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)	AR	D (95%CI)	l² (%)	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)		(-1.89 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				(-1.29 to 0.65)		.51
annual CV death rate				````		
Cardiovascular mortality						
<30	1,212	(831 to 2,242)	-0.83	(-1.20 to -0.44)	21	
30-49	621	(405 to 1,332)		(-2.47 to -0.75)	36	
≥50	NA			(-3.23 to 1.17)	29	
Overall	1,028	(756 to 1,605)		(-1.32 to -0.62)	26	
	,	(,,		(
Unadjusted analysis			-0.28	(-0.83 to 0.38)		.46
Adjusted analysis				(-0.95 to 0.27)		.27
Adjusted analysis including			-0.17	(-0.65 to 0.31)		.47
annual CV death rate			0111	(0.00 10 0.01)		
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				(-2.30 to -0.62)		.001
Adjusted analysis including				(-2.28 to -0.55)		.002
annual CV death rate				· · · · ·		
Stroke						
<30	1,170	(854 to 1,852)	-0.86	(-1.17 to -0.54)	19	
30-49	678	(472 to 1,205)		(-2.12 to -0.83)	18	
≥50	NA	-		(-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			-0.81	(-1.37 to -0.25)		.005
annual CV death rate				(

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

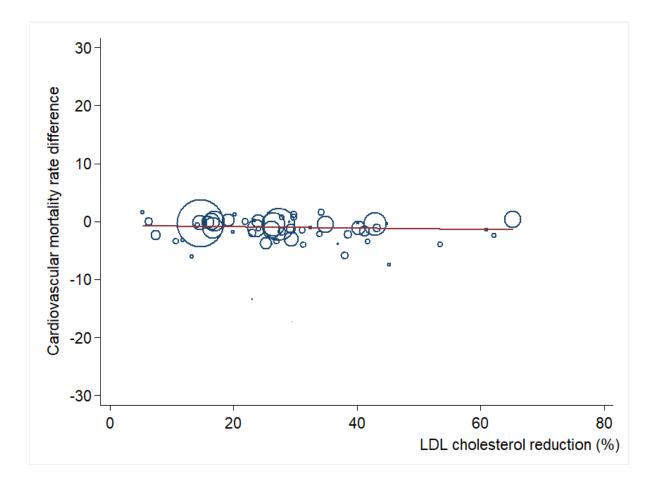
eTable 10. Unadjusted and adjusted meta-regression models for the association of percent LDL-C levels reduction and mortality and other cardiovascular outcomes expressed in rate ratios (RRs)

Percent LDL-C reduction (%)	Rate	ratio (95% CI)	l² (%)	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	0.99	(0.93 to 1.04)		.66
CV death rate				
Cardiovascular mortality	0.00	(0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0		
<30	0.88	(0.85 to 0.92)	1	
30-49	0.88	(0.80 to 0.95)	38	
≥50	0.87	```	42	
Overall	0.89	(0.85 to 0.92)	18	
Unadjusted analysis	1.02	(0.94 to 1.09)		.63
Adjusted analysis	1.02	· /		.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	· /	61	
≥50	0.69	` '	10	
Overall	0.09	(0.58 to 0.82) (0.73 to 0.81)	42	
Overall	0.77	(0.73 (0 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	0.92	(0.86 to 0.99)		.028
CV death rate	0.01	(0.00 10 0.00)		
Stroke				
<30	0.82	(0.77 to 0.86)	0	
30-49	0.82	( )	54	
≥50		(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	0.87	(0.79 to 0.95)		.003
CV death rate				

*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.

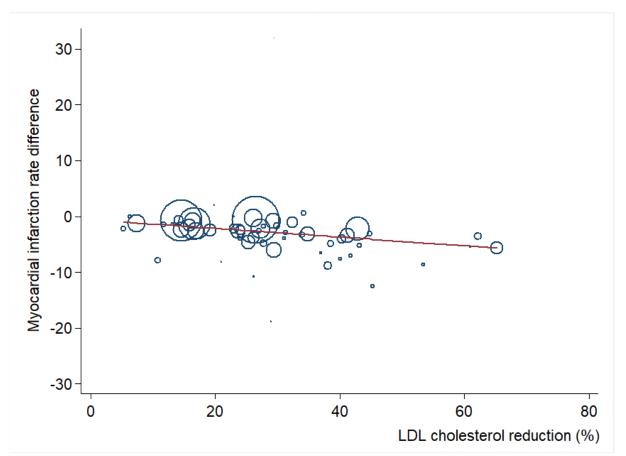
Change in ARD and 95% confidence intervals of more intensive vs less intensive LDL-C – lowering therapies plotted against percent LDL-C levels reduction. Size of the data markers is proportional to the weight in the meta-regression. The solid line represents the meta-regression slope of the change in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

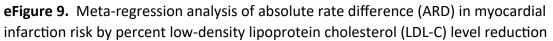


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**eFigure 8**. Meta-analysis of cardiovascular mortality risk stratified by percent low-density lipoprotein cholesterol (LDL-C) level reduction. Absolute rate difference (ARD) and 95% confidence intervals of more intensive vs less intensive LDL-C lowering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

Study. year	ES (96% CI)	% Weigl
<30 pp		
PLAC-I, 1995	-0.12 (-9.93, 9.69)	0.13
KAPS, 1995	0.74 (-2.83, 4.32)	0.87
WOSCOPS, 1995	-1.43 (-2.78, -0.09)	3.92
CAIUS, 1996	1.13 (-4.13, 6.39)	0.42
CARE, 1996	-1.75 (-4.68, 1.18)	1.23
POST CABG, 1997	0.68 (-3.69, 5.05)	0.60
LCAS, 1997	-1.85 (-8.18, 4.47)	0.30
LIPID, 1998	-3.74 (-5.71, -1.77)	2.35
AFCAPS/TexCAPS, 1998	-0.47 (-1.21, 0.27)	6.59
GISSI P. 2000	-3.24 (-8.46, 1.99)	0.43
PATE, 2001	1.59 (-4.07, 7.25)	0.37
ALLHAT, 2002	-0.17 (-2.09, 1.76)	2.44
LIPS. 2002	-3.44 (-7.09, 0.21)	0.83
HPS, 2002	-3.04 (-4.62, -1.46)	3.21
FLORIDA, 2002	-17.36 (-47.14, 12.42)	0.01
ALERT, 2003	-1.28 (-5.59, 3.03)	0.61
ALLIANCE, 2004	-3.36 (-7.17, 0.44)	0.77
PREVEND IT, 2004	-0.01 (-3.39, 3.37)	0.96
A to Z, 2004	-6.10 (-12.14, -0.05)	0.32
IDEAL, 2005	0.26 (-1.67, 2.19)	2.43
TNT, 2005	-1.17 (-2.51, 0.17)	3.94
ASPEN secondaire, 2006	-3.90 (-14.87, 7.08)	0.10
ASPEN primaire, 2006	1.24 (-2.14, 4.61)	0.96
MEGA, 2006	-0.32 (-0.83, 0.19)	7.81
SAGE, 2007	-13.50 (-29.97, 2.97)	0.04
SEARCH, 2010	-0.17 (-1.80, 1.47)	3.07
SHARP. 2011	-1.30 (-3.66, 1.07)	1.77
Nicholis , 2011	-0.00 (-2.84, 2.84)	1.30
STATCOPE, 2014	0.10 (-6.78, 6.98)	0.25
IMPROVE IT, 2015	-0.01 (-1.19, 1.17)	4.52
J STARS, 2015 HOPE-3, 2016	-0.01 (-1.44, 1.42) -0.49 (-1.48, 0.50)	3.63 5.33
HJ PROPER, 2017	-0.66 (-4.95, 3.63)	0.62
REAL CAD, 2018	-1.06 (-2.20, 0.07)	4.69
EWTOPIA, 2019	-1.00 (2220,007) -2.35 (-4.77, 0.06)	4.05
TRACE, 2019	-2.33 (4.77, 0.06) -0.01 (-1.82, 1.80)	2.67
TST, 2019	-2.00 (-4.88, 0.88)	1.27
Subtotal (I-squared = 21.5%, p = 0.125)	-0.82 (-1.20, -0.45)	72.49
30-49 pp		
4S, 1994	-5.90 (-8.93, -2.88)	1.17
ACAPS, 1994	-4.00 (-7.62, -0.37)	0.84
SCAT, 2000	1.63 (-1.90, 5.16)	0.89
PROSPER, 2002	-2.25 (-5.86, 1.36)	0.85
GREACE, 2002	-7.50 (-13.72, -1.28)	0.31
ASCOT-LLA, 2003	-0.50 (-1.94, 0.94)	3.61
PROVE IT TIMI22, 2004	-1.55 (-4.95, 1.85)	0.95
CARDS, 2004	-2.24 (-5.03, 0.55)	1.34
4D, 2005	-3.91 (-17.65, 9.84)	0.06
SPARCL, 2006	-1.72 (-3.97, 0.52)	1.93
CORONA, 2007	-0.34 (-9.39, 8.71)	0.15
JUPITER, 2008	-0.47 (-1.50, 0.55)	5.19
GISSI HF, 2008	-1.03 (-7.86, 5.80)	0.25
AURORA, 2009	-0.22 (-9.69, 9.25)	0.13
SPIRE-2, 2017	-1.13 (-4.04, 1.77)	1.25
KOREA, 2017	-3.50 (-7.66, 0.66)	0.66
ODYSSEY OUTCOME, 2018	-1.17 (-2.84, 0.50)	2.98 22.57
Subtotal (I-squared = 31.4%, p = 0.105)	-1.61 (-2.47, -0.75)	22.57
>50 pp		
SEAS. 2008	-2.44 (-7.38, 2.50)	0.47
ODYSSEY LONG TERM, 2015	-3.94 (-8.35, 0.46)	0.59
GLAGOV, 2016	-1.38 (-8.52, 5.77)	0.23
FOURIER, 2017	0.36 (-1.07, 1.79)	3.64
Subtotal (I-squared = 29.3%, p = 0.236)	-1.03 (-3.23, 1.17)	4.94
Overall (I-squared = 25.7%, p = 0.042)	-0.97 (-1.32, -0.62)	100.0
NOTE: Weights are from random effects analysis		



