

SUPPLEMENTAL MATERIAL

Table S1. Definition of the combined cardiovascular disease endpoint in the contributing statin trials from the Lipoprotein(a) Studies Collaboration.

Components of the combined cardiovascular disease endpoint	4D	CARDS	LIPID	MIRACL	4S
Fatal coronary heart disease	●	●	●	●	●
Non-fatal myocardial infarction	●	●	●	●	●
Unstable angina	-	●	●	●	-
Resuscitated cardiac arrest	-	●	-	-	●
Stroke	●	●	●	●	-
Coronary revascularization	●	●	-	●	●

Table S2. Trial-specific quartile definitions and hazard ratios for CVD in the contributing statin trials from the Lipoprotein(a) Studies Collaboration.

		Quartile 1	Quartile 2	Quartile 3	Quartile 4
"LDL-C"					
4D	Range, mg/dL	≤104	105-123	124-144	≥145
	HR (95% CI)	[Reference]	0.97 (0.92-1.02)	1.18 (1.12-1.24)	1.20 (1.14-1.26)
CARDS	Range, mg/dL	≤92	92-113	114-134	≥134
	HR (95% CI)	[Reference]	1.31 (1.16-1.47)	1.46 (1.30-1.65)	1.76 (1.57-1.97)
LIPID	Range, mg/dL	≤131	131-150	150-170	≥170
	HR (95% CI)	[Reference]	1.04 (1.03-1.04)	1.07 (1.07-1.08)	1.14 (1.13-1.14)
MIRACL	Range, mg/dL	≤101	102-122	123-146	≥147
	HR (95% CI)	[Reference]	1.08 (1.05-1.11)	0.93 (0.90-0.96)	0.99 (0.96-1.02)
4S	Range, mg/dL	≤170	170-187	189-207	≥208
	HR (95% CI)	[Reference]	1.20 (1.19-1.21)	1.10 (1.09-1.12)	1.25 (1.24-1.27)
LDL-C_{corr30}					
4D	Range, mg/dL	≤94	94-115	116-137	≥137
	HR (95% CI)	[Reference]	0.96 (0.91-1.02)	1.20 (1.14-1.26)	1.04 (0.99-1.10)
CARDS	Range, mg/dL	≤86	86-106	106-127	≥127
	HR (95% CI)	[Reference]	1.22 (1.08-1.37)	1.35 (1.20-1.51)	1.60 (1.43-1.79)
LIPID	Range, mg/dL	≤122	122-141	141-161	≥162
	HR (95% CI)	[Reference]	1.04 (1.04-1.05)	1.02 (1.02-1.03)	1.08 (1.08-1.09)
MIRACL	Range, mg/dL	≤94	94-115	115-139	≥140
	HR (95% CI)	[Reference]	0.83 (0.80-0.85)	0.90 (0.87-0.92)	0.83 (0.81-0.86)
4S	Range, mg/dL	≤165	165-183	183-200	≥200
	HR (95% CI)	[Reference]	1.15 (1.13-1.16)	1.10 (1.09-1.12)	1.16 (1.14-1.17)

LDL-C_{corr30} was estimated by subtracting 30% of Lp(a) mass from LDL-C. Quartiles were defined within each contributing trial based on trial-specific distributions. Hazard ratios were adjusted for age, sex, prior cardiovascular disease, diabetes, smoking, systolic blood pressure, and high-density lipoprotein cholesterol. CI=confidence interval; HR=hazard ratio.

Table S3. Descriptive summary of corrected LDL-C in the contributing statin trials from the Lipoprotein(a) Studies Collaboration assuming varying proportions of Lp(a) cholesterol content.

Variables	4D (n=1,224)	CARDS (n=2,232)	LIPID (n=7,862)	MIRACL (n=2,328)	4S (n=4,397)	Total (n=18,043)
LDL-C _{corr20} , mg/dL	119 (31)	108 (30)	145 (28)	120 (33)	185 (25)	135 (29)
LDL-C _{corr25} , mg/dL	117 (32)	107 (30)	143 (29)	119 (33)	184 (25)	134 (29)
LDL-C _{corr45} , mg/dL	111 (36)	103 (31)	138 (30)	114 (34)	180 (26)	129 (30)

