SUPPLEMENT PART II

Outcomes results

eTable 9. Unadjusted and adjusted meta-regression models for the association of percent LDL-C levels reduction and mortality and other cardiovascular outcomes expressed in absolute rate differences (ARDs) and annual number needed to treat (NNT)

Percent LDL-C reduction (%)	NNT (95% CI)		ARD (95%CI)		I² (%)	*P for trend**
All-cause mortality						
<30	982	(610 to 2,531)	-1.02	(-1.59 to -0.39)	28	
30-49	411	(277 to 800)	-2.43	(-3.61 to -1.25)	24	
≥50	NA		-0.36	(-2.59 to 1.87)	14	
Overall	754	(529 to 1,309)	-1.33	(-1.89 to -0.76)	31	
Unadjusted analysis			-0.27	(-1.24 to 0.71)		*.58*
Adjusted analysis			-0.44	(-1.43 to 0.55)		*.38*
Adjusted analysis including annual CV death rate			-0.32	(-1.29 to 0.65)		*.51*
Cardiovascular mortality						
<30	1,212	(831 to 2,242)	-0.83	(-1.20 to -0.44)	21	
30-49	621	(405 to 1,332)	-1.61	(-2.47 to -0.75)	36	
≥50	NA		-1.03	(-3.23 to 1.17)	29	
Overall	1,028	(756 to 1,605)	-0.97	(-1.32 to -0.62)	26	
Unadjusted analysis			-0.28	(-0.83 to 0.38)		*.46*
Adjusted analysis			-0.34	(-0.95 to 0.27)		*.27*
Adjusted analysis including annual CV death rate			-0.17	(-0.65 to 0.31)		*.47*
Myocardial infarction						
<30	464	(362 to 645)	-2.15	(-2.76 to -1.55)	59	
30-49	263	(201 to 384)	-3.79	(-4.98 to -2.60)	46	
≥50	187	(140 to 281)	-5.35	(-7.14 to -3.56)	0	
Overall	363	(300 to 459)	-2.76	(-3.33 to -2.18)	63	
Unadjusted analysis			-1.54	(-2.39 to -0.68)		*.001*
Adjusted analysis			-1.46	(-2.30 to -0.62)		*.001*
Adjusted analysis including annual CV death rate			-1.42	(-2.28 to -0.55)		*.002*
Stroke						
<30	1,170	(854 to 1,852)	-0.86	(-1.17 to -0.54)	19	
30-49	678	(472 to 1,205)	-1.48	(-2.12 to -0.83)	18	
≥50	NA		-0.67	(-4.07 to 2.73)	78	
Overall	907	(691 to 1,319)	-1.10	(-1.45 to -0.76)	39	
Unadjusted analysis			-0.77	(-1.27 to -0.27)		*.003*
Adjusted analysis			-0.82	(-1.32 to -0.28)		*.003*
Adjusted analysis including annual CV death rate			-0.81	(-1.37 to -0.25)		*.005*

* Meta-regression model for each 20% LDL-C reduction

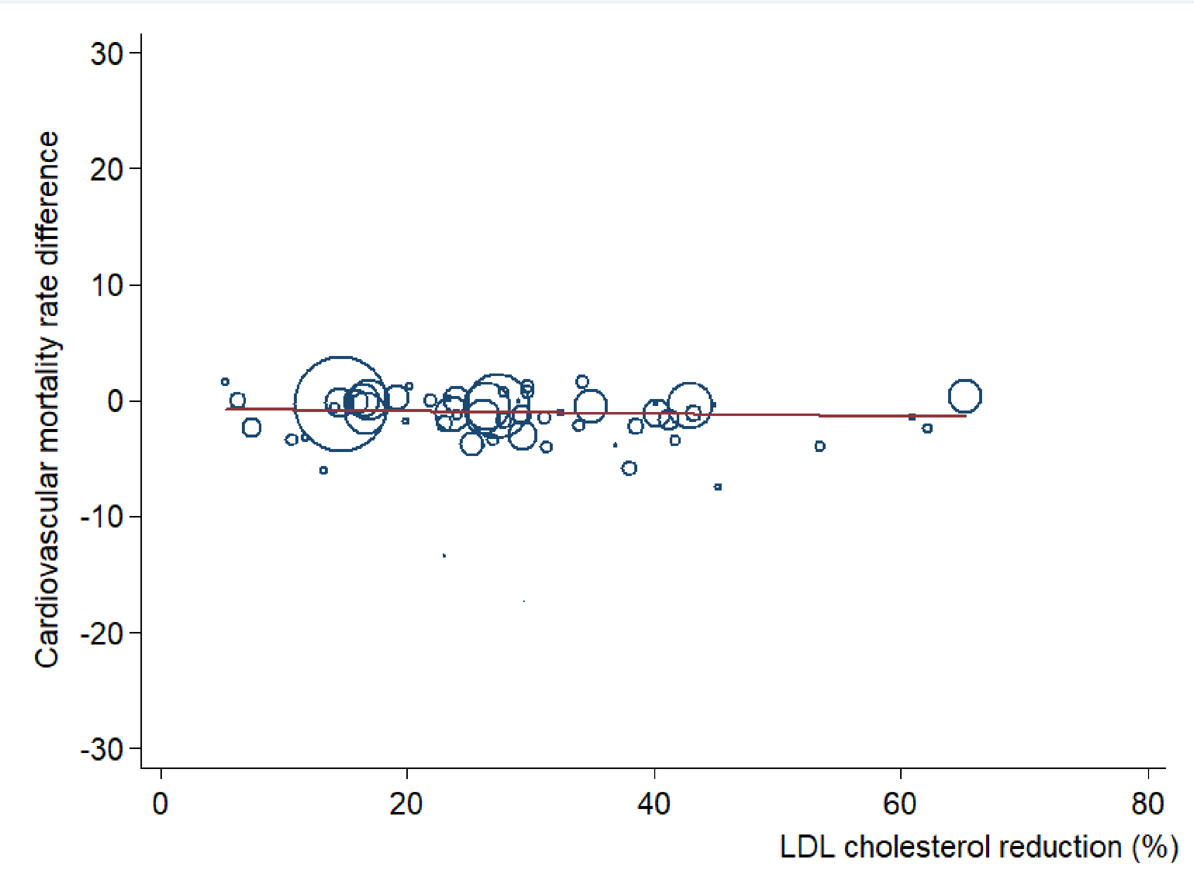
eTable 10. Unadjusted and adjusted meta-regression models for the association of percent LDL-C levels reduction and mortality and other cardiovascular outcomes expressed in rate ratios (RRs)

Percent LDL-C reduction (%)	Rate ratio (95% CI)		I² (%)	*P* for trend*
All-cause mortality				
<30	0.93	(0.89 to 0.97)	26	
30-49	0.90	(0.84 to 0.96)	46	
≥50	0.99	(0.82 to 1.21)	26	
Overall	0.92	(0.89 to 0.96)	34	
Unadjusted analysis	1.00	(0.94 to 1.06)		*.94*
Adjusted analysis	0.99	(0.95 to 1.05)		*.85*
Adjusted analysis including annual CV death rate	0.99	(0.93 to 1.04)		*.66*
Cardiovascular mortality				
<30	0.88	(0.85 to 0.92)	1	
30-49	0.88	(0.80 to 0.95)	38	
≥50	0.87	(0.63 to 1.22)	42	
Overall	0.89	(0.85 to 0.92)	18	
Unadjusted analysis	1.02	(0.94 to 1.09)		*.63*
Adjusted analysis	1.01	(0.95 to 1.07)		*.74*
Adjusted analysis including annual CV death rate	0.98	(0.92 to 1.05)		*.60*
Myocardial infarction				
<30	0.79	(0.75 to 0.83)	27	
30-49	0.74	(0.67 to 0.82)	61	
≥50	0.69	(0.58 to 0.82)	10	
Overall	0.77	(0.73 to 0.81)	42	
Unadjusted analysis	0.94	(0.87 to 1.02)		*.12*
Adjusted analysis	0.94	(0.87 to 1.01)		*.08*
Adjusted analysis including annual CV death rate	0.92	(0.86 to 0.99)		*.028*
Stroke				
<30	0.82	(0.77 to 0.86)	0	
30-49	0.82	(0.71 to 0.95)	54	
≥50	0.84	(0.44 to 1.61)	72	
Overall	0.82	(0.77 to 0.87)	34	
Unadjusted analysis	0.91	(0.82 to 0.99)		*.05*
Adjusted analysis	0.91	(0.83 to 1.01)		*.07*
Adjusted analysis including annual CV death rate	0.87	(0.79 to 0.95)		*.003*

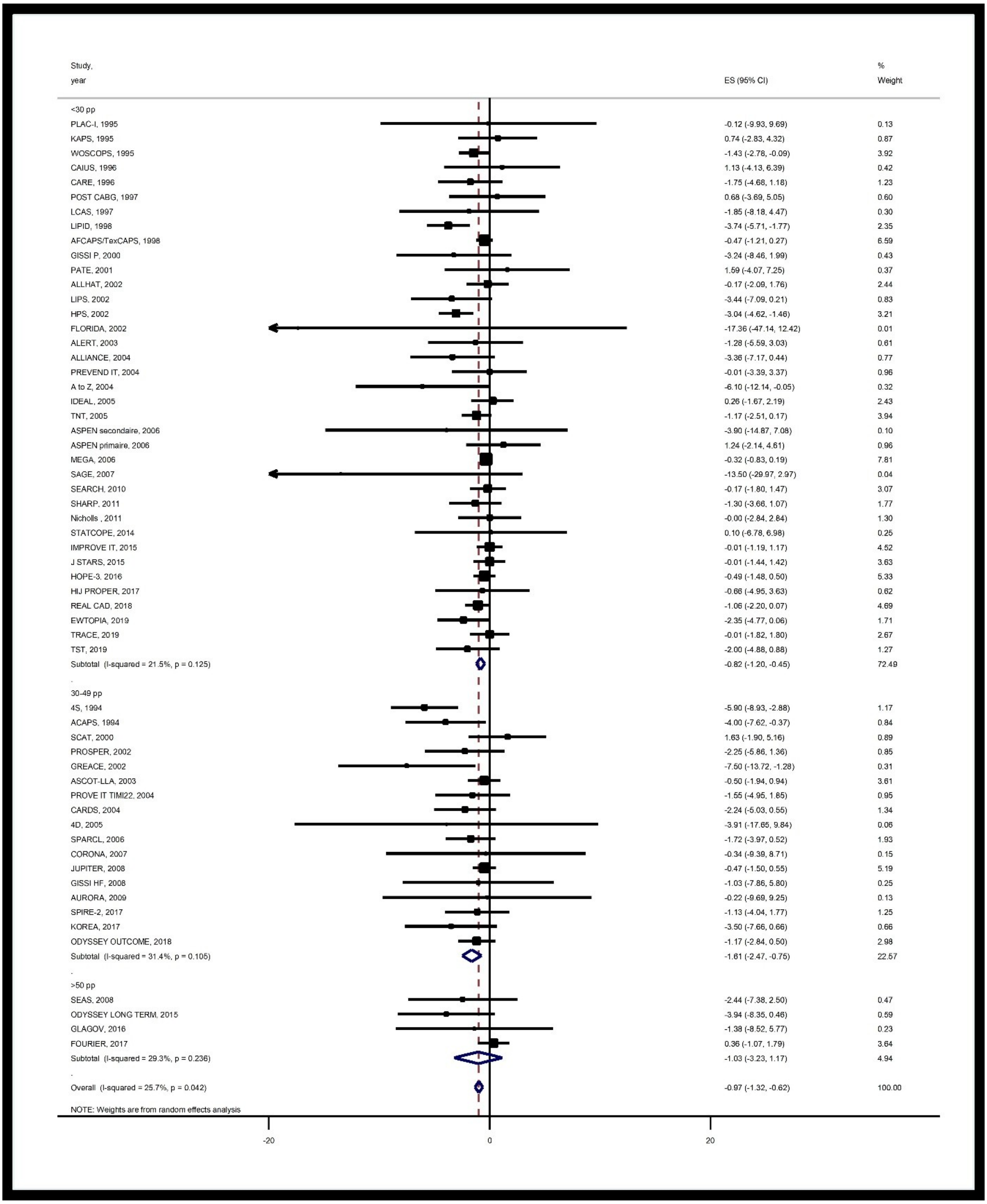
*Meta-regression model for each 20% LDL-C reduction

eFigure 7. Meta-regression analysis of absolute rate difference (ARD) in cardiovascular mortality risk by percent low-density lipoprotein cholesterol (LDL-C) level reduction.

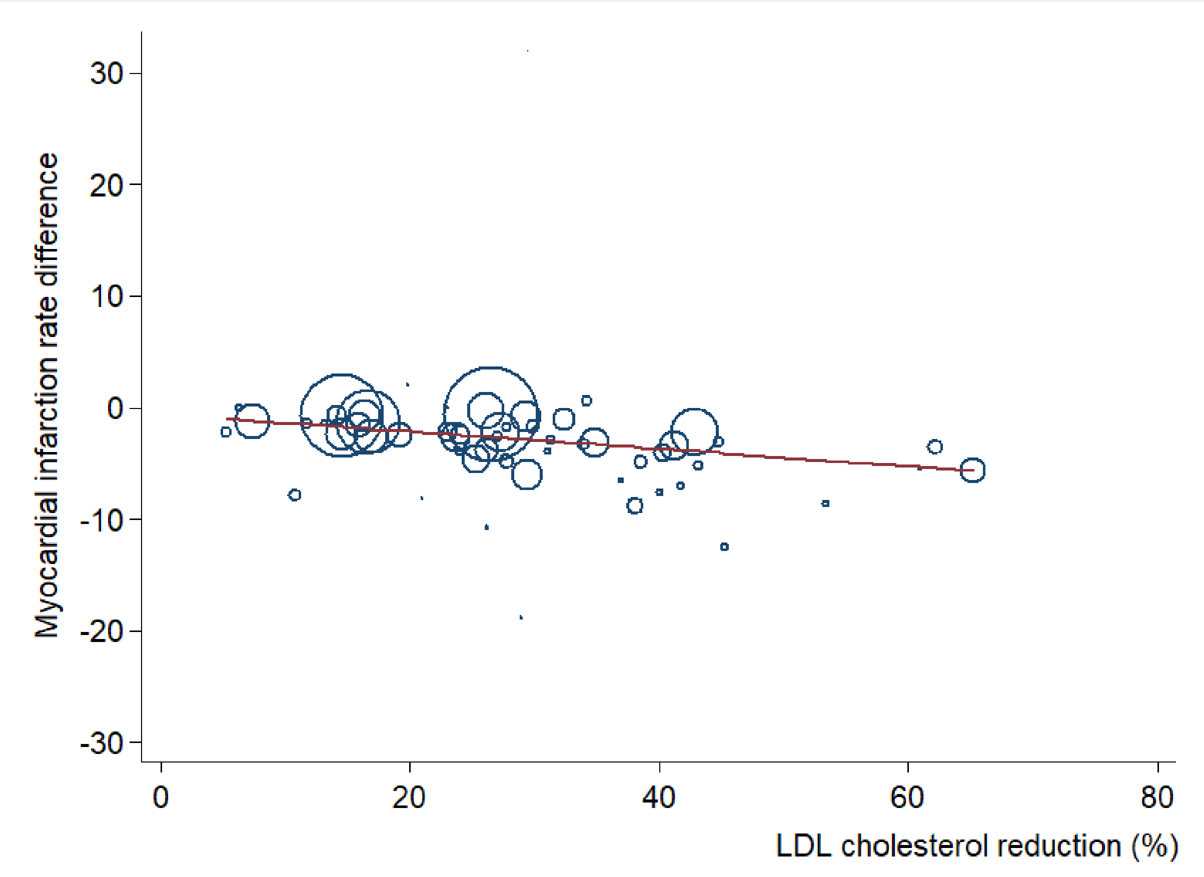
Change in ARD and 95% confidence intervals of more intensive vs less intensive LDL-C – lowering therapies plotted against percent LDL-C levels reduction. Size of the data markers is proportional to the weight in the meta-regression. The solid line represents the meta-regression slope of the change in ARD for treatment across increasing levels of percent LDL-C reduction.