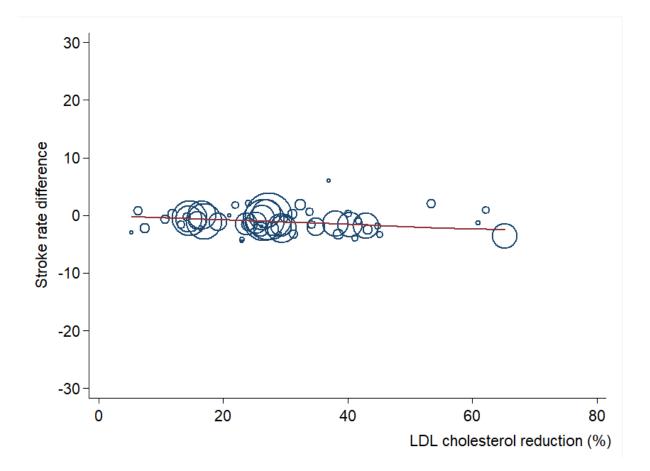


**eFigure 10**. Meta-analysis of myocardial infarction risk stratified by percent low-density lipoprotein cholesterol (LDL-C) level reduction. Absolute rate difference (ARD) and 95% confidence intervals of more intensive vs less intensive LDL-C lowering therapies and the weight of study data in the meta-analysis.

Study, gear	ES (95% CI)	% Weigh
<30 pp	1	
PLAC-I, 1995	-0.12 (-9.93, 9.69)	0.13
KAPS, 1995	0.74 (-2.83, 4.32)	0.87
WOSCOPS, 1995	-1.43 (-2.78, -0.09)	3.92
CAIUS, 1996	1.13 (-4.13, 6.39)	0.42
CARE, 1996	1.75 (-4.68, 1.18)	1.23
POST CABG, 1997	0.68 (-3.69, 5.05)	0.60
LCAS, 1997	-1.85 (-8.18, 4.47)	0.30
LIPID, 1998	-3.74 (-5.71, -1.77)	2.35
AFCAPS/TexCAPS, 1998	-0.47 (-1.21, 0.27)	6.59
GISSI P, 2000	-3.24 (-8.46, 1.99)	0.43
PATE, 2001	1.59 (-4.07, 7.25)	0.37
ALLHAT, 2002	-0.17 (-2.09, 1.76)	2.44
LIPS, 2002	-3.44 (-7.09, 0.21)	0.83
HPS, 2002	-3.04 (-4.62, -1.46)	3.21
FLORIDA, 2002	-17.36 (-47.14, 12.42)	0.01
ALERT, 2003	-1.28 (-5.59, 3.03)	0.61
ALLIANCE, 2004	-3.36 (-7.17, 0.44)	0.77
PREVEND IT, 2004	-0.01 (-3.39 -3.37)	0.96
A to Z, 2004	-6.10 (-12.14, -0.05)	0.32
DEAL, 2005	0.26 (-1.67, 2.19)	2.43
TNT, 2005	-1.17 (-2.51, 0.17)	3.94
ASPEN secondaire, 2006	-3.90 (-14.87, 7.08)	0.10
ASPEN primaire, 2006	1.24 (-2.14, 4.61)	0.96
MEGA, 2006	-0.32 (-0.83, 0.19)	7.81
SAGE, 2007	-13.50 (-29.97, 2.97)	0.04
SEARCH, 2010	-0.17 (-1.80, 1.47)	3.07
SHARP, 2011	-1.30 (-3.66, 1.07)	1.77
Nicholis , 2011	-0.00 (-2.84, 2.84)	1.30
STATCOPE, 2014	0.10 (-6.78, 6.98)	0.25
MPROVE IT, 2015	-0.01 (-1.19, 1.17)	4.52
J STARS, 2015	-0.01 (-1.44, 1.42)	3.63
HOPE-3, 2016	-0.49 (-1.48, 0.50)	5.33
HU PROPER, 2017	-0.66 (-4.95, 3.63)	0.62
REAL CAD, 2018	-1.06 (-2.20, 0.07)	4.69
EWTOPIA, 2019	-2.35 (-4.77, 0.06)	1.71
TRACE, 2019	-0.01 (-1.82, 1.80)	2.67
TST, 2019	-2.00 (-4.88, 0.88)	1.27
Subtotal (I-squared = 21.5%, p = 0.125)	0.82 (-1.20, -0.45)	72.49
	1	
30-49 pp	1	10000
45, 1994	-5.90 (-8.93, -2.88)	1.17
ACAPS, 1994	-4.00 (-7.62, -0.37)	0.84
5CAT, 2000	1.63 (-1.90, 5.16)	0.89
PROSPER, 2002	-2.25 (-5.86, 1.36)	0.85
GREACE, 2002	-7.50 (-13.72, -1.28)	0.31
ASCOT-LLA, 2003	-0.50 (-1.94, 0.94)	3.61
PROVE IT TIMI22, 2004	-1.55 (-4.95, 1.85)	0.95
CARDS, 2004	-2.24 (-5.03, 0.55)	1.34
4D, 2005	-3.91 (-17.65, 9.84)	0.06
SPARCL, 2006	-1.72 (-3.97, 0.52)	1.93
CORONA. 2007	-0.34 (-9.39, 8.71)	0.15
JUPITER, 2008	-0.47 (-1.50, 0.55)	5.19
GISSI HF, 2008	-1.03 (-7.66, 5.80)	0.25
AURORA, 2009	-0.22 (-9.69, 9.25)	0.13
SPIRE-2, 2017	-1.13 (-4.04, 1.77)	1.25
KOREA, 2017	-3.50 (-7.66, 0.66)	0.66
DDYSSEY OUTCOME, 2018	-1.17 (-2.84, 0.50)	2.98
Subtotal (I-squared = 31.4%, p = 0.105)	-1.61 (-2.47, -0.75)	22.57
- F0		
>50 pp		0.47
SEAS, 2008	-2.44 (-7.38, 2.50)	
DDYSSEY LONG TERM, 2015 GLAGOV, 2016	-3.94 (-8.35, 0.46)	0.59
	-1.38 (-8.52, 5.77)	0.23
	0.36 (-1.07, 1.79)	3.64
Subtotal (I-squared = 29.3%, p = 0.236)	-1.03 (-3.23, 1.17)	4.94
Overall (I-squared = 25.7%, p = 0.042)	-0.97 (-1.32, -0.62)	100.00
NOTE: Weights are from random effects analysis		
	1	
-20	0 20	

**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.

Study, year	ES (95% CI)	% Weight
<30 pp		
PLAC-I, 1995	-3.12 (-9.48, 3.25)	0.28
WOSCOPS, 1995	-0.32 (-1.51, 0.88)	3.66
CARE, 1996	-2.32 (-4.48, -0.15)	1.83
AFCAPS/TexCAPS, 1998	-0.18 (-0.81, 0.46)	5.33
LIPID, 1998	-1.29 (-2.67, 0.09)	3.20
GISSI P, 2000	0.24 (-2.78, 3.25)	1.09
PATE, 2001	-2.99 (-10.70, 4.71)	0.19
LIPS, 2002	0.30 (-0.74, 1.34)	4.10
HPS, 2002	-2.32 (-3.33, -1.31)	4.18
ALLHAT, 2002	-0.86 (-2.51, 0.79)	2.61
ALERT, 2003	2.08 (-2.20, 6.36)	0.59
A to Z, 2004	-1.66 (-5.12, 1.80)	0.86
REVERSAL, 2004	1.81 (-2.15, 5.77) -0.04 (-7.41, 7.32)	0.68
ALLIANCE, 2004	-0.04 (-7.4 (, 7.32) -0.72 (-3.93, 2.50)	0.21
IDEAL, 2005	-0.72 (-3.93, 2.50) -1.06 (-2.72, 0.60)	2.60
TNT, 2005	-1.54 (-2.86, -0.22)	3.34
ASPEN secondaire, 2006	-1.95 (-9.71, 5.81)	0.19
MEGA, 2006	-0.53 (-1.37, 0.31)	4.69
ASPEN primaire, 2006	-0.63 (-4.48, 3.23)	0.71
SAGE, 2007	-4.50 (-13.30, 4.30)	0.15
SEARCH, 2010	-0.59 (-1.71, 0.53)	3.86
Nicholis , 2011	0.72 (-2.46, 3.89)	1.00
SHARP, 2011	-1.93 (-3.35, -0.51)	3.09
J STARS, 2015	-2.22 (-7.68, 3.24)	0.38
IMPROVE IT, 2015	-1.12 (-1.95, -0.28)	4.73
HOPE-3, 2016 🛨	-0.82 (-1.54, -0.11)	5.08
HJ PROPER, 2017	-0.34 (-3.80, 3.12)	0.86
REAL CAD, 2018		4.07
EMPATHY, 2018	-2.42 (-4.410.43)	2.06
T\$T, 2019	-4.20 (-9.69, 1.30)	0.37
EWTOPIA, 2019	-2.26 (-5.39, 0.88)	1.02
TRACE, 2019	-1.61 (-3.83, 0.61)	1.76
Subtotal (I-squared = 18.8%, p = 0.173)	-0.86 (-1.17, -0.54)	69.76
30-49 pp		
ACAPS, 1994	-3.27 (-6.61, 0.07)	0.92
45, 1994	-1.41 (-2.56, -0.27)	3.80
SCAT, 2000	-1.63 (-5.16, 1.90)	0.83
GREACE, 2002	-3.33 (-7.50, 0.83)	0.62
PROSPER, 2002	0.54 (-2.90, 3.98)	0.87
ASCOT-ILA, 2003	-1.92 (-3.59, -0.25)	2.58 1.27
CARDS, 2004 PROVE IT TIMI22, 2004	-3.32 (-6.07, -0.57) 0.16 (-2.86, 3.17)	1.27
4D, 2005	6.01 (-0.99, 13.01)	0.23
SPARCL, 2006	-3.96 (-8.02, 0.10)	0.23
CORONA, 2007	-1.88 (-6.16, 2.40)	0.59
JUPITER. 2008	-1.83 (-2.97, -0.69)	3.80
GISSI HF, 2008	1.81 (-0.87, 4.48)	1.33
AURORA, 2009	0.34 (-3.60, 4.28)	0.69
KOREA, 2017	-1.00 (-5.38, 3.38)	0.57
SPIRE-2, 2017	-2.45 (-5.43, 0.52)	1.11
DDYSSEY OUTCOME, 2018	-1.55 (-2.75, -0.35)	3.64
Subtotal (I-squared = 18.5%, p = 0.237)	-1.47 (-2.12, -0.83)	24.58
>50 pp		
SEAS, 2008	0.87 (-2.96, 4.70)	0.72
DDYSSEY LONG TERM, 2015	2.04 (-1.19, 5.27)	0.97
GLAGOV, 2016	-1.38 (-7.41, 4.66)	0.31
FOURIER, 2017	-3.60 (-4.79, -2.40)	3.65
Subtotal (I-squared = 78.4%, p = 0.003)	-0.67 (-4.07. 2.73)	5.65
Overall (I-squared = 39.5%, p = 0.002)	-1.10 (-1.45, -0.76)	100.00
NOTE: Weights are from random effects analysis		
-20 0	20	
-20 0	20	