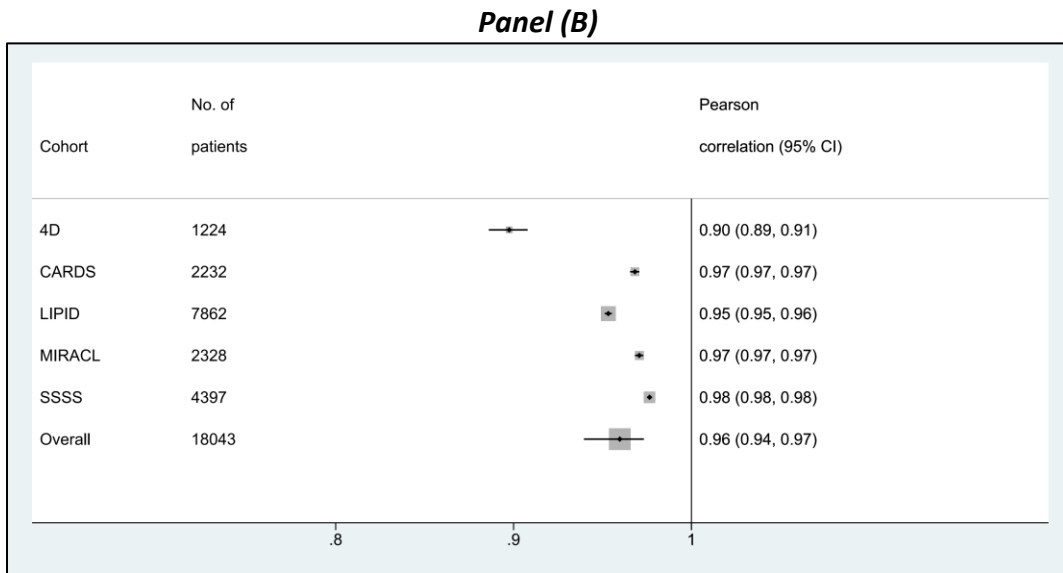
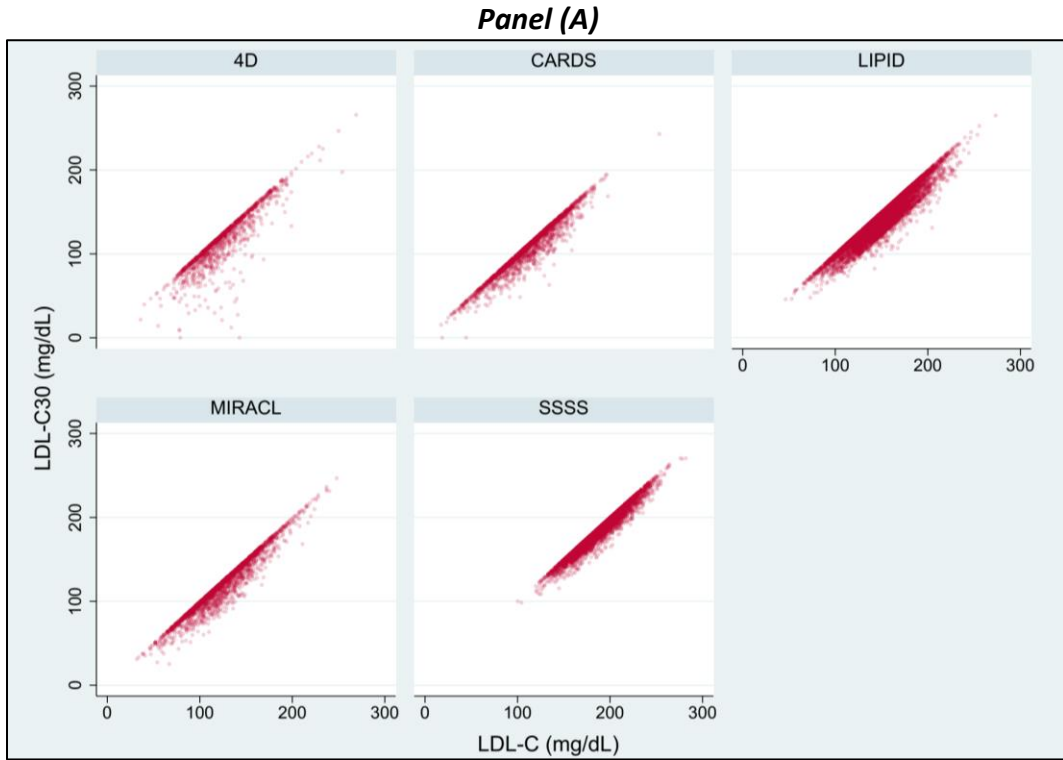
Data shown are means (standard deviations). LDL-C_{corr20}, LDL-C_{corr25}, and LDL-C_{corr45} were estimated by subtracting 20%, 25% and 45% of Lp(a) mass from “LDL-C”, respectively. Total means and standard deviations were calculated by pooling trial-specific estimates with random-effects meta-analysis.