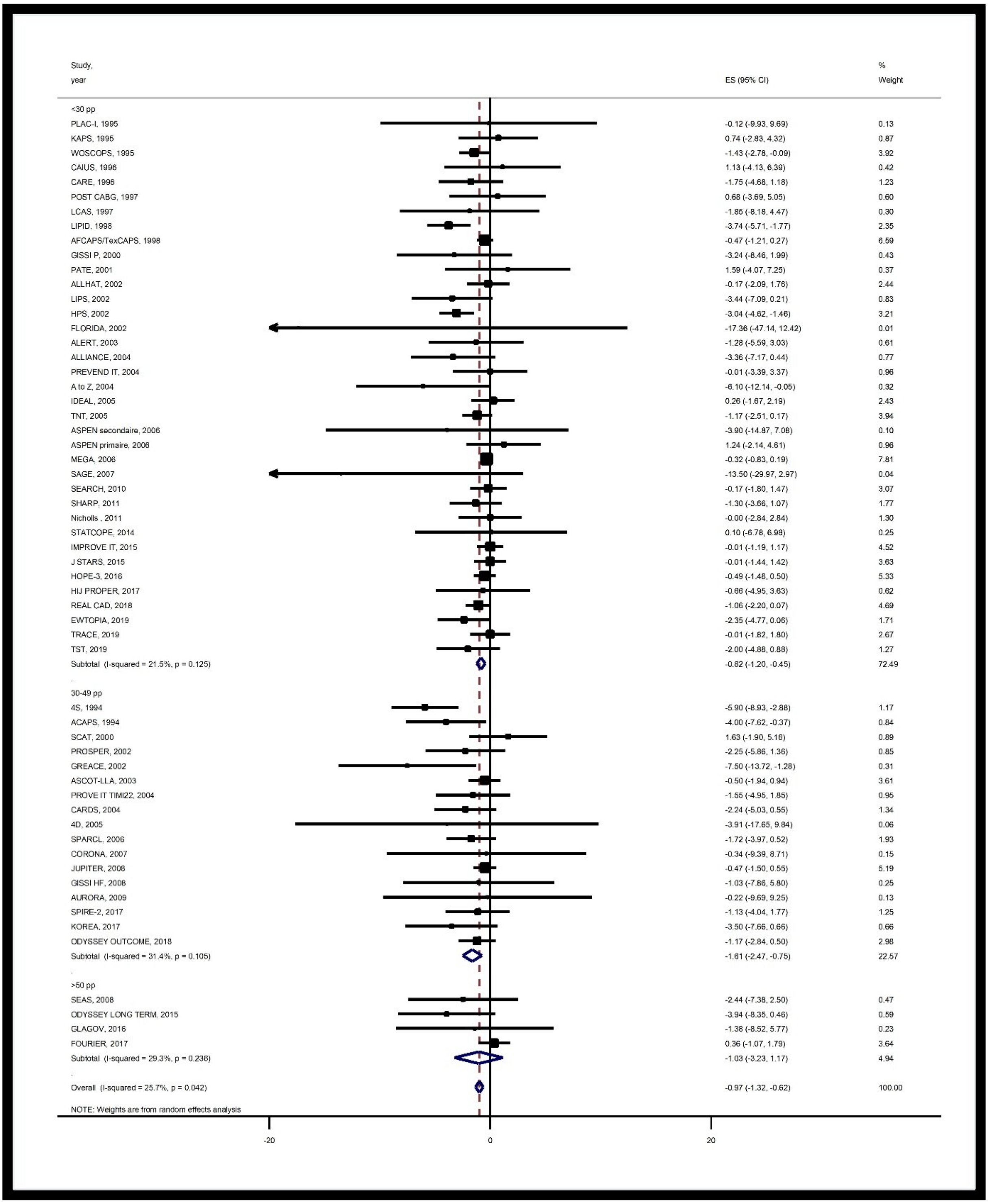
eFigure 8. Meta-analysis of cardiovascular mortality risk stratified by percent low-density lipoprotein cholesterol (LDL-C) level reduction. Absolute rate difference (ARD) and 95% confidence intervals of more intensive vs less intensive LDL-C lowering therapies and the weight of study data in the meta-analysis.



eFigure 9. Meta-regression analysis of absolute rate difference (ARD) in myocardial infarction risk by percent low-density lipoprotein cholesterol (LDL-C) level reduction

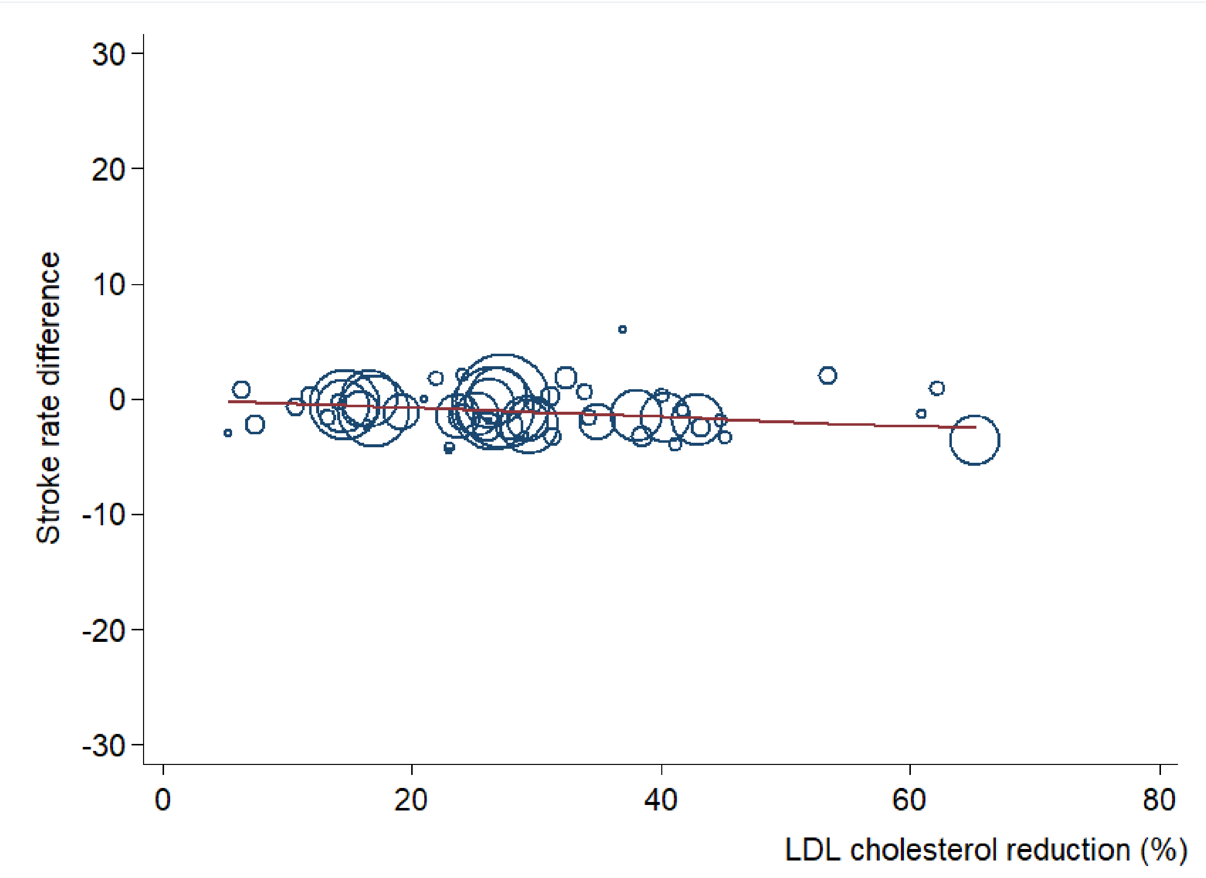


eFigure 10. Meta-analysis of myocardial infarction risk stratified by percent low-density lipoprotein cholesterol (LDL-C) level reduction. Absolute rate difference (ARD) and 95% confidence intervals of more intensive vs less intensive LDL-C lowering therapies and the weight of study data in the meta-analysis.

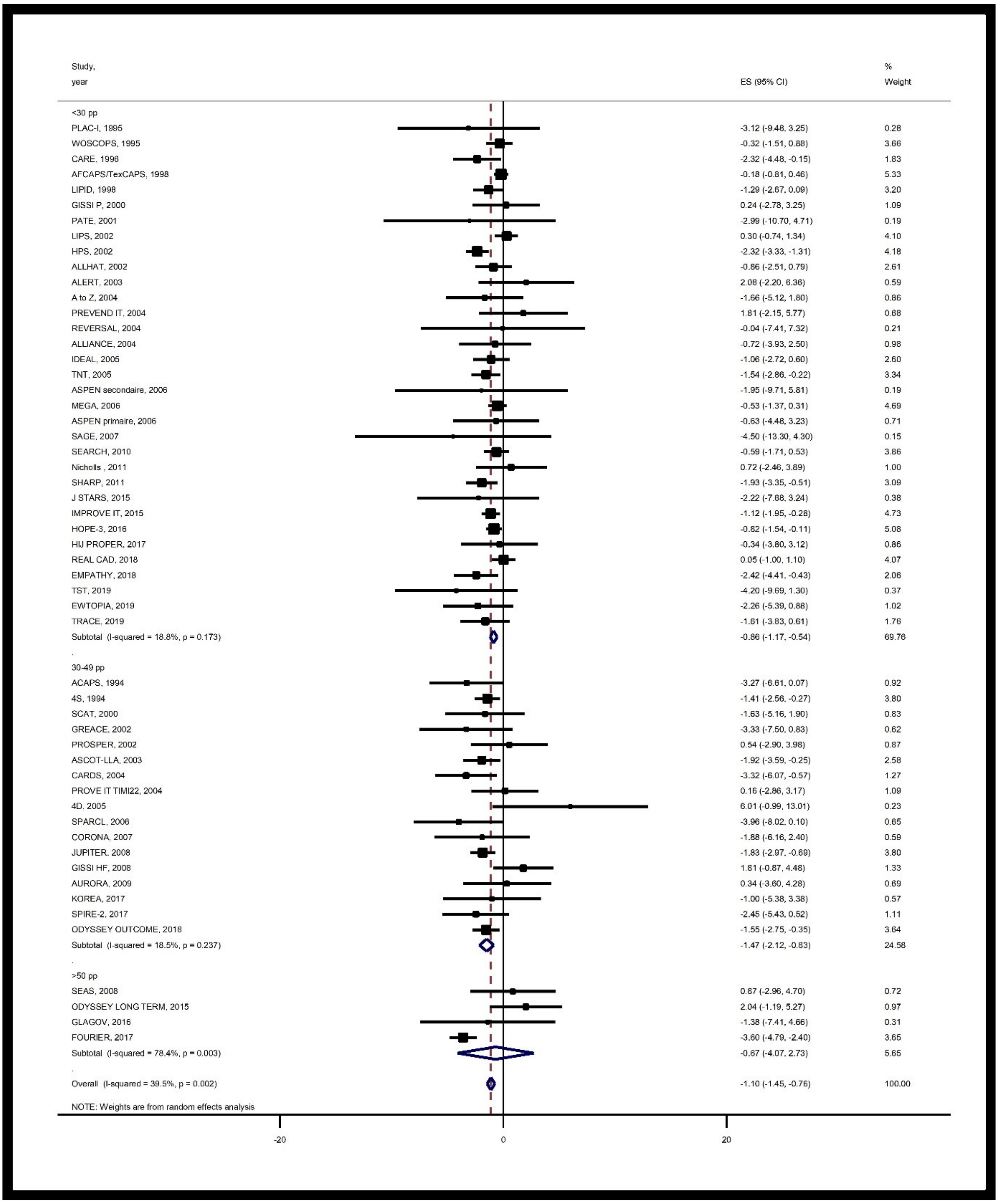


eFigure 11. Meta-regression analysis of absolute rate difference (ARD) in stroke risk by percent low-density lipoprotein cholesterol (LDL-C) Level reduction.

Change in ARD and 95% confidence intervals of more intensive vs less intensive LDL-C – lowering therapies plotted against percent LDL-C levels. Size of the data markers is proportional to the weight in the meta-regression. The solid line represents the meta-regression slope of the change in ARD for treatment across increasing levels of percent LDL-C reduction.



eFigure 12. Meta-analysis of stroke risk stratified by percent low-density lipoprotein cholesterol (LDL-C) level reduction. Absolute rate difference (ARD) and 95% confidence intervals of more intensive vs less intensive LDL-C lowering therapies and the weight of study data in the meta-analysis.



Absolute LDL-C reduction (eTables 11&12)

When LDL-C reduction was expressed as absolute reduction, unadjusted meta-regression showed that MI risk reduction was significantly associated with each 40 mg/dL LDL-C reduction (ARD -2.81 (-4.11 to -1.51), $P < .0001$; 16% increase in RR, $P = .002$). After adjustment including annual CV mortality rate, changes in RRs for MI risk were significant (15% increase in RR, $P = .014$) as well as changes in ARD (-2.29 (-3.73 to -0.86), $P = .002$). For stroke risk, meta-regression after adjustment was significant ($P = .009$ to .013). In contrast no relationship emerged between intensive LDL-C lowering therapy and increasing absolute LDL-C levels reduction for all-cause and CV mortality risk.

