SUPPLEMENTAL MATERIAL

This supplemental material has been provided by the authors to give readers additional information about their work.

Supplemental Methods

Covariates

Measurements followed similar protocols in both the ARIC Study and the CHS. At baseline, study participants provided information on education, race, smoking status, and prevalence of CHD. In the ARIC Study, prevalent CHD was defined if self-reported based on a previous physician-diagnosis or by the presence of previous myocardial infarction on ECG. Incident CHD was adjudicated by the ARIC Morbidity and Mortality Classification Committee as previously described.[1] In the CHS, prevalent CHD was defined as a positive history for MI, coronary revascularization, or angina using information from self-report and hospitalization records. A physical examination collected information on height and weight, and blood pressure was measured with a random-zero sphygmomanometer. Fasting glucose and lipids were measured from blood samples obtained during the exam. Diabetes was defined as a fasting glucose level of ≥126 mg/dl, use of an oral hypoglycemic agent or insulin, or in addition, in the ARIC Study, a non-fasting glucose of ≥200 mg/dl or a self-reported medical diagnosis of diabetes. In the ARIC Study and the CHS, hypertension was defined as use of medication to treat high blood pressure, systolic blood pressure ≥140mm Hg, or diastolic blood pressure ≥90 mm Hg. In ARIC, heart failure at baseline was defined as the reported use of medications to treat heart failure in the previous 2 weeks or the presence of heart failure according to Gothenburg criteria; incident heart failure during follow-up was defined as the presence of ICD-9-CM code 428 in any hospitalization or death certificate.[2] In CHS, heart failure confirmation required, in addition to physician diagnosis, one of the following: 1) documented heart failure symptoms (e.g., shortness of breath, fatigue, orthopnea, paroxysmal nocturnal dyspnea) and physical signs (e.g., edema, pulmonary rales, gallop rhythm) consistent with heart failure; 2) supporting clinical findings such as pulmonary edema on chest x-ray; or 3) therapy for heart failure, including diuretics, digitalis, angiotensin-converting enzyme inhibitors, or beta-blockers.

In ARIC, serum creatinine was assessed in 99% of subjects at their initial visit, while in CHS it was assessed in 97% subjects.[3] Kidney function was assessed by calculation of the estimated GFR (eGFR)

using the abbreviated Modification of Diet in Renal Disease (MDRD) Study equation: (eGFR (ml/min per 1.73 m^2) = 186.3*(serum creatinine in $mg/dl^{-1.154}$)*($age^{-0.203}$)*(0.742 if female)*(1.21 if black). Details about medication use were previously described for the CHS[4] and the ARIC Study.[5] Framingham risk score variables were obtained in both cohorts and included age, sex, total cholesterol, HDL cholesterol, blood pressure, diabetes, and smoking.[6]

Reader Agreement for LV Ejection Fraction and Segmental Wall Motion Scoring

To assess interreader and intrareader agreement for LV ejection fraction and segmental wall motion measurements, κ statistics and the percentage of agreement were calculated. For LV ejection fraction, 339 paired studies were read for assessment of interreader agreement and 310 paired studies for intrareader agreement. In addition, 477 and 239 paired studies were read for assessment of interreader and intrareader agreement, respectively, in scoring LV segmental wall motion. There was agreement on 94% (κ=0.32) of the paired interreader studies for LV ejection fraction, and the agreement for LV segmental wall motion was 92% (κ=0.45). The agreement was better for the paired intrareader studies (98% for LV ejection fraction and 95% for segmental wall motion, with κ=0.82 and 0.59, respectively).[7]

Supplemental Table 1. Non-sudden CVD death rate and hazard ratio (95% confidence interval) by echocardiographic correlates, ARIC, 1993-2002, and CHS 1989-2002