Table S4. Descriptive summary of Lp(a)-C and corrected LDL-C in patients from the clinical laboratory database assuming varying proportions of Lp(a) cholesterol content.

Variables	Categories of LDL-C					t statistic for trend ^a	P value for trend ^a
	<70 mg/dL (n=83,807)	70-<100 mg/dL (n=178,245)	100-<130 mg/dL (n=157,576)	130-<190 mg/dL (n=103,597)	≥190 mg/dL (n=7,919)		
Lp(a)-C ₂₀ , mg/dL	3 (1-7)	3 (1-9)	3 (2-10)	4 (2-11)	5 (2-14)	64	<0.0001
Lp(a)-C ₂₅ , mg/dL	4 (2-9)	4 (2-12)	4 (2-12)	5 (2-14)	6 (3-18)	64	<0.0001
Lp(a)-C ₄₅ , mg/dL	6 (3-16)	7 (3-21)	8 (4-22)	9 (4-25)	11 (5-32)	64	<0.0001
LDL-C _{corr20} , mg/dL	51 (11)	78 (12)	107 (12)	141 (17)	202 (27)	1,670	<0.0001
LDL-C _{corr25} , mg/dL	50 (12)	77 (13)	105 (13)	139 (18)	200 (28)	1,531	<0.0001
LDL-C _{corr45} , mg/dL	45 (16)	70 (19)	98 (20)	132 (24)	190 (34)	1,084	<0.0001

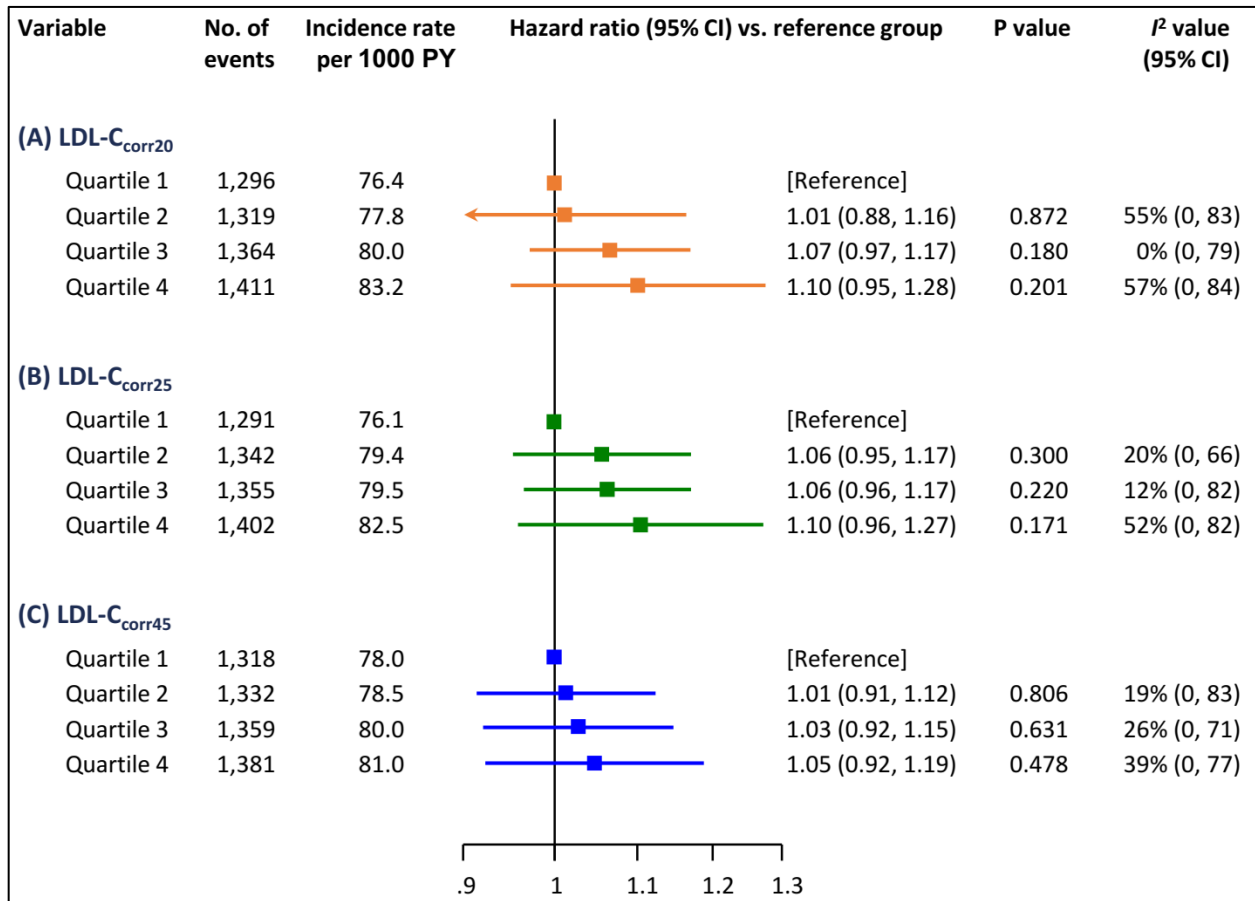
Data shown are means (standard deviations) or medians (interquartile ranges). Lp(a)-C₂₀, Lp(a)-C₂₅, and Lp(a)-C₄₅ were estimated as 20%, 25%, and 45% of Lp(a) mass, respectively. LDL-C_{corr20}, LDL-C_{corr25}, and LDL-C_{corr45} were estimated by subtracting Lp(a)-C₂₀, Lp(a)-C₂₅, and Lp(a)-C₄₅ from "LDL-C", respectively. ^at statistics and P values for trend were calculated using linear regression.

