Working Group on Future Research Opportunities in Multi-Ethnic Study of Atherosclerosis (MESA)

Hyatt Regency Bethesda
March 5, 2007

Welcome and Charge

Dr. Newman stated that the charge was to recommend areas of research that MESA can uniquely address during a continuation, based on knowledge of the field and an understanding of the resource that MESA has created and to provide some level of ranking of research ideas presented.

Background information about MESA

Dr. Bild presented a brief overview of the study, referring to the binder of materials that had been distributed, including the following:

- Original MESA Objective – To identify determinants of progression of subclinical to clinical cardiovascular disease (CVD)
- Cohort characteristics – age, gender, and ethnicity distribution and no prevalent CVD at baseline
- Subclinical CVD measures, including measures available to analyze progression
- Ancillary studies – 48 funded, many pending, in a wide range of disciplines
- Resources created -- a large data set and repository of blood and urine samples and DNA
- Publications – listing and selected reprints

NHLBI Strategic Plan

Dr. Bild reviewed the NHLBI Strategic Plan, including the process that led to the penultimate plan that was presented to the NHBL Advisory Council in February. She gave an overview of the three major goals and eight strategies in the plan and highlighted language relevant to goals and opportunities in MESA. These include:

- Delineate normal and pathologic mechanisms (e.g., identify biomarkers and characterize role)
- Enhance transmission of knowledge between basic and clinical arenas
- Identify key genetic variants, integrate phenotype and genotype data, and identify gene-environment interactions
- Study disease across the life span
- Develop approaches for risk stratification and their application and identify possible prevention strategies
- Advance personalized medicine, including provide environmental context
- Develop more precise measures of environmental exposures and more robust definitions of phenotypes
- Identify cost-effective approaches to prevention, diagnosis, and treatment
- Enhance understanding of the contributions of individual and societal factors in health disparities
- Support data-sharing

Strategies outlined in the Strategic Plan that align with MESA's strategies include:

- Enhance interdisciplinary work
- Increase the return from NHLBI population-based and outcomes research
- Support multi-disciplinary teams
- Develop and retain human capital – particularly by serving as a training ground for young investigators

Investigator Presentations

Dr. Burke -- Predictive value of subclinical CVD measures. He presented data on the predictive value of MR-measured LV mass for heart failure and coronary calcium for coronary heart disease events, on predictors of progression of coronary calcium, and on changes in risk factors observed in the cohort. He emphasized the opportunities that would be made

available by the accrual of more clinical events, including the conduct of subgroup analyses, identification of risk factors and subclinical disease measures that could be further investigated for their potential to prevent onset of clinical disease, identification of strategies to better identify intermediate risk groups, and the observation of whether there are differences across age, gender, and ethnic groups.

Dr. Lima -- Cardiac MRI measures of LV structure and function in MESA. He acknowledged his many collaborators, including trainees and junior investigators from the departments of Radiology, Cardiology, and School of Hygiene. He described the methods for measuring regional wall function, which is now considered the gold standard. In MESA, approximately 5000 participants had traditional MRI measures of LV mass, volume, and function. Approximately 2000 participants underwent an MRI tagging study using HARP methodology to quantify regional myocardial function. The primary measure of function analyzed is circumferential strain, though many other measures are also available. He reviewed several MESA findings, including associations of strain with smoking, blood pressure, carotid IMT, ethnicity (worse in African Americans than other groups), and gender (worse in men than women). After 4 years of follow-up, heart failure events in MESA (n=78) mimic the pattern by ethnicity observed for circumferential strain: most events occurred in African Americans and fewest in Chinese. Finally, he showed preliminary data indicating that diabetes is associated with worsening function over time.

Drs. Arnett and Divers -- Ancestral informative markers (AIMs) and self-reported ethnicity and LV mass. LVH phenotype varies among ethnicities, including size and remodeling. There is strong evidence from previous studies that there is a genetic component, with heritabilities of 30-60%. Principal component analysis of AIMs shows a distinct cluster for Chinese, less homogeneous clusters for whites and African Americans, and the greatest heterogeneity among Hispanics, with substantial overlap with the white and African American groups. Self-reported ethnicity and assigned ethnicity agreed well for African Americans and whites, but there was poor agreement among Hispanics. The principal component analysis removes the genetic background effect on LV mass and LV ejection fraction in epidemiologic and genetic studies. This method provides results that are similar to what we observe when the ancestry proportion estimates are used as control variables.

The investigators departed, with thanks from the Working Group members and NHLBI Project Office.

Plans for Renewal (MESA II)

Dr. Bild presented the plans for study renewal, including the general framework – cohort surveillance through 2014-15 and an Exam 5 in 2010-11. The cohort is projected to include 5,200 participants (90% of surviving participants), with an age range 54-93, and with a slightly altered ethnic composition based on current drop-out experience (43% white, 26% African American, 20% Hispanic, and 11% Chinese).

She presented the four proposed “anchoring” objectives, as well as other possible research areas, and invited the Working Group to provide feedback and additional suggestions. The four objectives include

1. To identify factors related to progression of subclinical to clinical CVD
2. To identify predictors of decline in ventricular function
3. To provide a platform for in-depth studies in CVD and other areas
4. To determine the basis for racial/ethnic differences in CVD

Noting that large observational cohort studies are able to address many objectives simultaneously, she provided a list of other research areas that could be addressed, including the following:

- Unrecognized MI
- Diabetes and glucose intolerance
- Renal function (estimates of glomerular filtration and albuminuria)
- Cognitive function
- Sleep disorders
- Right ventricular function
- Pulmonary function
- Carotid atheroma
- Coronary disease (CT angiography)
- Peripheral vascular disease
- Genetics and gene X environment interactions
- Proteomics
- Metabolomics (using fresh blood)
- Changes in diet, physical activity, and environmental factors

- Retinal vessels and disease

She presented data that address the feasibility of observing meaningful change in LV function over time, including cross-sectional data that show measurable differences in regional strain measures associated with risk factors and the projected number of expected new clinical heart failure cases: 300 by 2010. If regional dysfunction precedes clinical heart failure and represents the tip of the iceberg, then many more cases of significant dysfunction will be able to be identified. She also referred back to Dr. Lima's presentation, which demonstrated measurable changes in strain over 4 years.