The ARDs, NNTs and RRs for the 4 outcomes associated with intensive vs less intensive therapy across all trials varied by the extent of LDL-C level percentage reduction (<35 mg/dL, 35 to 65 mg/dL, and >65 mg/dL). MI risk was further reduced with increasing absolute LDL-C reduction which resulted in high ARDs, and low NNTs and RRs. Stroke risk was not reduced in trials with more than 65 mg/dL LDL-C reduction (ARD -0.55 (-2.57 to 1.47); RR 0.78 (0.44 to 1.39)).

eTable 11. Unadjusted and adjusted meta-regression models for the association of absolute LDL-C levels reduction and mortality and other cardiovascular outcomes expressed in absolute rate differences (ARDs) and annual number needed to treat (NNT)

Absolute LDL-C reduction (mg/dL)	NNT (95% CI)		ARD (95%CI)		I² (%)	*P for trend**
All-cause mortality						
<35	1,403	(803 to 5,495)	-0.71	(-1.25 to -0.18)	0	
35-65	592	(387 to 1,253)	-1.69	(-2.58 to -0.79)	35	
>65	201	(129 to 457)	-4.97	(-7.75 to -2.19)	15	
Overall	754	(529 to 1,309)	-1.33	(-1.89 to -0.76)	31	
Unadjusted analysis			-1.26	(-2.79 to 0.27)		*.10*
Adjusted analysis			-0.95	(-2.63 to 0.74)		*.26*
Adjusted analysis including annual CV death rate			-0.73	(-2.39 to 0.93)		*.38*
Cardiovascular mortality						
<35	1,969	(1,209 to 5,291)	-0.51	(-0.83 to -0.19)	0	
35-65	873	(600 to 1,602)	-1.15	(-1.67 to -0.62)	21	
>65	199	(141 to 342)	-5.02	(-7.12 to -2.92)	0	
Overall	1,027	(756 to 1,665)	-0.97	(-1.32 to -0.62)	26	
Unadjusted analysis			-0.96	(-1.94 to 0.02)		*.053*
Adjusted analysis			-0.79	(-1.85 to 0.27)		*.14*
Adjusted analysis including annual CV death rate			-0.46	(-1.31 to 0.39)		*.29*
Myocardial infarction						
<35	745	(568 to 1,080)	-1.34	(-1.76 to -0.93)	17	
35-65	280	(231 to 355)	-3.57	(-4.33 to -2.81)	34	
>65	129	(87 to 246)	-7.78	(-11.5 to -4.06)	56	
Overall	363	(300 to 459)	-2.76	(-3.33 to -2.18)	63	
Unadjusted analysis			-2.81	(-4.11 to -1.51)		*<.0001*
Adjusted analysis			-2.35	(-3.74 to -0.97)		*.001*
Adjusted analysis including annual CV death rate			-2.29	(-3.73 to -0.86)		*.002*
Stroke						
<35	1,143	(837 to 1,802)	-0.88	(-1.20 to -0.56)	0	
35-65	754	(499 to 1,541)	-1.33	(-2.01 to -0.65)	65	
>65	NA		-0.55	(-2.57 to 1.47)	50	
Overall	907	(691 to 1,319)	-1.10	(-1.45 to -0.76)	39	
Unadjusted analysis			-0.68	(-1.55 to 0.20)		*.13*
Adjusted analysis			-1.25	(-2.17 to -0.33)		*.009*
Adjusted analysis including annual CV death rate			-1.26	(-2.25 to -0.28)		*.013*

* Meta-regression model for each 40 mg/dL LDL-C absolute reduction

eTable 12. Unadjusted and adjusted meta-regression models for the association of absolute LDL-C levels reduction and mortality and other cardiovascular outcomes expressed in rate ratios (RRs)

Absolute LDL-C reduction (mg/dL)	**Rate ratio (95% CI)**		**I² (%)**	***P* for trend***
All-cause mortality				
<35	0.96	(0.92 to 1.00)	10	
35-65	0.92	(0.88 to 0.96)	31	
>65	0.73	(0.54 to 0.99)	63	
Overall	0.92	(0.89 to 0.96)	34	
Unadjusted analysis	0.95	(0.87 to 1.04)		*.31*
Adjusted analysis	0.99	(0.91 to 1.08)		*.77*
Adjusted analysis including annual CV death rate	0.97	(0.88 to 1.07)		*.56*
Cardiovascular mortality				
<35	0.93	(0.88 to 0.98)	0	
35-65	0.89	(0.85 to 0.94)	13	
>65	0.66	(0.53 to 0.82)	18	
Overall	0.89	(0.85 to 0.92)	18	
Univariable analysis	0.94	(0.83 to 1.05)		*.26*
Multivariable analysis	1.01	(0.91 to 1.12)		*.89*
Adjusted analysis including annual CV death rate	0.96	(0.86 to 1.07)		*.44*
Myocardial infarction				
<35	0.83	(0.79 to 0.88)	9	
35-65	0.76	(0.71 to 0.81)	38	
>65	0.56	(0.47 to 0.67)	3	
Overall	0.77	(0.73 to 0.81)	42	
Unadjusted analysis	0.84	(0.75 to 0.93)		*.002*
Adjusted analysis	0.89	(0.78 to 1.00)		*.056*
Adjusted analysis including annual CV death rate	0.85	(0.75 to 0.97)		*.014*
Stroke				
<35	0.83	(0.78 to 0.89)	0	
35-65	0.81	(0.72 to 0.91)	61	
>65	0.78	(0.44 to 1.39)	58	
Overall	0.82	(0.77 to 0.87)	34	
Unadjusted analysis	0.92	(0.78 to 1.08)		*.30*
Adjusted analysis	0.89	(0.75 to 1.05)		*.16*
Adjusted analysis including annual CV death rate	0.81	(0.69 to 0.95)		*.012*

*Meta-regression model for each 40 mg LDL-C reduction

Additional analyses

Baseline LDL-C levels (eTables 13&14)

The association between risk reduction and baseline LDL-C was further investigated.

In meta-regression analyses, when outcomes risks are expressed as ARDs, no relationship emerged between intensive LDL-C lowering therapy and increasing baseline LDL-C levels. In contrast RRs for all-cause and CV mortality as well as for MI risks associated with intensive LDL-C lowering therapy decreased by 6, 11 and 9% respectively for each 40 mg/dL increase in baseline LDL-C level. After multivariable adjustments the relationship remained significant only for CV mortality and MI (*P*= .009 to .015 and .006 to .01 respectively). In a meta-analysis by subgroups of baseline LDL-C level, when considering ARDs and NNTs, LDL-C lowering produced increasing benefits in the trials' participants with higher baseline LDL-C for mortality and MI risk. In contrast stroke risk reduction did not correlate with baseline LDL-C levels.

eTable 13. Unadjusted and adjusted meta-regression models for the association of baseline LDL-C levels and mortality and other cardiovascular outcomes expressed in absolute rate differences (ARDs) and annual number needed to treat (NNT)

Baseline LDL-C (mg/dL)	NNT	(95% CI)	ARD	(95%CI)	I² (%)	*P for trend**
All-cause mortality						
<100	NA		-0.75	(-1.59 to 0.10)	15	
100-129	1,015	(508 to 1,000,000)	-0.99	(-1.97 to -0.00)	12	
130-159	665	(411 to 1,748)	-1.50	(-2.44 to -0.57)	35	
≥160	321	(169 to 3,300)	-3.11	(-5.92 to -0.30)	51	
Overall	754	(529 to 1,309)	-1.33	(-1.89 to -0.71)	31	
Unadjusted analysis			-0.63	(-1.46 to 0.20)		*.14*
Adjusted analysis			-0.22	(-1.52 to 1.07)		*.73*
Adjusted analysis including annual CV death rate			-0.38	(-1.64 to 0.89)		*.55*
Cardiovascular mortality						
<100	1,661	(870 to 18,182)	-0.60	(-1.15 to -0.06)	0	
100-129	NA		-0.50	(-1.01 to 0.02)	0	
130-159	749	(512 to 1,393)	-1.34	(-1.95 to -0.72)	36	
≥160	515	(262 to 15,152)	-1.94	(-3.82 to -0.07)	54	
Overall	1,028	(756 to 1,605)	-0.97	(-1.32 to -0.62)	26	
Unadjusted analysis			-0.43	(-0.97 to 0.10)		*.11*
Adjusted analysis			-0.25	(-1.00 to 0.49)		*.50*
Adjusted analysis including annual CV death rate			-0.43	(-1.06 to 0.19)		*.17*
Myocardial infarction						
<100	333	(237 to 560)	-3.00	(-4.21 to -1.79)	61	
100-129	684	(463 to 1,311)	-1.46	(-2.16 to -0.76)	29	
130-159	334	(251 to 497)	-3.00	(-3.98 to -2.01)	62	
≥160	184	(113 to 487)	-5.44	(-8.82 to -2.05)	81	
Overall	363	(300 to 459)	-2.76	(-3.33 to -2.18)	63	
Unadjusted analysis			-0.59	(-1.54 to 0.35)		*.21*
Adjusted analysis			-0.27	(-1.48 to 0.95)		*.66*
Adjusted analysis including annual CV death rate			-0.33	(-1.57 to 0.92)		*.60*
Stroke						
<100	742	(449 to 2,132)	-1.35	(-2.23 to -0.47)	69	
100-129	962	(590 to 2,617)	-1.04	(-1.70 to -0.38)	30	
130-159	1,042	(662 to 2,439)	-0.96	(-1.51 to -0.41)	37	
≥160	898	(530 to 2,959)	-1.11	(-1.89 to -0.34)	0	
Overall	907	(661 to 1,319)	-1.10	(-1.45 to -0.76)	39	
Unadjusted analysis			0.24	(-0.26 to 0.75)		*.34*
Adjusted analysis			0.24	(-0.60 to 1.07)		*.57*

Adjusted analysis including annual CV death rate	0.26	(-0.62 to 1.13)	*.56*

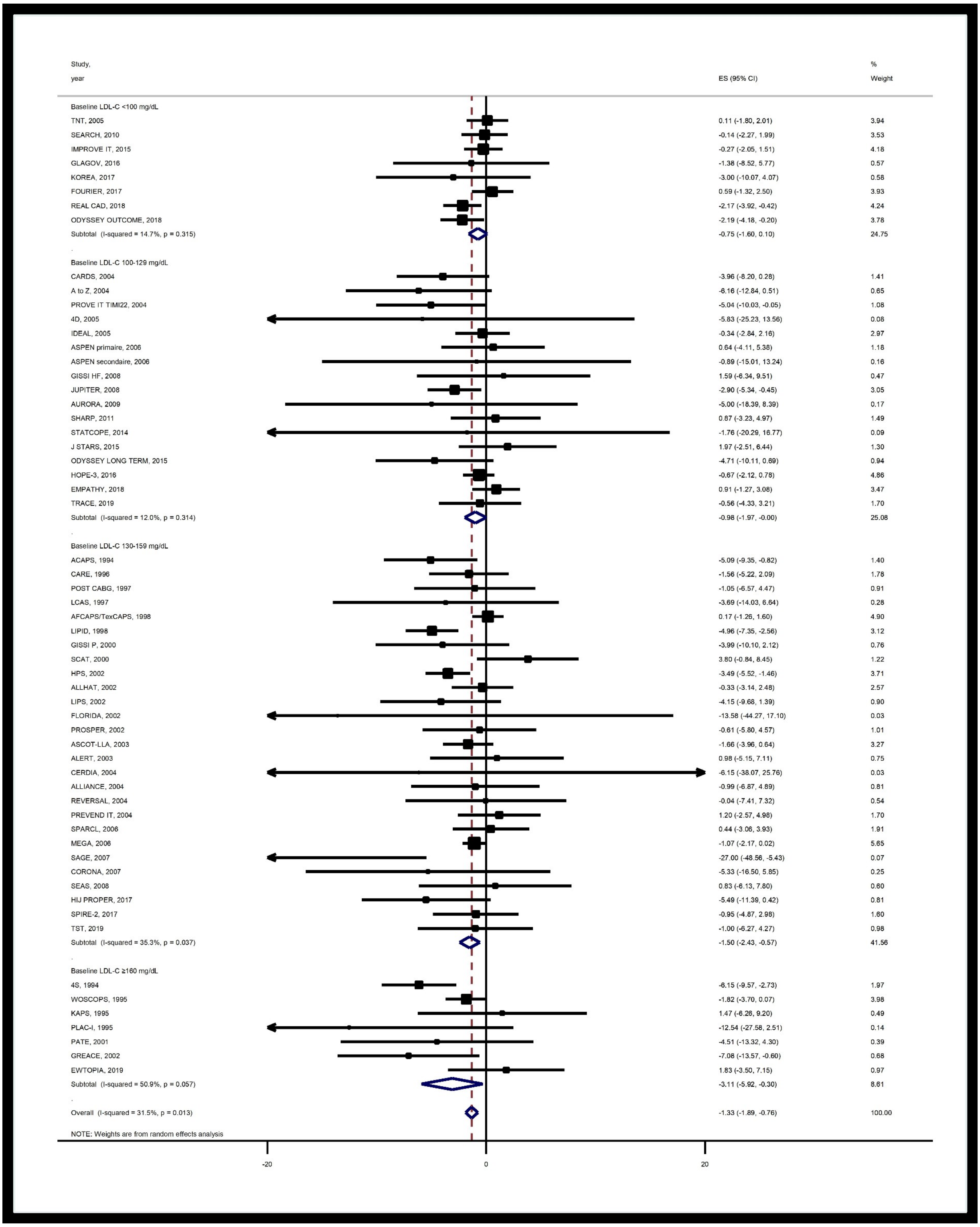
*Meta-regression model for each baseline 40 mg/dL LDL-C increase

eTable 14. Unadjusted and adjusted meta-regression models for the association of baseline LDL-C levels and mortality and other cardiovascular outcomes expressed in rate ratios (RRs)