Figure S1. Scatter plots (A) and Pearson correlation coefficients of LDL-C and LDL-C_{corr30} values in the contributing statin trials from the Lipoprotein(a) Studies Collaboration (n=18,043).



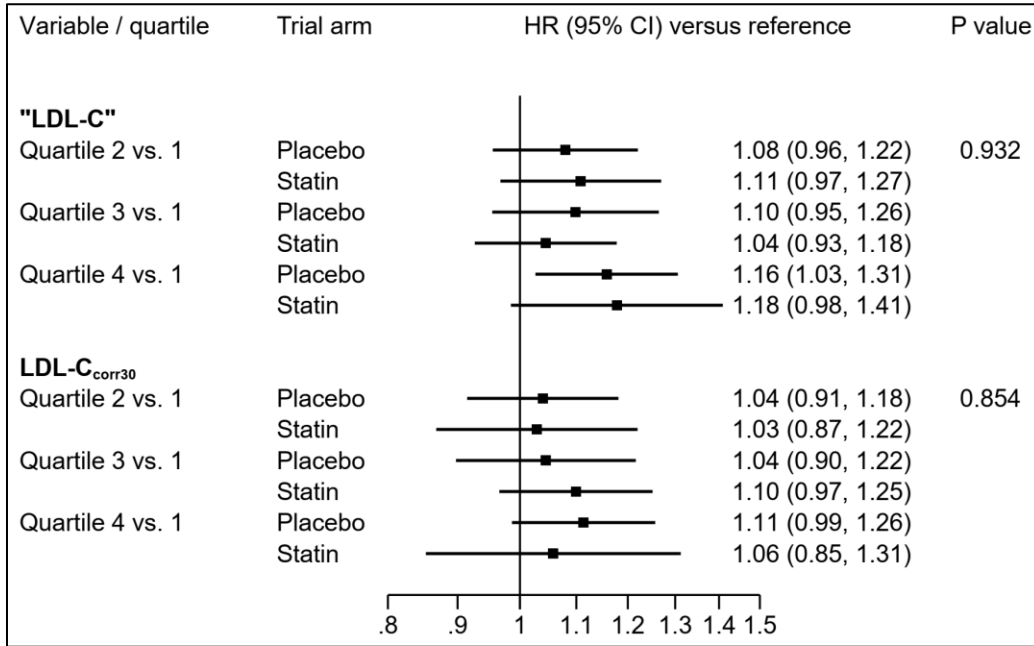
In Panel (b), the pooled Pearson correlation coefficient was estimated using random-effects meta-analysis using z-transformed study-specific correlation coefficients. CI=confidence interval.