### 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)	NN	IT (95% CI)	А	RD (95%CI)	l² (%)	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	. ,	15	
Overall	754	(529 to 1,309)	-1.33	(-1.89 to -0.76)	31	
e voitail	101	(020 10 2,000)	1.00	( 2100 10 0110)	01	
Unadjusted analysis			-1.26	(-2.79 to 0.27)		.10
Adjusted analysis			-0.95	(-2.63 to 0.74)		.26
Adjusted analysis including			-0.73	(-2.39 to 0.93)		.38
annual CV death rate			0.75	(2.00 to 0.00)		.00
annua ov dealn rate						
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	· · · ·	0	
Overall	1,027	(756 to 1,665)	-0.97	(-1.32 to -0.62)	26	
Overall	1,021	(750101,005)	0.57	(1.52 to 0.62)	20	
Unadjusted analysis			-0.96	(-1.94 to 0.02)		.053
Adjusted analysis			-0.79	(-1.85 to 0.27)		.14
Adjusted analysis including			-0.46	(-1.31 to 0.39)		.29
annual CV death rate			-0.40	(-1.51 (0 0.59)		.29
annoai CV dealinnale						
Myocardial infarction						
<35	745	(568 to 1,080)	-1.34	(-1.76 to -0.93)	17	
35-65	280	(231 to 355)	-3.57	· · · · ·	34	
>65	129	(87 to 246)		(-11.5 to -4.06)	56	
Overall	363	(300 to 459)	-2.76	(-3.33 to -2.18)	63	
e vorali	000		2.1.0	( 0100 10 2120)	00	
Unadjusted analysis			-2.81	(-4.11 to -1.51)		<.0001
Adjusted analysis			-2.35	(-3.74 to -0.97)		.001
Adjusted analysis including			-2.29	(-3.73 to -0.86)		.002
annual CV death rate			2.20	( 0.10 to 0.00)		.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	
		· · · · · · · · · · · · · · · · · · ·		<b>`</b>	-	10
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
ainuai CV uedin idie						

* 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)	l² (%)	P for trend*
All-cause mortality <35 35-65 >65 Overall Unadjusted analysis Adjusted analysis Adjusted analysis Adjusted analysis including annual CV death rate	0.96(0.92 to 1.00)0.92(0.88 to 0.96)0.73(0.54 to 0.99)0.92(0.89 to 0.96)0.95(0.87 to 1.04)0.99(0.91 to 1.08)0.97(0.88 to 1.07)	10 31 63 34	.31 .77 .56
Cardiovascular mortality <35 35-65 >65 Overall Univariable analysis Multivariable analysis Adjusted analysis including annual CV death rate	0.93(0.88 to 0.98)0.89(0.85 to 0.94)0.66(0.53 to 0.82)0.89(0.85 to 0.92)0.94(0.83 to 1.05)1.01(0.91 to 1.12)0.96(0.86 to 1.07)	0 13 18 18	.26 .89 .44
Myocardial infarction <35 35-65 >65 Overall Unadjusted analysis Adjusted analysis Adjusted analysis Adjusted analysis including annual CV death rate	0.83(0.79 to 0.88)0.76(0.71 to 0.81)0.56(0.47 to 0.67)0.77(0.73 to 0.81)0.84(0.75 to 0.93)0.89(0.78 to 1.00)0.85(0.75 to 0.97)	9 38 3 42	.002 .056 .014
Stroke <35 35-65 >65 Overall Unadjusted analysis Adjusted analysis Adjusted analysis Adjusted analysis including annual CV death rate	0.83(0.78 to 0.89)0.81(0.72 to 0.91)0.78(0.44 to 1.39)0.82(0.77 to 0.87)0.92(0.78 to 1.08)0.89(0.75 to 1.05)0.81(0.69 to 0.95)	0 61 58 34	.30 .16 .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 metaanalysis 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)	Α	RD (95%CI)	l² (%)	P for trend*
All-cause mortality <100 100-129 130-159 ≥160 Overall Unadjusted analysis Adjusted analysis Adjusted analysis including annual CV death rate	NA 1,015 665 321 754	(508 to 1,000,000) (411 to 1,748) (169 to 3,300) (529 to 1,309)	-0.75 -0.99 -1.50 -3.11 -1.33 -0.63 -0.22 -0.38	(-1.59 to 0.10) (-1.97 to -0.00) (-2.44 to -0.57) (-5.92 to -0.30) (-1.89 to -0.71) (-1.46 to 0.20) (-1.52 to 1.07) (-1.64 to 0.89)	15 12 35 51 31	.14 .73 .55
Cardiovascular mortality <100 100-129 130-159 ≥160 Overall Unadjusted analysis Adjusted analysis Adjusted analysis Adjusted analysis including annual CV death rate	1,661 NA 749 515 1,028	(870 to 18,182) (512 to 1,393) (262 to 15,152) (756 to 1,605)	-0.60 -0.50 -1.34 -1.94 -0.97 -0.43 -0.25 -0.43	(-1.15 to -0.06) (-1.01 to 0.02) (-1.95 to -0.72) (-3.82 to -0.07) (-1.32 to -0.62) (-0.97 to 0.10) (-1.00 to 0.49) (-1.06 to 0.19)	0 0 36 54 26	.11 .50 .17
Myocardial infarction <100 100-129 130-159 ≥160 Overall Unadjusted analysis Adjusted analysis Adjusted analysis Adjusted analysis including annual CV death rate	333 684 334 184 363	(237 to 560) (463 to 1,311) (251 to 497) (113 to 487) (300 to 459)	-3.00 -1.46 -3.00 -5.44 -2.76 -0.59 -0.27 -0.33	(-4.21 to -1.79) (-2.16 to -0.76) (-3.98 to -2.01) (-8.82 to -2.05) (-3.33 to -2.18) (-1.54 to 0.35) (-1.48 to 0.95) (-1.57 to 0.92)	61 29 62 81 63	.21 .66 .60
Stroke <100 100-129 130-159 ≥160 Overall Unadjusted analysis Adjusted analysis	742 962 1,042 898 907	(449 to 2,132) (590 to 2,617) (662 to 2,439) (530 to 2,959) (661 to 1,319)	-1.35 -1.04 -0.96 -1.11 -1.10 0.24 0.24	(-2.23 to -0.47) (-1.70 to -0.38) (-1.51 to -0.41) (-1.89 to -0.34) (-1.45 to -0.76) (-0.26 to 0.75) (-0.60 to 1.07)	69 30 37 0 39	.34 .57

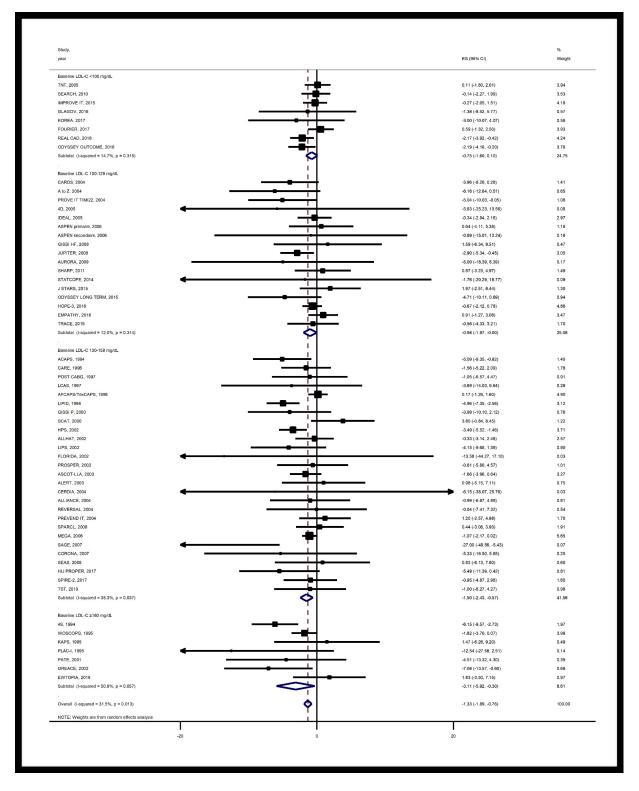
*Meta-regression model for each baseline 40 mg/dL LDL-C increase

