SUPPLEMENTAL MATERIAL

Reclassification from the **intermediate-low** (>5% to ≤10%10-year risk) category after adding the 9p21 genotype information to the ACRS model, and its implication on lipid therapy according to ATP III (Table 3 and Supplemental Table 3):

In whites in the ARIC study, of the individuals in the intermediate-low group (>5% to ≤10% 10-year risk), 32.1% (880 individuals) had LDL-C ≥130–159 mg/dL, and 29.6% (812 individuals) had LDL-C ≥160 mg/dL based on traditional risk factors alone (Table 3). If any of the individuals with LDL-C ≥130 mg/dL were to be reclassified to the intermediate-high category (>10% to ≤20% 10-year risk), both LDL-C therapy initiation and target goal levels would change for those who had LDL-C ≥160 mg/dL, with an optional target LDL-C <100mg/dL considered for those who had LDL-C ≥130–159 mg/dL. For the 27.6% (757 individuals) in the intermediate-low group (>5% to ≤10%10-year risk) with levels of LDL-C 100–129 mg/dL, reclassification to the intermediate-high category (>10% to ≤20% 10-year risk) would prompt a consideration for the optional target goal of LDL-C <100 mg/dL. Reclassification would not change therapy approach for the 10.7% (293 individuals) in the intermediate-low group (>5% to ≤10%10-year risk) with LDL-C <100 mg/dL, and thus, 9p21 genotype testing would not be recommended in that setting. The number of individuals in the intermediate-low risk group who were reclassified with baseline LDL-C levels in their categories is shown in Supplemental Table 3.

Reclassification from the **intermediate-high** (>10% to ≤20% 10-year risk) category after adding the 9p21 genotype information to the ACRS model, and its implication on lipid therapy according to ATP III (Table 3 and Supplemental Table 3):

In whites in the ARIC study, 17.6% (340 individuals) of the intermediate-high group (>10% to ≤20% 10-year risk) had LDL-C 100–129 mg/dL. If any of these individuals were to be reclassified to the high-risk group (>20% 10-year risk), LDL-C therapy initiation levels would change to LDL-C ≥100mg/dL, and target goal would now be LDL-C <100mg/dL. For the 76.5 % (1475 individuals) of the intermediate-high category (>10% to ≤20% 10-year risk) with LDL-C ≥130 mg/dL, individuals that would be reclassified to the high-risk category (>20% 10-year risk) would have a target LDL-C <100 mg/dL. Therapy approach would not change for the 5.9% (113 individuals) in the intermediate-high group (>10% to ≤20% 10-year risk) with LDL-C <100 mg/dL after reclassification to the high-risk category (>20% 10-year risk), and thus, 9p21 testing would not be recommended in that setting. In our study, over 94% (81 subjects) of the 86 subjects who were reclassified from the >10% to ≤20% 10-year risk (intermediate-high) to the >20% 10-year risk (high) category had LDL-C >100 mg/dL, potentially altering therapy approach (Supplemental Table 3). The number of individuals in the intermediate-high risk group who were reclassified with baseline LDL-C levels in their categories is shown in Supplemental Table 3.

Goodness-of-fit:

The observed number of CHD events were then compared to the expected events in the various groups defined by deciles of risk (Supplemental Table 4), calculating the

expected number from the one minus the fitted survival function, at the observed follow-up time for each person. In evaluating the goodness-of-fit, the model using the 9p21 allele in combination with traditional RF (Grønnesby-Borgan statistic chi square statistic 20.114, p=0.0172) did better than the model using traditional RF alone (Grønnesby-Borgan statistic chi square statistic 21.154, p<0.012). The large values of the statistic and significant 'p' values suggest that neither model was a very "good fit" when the observed and expected events were compared, although the model using 9p21 allele in combination with traditional RF was better as suggested by the smaller values of the chi-square test statistic.

Supplemental Table 1. Baseline characteristics of the ARIC white population eligible for the study in relation to the 9p21 possible genotypes (standard deviations in parenthesis)

	9p21-rs10757274 genotypes				
Characteristics	**AA (n=2,650)**	**AG (n=4,971)**	**GG (n=2,377)**	**P**	**Entire population (n=9,998)**
Age (years)	54.2(5.8)	54.2(5.7)	54.0(5.7)	0.58	54.1(5.7)
% Male	46.2	45.2	44.3	0.38	45.3
Body mass index (kg/m^2)	27.2(5.0)	26.8(4.8)	26.8(4.8)	0.014	26.9(4.8)
Systolic blood pressure (mm Hg)	118.7(17.0)	118.1(16.8)	118.1(16.8)	0.29	118.2(16.9)
Diastolic blood pressure (mm Hg)	71.9(10.1)	71.5(10.0)	71.5(9.9)	0.17	71.6(10.0)
Prevalent Hypertension (%)	26.0	25.5	24.7	0.55	25.4
Diabetes (%)	8.19	7.99	8.54	0.72	8.17
Total cholesterol (mg/dL)	214.3(39.0)	214.6(41.4)	213.1(39.9)	0.35	214.2(40.4)
Low-density lipoprotein cholesterol (mg/dL)	136.9(36.6)	136.9(38.4)	135.9(37.3)	0.56	136.7(37.7)
High-density lipoprotein cholesterol (mg/dL)	50.8(16.8)	51.3(17.1)	51.0(16.3)	0.47	51.1(16.8)
Triglycerides (mg/dL)	136.5(88.6)	135.1(93.4)	133.6(86.1)	0.52	135.1(90.4)
Current tobacco use (%)	25.0	24.6	23.9	0.64	24.5

