THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Mega JL, Stitziel NO, Smith JG, et al. Genetic risk, coronary heart disease events, and the clinical benefit of statin therapy: an analysis of primary and secondary prevention trials. *Lancet* 2015; published online March 4. http://dx.doi.org/10.1016/S0140-6736(14)61730-X.

Supplemental Methods.

Construction of the Genetic Risk Score

In each locus comprising the genetic risk score, the lead SNP or a proxy in linkage disequilibrium ($r^2 > 0.8$) was directly genotyped in MDCS, ASCOT, CARE, and PROVE IT-TIMI 22 (see Supplemental Table 2 for details). In JUPITER, genotypes for 11 of the loci were directly assessed using the Omni1-Quad platform as previously described.[1] Genotypes for the remaining loci were statistically imputed using 1000 Genomes Project data as previously described.[2] All imputed SNPs had an imputation Rsq≥0.88. Quality control (QC) procedures were applied to remove variants with missing genotypes in >5% of individuals and samples missing >5% of genotypes. A linear sum of the risk alleles weighted by the log of the odds ratio observed for each SNP in the original report comprised the genetic risk score. In JUPITER, the 1000 Genomes imputation data were used to infer any missing genotypes in individuals. In the other studies, missing genotypes in individuals were assigned the mean genotype value observed within the study.

[1] Chasman DI, Giulianini F, MacFadyen J, Barratt BJ, Nyberg F, Ridker PM. Genetic determinants of statin-induced low-density lipoprotein cholesterol reduction: the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial. Circ Cardiovasc Genet. 2012; **5**(2): 257-64.

[2] Chu AY, Guilianini F, Barratt BJ, Nyberg F, Chasman DI, Ridker PM. Pharmacogenetic determinants of statin-induced reductions in C-reactive protein. Circ Cardiovasc Genet. 2012; **5**(1): 58-65.

Scaling Factor

A scaling factor was created for each trial by which to multiply the event rate difference for statin versus placebo and upper and lower bounds of the 95% CI so that the event rate difference in the intermediate genetic risk score category for each trial was 1%. Then within each trial, meta-regression was performed across the genetic risk score categories to determine how the relative magnitude of absolute risk reduction with statin therapy varied by genetic risk score category. The coefficient represents the relative degree by which the absolute risk reduction with statin therapy varies when one shifts genetic risk score category. Meta-analysis was then performed combining the regression coefficients from the 4 trials. In terms of the clinical interpretation of the resultant number, a value of 0.50, for example, would indicate a 50% greater absolute risk reduction with statin therapy in patients with a high vs. an intermediate genetic risk score. If statin therapy in the average or intermediate population followed for a certain amount time would be expected to yield an 8% absolute risk reduction, enriching for patients with a high genetic risk score should yield a 12% absolute risk reduction.

Supplemental Table 1. Characteristics of Participants in the Studies

	MDCS	**JUPITER**	**ASCOT***	**CARE**	**PROVE IT-TIMI 22**
N	27,817	8,749	6,978	2,878	1,999
Age, yrs (mean, SD)	57.91 (7.63)	66.10 (7.77)	62.44 (8.48)	58.42 (9.31)	57.48 (11.06)
Sex, male (%)	38.7	67.8	79.7	86.1	77.5
Race, white (%)	Swedish nationality	100.0	95.1	93.5	90.0
Diabetes Mellitus (%)	4.1	0.4	21.7	13.6	16.9
Smoking (%)	28.7	13.2	32.7	16.7	38.1
Hypertension (%)	60.6	55.9	100.0	42.6	50.7
HDL Cholesterol, mg/dL (mean, SD)	53.4 (14.3)	52.14 (15.31)	49.93 (13.75)	38.70 (8.90)	39.87 (10.56)
LDL Cholesterol, mg/dL (mean, SD)	161.25 (38.3)	106.31 (17.33)	147.64 (36.79)	138.86 (14.62)	109.31 (30.03)
Follow up, yrs (mean, SD)	13.89 (3.48)	2.37 (1.05)	6.11 (1.03)	4.94 (0.72)	2.03 (0.57)

Continuous variables are presented as means with standard deviations and categorical variables are presented as proportions.

*Includes participants from the lipid-lowering randomized trial and from the blood pressure lowering trial who were not taking statins.

