Supplement

Study rationale:

Heart failure (HF) is a complex multi-system disease process which rests on a clinical diagnosis based on signs and symptoms, physical exam, biomarkers and imaging studies. Large scale epidemiologic studies have identified several cardiac and extra-cardiac predictors for HF. While identifying individual risk factors is important to understanding the pathophysiology of HF, integrative clinical risk prediction models provide more meaningful tools for clinicians and epidemiologists to implement preventive strategies to high risk patients.

The Multi-Ethnic Study of Atherosclerosis (MESA) was initiated by the National Heart, Lung, and Blood Institute to further understand the pathogenesis of cardiovascular disease by using advanced imaging methods to identify sub clinical cardiovascular disease and study its progression to clinically manifest disease. Cardiac magnetic resonance (CMR) imaging is capable of providing highly accurate and reproducible measures of left ventricular (LV) anatomy and identifies subtle changes providing important new information about the pathophysiology of subclinical disease. In the MESA study, LV mass by CMR has been shown to be a powerful predictor of HF, however it is of limited clinical use especially in a healthier population due to cost and availability. Therefore, for broader clinical application, a risk prediction model should be based on simple variables that can be easily obtained in primary care settings. In this study we looked at various parameters of individual risk factors (area under the curve, c-statistic, net reclassification index) to develop a HF risk prediction equation based on risk factors which would be readily available to primary care physicians in an outpatient setting to create a robust model for determining a 5-year risk for developing HF in patients who do not have existing

cardiac condition. It is to be noted that this model would not be useful in acutely ill patients, rather in "healthier" community dwelling individuals.

Study population:

The MESA cohort was drawn from six regions in the United States: Baltimore City and Baltimore County, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; New York, New York; and St. Paul, Minnesota. Except when random digit dialing was used, an informational brochure was mailed to households in targeted areas. Within 14 days, households were contacted by telephone; the language spoken in the home was determined; and a questionnaire was administered in English, Spanish, Cantonese, or Mandarin to introduce the study and collect eligibility information. Eligible MESA participants are defined as persons living within the defined geographic boundaries for each Field Center who are between the ages of 45 and 84 at enumeration, who are African-American, Chinese-American, White, or Hispanic, and who do not meet any of the exclusion criteria (see below). Target ethnic groups for each field center were chosen to maximize efficiency to detect ethnic differences and to allow the separation of the effect of ethnicity from that of study site. To augment recruitment of elderly members of minority groups, toward the end of the recruitment period, participants were asked to refer elderly persons to the study. MESA's primary hypotheses are concerned with the determinants and natural history of subclinical cardiovascular disease. Therefore, participants with known clinical disease were not recruited. Other exclusion criteria related to the long-term nature of the study or to incompatibility with certain components of the MESA exam. These exclusion criteria included clinical cardiovascular disease (physician diagnosis of heart attack, stroke, transient ischemic attack, heart failure, or angina), current atrial fibrillation, any

cardiovascular procedure (coronary artery bypass graft, angioplasty, valve replacement, pacemaker or defibrillator implantation, any surgery on the heart or arteries), pregnancy, active cancer treatment, weight >300 lbs, serious medical condition which precluded long term participation, nursing home residence, cognitive inability, inability to speak English, Spanish, Cantonese or Mandarin, plan to leave the community within five years, and chest CT within the past year. The MESA protocol, including information about the source populations from which recruitment occurred, detailed exclusion criteria, contact information for the investigators, and other information, is available on the World Wide Web at www.mesa-nhlbi.org

Supplement table 1: Race-specific c-statistic for incident HF in the MESA study

Ethnicity	c-statistic
White	0.84
Chinese-American	0.85
African American	0.90
Hispanic	0.88

Supplement table 2: Risk reclassification stratified by event status by the addition of LV mass index to the base model for HF categories <5%, 5-20% and >20%.

Model 1	Model 1+LV mass index			
Participants with event				
	<5% Risk	5%-20% Risk	>20% Risk	Total
<5% Risk	36	11	3	50
5%-20% Risk	5	26	10	41
>20% Risk	0	2	0	2
	41	39	13	
Participants without event				
	<5% Risk	5%-20% Risk	>20% Risk	Total
<5% Risk	3393	122	7	3522
5%-20% Risk	191	278	12	481
>20% Risk	0	14	14	28
Total	3584	414	33	

LV: left ventricle

Model 1: age, ethnicity, gender, body mass index, cigarette smoking, systolic blood pressure, heart rate, diabetes mellitus, total cholesterol and HDL cholesterol

Supplement table 3: Risk reclassification stratified by event status by the addition of NT-proBNP to the base model for HF categories <5%, 5-20% and >20%.

Model 1	Model 1+log(NT pro-BNP)			
Participants with event				
	<5% Risk	5%-20% Risk	>20% Risk	Total
<5% Risk	29	18	3	50
5%-20% Risk	4	23	14	41
>20% Risk	0	2	0	2
	33	43	17	
Participants without event				
	<5% Risk	5%-20% Risk	>20% Risk	Total
<5% Risk	3364	152	6	3522
5%-20% Risk	243	217	21	481
>20% Risk	0	13	15	28
Total	3607	382	42	

LV: left ventricle

Model 1: age, ethnicity, gender, body mass index, cigarette smoking, systolic blood pressure, heart rate, diabetes mellitus, total cholesterol and HDL cholesterol

Supplement table 4: Risk reclassification stratified by event status by the addition of LV mass index to the model containing NT proBNP for HF categories <5%, 5-20% and >20%.