**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)	l² (%)	P for trend*
All-cause mortality <100 100-129 130-159 ≥160 Overall	0.96(0.90 to 1.02)0.95(0.89 to 1.00)0.91(0.87 to 0.96)0.79(0.64 to 0.97)0.92(0.89 to 0.96)	30 21 21 53 34	
Unadjusted analysis Adjusted analysis Adjusted analysis including annual CV death rate	0.94(0.89 to 0.99)0.93(0.86 to 1.01)0.94(0.87 to 1.02)		.036 .09 .14
Cardiovascular mortality <100 100-129 130-159 ≥160 Overall Unadjusted analysis Adjusted analysis Adjusted analysis including annual CV death rate	0.95(0.88 to 1.02)0.94(0.88 to 1.00)0.86(0.82 to 0.91)0.66(0.57 to 0.78)0.89(0.85 to 0.92)0.89(0.83 to 0.95)0.88(0.79 to 0.97)0.89(0.80 to 0.97)	18 0 0 18	.001 .009 .015
Myocardial infarction <100 100-129 130-159 ≥160 Overall Unadjusted analysis Adjusted analysis Adjusted analysis Adjusted analysis including annual CV death rate	0.81(0.75 to 0.88)0.81(0.74 to 0.88)0.76(0.71 to 0.81)0.62(0.54 to 0.71)0.77(0.73 to 0.81)0.91(0.85 to 0.97)0.85(0.76 to 0.95)0.86(0.77 to 0.96)	53 25 26 0 42	.008 .006 .01
Stroke <100 100-129 130-159 ≥160 Overall Unadjusted analysis Adjusted analysis Adjusted analysis Adjusted analysis including annual CV death rate	0.77(0.65 to 0.91)0.83(0.72 to 0.97)0.84(0.78 to 0.90)0.73(0.59 to 0.91)0.82(0.77 to 0.87)1.05(0.94 to 1.17)0.99(0.86 to 1.16)1.03(0.89 to 1.19)	64 47 4 0 34	.35 .96 .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.

Study, rear		ES (95% CI)	% Weight
	11		
Baseline LDL-C <100 mg/dL			3.94
ENT, 2005		-1.17 (-2.51, 0.17)	
SEARCH, 2010 MPROVE IT, 2015	1	-0.17 (-1.80, 1.47)	3.07
SLAGOV, 2016		-0.01 (-1.19, 1.17) -1.38 (-8.52, 5.77)	0.23
FOURIER, 2017		0.36 (-1.07, 1.79)	3.64
KOREA, 2017		-3.50 (-7.66, 0.66)	0.66
REAL CAD, 2018		-1.06 (-2.20, 0.07)	4.69
DDYSSEY OUTCOME, 2018		-1.17 (-2.84, 0.50)	2.98
Subtotal (I-squared = 0.0%, p = 0.465)	6	-0.60 (-1.15, -0.06)	23.73
Baseline LDL-C 100-129 mg/dL			
CARDS, 2004	+	-2.24 (-5.03, 0.55)	1.34
A to Z, 2004		-6.10 (-12.14, -0.05)	0.32
PROVE IT TIMI22, 2004		-1.55 (-4.95, 1.85)	0.95
ID, 2005		-3.91 (-17.65, 9.84)	0.06
DEAL, 2005		0.26 (-1.67, 2.19)	2.43
ASPEN primaire, 2006		1.24 (-2.14, 4.61)	0.96
ASPEN secondaire, 2006		-3.90 (-14.87, 7.08)	0.10
IUPITER, 2008	<b>≓</b>	-0.47 (-1.50, 0.55)	5.19
3ISSI HF, 2008		-1.03 (-7.86, 5.80)	0.25
AURORA, 2009		-0.22 (-9.69, 9.25)	0.13
Nicholls , 2011		-0.00 (-2.84, 2.84)	1.30
SHARP, 2011		-1.30 (-3.66, 1.07)	1.77
STATCOPE, 2014		0.10 (-6.78, 6.98)	0.25
I STARS, 2015	······································	-0.01 (-1.44, 1.42)	3.63
DDYSSEY LONG TERM, 2015		-3.94 (-8.35, 0.46)	0.59
HOPE-3, 2016		-0.49 (-1.48, 0.50)	5.33
RACE, 2019		-0.01 (-1.82, 1.80)	2.67
Subtotal (I-squared = 0.0%, p = 0.806)	M	-0.50 (-1.01, 0.02)	27.30
Baseline LDL-C 130-159 mg/dL	1		
ACAPS, 1994		-4.00 (-7.62, -0.37)	0.84
CARE, 1996		-1.75 (-4.68, 1.18)	1.23
POST CABG, 1997		0.68 (-3.69, 5.05)	0.60
CAS, 1997		-1.85 (-8.18, 4.47)	0.30
.IPID, 1998	I	-3.74 (-5.71, -1.77)	2.35
AFCAPS/TexCAPS, 1998	- 4	-0.47 (-1.21, 0.27)	6.59
SCAT, 2000		1.63 (-1.90, 5.16)	0.89
SISSI P, 2000		-3.24 (-8.46, 1.99)	0.43
FLORIDA, 2002	←	-17.36 (-47.14, 12.42)	0.01
PROSPER, 2002		-2.25 (-5.86, 1.36)	0.85
ALLHAT, 2002		-0.17 (-2.09, 1.76)	2.44
HPS, 2002	- <b>e</b> -!	-3.04 (-4.62, -1.46)	3.21
LIPS, 2002		-3.44 (-7.09, 0.21)	0.83
ALERT, 2003	<del></del>	-1.28 (-5.59, 3.03)	0.61
ASCOT-LLA, 2003	- <del>)</del>	-0.50 (-1.94, 0.94)	3.61
PREVEND IT, 2004		-0.01 (-3.39, 3.37)	0.96
ALLIANCE, 2004		-3.36 (-7.17, 0.44)	0.77
MEGA, 2006	<b>—</b>	-0.32 (-0.83, 0.19)	7.81
SPARCL, 2006		-1.72 (-3.97, 0.52)	1.93
CORONA, 2007		-0.34 (-9.39, 8.71)	0.15
AGE, 2007	<	-13.50 (-29.97, 2.97)	0.04
EAS, 2008		-2.44 (-7.38, 2.50)	0.47
SPIRE-2, 2017		-1.13 (-4.04, 1.77)	1.25
HJ PROPER. 2017		-0.66 (-4.95, 3.63)	0.62
ST, 2019		-2.00 (-4.88, 0.88)	1.27
Subtotal (I-squared = 36.1%, p = 0.038)	•	-1.34 (-1.95, -0.72)	40.09
aseline LDL-C ≥160 mg/dL	il		
	i		
IS, 1994		-5.90 (-8.93, -2.88)	1.17
(APS, 1995		0.74 (-2.83, 4.32)	0.87
VOSCOPS, 1995		-1.43 (-2.78, -0.09)	3.92
PLAC-I, 1995 CAIUS, 1996		-0.12 (-9.93, 9.69)	0.13
AIUS, 1996 ATE, 2001		1.13 (-4.13, 6.39) 1.59 (-4.07, 7.25)	0.42
ATE, 2001 GREACE, 2002		1.59 (-4.07, 7.25) -7.50 (-13.72, -1.28)	0.37
WTOPIA, 2019		-7.30 (-13.72, -1.28) -2.35 (-4.77, 0.06)	1.71
ситоры, 2019 Subtotal (I-squared = 54.5%, p = 0.031)	~	-2.35 (-4.77, 0.05) -1.94 (-3.82, -0.07)	1.71 8.89
		-1.54 (-3.62, -0.07)	0.05
Overall (I-squared = 25.7%, p = 0.042)	0	-0.97 (-1.32, -0.62)	100.00
	Ť		
IOTE: Weights are from random effects analysis			
	1 1	I	