Supplemental Table 2. Components of the Genetic Risk Score by Study

Locus	MDCS	JUPITER	ASCOT	CARE	PROVE IT-TIMI 22
1p13.3 (SORT1)	rs599839	rs646776	rs646776	rs646776	rs646776
1p32.2 (PPAP2B)	rs17114036	rs17114036	rs17114036	rs17114036	rs17114036
1p32.3 (PCSK9)	rs11206510	rs11206510	rs11206510	rs11206510	rs11206510
1q41 (MIA3)	rs17465637	rs17465637	rs17465637	rs2133189	rs17465637
21q22.11 (KCNE2)	rs9982601	rs9305545	rs9305545	rs9982601	rs9305545
2q33.1 (WDR12)	rs6725887	rs6725887	rs6725887	rs35212307	rs6725887
3q22.3 (MRAS)	rs9818870	rs9818870	rs9818870	rs9818870	rs9818870
6p21.31 (ANKS1A)	rs17609940	N/A	N/A	rs17609940	rs17609940
6p24.1 (PHACTR1)	rs9349379	rs12526453	rs12526453	rs2327621	rs12526453
6q23.2 (TCF21)	rs12190287	rs1967917	rs1967917	rs12190287	rs12190287
6q25.3 (LPA)	rs3798220	rs3798220	rs3798220	rs3798220	rs3798220
6q25.3 (LPA)	rs10455872	rs10455872	rs10455872	rs10455872	rs10455872
7q32.2 (ZC3HC1)	rs11556924	rs11556924	rs11556924	rs11556924	rs11556924
9p21.3 (CDKN2A)	rs4977574	rs4977574	rs4977574	rs10757274	rs4977574
9q34.2 (ABO)	rs9411489	rs579459	rs579459	rs651007	rs579459
10q11.21 (CXCL12)	rs1746048	rs1746048	rs1746048	rs915083	rs1746048
10q24.32 (CYP17A1)	rs12413409	rs12411886	rs12411886	rs12411886	rs12411886
11q23.3 (APOA5)	rs964184	rs964184	rs964184	rs964184	rs964184
12q24 (HNF1A)	rs2259816	rs2259816	rs2259816	rs1169313	rs2259816
12q24.12 (SH2B3)	rs3184504	rs653178	rs653178	rs3184504	rs3184504
13q34 (COL4A1)	rs4773144	rs4773144	rs4773144	rs3809346	rs4773144
14q32.2 (HHIPL1)	rs2895811	rs2895811	rs2895811	rs2895811	rs2895811
15q25.1 (ADAMTS7)	rs3825807	rs3825807	rs3825807	rs3825807	rs3825807
17p11.2 (RASD1)	rs12936587	rs12936587	rs12936587	rs12936587	rs12936587
17p13.3 (SMG6)	rs216172	rs216172	rs216172	rs216172	rs216172
17q21.32 (UBE2Z)	rs46522	rs46522	rs46522	rs46522	rs46522
19p13.2 (LDLR)	rs1122608	rs1122608	rs1122608	rs1122608	rs1122608

The table includes either the lead SNP or proxy that was used.

Supplemental Table 3. Risk of Coronary Heart Disease Across Genetic Risk Score Quintiles

Study	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	HR per 1-SD	P value
Primary Prevention Populations							
MDCS	1.00	1.20 (1.06-1.37)	1.24 (1.08-1.42)	1.43 (1.27-1.62)	1.70 (1.51-1.91)	1.21 (1.17-1.26)	$2x10^{-25}$
JUPITER	1.00	1.02 (0.44-2.3)	0.98 (0.42-2.29)	1.72 (0.80-3.71)	1.32 (0.59-2.99)	1.08 (0.84-1.38)	0.55
ASCOT	1.00	1.69 (1.08-2.64)	1.45 (0.91-2.30)	1.59 (1.01-2.52)	2.10 (1.35-3.25)	1.28 (1.13-1.45)	0.0001
Meta-Analysis	*1.00*	*1.25 (1.05-1.50)*	*1.25 (1.10-1.42)*	*1.45 (1.29-1.62)*	*1.72 (1.53-1.92)*	*1.21 (1.17-1.26)*	*<0.0001*