Mitral Annular Calcification						
	ARIC			CHS		
	No	Yes	P-value	No	Yes	P-value
NSCD cases	63	6		272	325	
Person-years	16094	791		29696	20089	
Model 3: HR (95% CI)	1 (REF)	1.46 (0.63 – 3.38)	0.13	1 (REF)	1.81 (1.53 – 2.12)	<0.001
Model 4: HR (95% CI)	1 (REF)	1.04 (0.44 – 2.44)	0.93	1 (REF)	1.47 (1.24 – 1.73)	<0.001
Aortic Sclerosis						
	ARIC			CHS		
	No	Yes	P-value	No	Yes	P-value
NSCD cases	62	7		248	325	
Person-years	16011	879		27318	21277	
Model 3: HR (95% CI)	1 (REF)	1.48 (0.68 – 3.25)	0.33	1 (REF)	1.76 (1.49 – 2.07)	<0.001
Model 4: HR (95% CI)	1 (REF)	1.15 (0.52 – 2.58)	0.73	1 (REF)	1.46 (1.22 – 1.73)	<0.001
Reduced LV ejection fraction						
	ARIC			CHS		
	No	Yes	P-value	No	Yes	P-value
NSCD cases	52	17		864	170	
Person-years	16599	341		58667	4143	
Model 3: HR (95% CI)	1 (REF)	8.96 (4.76 – 16.88)	<0.0001	1 (REF)	2.14 (1.80 – 2.54)	<0.001
Model 4: HR (95% CI)	1 (REF)	4.61 (2.40 – 8.85)	<0.0001	1 (REF)	1.62 (1.33 – 1.97)	<0.001
Left atrium diameter										
	ARIC tertiles (cm)					CHS tertiles (cm)				
	<3.62	3.62 – 4.05	>4.05	Continuous per 1 SD	P-value+	<3.60	3.60 – 4.13	>4.13	Continuous per 1 SD	P-value+
NSCD cases	13	7	33			281	286	435		
Person-years	4578	4566	4628			20881	20997	19031		
Model 3: HR (95% CI)	1 (REF)	0.48 (0.19 – 1.21)	1.94 (1.01 – 3.74)	1.65 (1.31 – 2.09)	<0.0001	1 (REF)	0.94 (0.79 – 1.10)	1.37 (1.17 – 1.59)	1.25 (1.17 – 1.34)	<0.01
Model 4: HR (95% CI)	1 (REF)	0.47 (0.19 – 1.18)	1.67 (0.86 – 3.25)	1.51 (1.18 – 1.92)	0.0008	1 (REF)	0.90 (0.76 – 1.06)	1.08 (0.92 – 1.27)	1.06 (0.99 – 1.14)	0.08
Aortic root diameter										
	ARIC tertiles (cm)					CHS tertiles (cm)				
	<2.92	2.92 – 3.29	>3.29	Continuous per 1 SD	P-value+	<2.96	2.96 – 3.35	>3.35	Continuous per 1 SD	P-value+
NSCD cases	16	24	21			285	346	374		
Person-years	5190	4977	5146			21487	20747	18791		
Model 3: HR (95% CI)	1 (REF)	1.35 (0.72 – 2.55)	1.12 (0.58 – 2.15)	1.06 (0.82 – 1.36)	0.66	1 (REF)	1.13 (0.96 – 1.32)	1.14 (0.97 – 1.34)	1.06 (1.00 – 1.13)	0.07
Model 4: HR (95% CI)	1 (REF)	1.25 (0.66 – 2.36)	0.75 (0.38 – 1.49)	0.93 (0.71 – 1.20)	0.57	1 (REF)	1.08 (0.92 – 1.28)	1.13 (0.96 – 1.34)	1.05 (0.98 – 1.12)	0.18
LV mass index										
	ARIC tertiles (g/m^2.7)					CHS tertiles (g/m^2.7)				
	<41.4	41.4 – 53.1	>53.1	Continuous per 1 SD	P-value+	<33.07	33.07 – 42.20	>42.20	Continuous per 1 SD	P-value+
NSCD cases	8	6	30			148	188	297		
Person-years	4272	4305	4327			15391	15002	13197		
Model 3: HR (95% CI)	1 (REF)	0.63 (0.22 – 1.83)	2.22 (0.97 – 5.05)	1.19 (0.94 – 1.49)	0.15	1 (REF)	1.30 (1.04 – 1.61)	2.05 (1.68 – 2.50)	1.46 (1.37 – 1.56)	<0.001
Model 4: HR (95% CI)	1 (REF)	0.65 (0.22 – 1.88)	1.90 (0.84 – 4.30)	1.16 (0.91 – 1.49)	0.22	1 (REF)	1.13 (0.90 – 1.41)	1.34 (1.08 – 1.65)	1.18 (1.09 – 1.28)	<0.001