**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.

Baseline LDLC 4100 mgdL TNT. 2005 SEARCH, 2010 MPROVE IT. 72015 GLAGOV, 2016 FOURIER, 2017 ODYSSEY OUTCOME, 2018 REAL CAD, 2018 Subtral (4-quamet = 0.11%, p = 0.102) Baseline LDLC 100-129 mgdL AND Z, 2004 CARDS, 2005 CARDS, 2005 CARDS, 2005 CARDS, 2006 CARDS, 2006 CARDS, 2006 CARDS, 2010 CARDS,	$\begin{array}{c} 2.63  (4.51, .0.75) \\ .2.40  (4.09, .0.70) \\ .2.57  (4.22, .0.92) \\ .5.51  (+18, 74, 7.72) \\ .5.68  (7.40)  .3.49 \\ .7.00  (+15, 50, .3.49) \\ .7.00  (+15, 50, .3.49) \\ .4.00  (+2, 0.4)  .0.96) \\ .1.32  (22, 17, .0.46) \\ .1.32  (22, 17, .0.46) \\ .1.39  (9.01, 6.24) \\ .4.85  (6.89, .0.83) \\ .2.50  (+17, .0.27) \\ .6.46  (+7, 63, 4, 70) \\ .1.68  (6.77, .0.27) \\ .6.46  (+7, 63, 4, 70) \\ .1.69  (5.74, .237) \\ .1.79  (24.84, 1, 33) \\ .2.19  (4.34, .4.103) \\ .1.00  (4.35, 1, 152) \\ .7.56  (+15, 60,  (5.53) \\ .0.81  (+2.83, +100) \\ .0.22  (+30, 84) \\ .8.64  (+5.87, -1.42) \\ .0.76  (24.7, 0.89) \\ .0.68  (+17, -0.09) \\ .0.25  (+130, 1, 130) \\ .2.41  (-5.32, 0.49) \\ .1.46  (+2.16, -0.78) \end{array}$	3.01 3.21 3.25 0.18 2.74 0.67 1.98 4.04 19.08 0.46 0.51 1.41 2.86 0.51 1.41 3.76 3.76 3.76 3.76 3.46 0.045 3.66 0.64 3.21 4.24 4.24 4.24 4.24 4.24 4.24 4.24 4
SEARCH. 2010 IMPROVE IT. 2015 CUAGOV. 2016 FOURIER, 2017 OVYSSEY UTCOME, 2018 REAL CAO. 2018 Subtomi (1=squamed = 01.1%, p = 0.012) 	$\begin{array}{c} -2.40 \left( -4.09, -0.70 \right) \\ -2.57 \left( -42.2, -9.59 \right) \\ -5.55 \left( -18.7, 47, 72 \right) \\ -5.65 \left( -7.80, -3.49 \right) \\ -7.00 \left( -13.50, -3.56 \right) \\ -4.00 \left( -7.04, -9.69 \right) \\ -1.32 \left( -2.17, -0.49 \right) \\ -3.00 \left( -4.21, -1.79 \right) \\ \end{array}$	321 326 0.18 2.74 0.67 198 4.04 1908 0.51 1.41 2.06 0.25 1.39 0.16 3.76 3.76 3.76 3.76 3.06 0.46 0.46 0.46 0.46 3.21 4.20 0.44 0.64 0.51 3.21 3.21 3.21 3.21 3.21 3.21 3.21 3.2
IMPROVE IT, 2015 GLAGOV, 2016 FOURIER, 2017 KOREA, 2017 ODYSSEY OUTCOME, 2018 REAL CAD, 2016 Subtoal (4:equimed = 01.1%, p = 0.12) - Bealine LDLC 100.129 mg/dL PROVE IT TMIC2, 2024 A 10 Z, 2024 CARS, 2004 CARS, 2005 CARS, 2004 CARS, 2005 CARS,	$\begin{array}{c} -2.57 \left( + 22 962 \right) \\ -5.57 \left( + 32 962 \right) \\ -5.65 \left( 7.80 3.49 \right) \\ -7.00 \left( -15.0 - 3.69 \right) \\ -1.00 \left( 7.04 \right) - 969 \right) \\ -1.52 \left( 2.17 0.49 \right) \\ -3.00 \left( -4.21, -1.79 \right) \\ \end{array}$	326 0.18 2.74 0.67 1.98 4.04 1.908 0.46 0.46 0.46 0.46 0.46 0.46 0.46 0.46
GLAGOV. 2018 FOURIER, 2017 ODYSSEY OUTCOME, 2018 REAL CAD, 2016 Subtolal (4-squared = 61 11% p = 0.012) Baseline LDLC 100.129 mgidL PROVE IT TMIZ, 2004 A1 to 2, 2004 A1 to 2, 2004 A1 to 2, 2004 CARDS, 3004 ICEAL, 2005 40, 2005 SHARP, 2015 SHARP, 2015 SHARP, 2011 Nicholis, 2011 OVYSSEY LONG TERM, 2015 J STARS, 2015 HOPE-3, 2016 EINPATH, 2019 SHARD 42, 2019 SHARD 42	$\begin{array}{c} -5.51(-18.74,772)\\ -5.65(-7.80,-3.49)\\ -7.00(-15.50,-6.90)\\ -4.00(-7.04,-0.96)\\ -1.32(-21,-0.46)\\ -3.00(-7.04,-0.96)\\ -1.32(-21,-7.76)\\ -3.00(-7.04,-0.96)\\ -1.39(-9.01,-6.24)\\ -4.85(-88,-0.83)\\ -2.50(-4.73,-0.27)\\ -6.46(-17.63,-4.70)\\ -1.68(-6.74,-2.37)\\ -1.07(-24.81,-333)\\ -2.19(-3.34,-1.03)\\ -1.00(-35,1,-1.42)\\ -7.56(-15.66,-0.53)\\ -0.81(-2.83,-1.03)\\ -1.00(-35,1,-1.42)\\ -0.79(-24.7,-0.86)\\ -0.86(-1.77,-0.86)\\ -0.86(-1.77,-0.86)\\ -0.86(-1.77,-0.86)\\ -0.86(-1.77,-0.06)\\ -0.25(-1.60,-1.30)\\ -2.41(-5.32,-0.46)\\ \end{array}$	0.18 2.74 0.67 1.86 4.04 1.90 0.46 0.51 1.41 2.86 0.25 1.39 0.16 3.76 2.40 0.46 3.06 0.46 0.46 0.46 0.46 3.06 4.24 0.46 3.21 4.24 4.24 4.24 4.24 4.24 4.24 4.24 4
FOURIER, 2017 KOREA, 2017 OVYSSEY UTCOME, 2018 REAL CAD, 2018 Subtoal (4-squared = 81.1%, p = 0.012) Baseline LD.C 100.129 mg/dL PROVE IT IMIZ2, 2004 A 72, 2004 CARDS, 2004 CARDS, 2004 CARDS, 2004 CARDS, 2004 CARDS, 2004 CARDS, 2005 ASPEN secondaire, 2006 ASPEN secondaire, 2006 ASPEN secondaire, 2006 ASPEN secondaire, 2006 CISSI HF, 2008 AURORA, 2009 SUBTOAL 2015 CARDS, 2010 CARDS, 2	$\begin{array}{c} -5.65 (-7.80, -3.49)\\ -7.00 (-13.80, -5.69)\\ -4.00 (-7.04, -0.89)\\ -1.32 (-2.17, -0.46)\\ -3.00 (-4.21, -1.70)\\\\ \end{array}$	2,74 0,87 1,98 4,04 19,08 0,51 1,41 2,06 0,25 1,39 0,16 0,25 3,76 3,76 3,76 3,76 3,76 3,06 0,46 0,66 0,64 0,56 3,21 4,22 3,36
KOREA, 2017 ODYSSEY OUTCOME, 2018 Subtotal (4:equared = 01.1%; p = 0.012) Bearine LD.C 100.129 mgial PROVE IT MM22, 2004 A to 2, 2004 CARDS, 2004 CARDS	$\begin{array}{c} -7.00 (-12.80, -0.80) \\ +4.00 (-7.04, -0.66) \\ +3.22 (-2.17, -0.46) \\ -3.00 (+2.21, -1.70) \\ \end{array}$	0.67 198 4.04 19.08 0.46 0.51 1.41 2.08 0.25 1.59 0.16 0.376 0.45 0.04 0.45 0.04 0.45 0.06 0.06 0.06 0.06 0.06 0.05 0.05 0.0
ODYSEY OUTCOME, 2018 REAL 200, 2016 Baseline LDLC 100-129 mgilL PROVE IT TIMIC2, 2004 A to Z, 2004 A to Z, 2004 A to Z, 2004 CARDS, 2005 40, 2005 40, 2005 ASPEN secondaries, 2006 ASPEN secondaries, 2006 ASPEN secondaries, 2006 SHARP, 2011 Nicholis, 2011 OVYSEY (LOK TERM, 2015 J STARS, 2015 J STARS, 2015 HOFE-J, 2016 EINPATH, 2018 J Statical (L-squared = 28.7%, p = 0.130) 	$\begin{array}{c} 4.00(7,04,-0.96)\\ -1.32(2.17,-0.46)\\ -3.00(4.2,1,-1.70)\\ \end{array}\\\\ \begin{array}{c} -3.67(-12.02,4.08)\\ -1.39(9.01,6.24)\\ -4.86(88,-0.83)\\ -2.50(-4.73,-0.27)\\ -6.46(-17,63,4.70)\\ -1.96(-47,4,2.37)\\ -1.07(-24.49,1,333)\\ -2.19(-3.34,-1.03)\\ -1.00(-35,1,1.52)\\ -7.56(-15.66(-5.53)\\ -0.81(-2.83,1.00)\\ -0.02(-6.68,-6.44)\\ -8.64(-15.77,-4.26)\\ -0.79(-24.7,-0.86)\\ -0.88(-12.77,-0.86)\\ -0.88(-12.77,-0.86)\\ -0.88(-12.77,-0.86)\\ -0.82(-16.8,1.30)\\ -0.25(-16.8,1.30)\\ -0.24(-16.8,1.30)\\ \end{array}$	1,96 4,04 0,06 0,51 1,41 2,06 0,25 1,139 0,16 0,25 3,76 2,40 0,45 3,06 0,94 0,94 0,94 0,94 0,94 0,94 0,94 0,94
REAL CAD, 2018 Subtoal (4-squared = 81.1%, p = 0.012) Baseline LDL-C 100.129 mg/dL PROVE IT IMIZ2, 2004 A 02.2005 CARDS, 2004 CARDS, 2004 CARDS, 2004 CARDS, 2004 CARDS, 2005 CARDS, 2006	$\begin{array}{c} -1.32(2.17,-0.48)\\ -3.00(-4.21,-1.79)\\ \end{array}$	4,04 19,08 0,46 0,51 1,41 2,66 0,25 1,39 0,16 3,76 2,40 0,45 0,64 0,64 0,66 0,64 0,66 3,21 4,24 4,24 4,24 4,24 4,24 4,24 4,24 4
Subtolal (1-squared = 61.1%, p = 0.012)	-3.00(-4.21, -1.79) -3.97(-12.02, 4.08) -1.39(-9.01, 6.24) -4.86(-8.88, -0.83) -2.50(-4.73, -0.27) -6.46(-17.63, 4.70) -1.69(-5.74, 2.37) -1.079(-2.451, -3.33) -2.19(-3.34, -1.03) -1.00(-3.51, 1.52) -7.56(-15.86, -0.53) -0.61(-2.63, 1.00) -0.02(-6.68, 6.84) -8.64(-15.87, -1.42) -0.79(-2.47, 0.88) -0.68(-1.127, -0.09) -0.25(-1.80, 1.30) -2.5(-1.60, 1.30) -2.41(-6.32, 0.48)	9.08 0.46 0.51 1.41 2.86 0.25 1.39 0.16 0.45 0.64 0.64 0.66 0.66 3.21 4.24 4.23
Baseline LDL C 100-129 mg/dL PROVE IT TM/22, 2004 A 10 Z, 2004 A 1	$\begin{array}{c} -3.67 \left(-12.02, 4.08\right) \\ -1.39 \left(-9.01, 6.24\right) \\ -4.85 \left(+80, -0.85\right) \\ -2.50 \left(-4.73, -0.27\right) \\ -6.46 \left(+17.63, 4.70\right) \\ -1.69 \left(-5.74, 2.37\right) \\ -10.79 \left(-24.81, 3.33\right) \\ -2.19 \left(-3.34, -1.03\right) \\ -1.00 \left(-3.51, 1.52\right) \\ -7.56 \left(-15.06, 0.53\right) \\ -0.81 \left(-2.83, 1.00\right) \\ -0.02 \left(-60, 6.04\right) \\ -0.02 \left(-60, 6.04\right) \\ -0.07 \left(-2.47, -0.69\right) \\ -0.68 \left(-1.77, -0.69\right) \\ -0.68 \left(-1.27, -0.09\right) \\ -0.25 \left(-1.60, 1.30\right) \\ -2.41 \left(-5.32, 0.44\right) \end{array}$	0.46 0.51 1.41 2.26 0.25 3.76 3.76 3.46 0.45 0.46 0.46 3.26 3.21 4.22 3.36
PROVE IT TIMU2, 2004 A to Z, 2004 CARDS, 2004 CIERAL, 2005 40, 2005 ASPEIN secondarie, 2006 ASPEIN secondarie, 2006 ASPEIN secondarie, 2006 GISSI HF, 2008 AURORA, 2009 GISSI HF, 2008 AURORA, 2009 CIERAL, 2011 Nichols, 2011 OUYSSEY LONG TERM, 7015 DUTYSE, 2016 EMPATHY, 2018 TACE, 2019 Subtotal (Acquared = 28.7%, p = 0.130) - Subtotal (Acquared = 28.7%, p = 0.130)	$\begin{array}{c} -1.39(9.01,6.24)\\ -4.85(840,-0.85)\\ -2.50(-4.73,-0.27)\\ -6.46(+7.63,4.70)\\ -1.69(-5.74,2.57)\\ -1.07(-2.449,1.33)\\ -2.19(-3.34,-1.03)\\ -1.00(-3.57,1.52)\\ -7.56(+1.506,0.53)\\ -0.81(-2.63,1.00)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\$	0.51 1.41 2.68 0.25 1.39 0.16 3.76 2.40 0.45 3.08 0.04 0.68 3.21 3.21 3.23