Secondary Prevention Populations							
CARE	1.00	1.50 (0.91-2.46)	1.41 (0.85-2.34)	1.66 (1.01-2.72)	1.67 (1.01-2.76)	1.14 (0.98-1.32)	0.081
PROVE IT-TIMI 22	1.00	1.74 (0.94-3.23)	2.02 (1.11-3.66)	1.86 (1.01-3.43)	2.04 (1.10-3.80)	1.14 (0.95-1.36)	0.15
Meta-Analysis	*1.00*	*1.59 (1.08-2.34*	*1.64 (1.11-2.41)*	*1.74 (1.18-2.55)*	*1.81 (1.22-2.67)*	*1.14 (1.02-1.28)*	*0.0250*

These analyses were conducted among participants in MDCS and in the placebo or lower intensity statin treatment arms (PROVE IT-TIMI 22) of the applicable trials

Supplemental Table 4. Baseline Cholesterol Values Across Genetic Risk Score Categories

		Genetic Risk Score Categories		
		Low	**Intermediate**	**High**
JUPITER	LDL-C, mg/dL (mean, SD)	106.42 (17.31)	106.51 (17.08)	105.59 (18.08)
	HDL-C, mg/dL (mean, SD)	52.24 (15.50)	52.30 (15.36)	51.58 (14.97)
CARE	LDL-C, mg/dL (mean, SD)	137.80 (14.34)	139.72 (14.63)	139.03 (14.84)
	HDL-C, mg/dL (mean, SD)	38.99 (9.19)	38.03 (8.28)	39.10 (9.18)
PROVE IT-TIMI 22	LDL-C, mg/dL (mean, SD)	110.4 (31.10)	108.72 (30.35)	109.99 (27.90)
	HDL-C, mg/dL (mean, SD)	39.90 (10.13)	39.84 (10.51)	39.93 (11.13)

Data for ASCOT are not available.

Supplemental Table 5. Absolute and Percent Change in Cholesterol Values Across Genetic Risk Score Categories

		Genetic Risk Score Categories		
		Low	**Intermediate**	**High**
JUPITER Statin	Absolute Change LDL, mg/dL (mean, SD)	-50.32 (26.78)	-50.34 (24.36)	-50.42 (23.20)
	Percent Change LDL, (mean, SD)	-46 (29)	-47 (23)	-47 (22)
	Absolute Change HDL, mg/dL (mean, SD)	3.35 (8.58)	3.81 (8.59)	3.84 (8.34)
	Percent Change HDL, (mean, SD)	7.6 (1.6)	8.5 (1.7)	9.0 (1.7)
CARE Statin	Absolute Change LDL, mg/dL (mean, SD)	-46.39 (17.35)	-45.91 (18.93)	-43.71 (19.42)
	Percent Change LDL, (mean, SD)	-33.42 (11.93)	-32.73 (12.91)	-31.21 (13.47)
	Absolute Change HDL, mg/dL (mean, SD)	1.44 (4.99)	1.88 (4.48)	1.77 (4.49)
	Percent Change HDL, (mean, SD)	4.21 (12.14)	5.54 (11.86)	5.28 (11.94)
PROVE IT-TIMI 22 Pravastatin	Absolute Change LDL, mg/dL (mean, SD)	-18.06 (28.89)	-19.20 (31.30)	-16.44 (29.22)
	Percent Change LDL, (mean, SD)	-12.13 (30.32)	-13.45 (30.02)	-12.04 (27.00)
	Absolute Change HDL, mg/dL (mean, SD)	1.14 (9.13)	1.77 (7.74)	1.43 (8.11)

	Percent Change HDL, (mean, SD)	4.43 (22.93)	6.09 (20.63)	6.23 (19.46)
PROVE IT-TIMI 22 Atorvastatin	Absolute Change LDL, mg/dL (mean, SD)	-53.30 (35.18)	-49.34 (31.04)	-48.14 (31.24)
	Percent Change LDL, (mean, SD)	-44.37 (25.30)	-42.86 (24.15)	-41.69 (26.21)
	Absolute Change HDL, mg/dL (mean, SD)	-0.08 (8.06)	-0.07 (8.26)	-0.24 (8.22)
	Percent Change HDL, (mean, SD)	0.96 (19.68)	1.81 (20.80)	1.66 (20.40)

Data for ASCOT are not available.