Figure S2. Adjusted hazard ratios for cardiovascular disease risk according to quartiles of LDL-C_{corr20}, LDL-C_{corr25}, and LDL-C_{corr45} in the contributing statin trials from the Lipoprotein(a) Studies Collaboration (n=18,043).



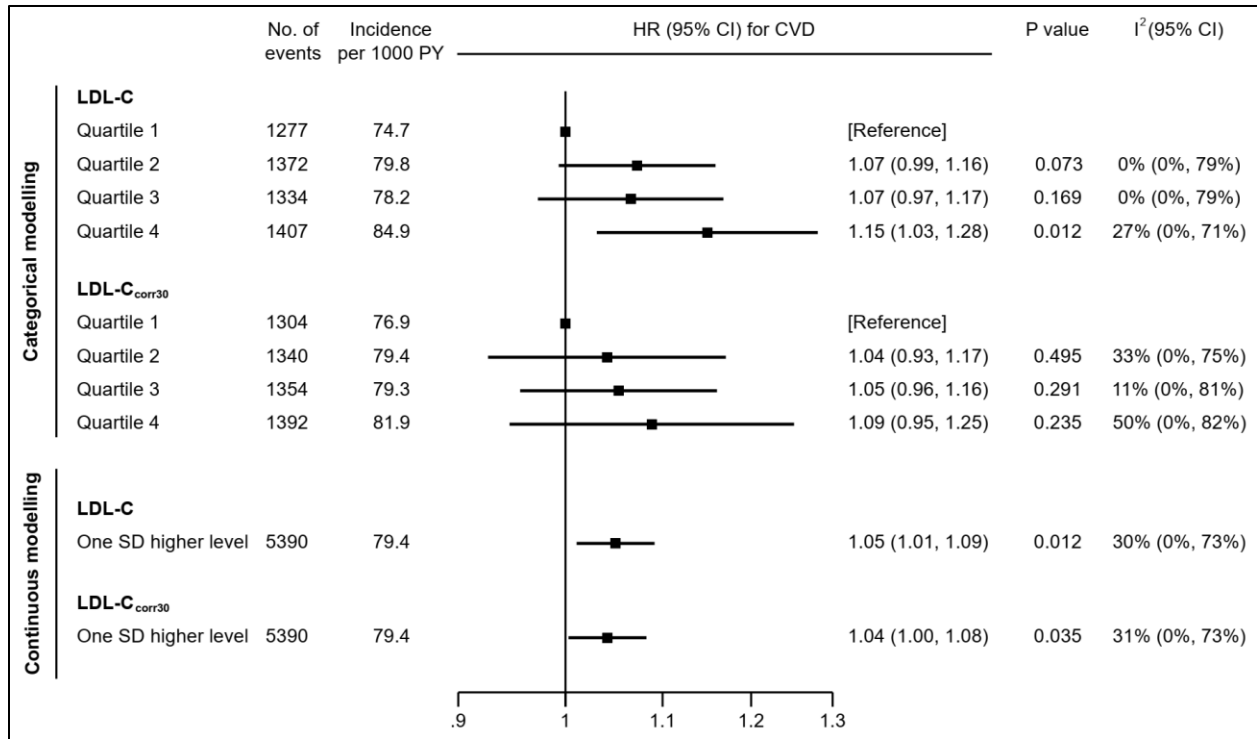
LDL-C_{corr20}, LDL-C_{corr25}, and LDL-C_{corr45} were estimated by subtracting 20%, 25% and 45% of Lp(a) mass from “LDL-C”, respectively. Quartiles were defined within each contributing trial based on trial-specific distributions. Hazard ratios were adjusted for age, sex, prior cardiovascular disease, diabetes, smoking, systolic blood pressure, and high-density lipoprotein cholesterol. CI=confidence interval; PY=person-years.

Figure S3. Adjusted hazard ratios for cardiovascular disease risk for quartiles of LDL-C and LDL-C_{corr30} according to allocation of statin vs. placebo in the contributing statin trials from the Lipoprotein(a) Studies Collaboration (n=18,043).