A ID Z, 2004 CARDS, 2004 (DEAL, 2005 40, 2005 40, 2005 ASPEH secondaire, 2006 ASPEH secondaire, 2007 ASPEH secondaire,	$\begin{array}{c} -1.39(9.01,6.24)\\ -4.85(840,-0.85)\\ -2.50(-4.73,-0.27)\\ -6.46(+7.63,4.70)\\ -1.69(-5.74,2.57)\\ -1.07(-2.449,1.33)\\ -2.19(-3.34,-1.03)\\ -1.00(-3.57,1.52)\\ -7.56(+1.506,0.53)\\ -0.81(-2.63,1.00)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\ -0.02(-60,0.64)\\$	0.51 1.41 2.68 0.25 1.39 0.16 3.76 2.40 0.45 3.08 0.04 0.68 3.21 3.21 3.23
CARDS, 2004 LIPEAL, 2005 ASPEN primare, 2006 ASPEN primare, 2006 ASPEN primare, 2006 ASPEN primare, 2006 CIRSI HF, 2008 AUROR A, 2009 SIARP, 2011 Nicholis, 2011 ODYSSEY LONG TERM, 2015 DYSSEY LONG TERM, 2016 DYSSEY LONG TERM, 2017 DYSSEY LONG TERM, 2016 DYSSEY LONG TERM, 2016 DY	$\begin{array}{c} 4.85( \pm .86, -0.83)\\ -2.50( \pm .73, -0.27)\\ -8.46( \pm .75, 0.3, 4.70)\\ -1.98( \pm .74, 2.37)\\ -10.79( \pm .24, 9.1, 3.33)\\ -2.19( \pm .34, 1, 0.5)\\ -1.00( \pm .55, 1, 1.52)\\ -7.56( \pm .56, 0, 6.53)\\ -0.61( \pm .26, 3.5, 1.00)\\ -0.02( \pm .66, 0, 6.4)\\ -0.02( \pm .66, 0, 6.4)\\ -0.79( \pm .24, 7.42)\\ -0.25( \pm .16, 0, 1.30)\\ -2.24( \pm .32, 0.46)\\ \end{array}$	1.41 2.66 0.25 1.39 0.16 3.76 2.40 0.45 3.08 0.64 0.64 0.64 3.21 4.24 3.36
UGEAL, 2005 4D, 2005 ASPEN yacondaire, 2006 ASPEN yacondaire, 2006 (ISSI HF, 2008 AURORA, 2009 SHARP, 2011 Nichails, 2011 OVSSEY L/CNG TERM, 2015 J STARS, 2015 HOFES, 2016 TRACE, 2019 Subticual (4:equawed = 28.7%, p = 0.130) 	$\begin{array}{c} -2.50 \left( -4.73 , -0.27 \right) \\ -8.48 \left( -175 , 9.470 \right) \\ -1.68 \left( -5.74 , 2.37 \right) \\ -10.79 \left( -24.91 , 3.33 \right) \\ -2.19 \left( -3.34 , -1.05 \right) \\ -1.00 \left( -3.51 , 1.52 \right) \\ -7.56 \left( -15.56 , 0.53 \right) \\ -0.81 \left( -28.3 , 1.00 \right) \\ -0.02 \left( -6.80 , 5.64 \right) \\ -8.64 \left( -15.87 , -4.27 \right) \\ -0.79 \left( -2.47 , 0.85 \right) \\ -0.68 \left( -1.27 , -0.09 \right) \\ -0.25 \left( -1.80 , 1.30 \right) \\ -2.41 \left( -5.32 , 0.49 \right) \end{array}$	2.88 0.25 1.99 0.16 3.76 2.40 0.45 3.08 0.64 0.64 0.64 3.21 4.24 3.36
40, 2005 ASPEL 9 secondaire, 2006 JUPITER, 2008 GIGSI HF, 2008 AURORA, 2009 SHARP, 2011 Nichils, 2011 OVYSSEY L (LNG TERM, 2015 J STARS, 2015 L STARS, 2015 MORE-3, 2019 SHARDAIL CH, 2019 SHAR	$\begin{array}{c} -6.46 \left(+7.63, 4.70\right) \\ -1.69 \left(5.74, 2.37\right) \\ -1.07 \left(2.248\right) , 3.33 \right) \\ -2.19 \left(3.34, -1.03\right) \\ -1.00 \left(3.51, 1.52\right) \\ -7.66 \left(+15.60, 0.53\right) \\ -7.66 \left(+15.60, 0.53\right) \\ -0.81 \left(2.83, 1.00\right) \\ -0.02 \left(6.68, 0.64\right) \\ -0.02 \left(4.77, 0.68\right) \\ -0.68 \left(-1.27, -0.08\right) \\ -0.25 \left(-1.80, 1.30\right) \\ -2.24 \left(-6.32, 0.44\right) \end{array}$	0.25 1.39 0.16 3.76 2.40 0.45 3.08 0.64 0.64 0.64 3.21 4.24 3.36
ASPEN primare, 2008	$\begin{array}{c} -1.68 (\leq 5/4, \leq 2.37) \\ -10.78 (\leq 2.4, 4, 1.33) \\ -2.19 (\leq 3.4, 4, 1.05) \\ -1.00 (\leq 3.5, 1.152) \\ -7.56 (=15.68, 0.53) \\ -0.61 (\leq 2.63, 1.00) \\ -0.02 (< 6.68, 0.64) \\ -8.64 (=15.87, -1.42) \\ -0.79 (\leq 2.47, 0.69) \\ -0.68 (=1.27, -0.09) \\ -0.25 (=1.60, 1.30) \\ -2.25 (=1.60, 1.30) \\ -2.41 (\leq 3.2, 0.46) \end{array}$	1.39 0.16 3.76 2.40 0.45 3.08 0.64 0.66 3.21 4.24 3.36
ASPEN secondaire, 2006	$\begin{array}{c} -10.79(24.91,3.33)\\ -2.19(3.34,-1.05)\\ -1.00(3.51,1.52)\\ -7.56(15.60,0.33)\\ -0.81(2.83,1.00)\\ -0.02(2.68,0.64)\\ -8.64(15.87,-1.42)\\ -0.79(2.47,0.85)\\ -0.68(1.77,-0.69)\\ -0.25(1.80,1.30)\\ -2.24(1.(5.32,0.49))\end{array}$	0.16 3.76 2.40 0.45 3.08 0.64 0.68 3.21 4.24 3.36
JUPTER, 2008 GISSI HF, 2008 GISSI HF, 2008 HARCRA, 2009 SHARP, 2011 UNDMILE, 2019 UNDMILE, 2019 UNDMILE, 2019 UNDMILE, 2019 SHARCRA, 2015 UNDMILE, 2019 UNDM	$\begin{array}{c} -2.19(-3.34,-1.03)\\ -1.00(-351,-152)\\ -7.66(-15.66,0,63)\\ -0.81(-2.63,1.00)\\ -0.02(-6.08,0.64)\\ -8.64(-15.87,-1.42)\\ -0.79(-2.47,0.86)\\ -0.86(-127,-0.06)\\ -0.86(-127,-0.06)\\ -0.25(-1.80,1.30)\\ -2.41(-5.32,0.46)\end{array}$	3.76 2.40 0.45 3.08 0.64 0.56 3.21 4.24 3.36
GISSIHF.2008 AURORA.2009 SHARP,2011 ODYSSEY LONG TERM,2015 DIFARS.2015 HORE-3,2015 EMPATHY.2018 TRACE.2019 Subtoal (Acquared = 28.7%, p = 0.130) - Basime LDLC 150-159 mgtiL	$\begin{array}{c} -1.00 \ (3.51, 1.52) \\ -7.66 \ (150, 0.63) \\ -0.61 \ (2.63, 1.00) \\ -0.02 \ (6.68, 0.64) \\ -8.64 \ (15.87, -1.42) \\ -0.79 \ (2.47, 0.68) \\ -0.68 \ (-127, -0.09) \\ -0.25 \ (-1.80, 1.30) \\ -2.21 \ (-1.62, 0.48) \end{array}$	2.40 0.45 3.08 0.64 0.56 3.21 4.24 3.36
AURORA, 2009 SHARP, 2011 DDYSSEY LONG TERM, 2015 USTARS, 2015 MOPE-3, 2016 EMPATHY, 2016 TRACE, 2019 Subticual (4-quared = 28.7%, p = 0.180) Subticual (4-quared = 28.7%, p = 0.180) Baseline LDL-C 130-189 mg/dL	-7.50 (-15.06, 0.53) -0.81 (-28.3, 1.00) -0.02 (-0.69, 6.84) -8.64 (-15.97, -1.42) -0.79 (-2.47, 0.85) -0.68 (-127, -0.06) -0.25 (-1.80, 1.30) -2.41 (-5.32, 0.49)	0.45 3.08 0.64 0.56 3.21 4.24 3.36
SHARP, 2011	$\begin{array}{c} -0.81(+2.83, +0.0)\\ -0.02(+0.80, 6.64)\\ -0.80(+1.65, 87, -4.22)\\ -0.79(+2.47, -0.89)\\ -0.68(+1.27, -0.09)\\ -0.25(+1.80, +3.00)\\ -2.241(+5.32, -0.46)\end{array}$	3.08 0.64 0.56 3.21 4.24 3.36
Nichilis 2211 ODYSSEY LONG TERM, 2015 DSTARS, 2015 EMPATHY, 2018 EMPATHY, 2018 Subtotal (1-aquared = 28.7%, p = 0.130) . Beavine LDLC 130-159 mg/dL	-0.02 (-8.68, 6.64) -8.64 (-15.87, -1.42) -0.79 (-2.47, 0.89) -0.68 (-1.27, -0.09) -0.25 (-1.60, 1.30) -2.41 (-5.32, 0.49)	0.84 0.56 3.21 4.24 3.36
ODYSSEY LONG TERM, 2015       JSTARS, 2015       HOPE-3, 2016       EMPATHY, 2018       TRACE, 2019       Subtoal (1-squared = 28.7%, p = 0.130)       Baseline LDL-C 130-159 mg/dL	-8.64 (-15.87, -1.42) -0.79 (-2.47, 0.89) -0.68 (-1.27, -0.99) -0.25 (-1.80, 1.30) -0.25 (-1.80, 1.30) -2.41 (-5.32, 0.49)	0.56 3.21 4.24 3.36
J STARS, 2015 HOPE-3, 2016 EMPATHY, 2018 TRACE, 2019 Subcidial (1-4quared = 28.7%, p = 0.130) Subcidial (1-50-159 mg/dL	-0.79 (-2.47, 0.89) -0.88 (-1.27, -0.09) -0.25 (-1.80, 1.30) -2.41 (-5.32, 0.49)	3.21 4.24 3.36
MOPE-3, 2018 EMPATHY. 2018 TRACE, 2019 Subtrial (L4quared = 28.7%, p = 0.130) Baseline LDL-C 130-159 mg/dL	-0.68 (-1.27, -0.09) -0.25 (-1.80, 1.30) -2.41 (-5.32, 0.49)	4.24 3.36
EMPATHY. 2018 TRACE, 2019 Subtolal (!4cquared = 28.7%, p = 0.130) . Baseline LDL-C 130-159 mg/dL	-0.25 (-1.80, 1.30) -2.41 (-5.32, 0.49)	3.36
TRACE, 2019 Subtitual (1-4quared = 28.7%, p = 0.130) Subtitual (1-5quared = 28.7%, p = 0.130) Sasalime LDL-C 130-159 mg/dL	-2.41 (-5.32, 0.49)	
Subtotal (1-squared = 28.7%, p = 0.130) Baseline LDL-C 130-159 mg/dL		
Baseline LDL-C 130-159 mg/dL	-1.40 (-2.16, -0.78)	2.08 30.61
		30.61
ACAPS, 1994		
	-2.91 (-8.23, 2.41)	0.93
CARE, 1996	-4.83 (-8.43, -1.24)	1.62
POST CABG, 1997	-1.74 (-7.58, 4.10)	0.80
LCAS, 1997	1.96 (-14.79, 18.71)	0.12
	-4.65 (-6.67, -2.64)	2.87
AFCAPS/TexCAPS, 1998	-2.22 (-3.62, -0.81)	3.50
SCAT, 2000	0.54 (-4.34, 5.42)	1.06
GISSI P, 2000	-1.51 (-6.24, 3.23)	1.11
PROSPER, 2002	-3.25 (-7.86, 1.35)	1.16
	31.97 (-10.56, 74.51)	
HPS, 2002	-6.12 (-7.87, -4.37) -1.60 (-3.83, 0.63)	3.14
LIPS, 2002	-1.60 (-3.83, 0.63) -2.58 (-7.53, 2.36)	
LIPS. 2002 ASCOT-LLA, 2003	-2.58 (-7.53, 2.36) -3.22 (-5.08, -1.38)	1.04 3.05
ALERT, 2003	-3.22 (-5.06, -1.38) -3.71 (-7.58, 0.16)	3.05
ALLIANCE, 2004	-7.91 (-12.42, -3.40)	1.48
REVERSAL, 2004	-7.91 (-12.42, -3.40) -8.20 (-25.51, 9.10)	0.11
MEGA, 2006	-8.20 (-25.51, 9.10) -0.74 (-1.41, -0.08)	4.18
SPARCL, 2006	-3.36 (-5.25, -1.47)	3.00
CORONA, 2007	-3.10 (-7.95, 1.75)	1.07
SAGE, 2007	-0.08 (-24.97, 24.81)	0.05
SAGE, 2007	-3.59 (-7.31, 0.12)	1.56
SPIRE-2, 2017	-5.28 (-10.71, 0.12)	0.90
HU PROPER, 2017	-0.63 (-3.49, 2.24)	2.12
TST, 2019	-2.20 (-4.99, 0.60)	2.12
Subtotal (I-squared = 61.8%, p = 0.000)	-3.00 (-3.98, -2.01)	40.90
Beseine LDL-© ≿180 mg/dL		
4S, 1994	-8.82 (-12.22, -5.42)	1.74
WOSCOPS, 1995	-3.80 (-6.06, -1.54)	2.63
	-18.88 (-38.97, 1.20)	0.08
PATE, 2001	-2.28 (-7.28, 2.73)	1.02
GREACE, 2002	-12.50 (-19.43, -5.57)	0.60
EWTOPIA, 2019	-1.31 (-2.88, 0.25)	3.34
Subtotal (i-squared = 80.6%, p = 0.000)	-5.44 (-8.82, -2.05)	9.41
Overall (I-squared = 63.1%, p = 0.000)	-2.76 (-3.33, -2.18)	100.00
NOTE: Weights are from random effects analysis		
-20 0	20	