Supplemental Table 2. Baseline characteristics of the ARIC white population eligible for the study in relation to incident CHD status (standard deviations in parenthesis)

		Incident CHD case status		
Characteristics		**Noncases (n=8,649)**	**Cases (n=1,349)**	**P**
Age (years)		53.9(5.7)	55.5(5.5)	<0.0001
% Male		41.67	68.35	<0.0001
Body mass index (kg/m^2)		26.8(4.8)	27.9(4.6)	<0.0001
Systolic blood pressure (mm Hg)		117.4(16.6)	124.0(17.6)	<0.0001
Diastolic blood pressure (mm Hg)		71.3(9.9)	73.5(10.7)	<0.0001
Diabetes (%)		6.42	19.42	<0.0001
Total cholesterol (mg/dL)		212.6(40.1)	224.3(41.2)	<0.0001
Low-density lipoprotein cholesterol (mg/dL)		134.7(37.2)	149.9(37.8)	<0.0001
High-density lipoprotein cholesterol* (mg/dL)		52.4(17.0)	43.0(12.6)	<0.0001
Triglycerides (mg/dL)		130.7(86.6)	163.6(107.7)	<0.0001
Current tobacco use (%)		23.5	31.1	<0.0001
Prevalent Hypertension (%)		23.5	38.0	<0.0001
Rs10757274 genotype (%)	AA	27.1	22.7	<0.002
	AG	49.5	51.2	<0.002
	GG	23.4	26.2	<0.002

*HDL in male cases (n=922), mean 40.1(10.9) HDL in male non-cases (n=3604), mean 43.8(12.5) HDL in female cases (n=427) mean 49.3(13.7), HDL in female non-cases (n=5045) mean 58.5(17.2)

Supplemental Table 3. Baseline LDL-C levels in subjects reclassified by the addition of the 9p21 genotype to traditional risk factors-based ARIC Cardiovascular Risk Score (ACRS) risk model. LDL-C levels are in mg/dL

	LDL-C of Individuals Reclassified to the Immediate Upper Risk Category(CHD risk)			**LDL-C of the Reclassified to the Immediate Lower Risk Category (CHD risk)**		
LDL-C	(<5%*) reclassified to (>5% to ≤10%)	(>5% to ≤10%) reclassified to >10% to ≤20%	>10% to ≤20% reclassified to (>20%)	(>5% to ≤10%) reclassified to (<5%)	>10% to ≤20% reclassified to (>5% to ≤10%)	(>20%) reclassified to >10% to ≤20%
<100	12.90% (n=20)	11.03% (n=16)	5.81% (n=5)	16.49% (n=31)	5.66% (n=9)	6.25% (n=4)
100–130	29.03% (n=45)	17.24% (n=25)	16.28% (n=14)	31.38% (n=59)	27.04% (n=43)	18.75% (n=12)
130–160	36.77% (n=57)	33.10% (n=48)	41.86% (n=36)	23.40% (n=44)	38.36% (n=61)	35.94% (n=23)
>160	21.29% (n=33)	38.62% (n=56)	36.05% (n=31)	28.72% (n=54)	28.93% (n=46)	39.06% (n=25)
Total	(n=155)	(n=145)	(n=86)	(n=188)	(n=159)	(n=64)

* Percentage reflects 10-year CHD risk

Supplemental Table 4. OBSERVED and EXPECTED CHD events in decile groups of risk using traditional risk factors alone and traditional risk factors + 9p21 allele

Deciles	Traditional Risk Factors Alone		Traditional Risk Factors + 9p21 Allele	
	Observed (n)	Expected (n)	Observed (n)	Expected (n)
1	12	21.16	16	20.38
2	28	36.59	24	35.77
3	55	51.69	51	51.05
4	62	70.58	69	69.71
5	98	92.84	82	92.37
6	116	117.63	120	117.5
7	158	148.89	166	147.97
8	208	184.07	213	184.98
9	352	242.838	242	243.81
10	360	382.67	366	385.43
Total	1349	1349	1349	1349