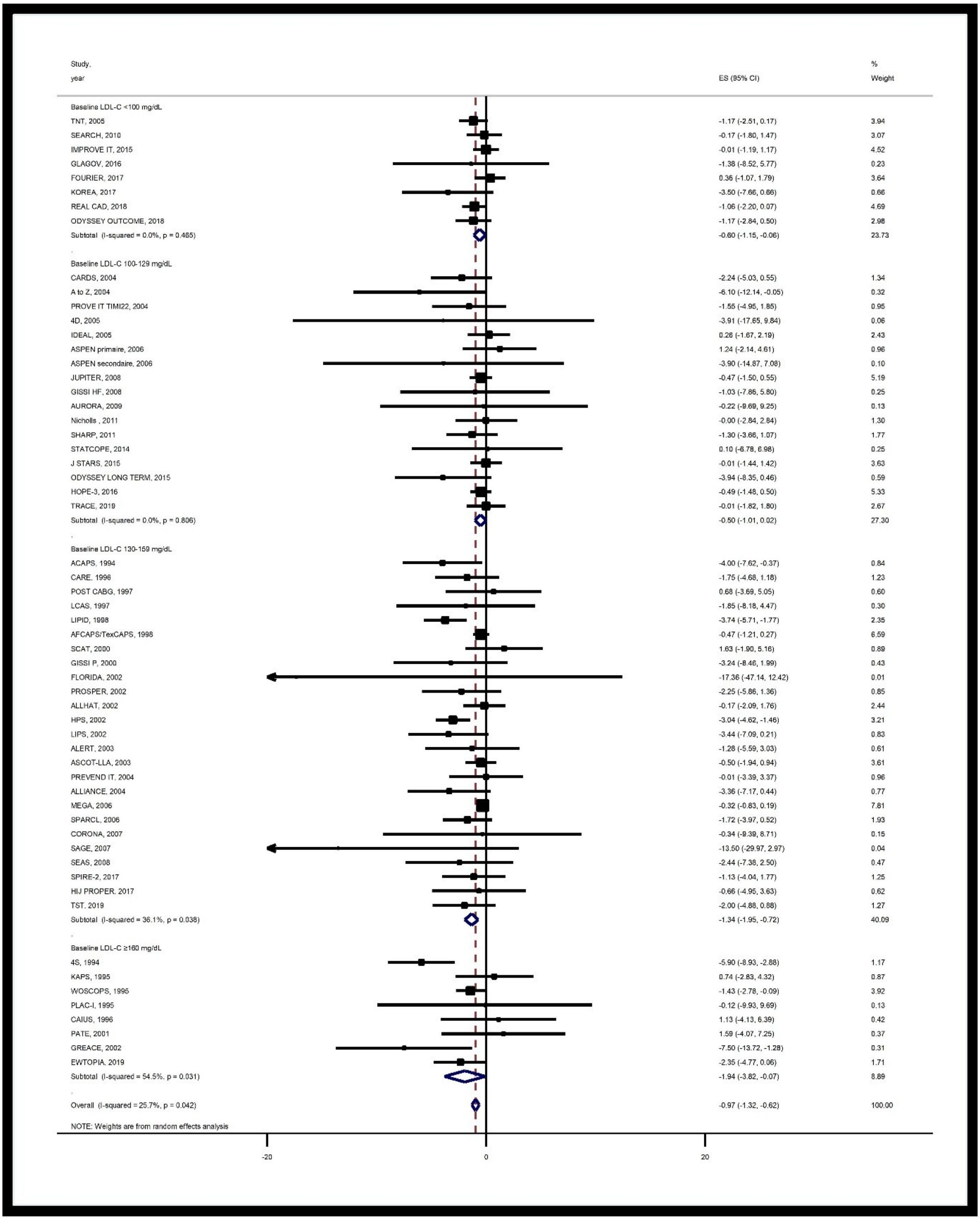
Baseline LDL-C (mg/dL)	Rate ratio (95% CI)		I² (%)	*P* for trend*
All-cause mortality				
<100	0.96	(0.90 to 1.02)	30	
100-129	0.95	(0.89 to 1.00)	21	
130-159	0.91	(0.87 to 0.96)	21	
≥160	0.79	(0.64 to 0.97)	53	
Overall	0.92	(0.89 to 0.96)	34	
Unadjusted analysis	0.94	(0.89 to 0.99)		*.036*
Adjusted analysis	0.93	(0.86 to 1.01)		*.09*
Adjusted analysis including annual CV death rate	0.94	(0.87 to 1.02)		*.14*
Cardiovascular mortality				
<100	0.95	(0.88 to 1.02)	18	
100-129	0.94	(0.88 to 1.00)	0	
130-159	0.86	(0.82 to 0.91)	0	
≥160	0.66	(0.57 to 0.78)	0	
Overall	0.89	(0.85 to 0.92)	18	
Unadjusted analysis	0.89	(0.83 to 0.95)		*.001*
Adjusted analysis	0.88	(0.79 to 0.97)		*.009*
Adjusted analysis including annual CV death rate	0.89	(0.80 to 0.97)		*.015*
Myocardial infarction				
<100	0.81	(0.75 to 0.88)	53	
100-129	0.81	(0.74 to 0.88)	25	
130-159	0.76	(0.71 to 0.81)	26	
≥160	0.62	(0.54 to 0.71)	0	
Overall	0.77	(0.73 to 0.81)	42	
Unadjusted analysis	0.91	(0.85 to 0.97)		*.008*
Adjusted analysis	0.85	(0.76 to 0.95)		*.006*
Adjusted analysis including annual CV death rate	0.86	(0.77 to 0.96)		*.01*
Stroke				
<100	0.77	(0.65 to 0.91)	64	
100-129	0.83	(0.72 to 0.97)	47	
130-159	0.84	(0.78 to 0.90)	4	
≥160	0.73	(0.59 to 0.91)	0	
Overall	0.82	(0.77 to 0.87)	34	
Unadjusted analysis	1.05	(0.94 to 1.17)		*.35*
Adjusted analysis	0.99	(0.86 to 1.16)		*.96*
Adjusted analysis including annual CV death rate	1.03	(0.89 to 1.19)		*.71*

*Meta-regression model for each 40 mg/dL increase in baseline LDL-C levels

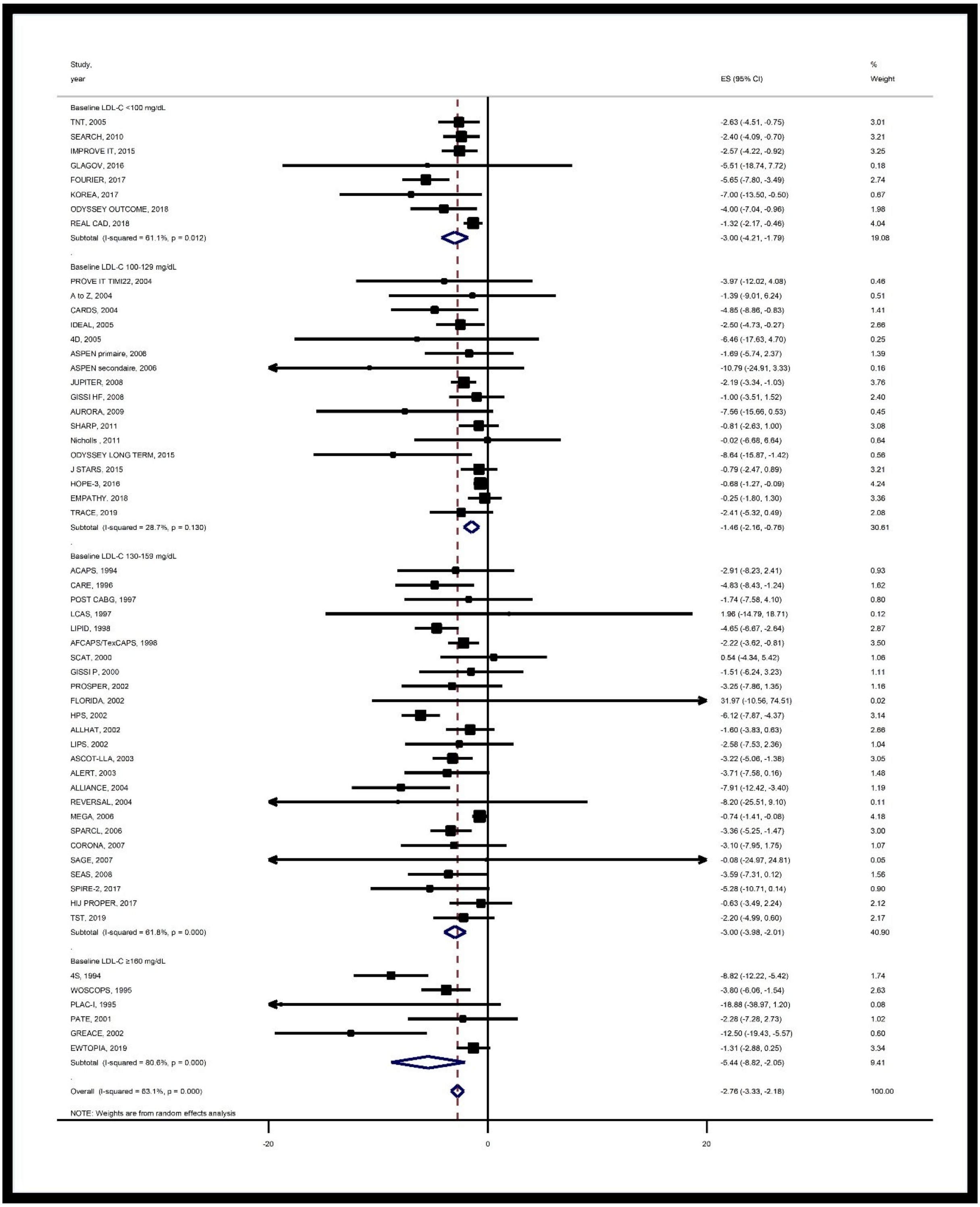
eFigure 13. Meta-analysis of all-cause mortality risk stratified by baseline LDL-C levels. Absolute rate difference (ARD) and 95% confidence intervals of more intensive vs less intensive LDL-C lowering therapies and the weight of study data in the meta-analysis.



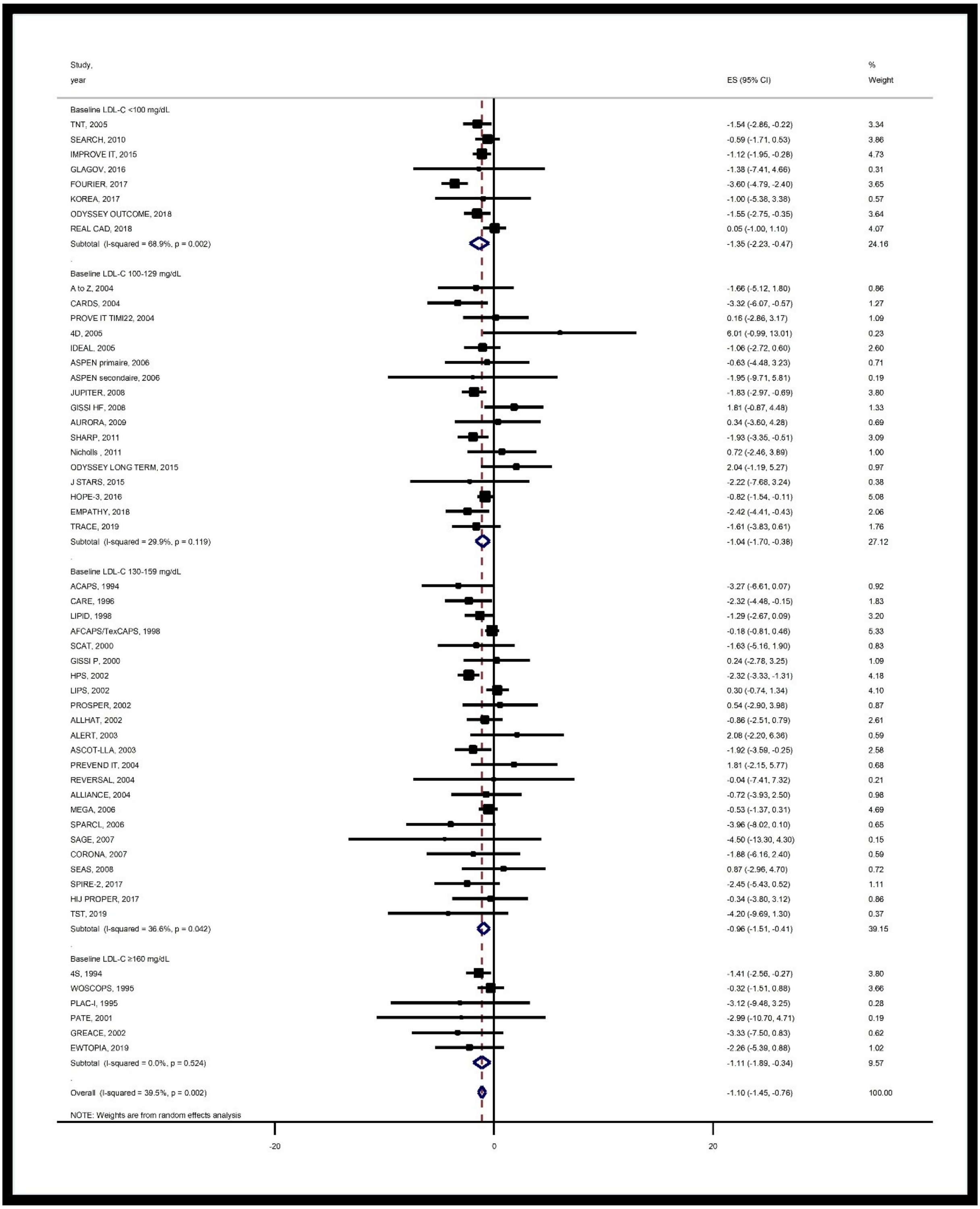
eFigure 14. Meta-analysis of cardiovascular mortality risk stratified by baseline low-density lipoprotein cholesterol (LDL-C) levels. Absolute rate difference (ARD) and 95% confidence intervals of more intensive vs less intensive low-density lipoprotein cholesterol (LDL-C)–lowering therapies and the weight of study data in the meta-analysis.



eFigure 15. Meta-analysis of myocardial infarction risk stratified by baseline low-density lipoprotein cholesterol (LDL-C) levels. Absolute rate difference (ARD) and 95% confidence intervals of more intensive vs less intensive LDL-C lowering therapies and the weight of study data in the meta-analysis.



eFigure 16. Meta-analysis of stroke risk stratified by baseline low-density lipoprotein cholesterol (LDL-C) levels. Absolute rate difference (ARD) and 95% confidence intervals of more intensive vs less intensive LDL-C lowering therapies and the weight of study data in the meta-analysis.