	Mitral E to A					
	ARIC (m/s)			CHS (m/s)		
	<0.70	0.70 – 1.5	>1.5	<0.70	0.70 – 1.5	>1.5
NSCD cases	9	35	9	281	619	85
Person-years	1270	13294	1030	10106	47699	3170
Model 3: HR	1.29	1 (REF)	4.18	2.18	1 (REF)	1.87
(95% CI)	(0.60 – 2.81)		(1.98 – 8.82)	(1.89 – 2.52)		(1.48 – 2.35)
Model 4: HR	0.96	1 (REF)	3.37	1.73	1 (REF)	1.40
(95% CI)	(0.42 – 2.18)		(1.57 – 7.25)	(1.49 – 2.01)		(1.08 – 1.82)

	Mitral Peak E			
	ARIC (m/s)		CHS (m/s)	
	Continuous per 1 SD	P-value+	Continuous per 1 SD	P-value+
Model 3: HR	1.30	0.03	1.04	0.520
(95% CI)	(1.02 – 1.65)		(0.92 – 1.18)	
Model 4: HR	1.28	0.03	1.04	0.514
(95% CI)	(1.02 – 1.61)		(0.92 – 1.18)	

ARIC=Atherosclerosis Risk in Communities Study; CHD=coronary heart disease; CHS=Cardiovascular Health Study; CVD=cardiovascular disease; eGFR=estimated glomerular filtration rate; HDLc=high density lipoprotein cholesterol; LV=left ventricular; NSCD=non-sudden CVD death

+P-value is for continuous variable, per 1 SD

Model 3: Cox proportional hazards model adjusting for Framingham risk score as one variable: (sex, age, total cholesterol, HDLc, blood pressure, diabetes and smoking), and also prevalent CHD + eGFR

Model 4: Model 3 + time-dependent heart failure, time-dependent CHD

Supplemental Table 2. SCD hazard ratios (95% confidence interval) by continuous variable using select echocardiographic variables from Table 3.

	Left atrium diameter			
	ARIC (cm)		**CHS (cm)**	
	Continuous, per 1 SD	**p-value[+]**	**Continuous, per 1 SD**	**p-value[+]**
Model 1: HR (95% CI)	1.48 (1.10 – 1.99)	0.01	1.24 (1.09 – 1.40)	0.001
Model 2: HR (95% CI)	1.38 (1.02 – 1.88)	0.04	1.19 (1.05 – 1.35)	0.007
Model 3: HR (95% CI)	1.34 (0.99 – 1.83)	0.06	1.18 (1.04 – 1.34)	0.009
Model 4: HR (95% CI)	1.24 (0.92 – 1.66)	0.16	1.13 (0.99 – 1.29)	0.07
	Aortic root diameter			
	ARIC (cm)		**CHS (cm)**	
	Continuous, per 1 SD	**p-value[+]**	**Continuous, per 1 SD**	**p-value[+]**
Model 1: HR (95% CI)	1.38 (1.00 – 1.90)	0.05	1.02 (0.89 – 1.17)	0.77
Model 2: HR (95% CI)	1.40 (1.07 – 1.85)	0.02	1.12 (0.99 – 1.27)	0.07
Model 3: HR (95% CI)	1.37 (1.03 – 1.81)	0.03	1.12 (0.99 – 1.27)	0.08
Model 4: HR (95% CI)	1.28 (0.95 – 1.73)	0.10	1.07 (0.94 – 1.22)	0.32
	LV mass index			
	ARIC (g/m^2.7)		**CHS (g/m^2.7)**	
	Continuous, per 1 SD	**p-value[+]**	**Continuous, per 1 SD**	**p-value[+]**
Model 1: HR (95% CI)	1.50 (1.20 – 1.88)	0.0004	1.51 (1.33 – 1.70)	<0.001
Model 2: HR (95% CI)	1.31 (1.04 – 1.64)	0.02	1.38 (1.22 – 1.57)	<0.001
Model 3: HR (95% CI)	1.28 (1.01 – 1.63)	0.04	1.38 (1.22 – 1.57)	<0.001
Model 4: HR (95% CI)	1.29 (1.01 – 1.66)	0.04	1.31 (1.13 – 1.53)	0.001