Supplemental Table 6. Risk of Coronary Heart Disease with Statin Therapy Across Genetic Risk Score Quintile

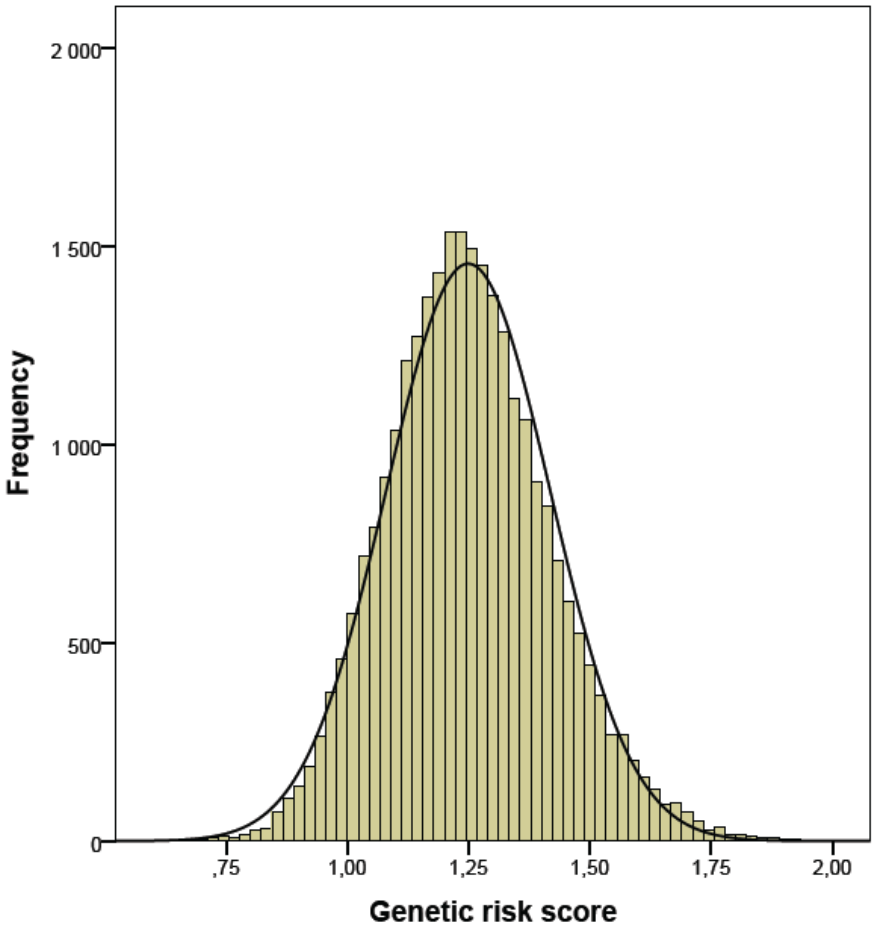
	Quintile	# of Events, Control	# of Individuals, Control	Event Rate, Control (%)	# of Events, Statin	# of Individuals, Statin	Event Rate, Statin (%)	Hazard Ratio	ARR (%)
JUPITER	1	10	865	1.16	7	878	0.80	0.68	0.36
	2	12	904	1.33	9	838	1.07	0.80	0.26
	3	12	862	1.39	11	880	1.25	1.01	0.14
	4	19	885	2.22	8	887	0.90	0.43	1.32
	5	14	864	1.62	6	878	0.68	0.41	0.94
ASCOT	1	13	432	3.00	8	412	1.94	0.64	1.06
	2	18	402	4.48	11	442	2.49	0.55	1.99
	3	13	381	3.41	14	462	3.03	0.89	0.38
	4	17	404	4.21	12	440	2.73	0.65	1.48
	5	28	426	6.57	15	418	3.59	0.54	2.98

CARE	1	26	278	9.35	22	297	7.41	0.79	1.95
	2	41	291	14.09	26	285	9.12	0.64	4.97
	3	37	298	12.42	28	277	10.11	0.82	2.31
	4	41	288	14.24	38	288	13.19	0.91	1.04
	5	38	277	13.72	23	299	7.69	0.54	6.03
PROVE IT-TIMI 22*	1	20	213	9.39	21	186	11.29	1.24	-1.90
	2	26	206	12.62	15	194	7.73	0.61	4.89
	3	33	205	16.10	18	195	9.23	0.57	6.87
	4	29	194	14.95	22	206	10.68	0.70	4.27
	5	28	188	14.89	17	212	8.02	0.51	6.87