**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.

Study,		%
ear	ES (95% CI)	Weight
Baseline LDL-C <100 mg/dL	!	
FNT, 2005	-1.54 (-2.86, -0.22)	3.34
SEARCH, 2010	-0.59 (-1.71, 0.53)	3.86
MPROVE IT, 2015	-1.12 (-1.95, -0.28)	4.73
GLAGOV, 2016	-1.38 (-7.41, 4.66)	0.31
FOURIER, 2017	-3.60 (-4.79, -2.40)	3.65
KOREA, 2017	-1.00 (-5.38, 3.38)	0.57
DDVSSEY OUTCOME, 2018	-1.55 (-2.75, -0.35)	3.64
REAL CAD, 2018	0.05 (-1.00, 1.10)	4.07
Subtotal (I-squared = 68.9%, p = 0.002)	-1.35 (-2.23, -0.47)	24.16
Baseline LDL-C 100-129 mg/dL		
A to Z, 2004	-1.66 (-5.12, 1.80)	0.86
CARDS, 2004	-3.32 (-6.07, -0.57)	1.27
PROVE IT TIMI22, 2004	0.16 (-2.86, 3.17)	1.09
4D, 2005	6.01 (-0.99, 13.01)	0.23
DEAL, 2005	-1.06 (-2.72, 0.60)	2.60
ASPEN primaire, 2006	-0.63 (-4.48, 3.23)	0.71
SPEN secondaire, 2006	-1.95 (-9.71, 5.81)	0.19
JUPITER, 2008	-1.83 (-2.97, -0.69)	3.80
3ISSI HF, 2008	1.81 (-0.87, 4.48)	1.33
AURORA, 2009	0.34 (-3.60, 4.28)	0.69
SHARP, 2011 -	-1.93 (-3.35, -0.51)	3.09
Nicholls , 2011	0.72 (-2.46, 3.89)	1.00
DDYSSEY LONG TERM, 2015	2.04 (-1.19, 5.27)	0.97
J STARS, 2015	-2.22 (-7.68, 3.24)	0.38
HOPE-3, 2016	-0.82 (-1.54, -0.11)	5.08
EMPATHY, 2018	-2.42 (-4.41, -0.43)	2.06
FRACE, 2019	-1.61 (-3.83, 0.61)	1.76
Subtotal (I-squared = 29.9%, p = 0.119)	-1.04 (-1.70, -0.38)	27.12
Baseline LDL-C 130-159 mg/dL		
ACAPS, 1994	-3.27 (-6.61, 0.07)	0.92
CARE, 1996	-2.32 (-4.48, -0.15)	1.83
.IPID, 1998	-1.29 (-2.67, 0.09)	3.20
AFCAPS/TexCAPS, 1998	-0.18 (-0.81, 0.46)	5,33
SCAT, 2000	-1.63 (-5.16, 1.90)	0.83
GISSI P, 2000	0.24 (-2.78, 3.25)	1.09
HPS, 2002	-2.32 (-3.33, -1.31)	4.18
.IPS, 2002	0.30 (-0.74, 1.34)	4.10
PROSPER, 2002	0.54 (-2.90, 3.98)	0.87
ALLHAT, 2002	-0.86 (-2.51, 0.79)	2.61
ALERT, 2003	2.08 (-2.20, 6.36)	0.59
ASCOT-LLA, 2003	-1.92 (-3.59, -0.25)	2.58
PREVEND IT, 2004	1.81 (-2.15, 5.77)	0.68
REVERSAL, 2004	-0.04 (-7.41, 7.32)	0.21
ALLIANCE, 2004	-0.72 (-3.93, 2.50)	0.98
VIEGA, 2006	-0.53 (-1.37, 0.31)	4.69
SPARCL, 2006	-3.96 (-8.02, 0.10)	0.65
SAGE. 2007	-4.50 (-13.30, 4.30)	0.15
CORONA 2007	-1.88.(-6.16.2.40)	0.59
SEAS 2008	0 87 (-2 96 4 70)	0.72
SPIRE-2, 2017	-2.45 (-5.43, 0.52)	1.11
HJ PROPER, 2017	-0.34 (-3.80, 3.12)	0.86
FST, 2019	4.20 (-9.69, 1.30)	0.37
	-0.96 (-1.51, -0.41)	39.15
Baseline LDL-C ≥160 mg/dL	-	
18, 1994	-1.41 (-2.56, -0.27)	3.80
NOSCOPS, 1995	-0.32 (-1.51, 0.88)	3.66
PLAC-1, 1995	-3.12 (-9.48, 3.25)	0.28
PATE, 2001	-3.12 (-5.46, 3.23) -2.99 (-10.70, 4.71)	0.28
GREACE, 2002	-3.33 (-7.50, 0.83)	0.62
EWTOPIA, 2019	-2.26 (-5.39, 0.88)	1.02
Subtotal (I-squared = 0.0%, p = 0.524)	-2.20 (-5.33, 0.68)	9.57
	Ĩ	
Dverall (I-squared = 39.5%, p = 0.002)	-1.10 (-1.45, -0.76)	100.00
NOTE: Weights are from random effects analysis	1	
-20	0 20	