Achieved LDL-C levels (eTables 15&16)

We investigated the relationship between achieved LDL-C levels and the risk reduction of outcomes. Overall, when expressed in terms of ARDs, clinical benefits did not consistently differ between trials that achieved LDL-C levels below 70 and even 55 mg/dL and those with achieved LDL-C greater than 70 or 116 mg/dL. In univariate meta-regression, a significant univariate trend was found toward decrease in RRs for all-cause and CV mortality according to each lower 40 mg/dL achieved LDL-C levels (*P*= .04, < .001 and .05 respectively). These relationships did not remain significant after multivariable adjustments. Of note RR for stroke risk associated with intensive LDL-C lowering therapy increased by 8% for lower achieved LDL-C levels.

eTable 15. Unadjusted and adjusted meta-regression models for the association of achieved LDL-C levels and mortality and other cardiovascular outcomes expressed in absolute rate differences (ARDs) and annual number needed to treat (NNT)

Achieved LDL-C (mg/dL)	NNT (95% CI)		ARD (95%CI)		I² (%)	*P for trend*
All-cause mortality						
≥116	479	(262 to 2,793)	-2.09	(-3.82 to -0.36)	49	
100-115	NA		-1.55	(-3.83 to 0.72)	64	
70-99	1,130	(673 to 3,496)	-0.89	(-1.49 to -0.29)	0	
55-69	298	(198 to 601)	-3.36	(-5.06 to -1.66)	7	
<55	NA		-0.60	(-1.99 to 0.79)	23	
Overall	754	(529 to 1,309)	-1.33	(-1.89 to -0.76)	31	
Unadjusted analysis			-0.44	(-1.33 to 0.45)		*.32*
Adjusted analysis			0.46	(-1.26 to 2.18)		*.60*
Adjusted analysis including annual CV death rate			0.24	(-1.47 to 1.96)		*.78*
Cardiovascular mortality						
≥116	675	(362 to 5,025)	-1.48	(-2.77 to -0.19)	58	
100-115	787	(405 to 13,514)	-1.27	(-2.47 to -0.07)	54	
70-99	1,066	(732 to 1,968)	-0.94	(-1.37 to -0.51)	0	
55-69	615	(373 to 1,757)	-1.63	(-2.68 to -0.57)	0	
<55	NA		-0.18	(-0.86 to 0.49)	0	
Overall	1,028	(756 to 1,605)	-0.97	(-1.32 to -0.62)	26	
Unadjusted analysis			-0.33	(-0.89 to 0.23)		*.24*
Adjusted analysis			0.18	(-0.86 to 1.21)		*.74*
Adjusted analysis including annual CV death rate			-0.12	(-0.94 to 0.70)		*.77*
Myocardial infarction						
≥116	263	(165 to 648)	-3.79	(-6.06 to -1.54)	82	
100-115	422	(272 to 942)	-2.37	(-3.68 to -1.06)	42	
70-99	392	(297 to 575)	-2.55	(-3.37 to -1.74)	65	
55-69	352	(229 to 755)	-2.84	(-4.36 to -1.32)	4	
<55	304	(210 to 547)	-3.29	(-4.76 to -1.83)	51	
Overall	363	(300 to 459)	-2.76	(-3.33 to -2.18)	63	
Unadjusted analysis			-0.05	(-1.04 to 0.94)		*.92*
Adjusted analysis			1.58	(0.15 to 3.00)		*.03*
Adjusted analysis including annual CV death rate			1.39	(-0.09 to 2.89)		*.065*
Stroke						
≥116	1,321	(762 to 4,950)	-0.76	(-1.31 to -0.20)	0	
100-115	NA		-0.70	(-1.54 to 0.13)	27	
70-99	863	(598 to 1,550)	-1.16	(-1.67 to -0.64)	41	
55-69	1,121	(569 to 41,667)	-0.89	(-1.76 to -0.02)	0	
<55	543	(319 to 1,848)	-1.84	(-3.14 to -0.54)	69	
Overall	907	(691 to 1,319)	-1.10	(-1.45 to -0.76)	39	
Unadjusted analysis			0.50	(0.00 to 1.00)		*.04*

Adjusted analysis	1.02	(0.05 to 1.98)	*.04*
Adjusted analysis including annual CV death rate	1.08	(0.06 to 2.11)	*.04*

*Meta-regression model for each achieved 40 mg/dL LDL-C decrease

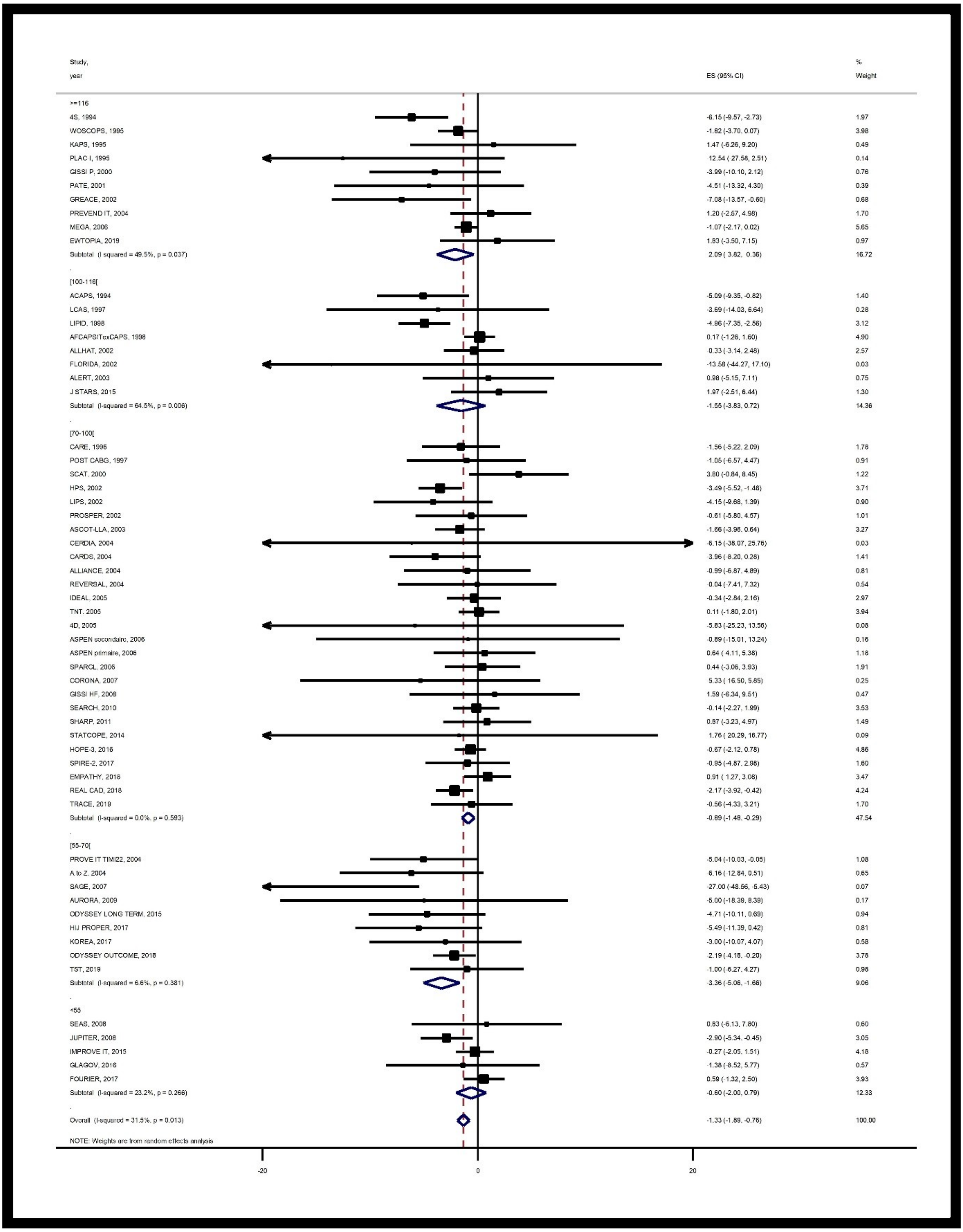
eTable 16. Unadjusted and adjusted meta-regression models for the association of achieved LDL-C levels and mortality and other cardiovascular outcomes expressed in rate ratios

Achieved LDL-C (mg/dL)	Rate ratio (95% CI)		I² (%)	*P* for trend*
All-cause mortality				
≥116	0.79	(0.68 to 0.92)	37	
100-115	0.93	(0.80 to 1.09)	56	
70-99	0.95	(0.92 to 0.98)	0	
55-69	0.82	(0.72 to 0.93)	43	
<55	0.97	(0.89 to 1.06)	28	
Overall	0.92	(0.89 to 0.96)	34	
Unadjusted analysis	0.94	(0.88 to 0.99)		*.04*
Adjusted analysis	0.99	(0.89 to 1.09)		*.79*
Adjusted analysis including annual CV death rate	0.99	(0.89 to 1.11)		*.91*
Cardiovascular mortality				
≥116	0.68	(0.59 to 0.79)	0	
100-115	0.84	(0.72 to 0.98)	26	
70-99	0.91	(0.87 to 0.95)	0	
55-69	0.85	(0.4 to 0.98)	20	
<55	0.99	(0.90 to 1.09)	0	
Overall	0.89	(0.85 to 0.92)	18	
Unadjusted analysis	0.88	(0.82 to 0.94)		*<.001*
Adjusted analysis	0.94	(0.83 to 1.05)		*.26*
Adjusted analysis including annual CV death rate	0.96	(0.86 to 1.08)		*.53*
Myocardial infarction				
≥116	0.63	(0.55 to 0.72)	6	
100-115	0.78	(0.66 to 0.93)	50	
70-99	0.78	(0.74 to 0.82)	16	
55-69	0.86	(0.79 to 0.95)	12	
<55	0.72	(0.59 to 0.87)	72	
Overall	0.77	(0.73 to 0.81)	42	
Unadjusted analysis	0.92	(0.85 to 1.00)		*.052*
Adjusted analysis	1.01	(0.87 to 1.18)		*.87*
Adjusted analysis including annual CV death rate	1.03	(0.88 to 1.20)		*.70*
Stroke				
≥116	0.78	(0.64 to 0.94)	0	
100-115	0.89	(0.79 to 1.02)	8	
70-99	0.83	(0.76 to 0.90)	37	
55-69	0.83	(0.72 to 0.96)	0	
<55	0.68	(0.50 to 0.92)	72	
Overall	0.82	(0.77 to 0.87)	34	
Unadjusted analysis	1.07	(0.96 to 1.19)		*.22*
Adjusted analysis	1.06	(0.88 to 1.29)		*.53*
Adjusted analysis including	1.15	(0.96 to 1.38)		*.13*

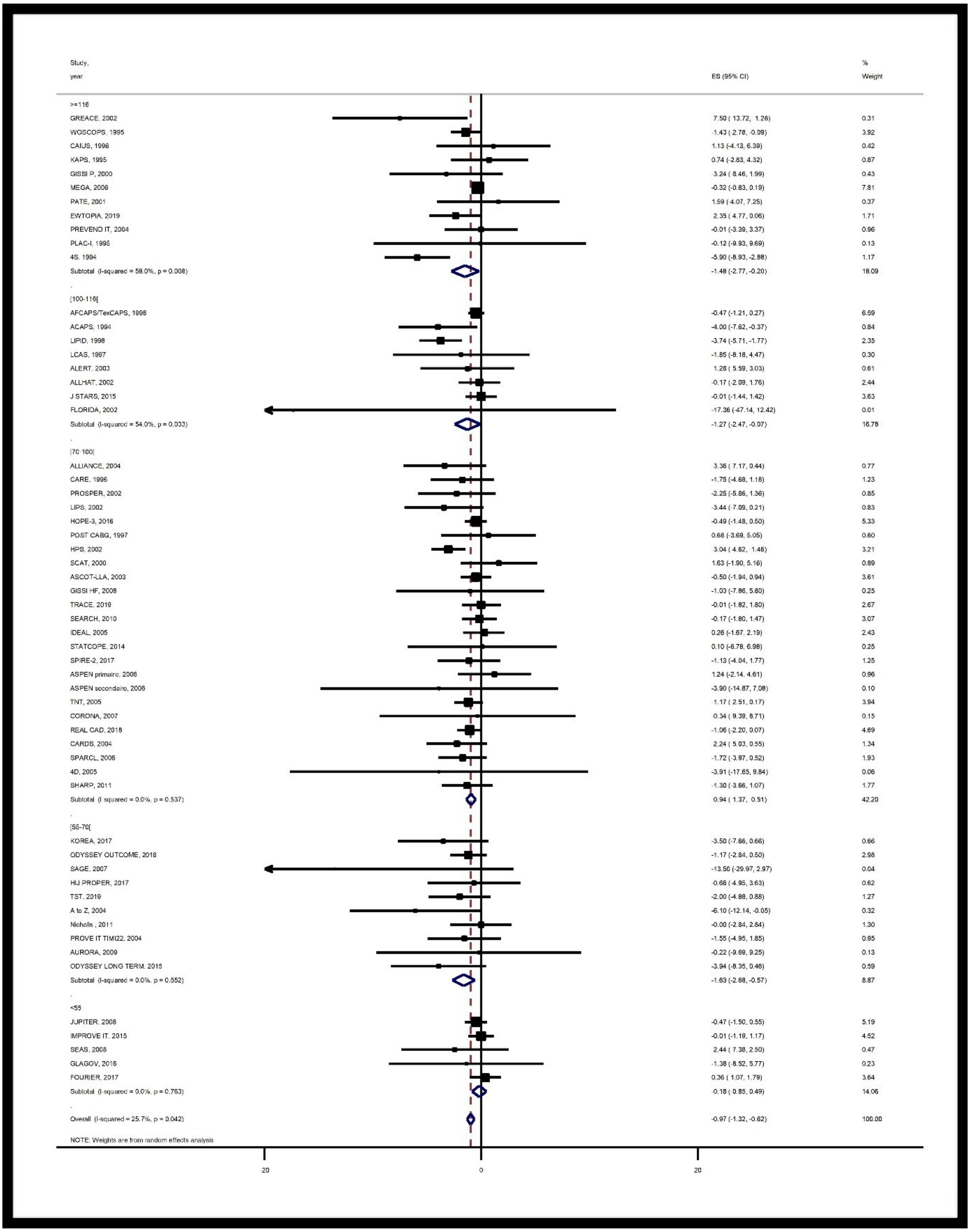
annual CV death rate

*Meta-regression model for each 40 mg/dL increase in achieved LDL-C levels

eFigure 17. Meta-analysis of all-cause mortality risk stratified by achieved LDL-C levels in the more intensive low-density lipoprotein cholesterol (LDL-C)–lowering arms. Absolute rate difference (ARD) and 95% confidence intervals of more intensive vs less intensive LDL-C lowering therapies and the weight of study data in the meta-analysis.