(Model 1, log NT proBNP)	(Model 1, log NT proBNP)+LV mass index			
Participants with event				
	<5% Risk	5%-20% Risk	>20% Risk	Total
<5% Risk	31	2	0	33
5%-20% Risk	3	38	2	43
>20% Risk	0	2	15	17
	34	42	17	
Participants without event				
	<5% Risk	5%-20% Risk	>20% Risk	Total
<5% Risk	3564	43	0	3607
5%-20% Risk	79	296	7	382
>20% Risk	0	10	32	42
Total	3643	349	39	

LV: left ventricle

Model 1: age, ethnicity, gender, body mass index, cigarette smoking, systolic blood pressure, heart rate, diabetes mellitus, total cholesterol and HDL cholesterol

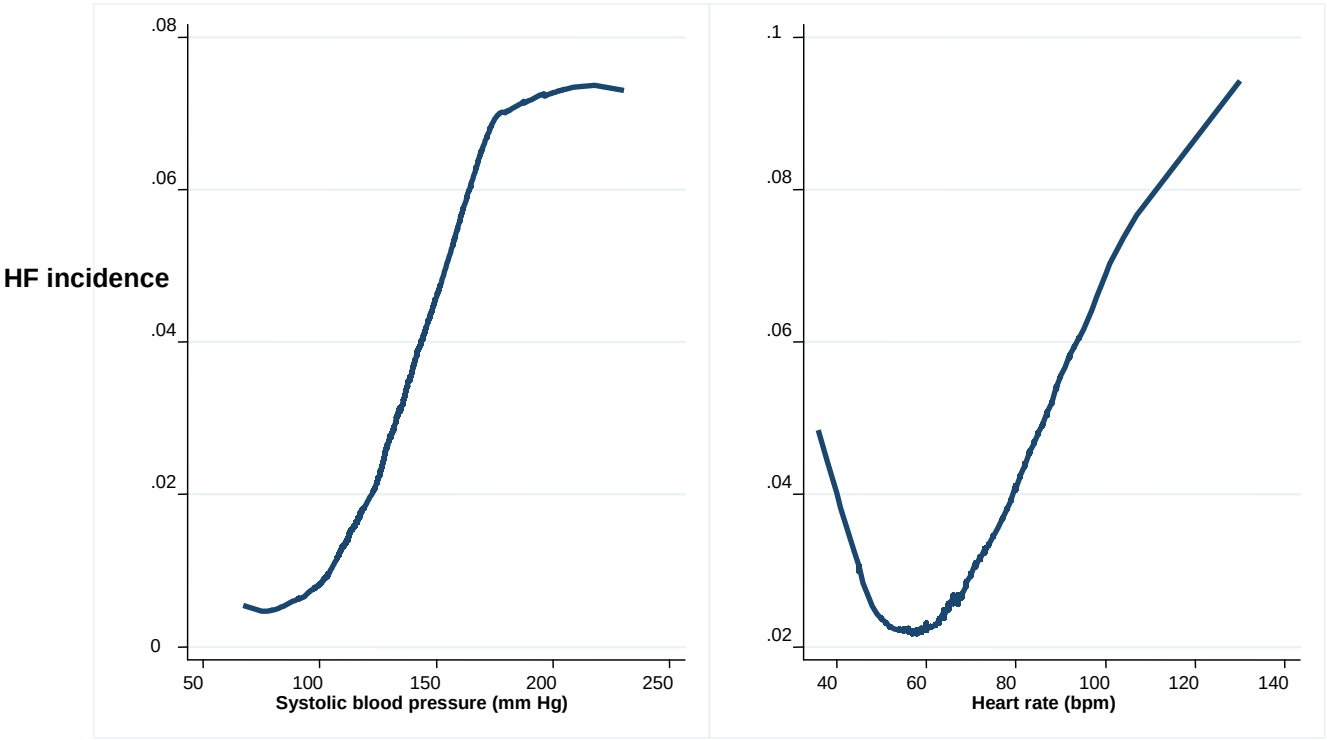
Supplement table 5: Risk reclassification stratified by event status by the addition of NT-proBNP to the model containing LV mass index for HF categories <5%, 5-20% and >20%.

(Model 1, LV mass index)	(Model 1, LVMI)+ log NT-proBNP			
Participants with event				
	<5% Risk	5%-20% Risk	>20% Risk	Total
<5% Risk	28	12	1	41
5%-20% Risk	6	27	6	39
>20% Risk	0	3	10	13
	34	42	17	
Participants without event				
	<5% Risk	5%-20% Risk	>20% Risk	Total
<5% Risk	3472	111	1	3584
5%-20% Risk	171	224	19	414
>20% Risk	0	14	19	33
Total	3643	349	39	

LV: left ventricle

Model 1: age, ethnicity, gender, body mass index, cigarette smoking, systolic blood pressure, heart rate, diabetes mellitus, total cholesterol and HDL cholesterol

Supplement figure 1: Non-linear relationship between systolic blood pressure and heart rate with incident HF.



Heart rate exhibits a nonlinear J shaped association with incident HF with highest rates at either extremes. Systolic blood pressure exhibits a sigmoidal nonlinear relation with incident HF.

Supplement figure 2: Relationship between incident HF and LV mass index by race (White vs. Black participants; overall represents all MESA population).