CMR in Clinical Trials: Prognostic Value of CMR versus Traditional Risk Factors

Aditya Jain, MD, MPH[1], David A. Bluemke, MD, PhD[1,2]
[1]Department of Radiology, Johns Hopkins University, Baltimore, MD
[1,2]-Radiology and Imaging Sciences, Clinical Center and National Institute of Biomedical Imaging and Bioengineering, National Institutes of Health, Bethesda, MD, USA

Adapted from: Cardiovascular imaging for assessing cardiovascular risk in asymptomatic men versus women: the multi-ethnic study of atherosclerosis (MESA).
Jain A, McClelland RL, Polak JF, Shea S, Burke GL, Bild DE, Watson KE, Budoff MJ, Liu K, Post WS, Folsom AR, Lima JA, Bluemke DA. Circ Cardiovasc Imaging. 2011

Introduction:

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in both men and women. Cardiac magnetic resonance (CMR) is a well-validated for non-invasive diagnostic and prognostic testing, and is used to assess left ventricular function, mass [5] and volumes [6]. Other alternative imaging metrics for assessment of cardiovascular risk include coronary artery calcium (CAC) [3], carotid intima-media thickness (IMT) [4]. However, there is limited population-based evidence on the independent and incremental utility of these imaging tests in CVD risk assessment [7]. Gender differences in the prevalence, presentation and prognosis of CVD, as well as in the role of traditional risk factors in determining its risk are increasingly recognized, which necessitates accrual of gender-specific information for the optimal prevention and management of CVD [1, 2].

In this review, we will compare these noninvasive imaging tests for their overall- and gender-specific predictive value of incident CVD. The incremental value of CMR relative to traditional risk factors is discussed. Data from the Multi-Ethnic Study of Atherosclerosis (MESA) will be used primarily to illustrate the role of CMR in relationship to traditional risk factors and other imaging tests.

Association of imaging measures with incident CVD:

Coronary heart disease. As seen in Table 1, log CAC score showed the highest HR for incident coronary heart disease (CHD) and cardiovascular disease (CVD) in the MESA population [Hazard ratio (HR) 2.3 and 1.7, respectively].

In men, HR's for CHD and CVD were 2.4 and 1.9, respectively. For women, the corresponding values were 2.2 and 1.9.

Stroke: Although both LV mass and LV mass/volume ratio were associated with the highest hazard ratio for incident stroke in the overall cohort (HR 1.3 for both), LV mass/volume ratio showed the highest HR for men (1.4), where as LV mass was higher for women (HR 1.5).

Heart failure. LV mass gave the highest HR for HF overall (HR 1.8). For men, the HR was 1.8, and for women, 1.7.

Table 1. Hazard ratios (HRs) and 95% Confidence Intervals for Incident CVD by Imaging Measures of Subclinical Disease Treated as Continuous Variables

	Overall (n=4965)	Men (n=2365)	Women (n=2600)
CHD			
CAC score	**2.3 (1.9, 2.8)‡**	**2.4 (1.9, 2.9)‡**	**2.2 (1.5, 3.1)‡**
Carotid IMT	1.1 (0.9, 1.3)	1.0 (0.9, 1.2)	1.3 (1.0, 1.7)
LV mass	1.1 (0.9, 1.2)	1.1 (0.9, 1.3)	1.0 (0.8, 1.3)
LV mass/volume	1.1 (0.9, 1.3)	1.2 (0.9, 1.3)	1.1 (0.8, 1.5)
Stroke (n=65)			
CAC score	1.0 (0.8, 1.4)	1.3 (0.8, 2.1)	0.9 (0.6, 1.3)
Carotid IMT	1.0 (0.8, 1.3)	1.1 (0.8, 1.6)	0.9 (0.6, 1.3)
LV mass	**1.3 (1.1, 1.7)‖**	1.2 (0.8, 1.6)	**1.5 (1.1, 1.9)‖**
LV mass/volume	**1.3 (1.1, 1.6)‖**	**1.4 (1.0, 1.9)§**	1.3 (0.9, 1.7)
Heart Failure (n=91)			
CAC score	1.4 (1.1, 1.7)§	1.4 (0.9, 1.9)	1.4 (0.9, 2.2)
Carotid IMT	0.9 (0.7, 1.1)	0.8 (0.6, 1.1)	1.0 (0.7, 1.5)
LV mass	**1.8 (1.6, 2.1)‡**	**1.9 (1.6, 2.2)‡**	**1.7 (1.3, 2.2)‡**
LV mass/volume	1.1 (0.9, 1.3)	1.1 (0.8, 1.3)	1.2 (0.9, 1.7)
All CVD (n=297)			
CAC score	**1.7 (1.5, 1.9)‡**	**1.9 (1.6, 2.3)‡**	**1.5 (1.2, 1.8)‡**
Carotid IMT	1.0 (0.9, 1.1)	0.9 (0.8, 1.1)	1.1 (0.9, 1.3)
LV mass	1.3 (1.2, 1.5)‡	1.4 (1.2, 1.5)‡	1.2 (1.0, 1.5)
LV mass/volume	1.1 (1.0, 1.2)§	1.1 (1.0, 1.3)§	1.1 (0.9, 1.3)

*adjusted for traditional risk factors (age, gender, ethnicity, BMI, systolic BP, total and HDL cholesterol, diabetes, cigarette smoking, hypertension, and lipid medication); ‡p≤0.001;p≤0.01;§p<0.05

CAC score refers to the natural logarithm of (CAC + 1) values; carotid IMT refers to a composite z score for overall maximal IMT;