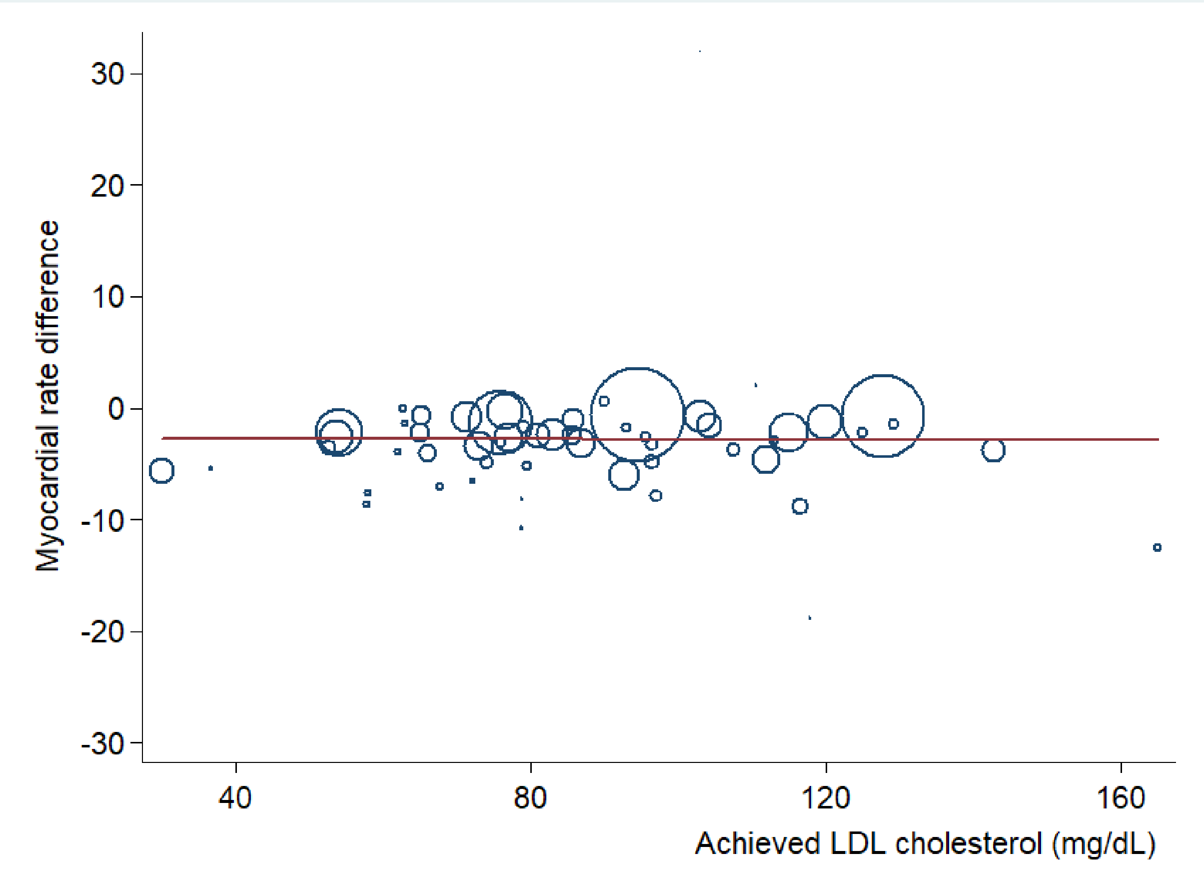


eFigure 18. Meta-analysis of cardiovascular mortality risk stratified by achieved low-density lipoprotein cholesterol (LDL-C) levels in the more intensive LDL-C lowering arms. Absolute rate difference (ARD) and 95% confidence intervals of more intensive vs less intensive LDL-C lowering therapies and the weight of study data in the meta-analysis.

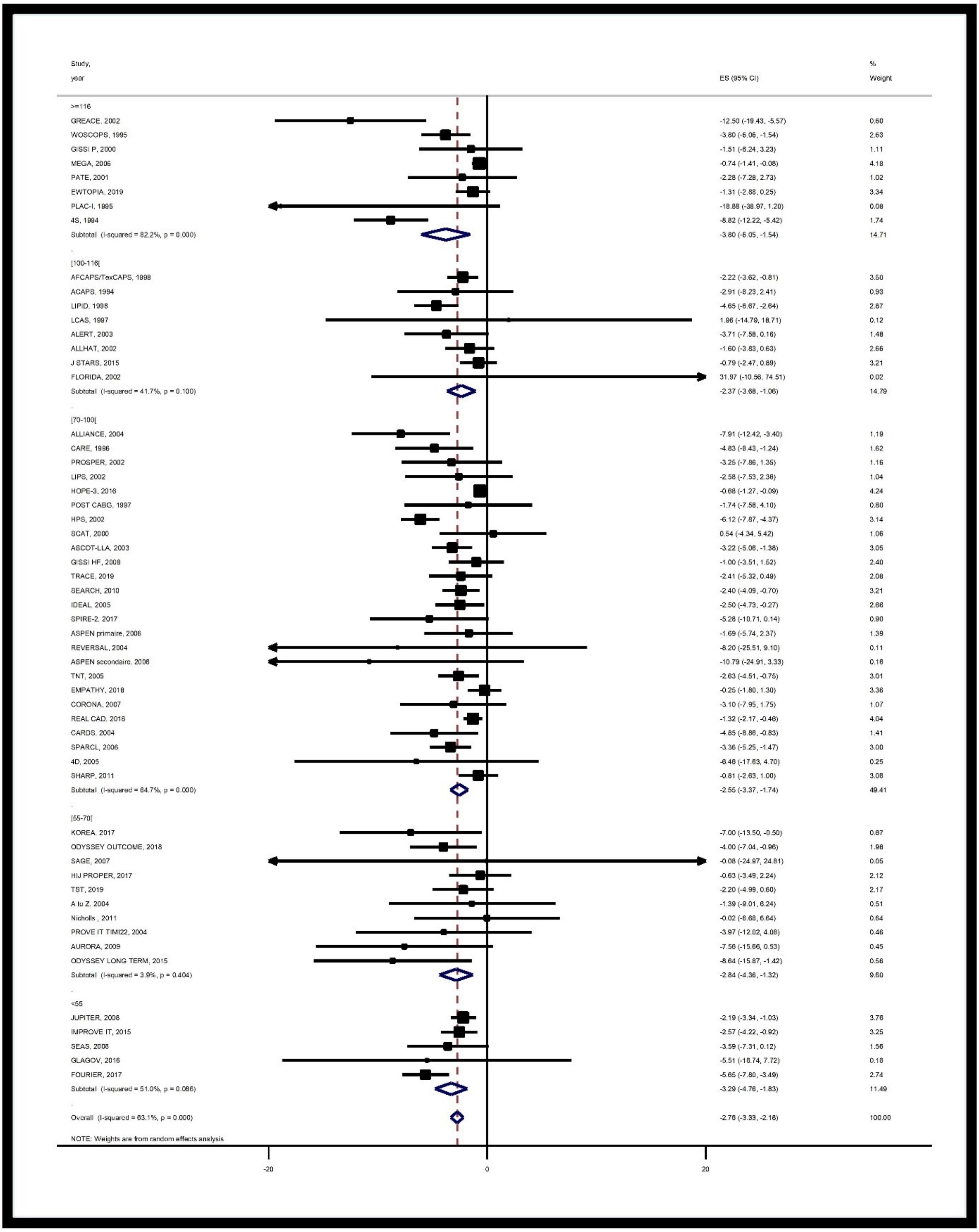


eFigure 19. Meta-regression analysis of absolute rate difference (ARD) in myocardial infarction risk by achieved low-density lipoprotein cholesterol (LDL-C) level reduction.

Change in ARD and 95% confidence intervals of more intensive vs less intensive LDL-C – lowering therapies plotted against achieved LDL-C levels. Size of the data markers is proportional to the weight in the meta-regression. The solid line represents the meta-regression slope of the change in ARD for treatment across increasing levels of achieved LDL-C.

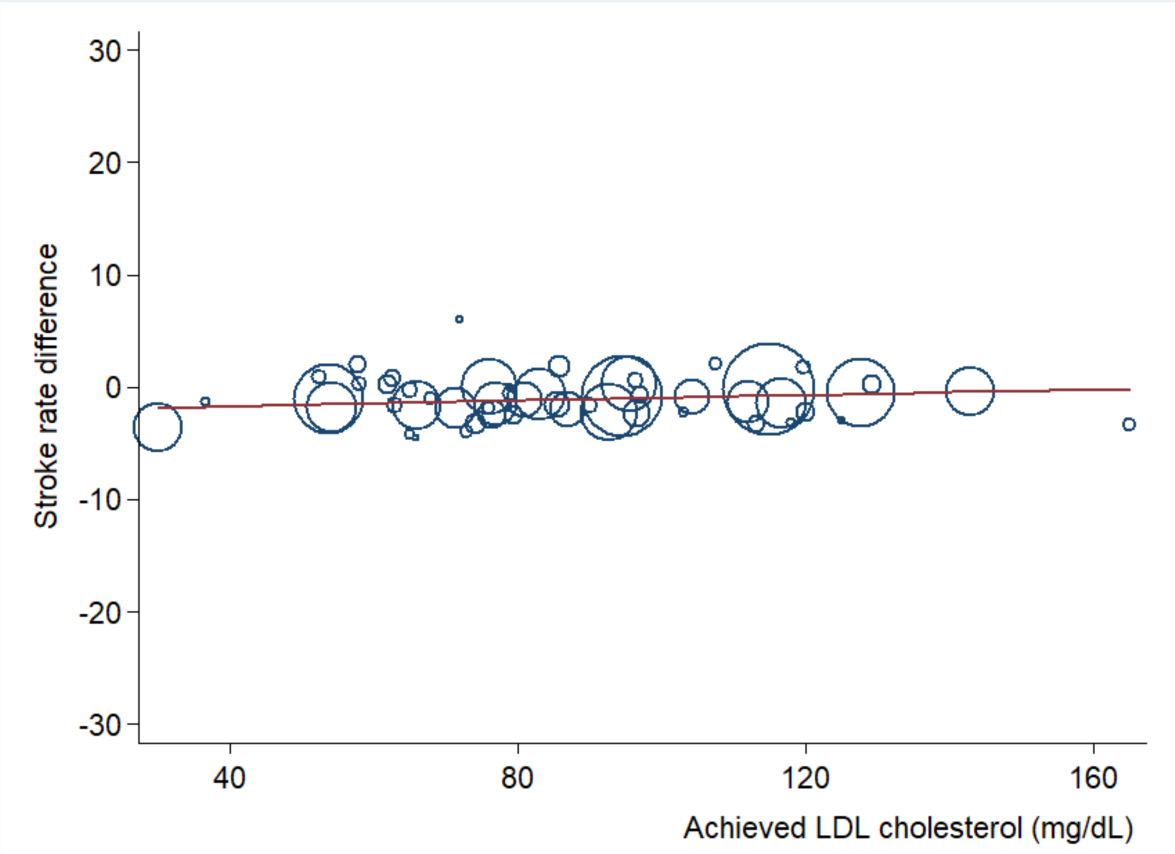


eFigure 20. Meta-analysis of myocardial infarction risk stratified by achieved LDL-C levels in the more intensive low-density lipoprotein cholesterol (LDL-C)–lowering arms. Absolute rate difference (ARD) and 95% confidence intervals of more intensive vs less intensive LDL-C lowering therapies and the weight of study data in the meta-analysis.

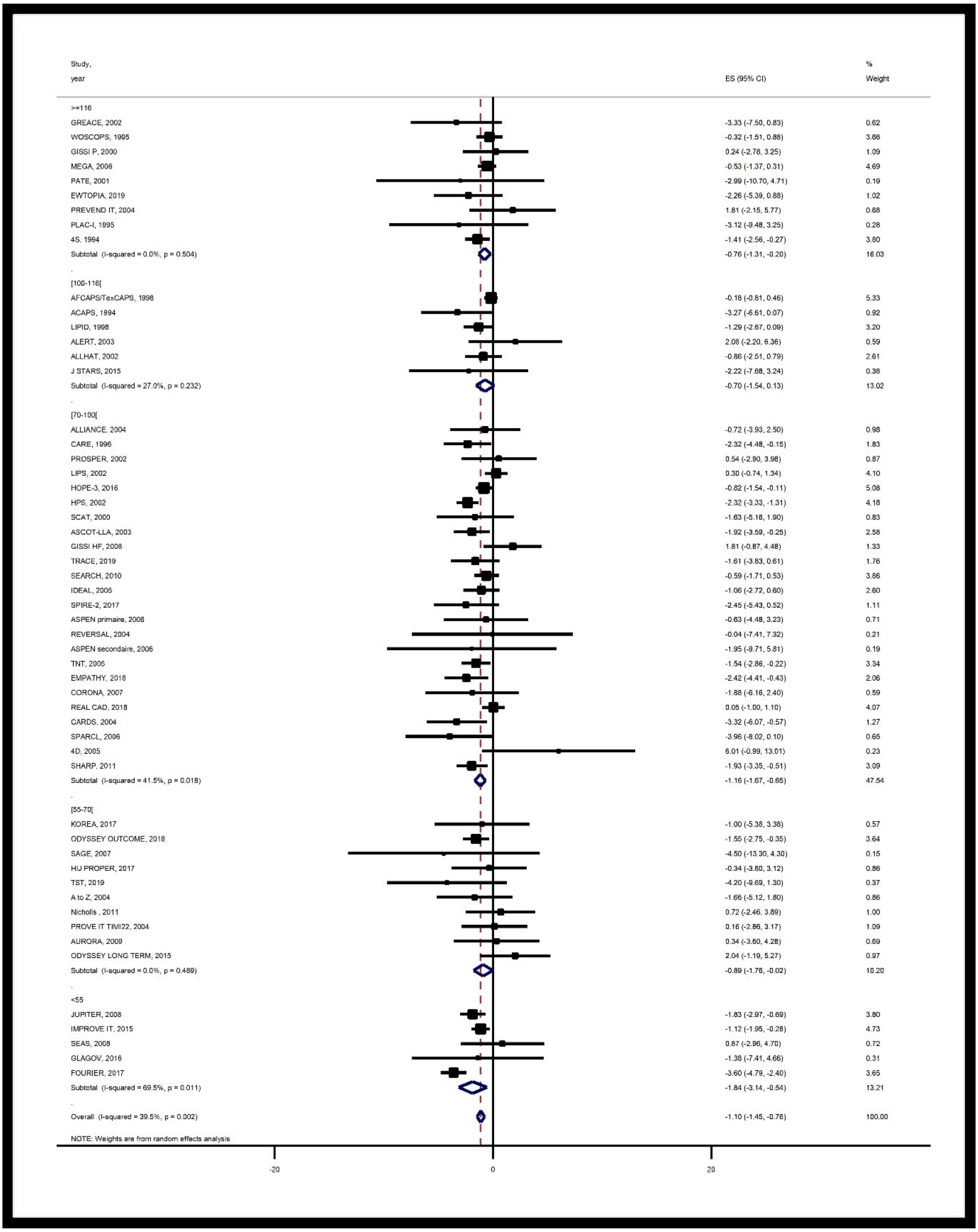


eFigure 21. Meta-regression analysis of absolute rate difference (ARD) in stroke risk by achieved LDL-C levels in the more intensive low-density lipoprotein cholesterol (LDL-C) lowering arms.