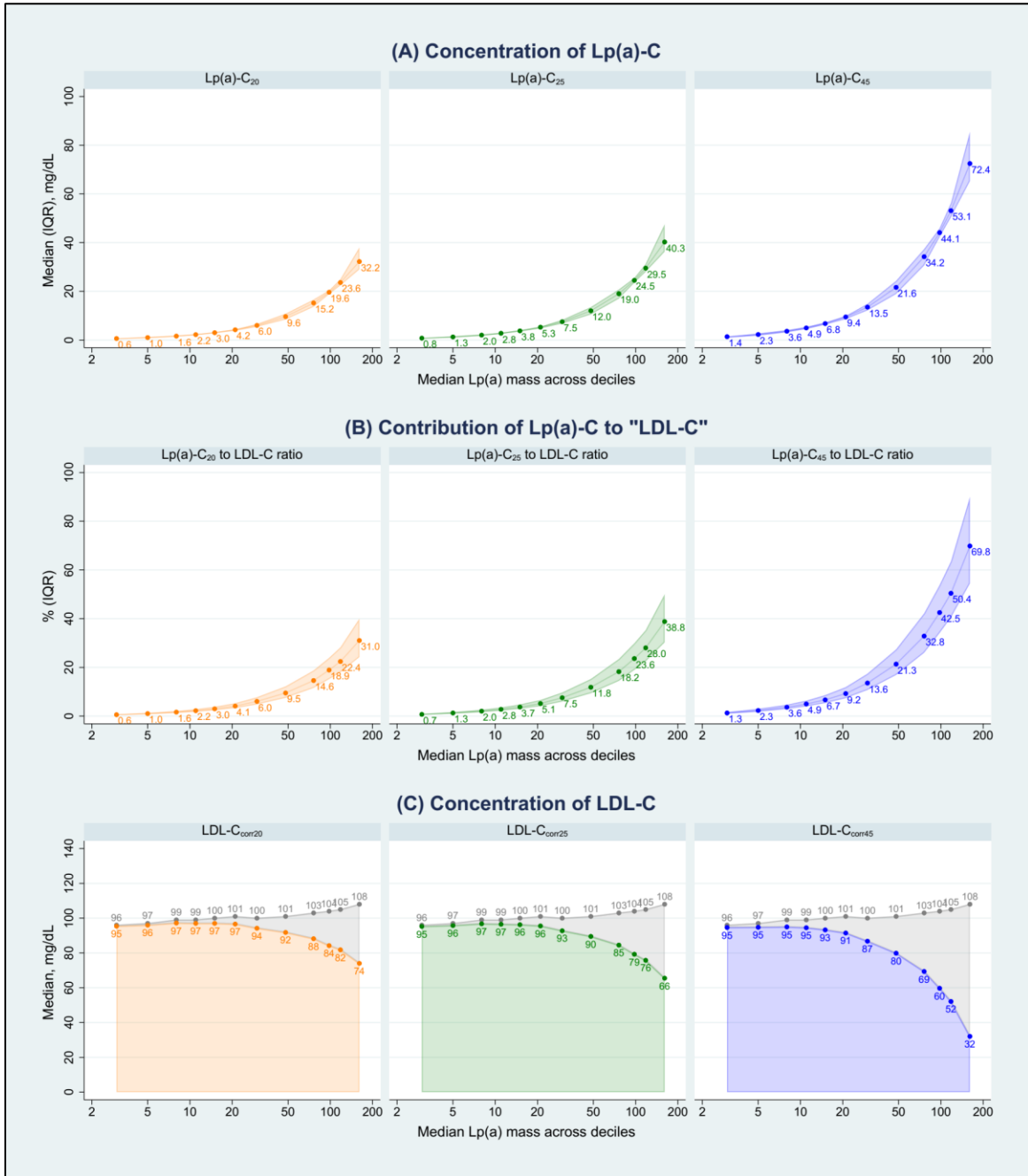
LDL-C_{corr30} was estimated by subtracting 30% of Lp(a) mass from "LDL-C". Quartiles were defined within each contributing trial based on trial-specific distributions. Hazard ratios were adjusted for age, sex, prior cardiovascular disease, diabetes, smoking, systolic blood pressure, and high-density lipoprotein cholesterol. CI=confidence interval; HR=hazard ratio.