LV mass was adjusted for body size when implied as a separate imaging measure but not in LV mass-volume ratio; HR expresses hazard in relation to one standard deviation increment of the respective imaging measure

BOLD script refers to imaging measure(s) showing the highest HR for each event type

Table 2 shows the area under the curve (AUC) statistics for incident CVD prediction. As compared to traditional risk factors alone, AUC values for future CHD, HF, and CVD showed the highest improvement after adding CAC, LV mass, and CAC respectively in the overall cohort (0.766 vs. 0.815, p<0.0001; 0.818 vs. 0.853, p=0.02; 0.773 vs. 0.797, p<0.001 respectively) and in men (0.714 vs. 0.785, p<0.0001; 0.790 vs. 0.845, p<0.01; 0.738 vs. 0.777, p<0.01 respectively). For women, CAC added most to AUC for CHD prediction (0.805 vs. 0.835, p=0.04).

Table 2. Area under the ROC Curve (AUC) for Incident CVD by Imaging for Subclinical Disease

Measure	Overall (n=4965)	Men (n=2365)	Women (n=2600)
CHD (n=187)			
Base model[*]	0.766	0.714	0.805
Base model + CAC	**0.815[†]**	**0.785[†]**	**0.835[§]**
Base model + Carotid IMT	0.777[§]	0.720	0.820
Base model + LV mass	0.768	0.722	0.805
Base model + LV mass/volume	0.772[§]	0.725	0.809
Base model + CAC + IMT + LV mass	**0.817[†]**	**0.787[†]**	0.837
Stroke (n=65)			
Base model	0.835	0.834	0.858
Base model + CAC	0.836	0.838	0.857
Base model + Carotid IMT	0.835	0.833	0.856
Base model + LV mass	0.843	0.839	0.869
Base model + LV mass/volume	0.843	0.841	0.864
Base model + CAC + IMT + LV mass	0.844	0.840	0.867
Heart Failure (n=91)			
Base model	0.818	0.790	0.851
Base model + CAC	0.826	0.794	0.862
Base model + Carotid IMT	0.818	0.791	0.851
Base model + LV mass	**0.853[§]**	**0.845[‖]**	0.868
Base model + LV mass/volume	0.818	0.790	0.858
Base model + CAC + IMT + LV mass	**0.856[§]**	**0.849[‖]**	0.881
All CVD (n=297)			
Base model	0.773	0.738	0.806
Base model + CAC	**0.797[‡]**	**0.777[‖]**	0.819
Base model + Carotid IMT	0.775	0.739	0.810
Base model + LV mass	0.785[§]	0.757[§]	0.811
Base model + LV mass/volume	0.777	0.745	0.806
Base model + CAC + IMT + LV mass	**0.806[†]**	**0.790[†]**	**0.824[§]**

[*]consists of traditional risk factors only; [†]p≤0.0001; [‡]p<0.001; p<0.01; [§]p<0.05
p-values stand for comparison with the respective base model
CAC score refers to the natural logarithm of (CAC + 1) values; carotid IMT refers to a composite z score for overall maximal IMT; LV mass was adjusted for body size when implied as a separate imaging measure but not in LV mass-volume ratio
BOLD script refers to imaging measure(s) leading to the highest increment in AUC when added to the base model

Net reclassification improvement (NRI) is a method to assess the percentage impact of each of additive factor to the regression model. The addition of CAC to traditional risk factors resulted in the highest improvement in CHD prediction among all imaging measures (NRI for CAC, 24%, p<0.001; carotid IMT, 4%, p=0.27; LV mass, 2%, p=0.58; LV mass/volume, 6%, p=0.06;

results not shown in tables).

Summary:

Among imaging measures, CAC was shown to be most strongly associated with CHD and CVD, LV mass and LV concentric remodeling were most strongly associated with stroke, and LV mass showed the strongest association with HF after adjustment for traditional risk factors. In general, these relationships were present for both men and women. According to AUC analysis, CAC provided the highest incremental CHD prediction in both men and women, and LV mass added the most to HF prediction beyond traditional risk factors in men compared to the other imaging measures.

A number of prior studies have reported a strong positive association between CAC score and incident CHD after inclusion of conventional coronary risk factors [3]. A prospective analysis in MESA has addressed the potential utility of CAC vs. IMT for CVD risk prediction before, and also found that CAC better predicted CHD and total CVD than did IMT [8]. Similarly, CAC has been previously shown to significantly improve CHD risk classification in MESA using NRI statistic in detail [18]. Previous ECG- and echocardiography-based studies have demonstrated LVH and abnormal LV geometry to confer an independent, increased risk of stroke [19, 20]. Although the highest quartile of IMT was linked to an increased risk of CHD independent of traditional risk factors as well as other imaging tests, IMT did not show an independent association with stroke, in contrast to prior reports [4, 8]. This could be variously attributable to methodological differences among these studies with respect to population demographics, carotid segment definition, ultrasound protocols, adjustment for confounding covariates, and/or definition and number of clinical end points.

Gender and Ethnic Considerations: Imaging measures of subclinical CVD are associated similarly with incident CVD in men and women as indicated by the lack of any effect modification by gender. This is despite the multifactorial influence of female reproductive hormones on the cardiovascular system, and lower sensitivity and specificity of imaging modalities for disease detection in women due to smaller vessels and heart size [15, 21], and the resulting potential for larger errors in measurements. In general, the majority of available data is regarding Caucasian men. More recent studies such as MESA indicate that imaging phenotypes cardiovascular risk somewhat independently of ethnicity and gender.

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