Change in ARD and 95% confidence intervals of more intensive vs less intensive LDL-C – lowering therapies plotted against achieved LDL-C level in the more intensive treatment group. Size of the data markers is proportional to the weight in the meta-regression. The solid line represents the meta-regression slope of the change in ARD for treatment across increasing levels of achieved LDL-C levels.



eFigure 22. Meta-analysis of stroke risk stratified by achieved low-density lipoprotein cholesterol (LDL-C) levels in the more intensive LDL-C lowering arms. Absolute rate difference (ARD) and 95% confidence intervals of more intensive vs less intensive LDL-C lowering therapies and the weight of study data in the meta-analysis.



Cardiovascular mortality rate of randomized populations (eTables 17&18)

We investigated the relationship between the risk of CV mortality of randomized populations in less intensive LDL-C lowering arms and the risk reduction of outcomes. When expressed in terms of ARDs, clinical benefits in terms of mortality but not for MI and stroke increased significantly in randomized populations with higher CV mortality rates. Expressed in terms of RRs only stroke risk was related to CV mortality rate after adjustment but with a 6% decrease in RR (*P*= .013).

eTable 17. Unadjusted and adjusted meta-regression models for the association of annual CV mortality rates and mortality and other cardiovascular outcomes expressed in absolute rate differences (ARDs) and annual number needed to treat (NNT)

Annual CV mortality rate (‰)	NNT (95% CI)		ARD (95%CI)		I² (%)	*P for trend**
All-cause mortality						
<5	935	(559 to 2,833)	-1.07	(-1.79 to -0.35)	20	
5-9.999	NA		-0.85	(-1.88 to 0.17)	17	
10-14.999	NA		-0.86	(-1.91 to 0.19)	0	
≥15	262	(186 to 443)	-3.82	(-5.39 to -2.26)	20	
Overall	708	(503 to 1,193)	-1.41	(-1.99 to -0.84)	32	
Unadjusted analysis			-0.83	(-1.60 to -0.07)		*.03*
Adjusted analysis			-0.74	(-1.57 to 0.09)		*.08*
Cardiovascular mortality						
<5	2,105	(462 to 5,814)	-0.48	(-0.78 to -0.17)	0	
5-9.999	1,221	(713 to 4,255)	-0.82	(-1.40 to -0.24)	0	
10-14.999	NA		-0.69	(-1.49 to 0.12)	0	
≥15	305	(238 to 424)	-3.28	(-4.21 to -2.36)	0	
Overall	1,028	(756 to 1,605)	-0.97	(-1.32 to -0.62)	26	
Unadjusted analysis			-0.88	(-1.33 to -0.43)		*<.0001*
Adjusted analysis			-0.87	(-1.37 to -0.38)		*.001*
Myocardial infarction						
<5	632	(462 to 999)	-1.58	(-2.16 to -1.00)	44	
5-9.999	343	(262 to 499)	-2.91	(-3.82 to -2.00)	27	
10-14.999	322	(239 to 490)	-3.11	(-4.18 to -2.04)	17	
≥15	233	(160 to 424)	-4.29	(-6.23 to -2.36)	68	
Overall	352	(292 to 444)	-2.84	(-3.43 to -2.25)	63	
Unadjusted analysis			-0.29	(-0.80 to 0.21)		*.25*
Adjusted analysis			-0.31	(-0.84 to 0.22)		*.24*
Stroke						
<5	1,449	(910 to 3,559)	-0.69	(-1.01 to -0.28)	18	
5-9.999	665	(409 to 1,773)	-1.50	(-2.44 to -0.56)	60	
10-14.999	1,006	(622 to 2,632)	-0.99	(-1.61 to -0.38)	0	
≥15	799	(500 to 2,004)	-1.25	(-2.00 to -0.50)	28	
Overall	928	(700 to 1,374)	-1.08	(-1.43 to -0.73)	40	
Unadjusted analysis			0.17	(-0.19 to 0.52)		*.35*
Adjusted analysis			0.23	(-0.16 to 0.61)		*.24*

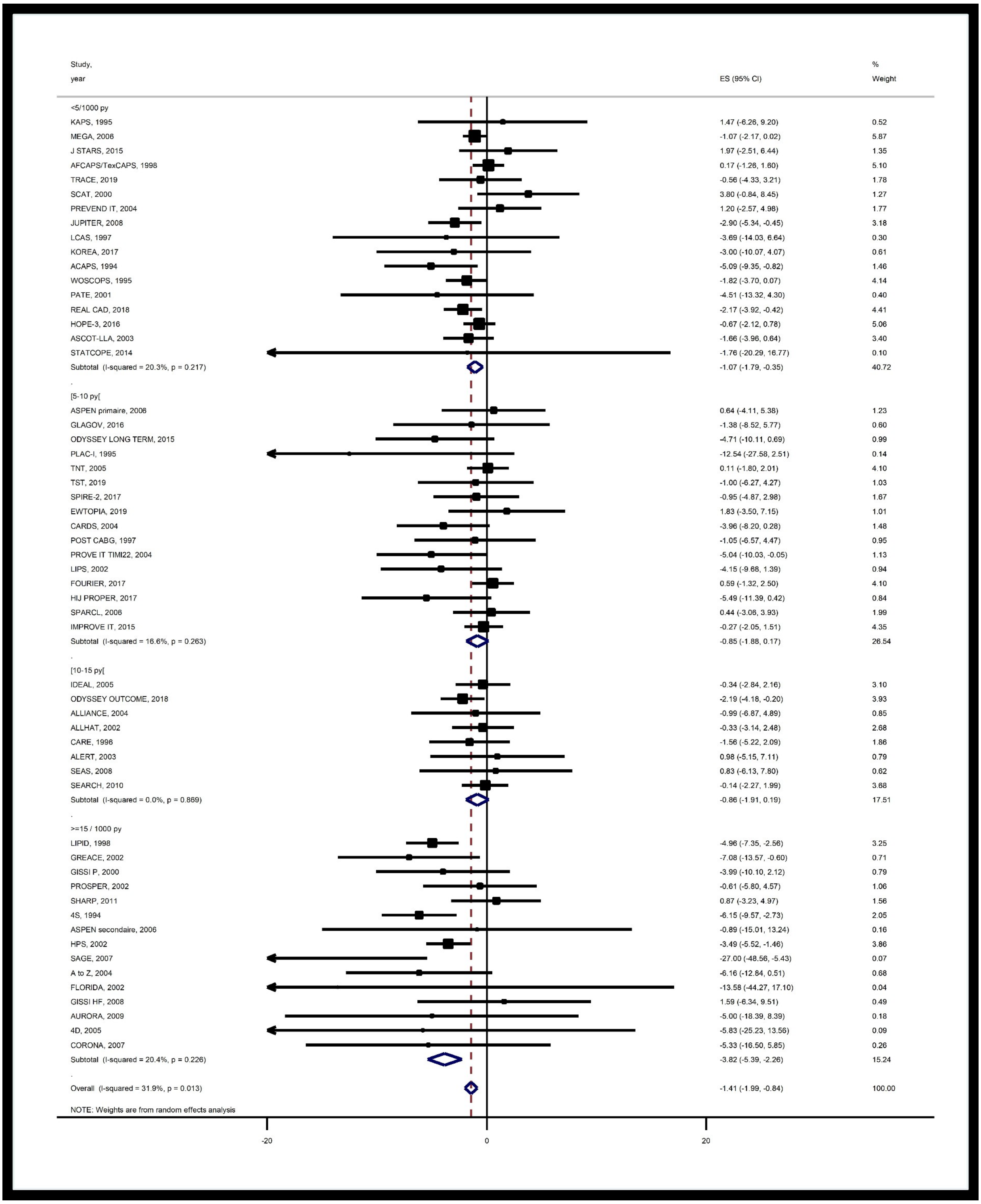
*Meta-regression model for each 10‰ increase in annual CV mortality rate

eTable 18. Unadjusted and adjusted meta-regression models for the association of annual CV mortality rates and mortality and other cardiovascular outcomes expressed in rate ratios

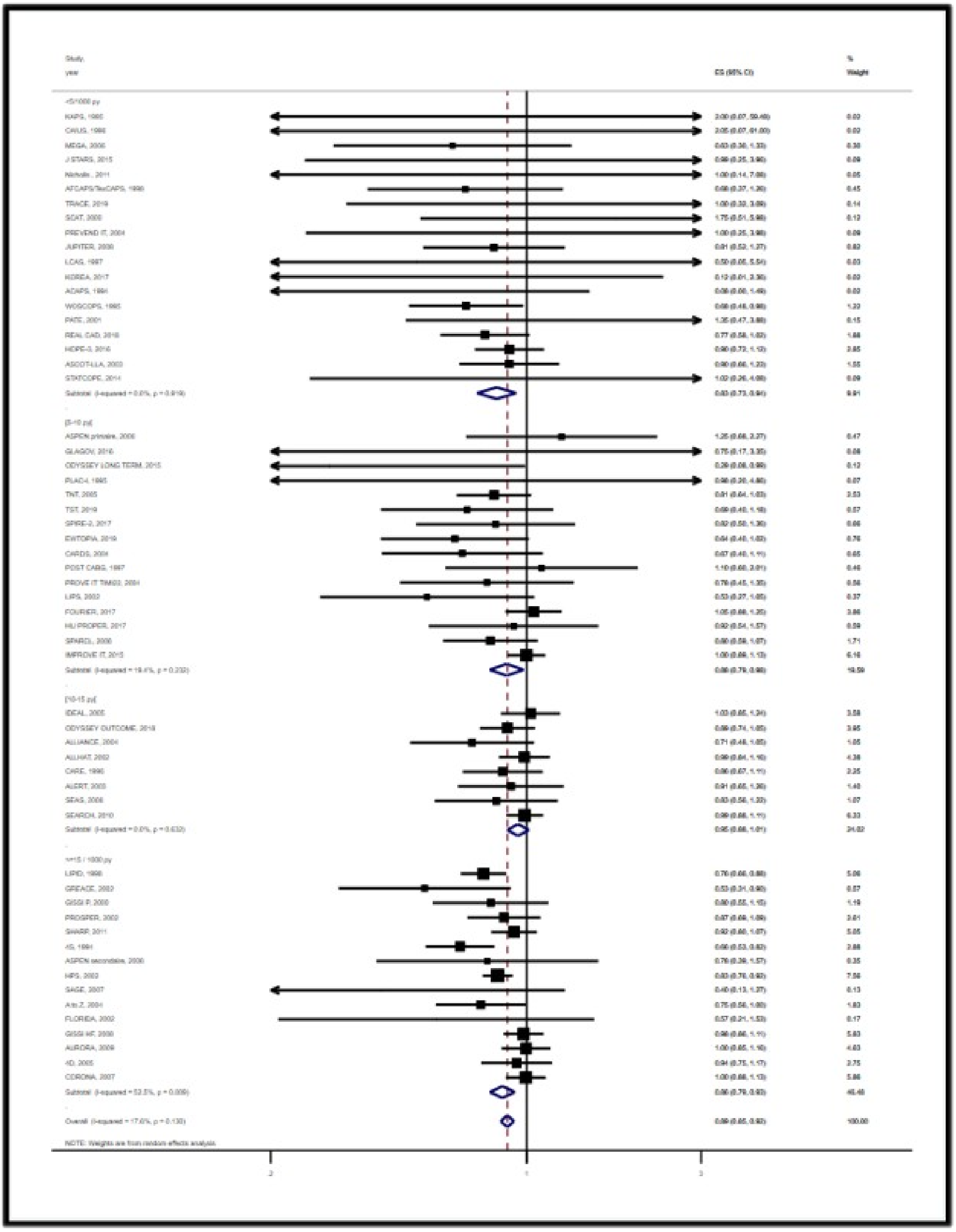
Annual CV mortality rate (‰)	Rate ratio (95% CI)		I² (%)	*P* for trend*
All-cause mortality				
<5	0.86	(0.80 to 0.94)	4	
5-9.999	0.95	(0.88 to 1.02)	23	
10-14.999	0.97	(0.92 to 1.02)	0	
≥15	0.89	(0.84 to 0.96)	62	
Overall	0.92	(0.89 to 0.95)	36	
Unadjusted analysis	1.01	(0.99 to 1.03)		*.33*
Adjusted analysis	1.01	(0.99 to 1.02)		*.49*
Cardiovascular mortality				
<5	0.83	(0.73 to 0.94)	0	
5-9.999	0.88	(0.79 to 0.98)	19	
10-14.999	0.95	(0.88 to 1.01)	0	
≥15	0.86	(0.79 to 0.93)	52	
Overall	0.89	(0.85 to 0.92)	18	
Unadjusted analysis	1.02	(0.99 to 1.04)		*.06*
Adjusted analysis	1.02	(0.99 to 1.04)		*.07*
Myocardial infarction				
<5	0.63	(0.57 to 0.71)	0	
5-9.999	0.76	(0.70 to 0.83)	28	
10-14.999	0.82	(0.76 to 0.89)	38	
≥15	0.80	(0.73 to 0.88)	55	
Overall	0.77	(0.73 to 0.81)	43	
Unadjusted analysis	1.04	(1.00 to 1.07)		*.025*
Adjusted analysis	1.03	(0.99 to 1.06)		*.08*
Stroke				
<5	0.78	(0.69 to 0.88)	0	
5-9.999	0.75	(0.67 to 0.85)	32	
10-14.999	0.88	(0.80 to 0.97)	14	
≥15	0.87	(0.76 to 1.00)	54	
Overall	0.82	(0.77 to 0.87)	34	
Unadjusted analysis	1.05	(1.01 to 1.09)		*.007*
Adjusted analysis	1.06	(1.01 to 1.10)		*.013*