ARIC=Atherosclerosis Risk in Communities Study; CHD=coronary heart disease; CHS=Cardiovascular Health Study; eGFR=estimated glomerular filtration rate; HDLc=high density lipoprotein cholesterol; SCD=sudden cardiac death

+P-value is for continuous variable, per 1 SD

Model 1: Cox proportional hazards model adjusted for age, sex, **race (in CHS only)

Model 2: Cox proportional hazards model adjusting for Framingham risk score as one variable: (sex, age, total cholesterol, HDLc, blood pressure, diabetes and smoking), and also prevalent CHD

Model 3: Model 2 + eGFR

Model 4: Model 3 + time-dependent heart failure, time-dependent CHD

Supplemental Table 3. C-statistic of sudden cardiac death with echocardiographic variables added to the Framingham risk score (fractional shortening replacing reduced ejection fraction).

	ARIC C-statistic (95% CI)	CHS C-statistic (95% CI)
Framingham risk score	0.608 (0.526-0.690)	0.669 (0.638-0.700)
FRS + Univariate: (each variable added to the score separately)		
Mitral annular calcification	0.648 (0.567-0.729)	0.677 (0.633-0.721)
LV fractional shortening, continuous	0.663 (0.555-0.770)	0.654 (0.610-0.699)
Aortic sclerosis	0.620 (0.535-0.705)	0.671 (0.628-0.714)
Left atrium diameter, continuous	0.608 (0.522-0.694)	0.669 (0.637-0.702)
Left atrium diameter, tertiles	0.619 (0.537-0.702)	0.669 (0.637-0.701)
Aortic root diameter, continuous	0.682 (0.609-0.756)	0.666 (0.635-0.697)
Aortic root diameter, tertiles	0.637 (0.564-0.710)	0.666 (0.635-0.697)
LV mass index, continuous	0.648 (0.542-0.755)	0.687 (0.645-0.728)
LV mass index, tertiles	0.623 (0.538-0.707)	0.670 (0.628-0.712)
Mitral E/A, continuous	0.629 (0.542-0.715)	0.666 (0.634-0.698)
Mitral E/A, categories	0.633 (0.553-0.713)	0.671 (0.639-0.703)
Mitral Peak E, continuous	0.644 (0.552-0.735)	0.668 (0.635-0.700)
FRS + Multivariate: (with fractional shortening replacing reduced EF)	0.778 (0.669-0.887)	0.733 (0.679-0.787)

Supplemental Figures and Legends

Supplemental Figure 1

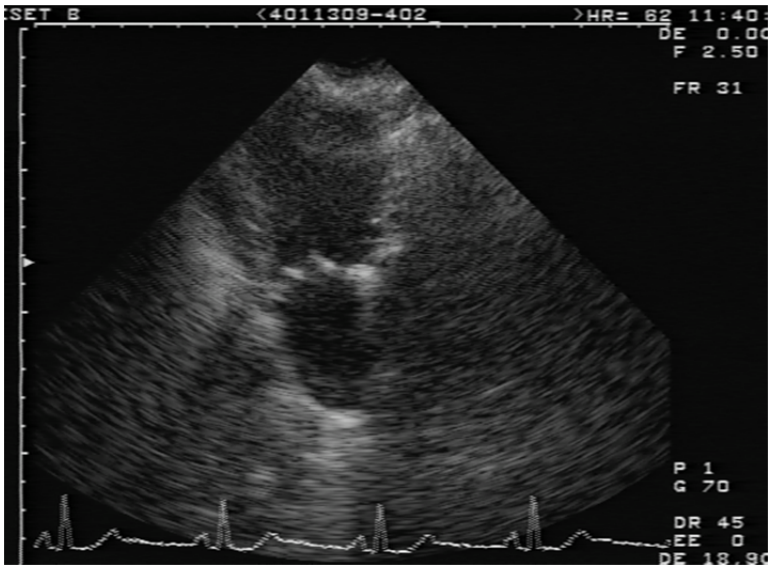


Image demonstrating mitral annular calcification.