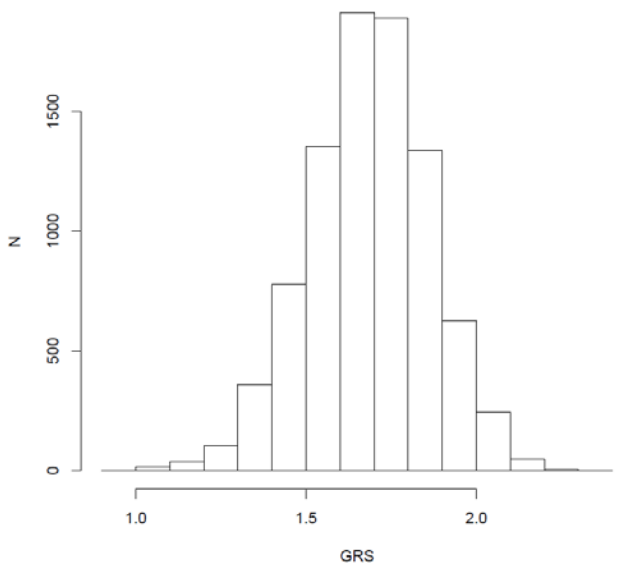
*In PROVE IT-TIMI 22, the control group is moderate intensity statin therapy (pravastatin 40 mg) and the statin group is high intensity statin therapy (atorvastatin 80 mg). ARR indicates absolute risk reduction.