*Meta-regression model for each 10‰ increase in annual CV mortality rate

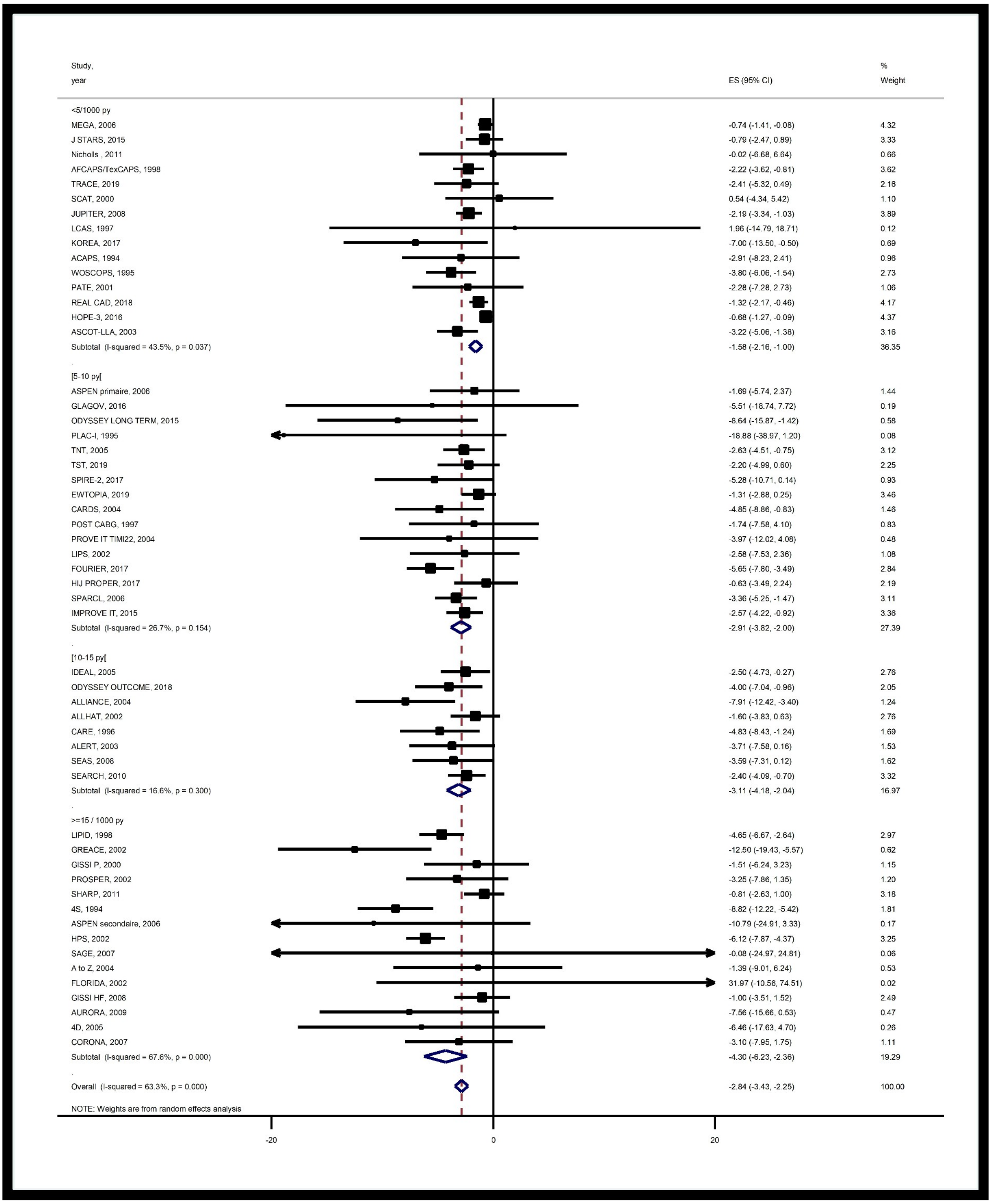
eFigure 23. Meta-analysis of all-cause mortality risk stratified by annual CV mortality rates in the less intensive LDL-C lowering arms. Absolute rate difference (ARD) and 95% confidence intervals of more intensive vs less intensive LDL-C lowering therapies and the weight of study data in the meta-analysis.



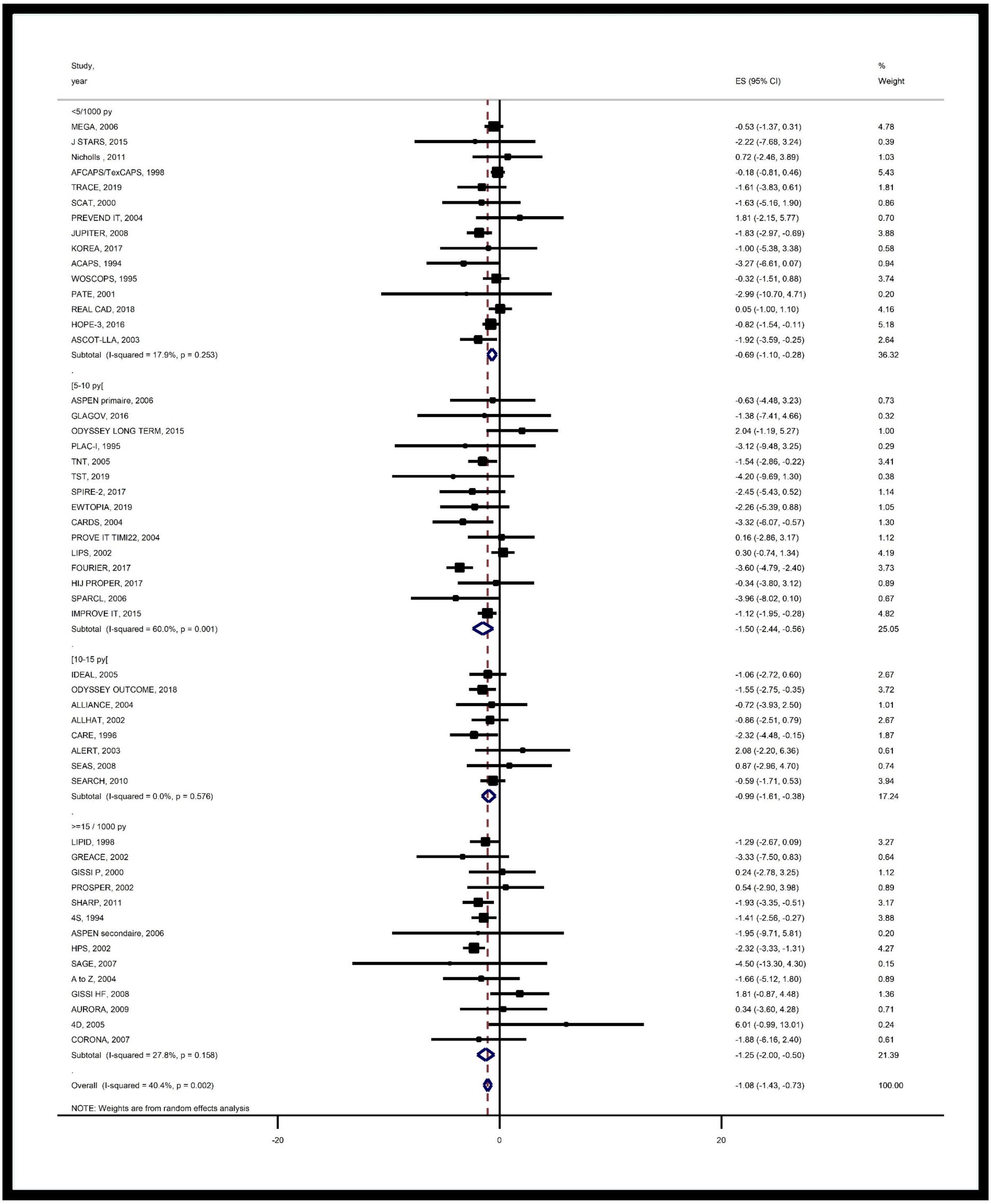
eFigure 24. Meta-analysis of CV mortality risk stratified by annual CV mortality rates in the less intensive LDL-C lowering arms. Absolute rate difference (ARD) and 95% confidence intervals of more intensive vs less intensive LDL-C lowering therapies and the weight of study data in the meta-analysis.



eFigure 25. Meta-analysis of myocardial infarction risk stratified by annual CV mortality rates in the less intensive LDL-C lowering arms. Absolute rate difference (ARD) and 95% confidence intervals of more intensive vs less intensive LDL-C lowering therapies and the weight of study data in the meta-analysis.



eFigure 26. Meta-analysis of stroke risk stratified by annual CV mortality rates in the less intensive LDL-C lowering arms. Absolute rate difference (ARD) and 95% confidence intervals of more intensive vs less intensive LDL-C lowering therapies and the weight of study data in the meta-analysis.



Non-cardiovascular mortality

Fifty-five studies reported the incidence of non-CV death. Pooled analysis showed that 6,292 of 158,655 patients (3.97%) receiving intensive LDL-C–lowering strategy vs 6,405 of 157,816 (4.06%) receiving less intensive strategy died from non-CV cause (ARD -0.23 (-0.57 to 0.11); RR 0.978 (95% CI 0.937 to 1.020), *P*= .19; I^2 16%; Tau^2 0.0035). Non-CV death was not altered neither by the extent of LDL-C reduction in percentage or absolute values nor by the baseline LDL-C or achieved LDL-C values in both unadjusted and adjusted analyses.

Comparisons with previous meta-analyses with regard to the studies not included in the present meta-analysis

A) Comparisons with the Navarese' study (Primary and secondary prevention of CVD) published in JAMA 2018[22] we did not include :

- the OSLER-1&-2 trials[23] (which compared evolocumab and placebo in 4465 patients due to the short median follow-up (11.1 months)

In Navarese et al's study[22], the primary measurement was baseline LDL, whereas in our study it was percentage of LDL reduction. Navarese et al. included randomized trials with at least 1000 patients whereas we included those with at least 100 patients. A total of 34 trials and 270 288 patients in their meta-analysis comparing the effects of more or less intense statin therapy on total and cardiovascular mortality in both primary and secondary cardiovascular prevention similar to our study. The coprimary end points were total mortality and cardiovascular mortality and secondary endpoints included where cardiovascular events, whereas we included non-CV mortality as endpoint. Our inclusion criteria enabled enrolling patients with left ventricular dysfunction, kidney disease or aortic stenosis as well as those with rheumatoid arthritis, chronic obstructive pulmonary disease, which weren't included in

Navarese et al's work. Although we found similar findings to Navarese's work regarding all-cause mortality in terms of rate ratios, our meta-regression results differ as we did not find a significant relationship for all-cause and cardiovascular mortality. Additionally, our study is the first to adjust for annual cardiovascular mortality rates. We also provided the ARDs and NNTs to offer additional clinically relevant information to clinicians.

B) Comparisons with the Chou' study (Primary prevention of CVD)[24] published in JAMA 2016, we did not include:

- the 2005 HYRIM trial[25] investigated the effect of fluvastatin treatment and lifestyle intervention on development of carotid intima–media thickness (IMT) in 287 hypertensive patients: nine patients died during the course of the study; four in the fluvastatin alone or with lifestyle intervention arm and five in placebo- or lifestyle intervention-treated patients.

- the 2010 METEOR trial[26] evaluating the Effects of Rosuvastatin 40 mg on Intima-Media Thickness in 984 participants: 1 death occurred during the study; the cause was reported to be Creutzfeldt-Jakob disease.

C) Comparisons with 2013 Cochrane study (Statins for the primary prevention of cardiovascular disease[27]; we did not include:

- the 1996 CELL trial[28]: among the 681 subjects randomized "intensive advice" versus "usual advice" one-third received pravastatin

- the 2007 METEOR trial[26] evaluating the Effects of Rosuvastatin 40 mg on Intima-Media Thickness in 984 participants: 1 death occurred during the study; the cause was reported to be Creutzfeldt-Jakob disease.

- the 2007 HYRIM trial[25] investigated the effect of fluvastatin treatment and lifestyle intervention on development of carotid intima–media thickness (IMT) in 287 hypertensive patients: nine patients died during the course of the study; four in the fluvastatin alone or with lifestyle intervention arm and five in placebo- or lifestyle intervention-treated patients.

- the 2010 PHYLLIS trial[29] investigating the possibility that statins reduce blood pressure did not report neither death nor clinical events in 253 hypertensive patients.

- the 2003 Derosa's trial[30] randomized 99 subjects placebo, fluvastatin, orlistat or both

D) Comparisons with the Wang's meta analysis[31]; we did not include :

- The neutral 2015 ALPS-AMI trial[32] which compared the lipophilic atorvastatin 10-20 mg and the hydrophilic pravastatin 10-20 mg in 508 japanese patients with acute MI (9 versus 14 deaths and 3 versus 3 CV deaths)

- The 1995 REGRESS trial[33] which assess in 11 centers in Netherlands pravastatin on progression and regression of coronary atherosclerosis in 885 male patients with a serum cholesterol level between 4 and 8 mmol/L (155 and 310 mg/dL) by quantitative coronary arteriography did not report death of all-cause and cardiovascular cause

- The 2017 SPIRE-1 trial[34] that evaluated bococizumab versus placebo during a short follow up period (0.6 year)

- the 2005 HYRIM trial[25] investigated the effect of fluvastatin treatment and lifestyle intervention on development of carotid intima–media thickness (IMT) in 287 hypertensive patients: nine patients died during the course of the study; four in the fluvastatin alone or with lifestyle intervention arm and five in placebo- or lifestyle intervention-treated patients.

- the OSLER-1&-2 trials[23] which compared evolocumab and placebo in 4465 patients due to the short median follow-up (11.1 months)

- the neutral 2013 PEARL study[35] (which compared pivastatin versus usual care in 574 Japanese patients with Heart Failure due to coronary artery disease in 27%

- the 2001 BCAPS study[36] which compared the effects of low-dose metoprolol CR/XL (25 mg once daily) and fluvastatin (40 mg once daily) on the rate of progression of carotid intima-media thickness in 793 clinically healthy, symptom-free subjects with carotid plaque. The cardiovascular event rate tended to be lower in patients treated with metoprolol CR/XL compared with patients not treated with metoprolol CR/XL (5 versus 13 patients, P=0.055).

E) Comparisons with the Nacis's meta analysis[37]:

Naci and coworkers also found that statins were significantly more effective than controls in reducing all-cause mortality (OR 0.87, 95% credible interval 0.82-0.92) and major coronary events (OR 0.69, 95% CI 0.64-0.75). The investigators included smaller trials (50 patients in each arm) with shorter duration (at least 4 weeks) but also included trials testing ezetimibe or PCSK9-inhibiting monoclonal antibodies. This study rather highlighted potential differences between individual statins, with atorvastatin, fluvastatin and simvastatin achieving better results in terms of reducing both the risk of all-cause mortality and major coronary events. The authors did not investigate subgroups of patients in their analysis and our study did not investigate differences in statins. In our opinion Naci's study is complementary to our findings.

Additional excluded studies

- the 1994 CRISP trial[38] did not report death and did not detail CV events in 431 subjects over 65 years old randomized placebo, 20-mg lovastatin, and 40-mg lovastatin.
- the 2009 Mok trial[39] evaluated effects of simvastatin 20 mg versus placebo on asymptomatic middle cerebral artery (MCA) stenosis progression: the all-cause mortality was significantly less in the active group (n = 0) relative to that in the placebo group (n = 7, p = 0.014). The causes of death for these 7 cases in the placebo group were vascular-related for 4 patients and non-vascular-related for the remaining 3 cases (asthmatic attack, septicemia, cholangiocarcinoma).
- the 2006 Schmermund trial[40] did not report death in 471 patients with coronary artery calcification assigned to atorvastatin 10 or 80 mg.
- the neutral 2005 St. Francis Heart Study RCT evaluating the efficacy of atorvastatin in subjects with elevated coronary calcium scores could not be incorporated in the present analysis because the clinical endpoints could not be detailed (request being left without a response).[41]

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