Supplemental Figure 2

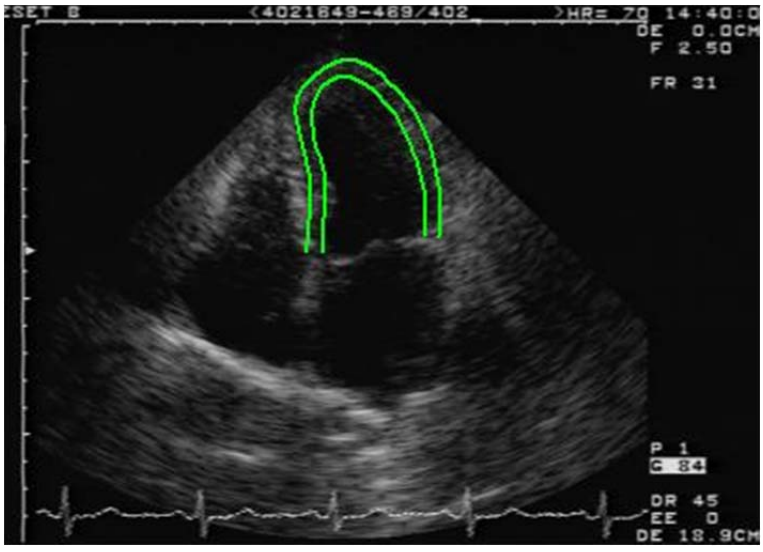


Image demonstrating increased left ventricular mass.

Supplemental Figure 3

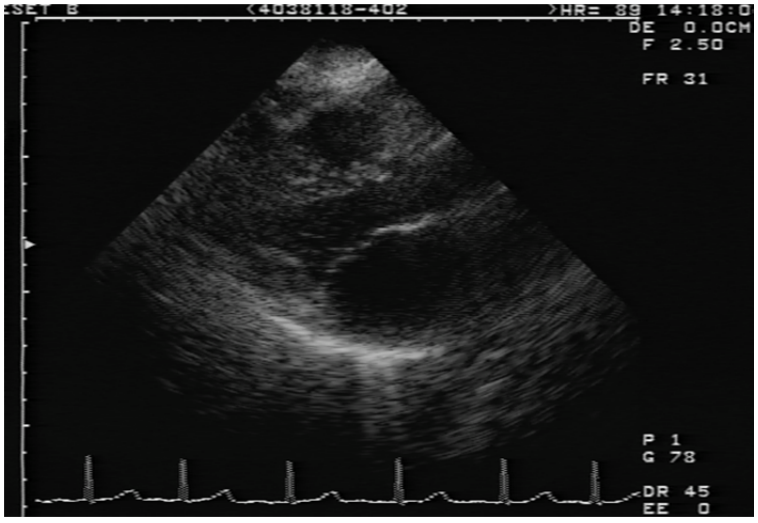


Image demonstrating increased left atrial diameter.

