and examine facilitators and barriers to seeking medical care in a timely manner. The study could ask participants simple questions about barriers to accessing health care and acquiring medications. Questions about time to treatment for heart failure could be included as well by looking at time from onset of acute and/or premonitory symptoms to presentation for care. Similar information would also be important to collect for the ARIC dementia study. Some of the study components can be studied in particular demographic or clinical subgroups if interest.

Depression may be a risk factor for the development of heart failure, which has not been well demonstrated because the appropriate longitudinal study has not been done. The ARIC study is ideally suited for testing this hypothesis. A measure of depressive symptoms could be added to the assessment. The ARIC study also may consider assessing the impact of anxiety on the CVD outcomes.

Other Topic Areas

As the cohort has transitioned from middle age to old age, ARIC should now focus on studying triggers of events and determining correlates in progression of subclinical to clinical events. In both ARIC and CHS studies, a small group of participants had clinical exams within 30 days before events, which may provide opportunities for further investigation.

The panel indicated that healthy aging could be assessed in the context of heart failure, obesity, or in general. Sample questions include: What does healthy aging mean to the cohort? How can we define it? How would participants define it? What kind of bio-repository would be needed for the future to investigate this and other research questions?

The panel pointed out that there is a controversy whether diastolic heart failure is a distinct entity or other factors such as vascular stiffness and neurohormonal may influence it. It is important to consider vascular aging as well as assess kidney and brain vascular beds. Vascular stiffness is strongly correlated with other factors. This could be a unifying theme for the exam. The panel suggested that the study use a vascular stiffness approach rather than a dementia approach to identify dementia cases and do case-control MRIs. The exam should include determinations of cystatin C, microalbuminuria, and body composition. It is necessary to

have less of an organ approach and more of a system approach to look at aging in the vascular beds. There may be a global phenotype of vascular aging that has not yet been identified. Visceral fat and metabolic changes with increasing inflammation might be a major part of the system.

The ARIC study can also better characterize correlates of body composition to answer several research questions. Does overweight at this age have health implications, does it matter what people weighed in middle age, and should people be pressured to lose weight or is being overweight protective in this group? This issue has remained unclear. Since obesity comprises 65-70% of all heart failure patients in some studies, data are needed to help clarify guidelines in this area. The Health ABC study showed large body composition differences by race, and therefore body composition measures by computed tomography (CT) scan are very important. Characterizing cardiac sarcopenia and fatty infiltration could also be pursued.

The panel emphasized the value of research in improving clinical practice and public health. The importance of translation of knowledge from epidemiologic studies to actual clinical practice was discussed. The panel recommended that the NHLBI make efforts to complement research activities in ARIC with those in its other programs and speed up the process to make it more informative for clinical practice and prevention programs.

[Back to Table of Contents](#)

Recommendations and Priorities

The Working Group acknowledged that the ARIC study is a valuable resource for research on the progression of subclinical to clinical cardiovascular disease and heart failure. The group endorsed the major topic areas as presented for the next possible exam in ARIC, including heart failure diagnosis and screening, triggers and modifiers in heart failure development, and outcomes associated with heart failure. The Working Group provided the following recommendations and priorities for future research in the ARIC study, especially in a possible clinical examination.

For the cohort study, an exam is needed to:

- Characterize phenotype and staging of heart failure by echocardiography and biomarkers, and develop novel criteria for heart failure diagnosis and screening in the community-based population. The exam needs to be straightforward and reproducible across all four field centers. A core lab is needed for an echocardiography component. The study may consider cardiac MRI for structure and function in a subset for better data quality and reproducibility.
- Consider alternative study designs, for example, splitting the participants into 3 groups: one group receiving echocardiogram to delineate antecedents of left ventricular systolic and diastolic dysfunction and their associations with prior and subsequent heart failure; the second group receiving a stress test to measure blood pressure, heart rate, physical fitness, and ECG responses to exercise; and the third for both to examine the relation between direct cardiac measures and exercise findings.
- Identify risk markers, triggers, and precipitating factors in progression of heart failure (stages A to D), including ventricular and vascular stiffness; interplay of renal insufficiency, diabetes, ambulatory blood pressure, and atrial fibrillation; infection; genomics, proteomic, and metabolic determinants; quality of care and patient compliance; physical activity, nutrition, psychological distress, and cognition.
- Determine the contributions of ventricular and vascular stiffness, diabetes, and renal insufficiency, and their interactions, to the initiation and progression of diastolic heart failure.
- Study healthy aging in a systematic approach to develop a global phenotype of vascular aging and to assess visceral fat and metabolic changes with increasing inflammation.
- Examine the impact of body composition and body weight changes from middle to old age on the progression and development of heart failure.
- Follow up participants with significant clinical results from the exam to assess the impact of results reporting on physicians' management of heart failure and outcomes.

Suggested exam components:

- Echocardiography (LV systolic function/mass, tissue Doppler and speckle tracking)
- Pulse wave velocity and central aortic pressure
- Anthropometry
- 6-minute walk test or treadmill stress test
- Ambulatory blood pressure monitoring
- Electrocardiogram and Holter monitor
- BNP, NT-pro-BNP, Cystatin-C, microalbuminuria

- CT for body composition
- Medical history and medication use
- Life style, diet, depression, and psychosocial factors
- Activities of daily living and quality of life measures
- Cognitive function assessment

For Community Surveillance:

- More actively characterize cause of death
- Include heart failure management questions, self care attitudes and practices
- Attempt to speed up the data collection process
- Regularly release the surveillance results in web-based reports rather than in papers published on an irregular basis
- Consider active surveillance if considering a trigger-type study

[Back to Table of Contents](#)

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[Back to Table of Contents](#)

[HOME](#) | [SEARCH](#) | [ACCESSIBILITY](#) | [SITE INDEX](#) | [OTHER SITES](#) | [PRIVACY STATEMENT](#) | [FOIA](#) | [CONTACT US](#)



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