Supplemental Figure 1. Distribution of the Genetic Risk Score

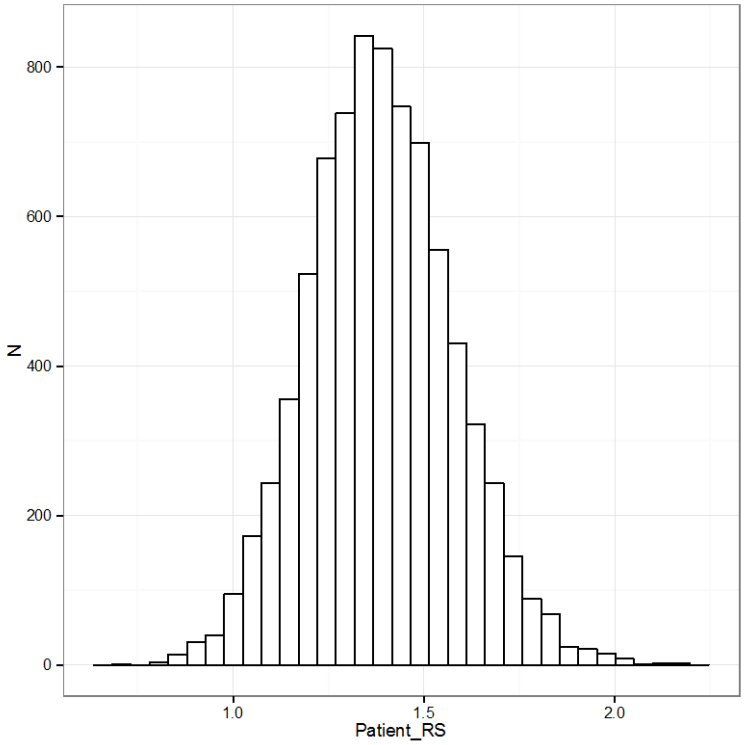
MDCS



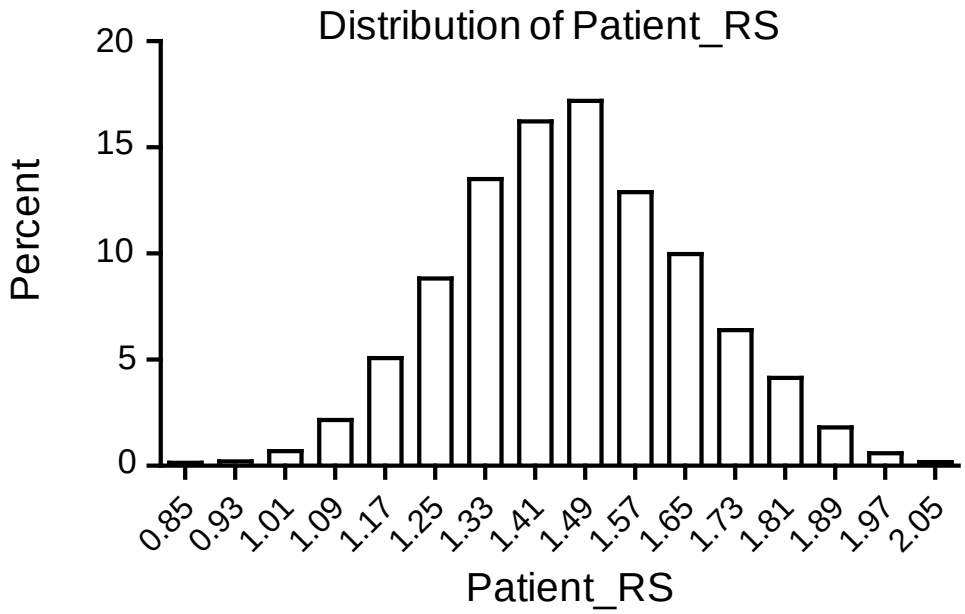
JUPITER



ASCOT



CARE


Distribution of Patient_RS
Percent
20
15
10
5
0
0.85
0.93
1.01
1.09
1.17
1.25
1.33
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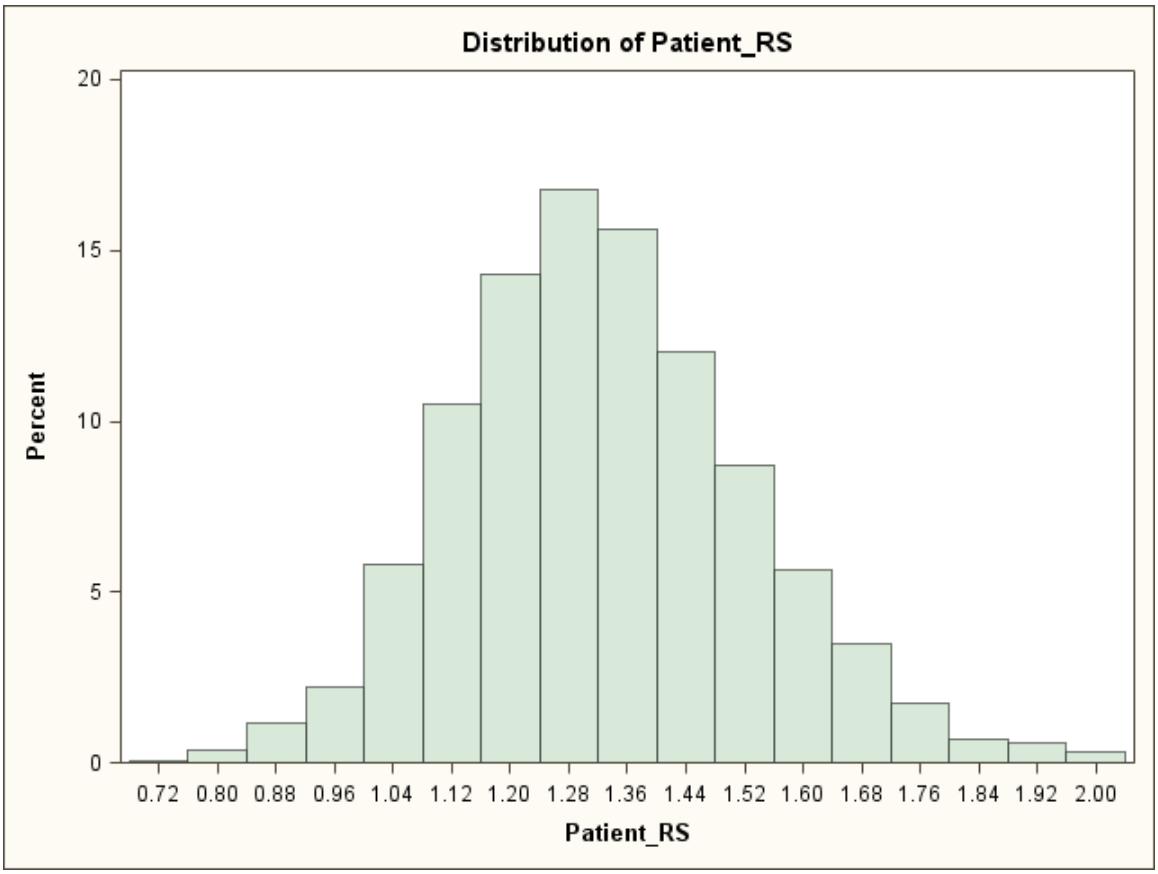
1.89
1.97
2.05
Patient_RS

PROVE IT-TIMI 22



Supplemental Figure 2. Magnitude of the Absolute Risk Difference of Coronary Heart Disease with Statin Therapy Across Genetic Risk Score Categories