Supplemental Figure 4

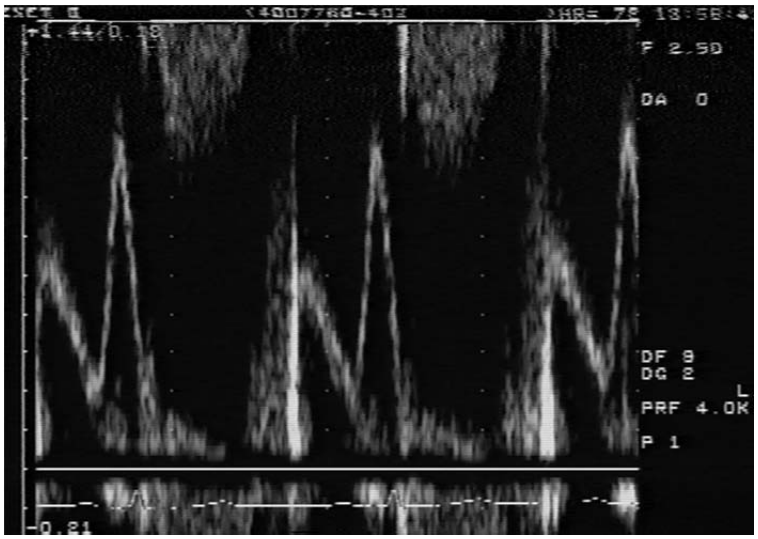
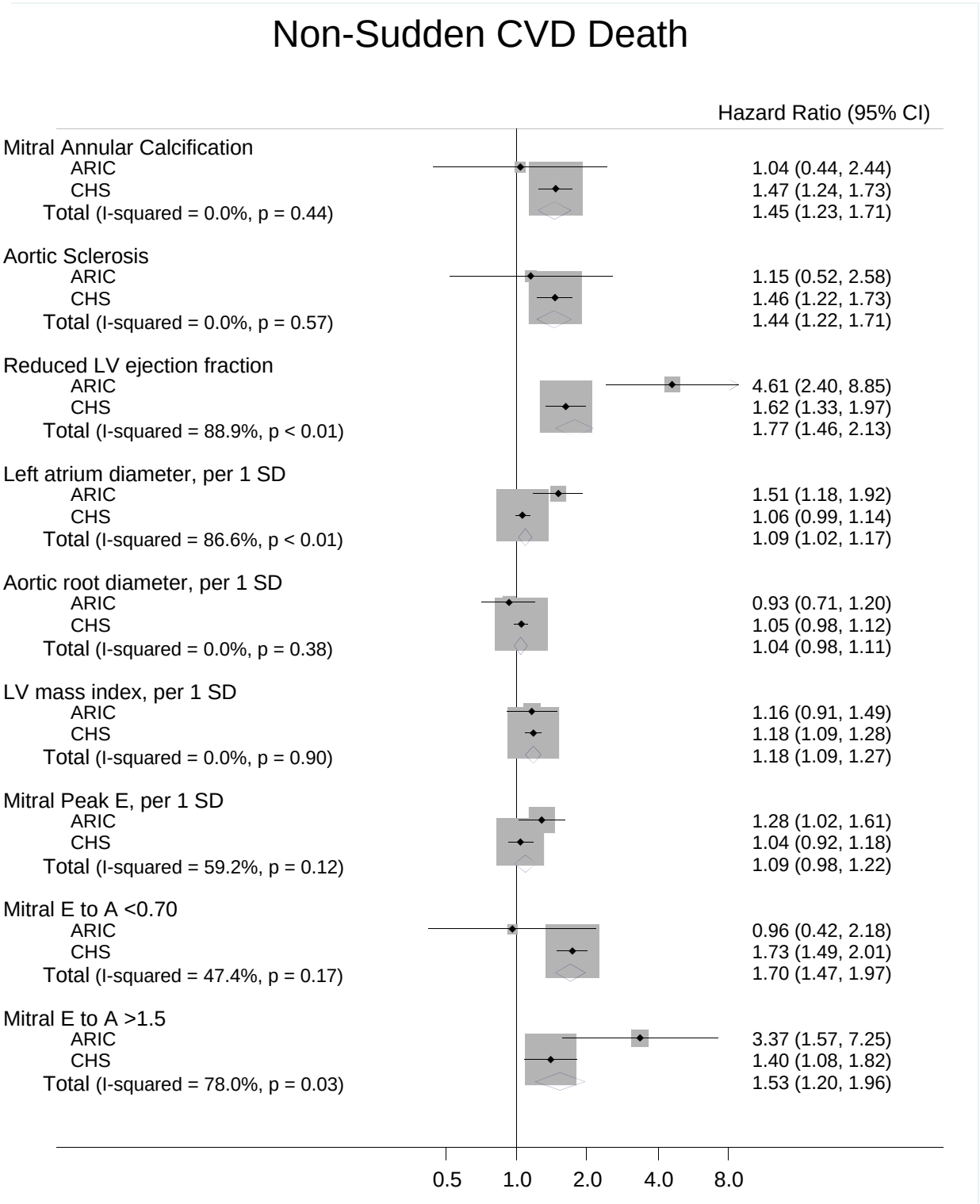


Image demonstrating mitral inflow E/A velocity ratio <0.7.

Supplemental Figure 5



Forest plot of the meta-analyzed and risk-adjusted hazard ratios for non-sudden cardiovascular disease deaths in ARIC and CHS, using CHD and heart failure as time-dependent variables (Model 4)

Supplemental References

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