She presented the proposed timeline and noted that MESA Air is planning to repeat coronary calcium and carotid IMT measures in half the cohort in 2010 in conjunction with a MESA Exam 5. Finally, she described the process for further review of the MESA initiative by the NHLB Advisory Council, and the subsequent review and acquisition process, if the initiative is approved. RFPs specify the statement of work, while the researchers' proposals provide details about how the work would be performed, along with all relevant technical information. There is a period of protocol development after awards are made.

Discussion by Working Group

The Working Group acknowledged that MESA is unique because of its multiple ethnic groups and precise characterization of subclinical CVD. The Group endorsed the four main objectives as presented, including continued evaluation of the predictive value of subclinical CVD and other measures and studying the natural history and predictors of change in left ventricular function and development of heart failure. They also stated that providing a platform for additional in-depth studies and evaluating variation by race/ethnicity were important features of MESA. The Working Group discussed the proposed research areas and suggested others. While there was not enough time for a detailed discussion of all possible components and priorities the following feedback and approximate priorities were provided.

Highest priority:

- Continue surveillance for clinical CVD events in order to take advantage of the data that have been collected and allow research questions related to progression of and predictive value of subclinical disease measures and other measures in important subgroups, including age, ethnicity, and gender, to be addressed.

High priority:

- Perform repeat cardiac MRI on the entire available cohort, including tagging to measure regional dysfunction, to allow the study of change over time. Tagging would also allow excellent study of diastolic function.
- Perform gadolinium enhancement to identify unrecognized myocardial infarction.
- Perform echocardiography in a subset to compare its clinical utility with MRI.
- Measure serum brain natriuretic peptide (BNP) as a predictor of HF.
- Perform studies to characterize sleep, including actigraphy (to measure sleep duration), oximetry (to measure blood oxygen desaturation), and sleep-disordered breathing. MESA could fill in gaps not addressed by the Sleep Heart Health Study, including evaluating sleep and nocturnal hypoxemia in relation to heart failure.
- Measure physical functioning as it relates subclinical cardiovascular disease.
- Perform brain MRI to identify lacunar strokes, white matter disease, and other abnormalities as objective measures of brain pathology as related to subclinical cardiovascular disease. It was noted that vascular disease of the brain is as important as vascular disease of the heart in elderly people.
- Assess cognitive function (a 30-minute assessment was recommended) to relate cross-sectionally or retrospectively to other data and as a baseline for possible future measures. Include an assessment of depression and executive functioning. Test performance may be influenced by culture or education; attention should be paid to this when selecting tests. The most useful design is to obtain change over time in individuals.
- Re-evaluate diet, physical activity, and other environmental factors.

Enthusiasm also expressed:

- Repeat coronary calcium measurement in the entire cohort.
- In conjunction with coronary calcium measurement, CT angiography in a subset (perhaps 50%) to identify and quantify non-calcified plaque. Coronary calcium measurement may be particularly valuable in women, who develop it later than men. Consider comparing participants who undergo CTA to those who do not to gain an understanding of the clinical impact of the measurement itself. There was much discussion about CTA with a wide range of level of enthusiasm and caution expressed about the risk of iodine-contrast agent-induced renal failure and anaphylaxis, difficulty handling clinically significant findings (without some relevant guidelines being in place), and interfering with the natural history of atherosclerosis.

- Measure visceral adiposity and liver fat from CT or MRI of the abdomen.
- Re-evaluate carotid plaque characteristics with MRI.
- Measure hemodynamics, such as vascular compliance or stiffness.
- Perform electrocardiogram.
- Measure ankle-brachial index.
- Include provocative testing, such as with a simple exercise test.
- Evaluate renal function.

Other comments:

- Study whether further evaluation of the “intermediate risk” group can enhance risk prediction.
- Determine which tests for subclinical disease assessment might be useful clinically.
- Gadolinium used for carotid MR imaging has had good acceptance in the MESA substudy and in an ancillary study and in the Icelandic Heart Study. However, there are recent reports of dermopathy in renal failure patients.
- Speed up events investigations to take better advantage of these data.
- Prepare for changes in CT (e.g., 128- and 256-slice scanners) and MRI technology (e.g., 3 Tesla magnets).
- Genetics is a currently active area in MESA and will continue to be so; additional phenotyping will enhance the value of the genetics studies.
- Ascertainment and definitions of heart failure should be carefully considered.
- Consider PET scanning in a substudy (though concern was expressed about radiation).
- Future MRI may be able to assess non-ischemic fibrosis in heart failure without gadolinium.
- Getting good measures of diastolic dysfunction will allow the study of questions of why some people with diastolic dysfunction become symptomatic and some do not.
- MR of the head could include upper airway images.
- Include costs in the renewal for sharing of images.
- Perform whole genome amplification to assure an abundant supply of DNA.
- Consider the value of follow-up after Exam 5 to evaluate how Exam 5 measures relate to subsequent outcomes and change, particularly in cognition. (The current plan for renewal has 3 years of surveillance after Exam 5.)

Drs. Newman and Bild thanked the Working Group members for their valuable time and contributions.

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