Figure S4. Association of “LDL-C” with cardiovascular disease risk in a multivariable model further adjusted for $\log_e \text{Lp(a)}$ in the contributing statin trials from the Lipoprotein(a) Studies Collaboration (n=18,043).



“LDL-C” quartiles were defined within each contributing trial based on trial-specific distributions. Multivariable adjustment models were adjusted for age, sex, prior cardiovascular disease, diabetes, smoking, systolic blood pressure, high-density lipoprotein cholesterol, and $\log_e \text{Lp(a)}$. CI=confidence interval; CVD=cardiovascular disease; HR=hazard ratio; PY=person years; SD=standard deviation.

Figure S5. Estimated Lp(a)-C₂₀, Lp(a)-C₂₅, and Lp(a)-C₄₅, contribution to LDL-C, and corrected LDL-C values in patients from the clinical laboratory database assuming varying proportions of Lp(a) cholesterol content.



Analysis is based on the Health Diagnostic Laboratory data. Lp(a)-C₂₀, Lp(a)-C₂₅, and Lp(a)-C₄₅ were estimated as 20%, 25%, and 45% of Lp(a) mass, respectively. LDL-C_{corr20}, LDL-C_{corr25}, and LDL-C_{corr45} were estimated by subtracting Lp(a)-C₂₀, Lp(a)-C₂₅, and Lp(a)-C₄₅ from "LDL-C", respectively. Groups plotted are deciles of Lp(a) mass, with the top decile further divided into thirds. IQR=interquartile-range.

Figure S6. Reassignment to lower LDL-C categories upon correction to LDL-C_{corr20}, LDL-C_{corr25}, and LDL-C_{corr45} of patients from the clinical laboratory database.

(A) Reclassification with LDL-C_{corr20}								
		No. of people in categories of LDL-C_{corr20} mg/dL					Reclassified to lower category	
		<70	70-<100	100-<130	130-<190	≥190	No. of people	Row % (95% CI)
„LDL-C“, mg/dL	<70	83,807	0	0	0	0	NA	NA
	70-<100	37,949	140,296	0	0	0	37,949	21.3% (21.1-21.5)
	100-<130	1,029	39,860	116,687	0	0	40,889	25.9% (25.7-26.2)
	130-<190	13	629	24,461	78,494	0	25,103	24.2% (24.0-24.5)
	≥190	0	0	0	2,573	5,346	2,573	32.5% (31.5-33.5)

(B) Reclassification with LDL-C_{corr25}								
		No. of people in categories of LDL-C_{corr25} mg/dL					Reclassified to lower category	
		<70	70-<100	100-<130	130-<190	≥190	No. of people	Row % (95% CI)
„LDL-C“, mg/dL	<70	83,807	0	0	0	0	NA	NA
	70-<100	46,078	132,167	0	0	0	46,078	25.9% (25.6-26.1)
	100-<130	2,648	45,701	109,227	0	0	48,349	30.7% (30.5-30.9)
	130-<190	42	1,631	27,935	73,989	0	29,608	28.6% (28.3-28.9)
	≥190	0	0	8	2,891	5,020	2,899	36.6% (35.5-37.7)

(C) Reclassification with LDL-C_{corr45}								
		No. of people in categories of LDL-C_{corr45} mg/dL					Reclassified to lower category	
		<70	70-<100	100-<130	130-<190	≥190	No. of people	Row % (95% CI)
„LDL-C“, mg/dL	<70	83,807	0	0	0	0	NA	NA
	70-<100	70,483	107,762	0	0	0	70,483	39.5% (39.3-39.8)
	100-<130	15,051	55,184	87,341	0	0	70,235	44.6% (44.3-44.8)
	130-<190	1,832	8,186	33,866	59,713	0	43,884	42.4% (42.1-42.7)
	≥190	6	41	240	3,661	3,971	3,948	49.9% (48.7-51.0)

Analysis is based on the Health Diagnostic Laboratory data. Lp(a)-C₂₀, Lp(a)-C₂₅, and Lp(a)-C₄₅ were estimated as 20%, 25%, and 45% of Lp(a) mass, respectively. LDL-C_{corr20}, LDL-C_{corr25}, and LDL-C_{corr45} were estimated by subtracting Lp(a)-C₂₀, Lp(a)-C₂₅, and Lp(a)-C₄₅ from “LDL-C”, respectively. CI=confidence interval; NA=not available.