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

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

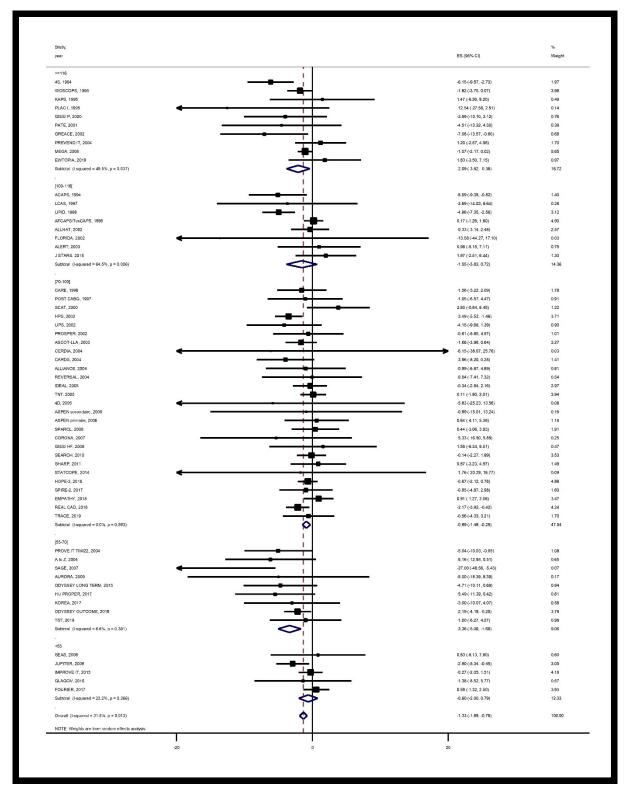
*Meta-regression model for each achieved 40 mg/dL LDL-C decrease

Achieved LDL-C (mg/dL)	Rate ratio (95%	CI) I ² (%)	P for trend*
All-cause mortality ≥116 100-115 70-99 55-69 <55 Overall Unadjusted analysis Adjusted analysis Adjusted analysis Adjusted analysis including annual CV death rate	<ul> <li>0.79 (0.68 to 0.</li> <li>0.93 (0.80 to 1.</li> <li>0.95 (0.92 to 0.</li> <li>0.82 (0.72 to 0.</li> <li>0.97 (0.89 to 1.</li> <li>0.92 (0.89 to 0.</li> <li>0.94 (0.88 to 0.</li> <li>0.99 (0.89 to 1.</li> <li>0.99 (0.89 to 1.</li> <li>0.99 (0.89 to 1.</li> </ul>	09) 56 98) 0 93) 43 06) 28 96) 34 99) 09)	.04 .79 .91
Cardiovascular mortality ≥116 100-115 70-99 55-69 <55 Overall Unadjusted analysis Adjusted analysis Adjusted analysis Adjusted analysis including annual CV death rate	0.68       (0.59 to 0.         0.84       (0.72 to 0.         0.91       (0.87 to 0.         0.85       (0.4 to 0.9         0.99       (0.90 to 1.         0.89       (0.85 to 0.         0.88       (0.82 to 0.         0.94       (0.83 to 1.         0.96       (0.86 to 1.)	98) 26 95) 0 8) 20 09) 0 92) 18 94) 05)	<.001 .26 .53
Myocardial infarction ≥116 100-115 70-99 55-69 <55 Overall Unadjusted analysis Adjusted analysis Adjusted analysis including annual CV death rate	0.63       (0.55 to 0.         0.78       (0.66 to 0.         0.78       (0.74 to 0.         0.86       (0.79 to 0.         0.72       (0.59 to 0.         0.77       (0.73 to 0.         0.92       (0.85 to 1.         1.01       (0.87 to 1.         1.03       (0.88 to 1.	93)       50         82)       16         95)       12         87)       72         81)       42         00)       18)	.052 .87 .70
Stroke ≥116 100-115 70-99 55-69 <55 Overall Unadjusted analysis Adjusted analysis Adjusted analysis including	0.78 (0.64 to 0. 0.89 (0.79 to 1. 0.83 (0.76 to 0. 0.83 (0.72 to 0. 0.68 (0.50 to 0. 0.82 (0.77 to 0. 1.07 (0.96 to 1. 1.06 (0.88 to 1. 1.15 (0.96 to 1.	02) 8 90) 37 96) 0 92) 72 87) 34 19) 29)	.22 .53 .13

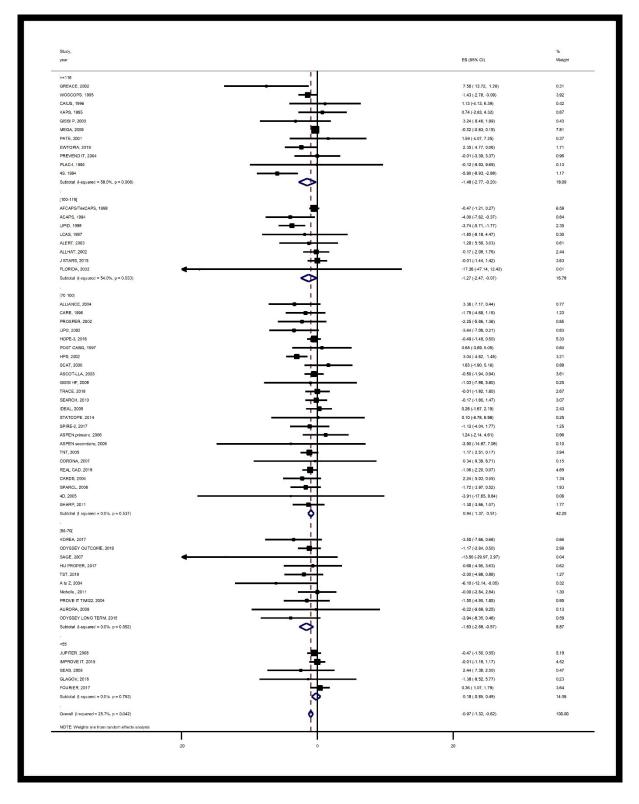
**eTable 16**. Unadjusted and adjusted meta-regression models for the association of achieved LDL-C levels and mortality and other cardiovascular outcomes expressed in rate ratios

*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.



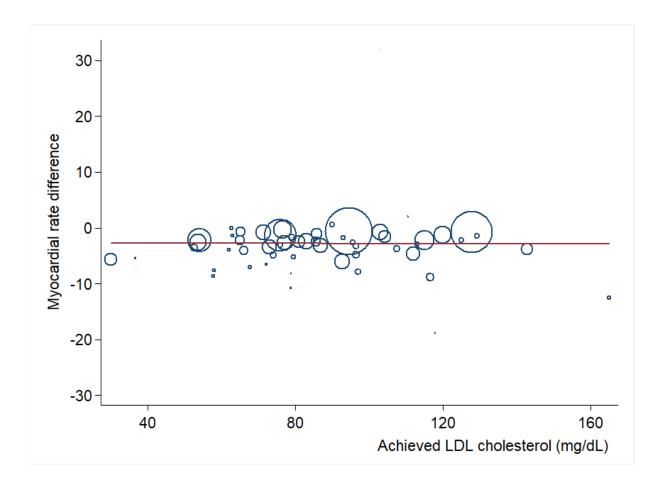
**eFigure 18**. Meta-analysis of cardiovascular mortality risk stratified by achieved low-density lipoprotein cholesterol (LDL-C) levels in the more intensive LDL-C lowering arms. Absolute rate difference (ARD) and 95% confidence intervals of more intensive vs less intensive LDL-C lowering therapies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



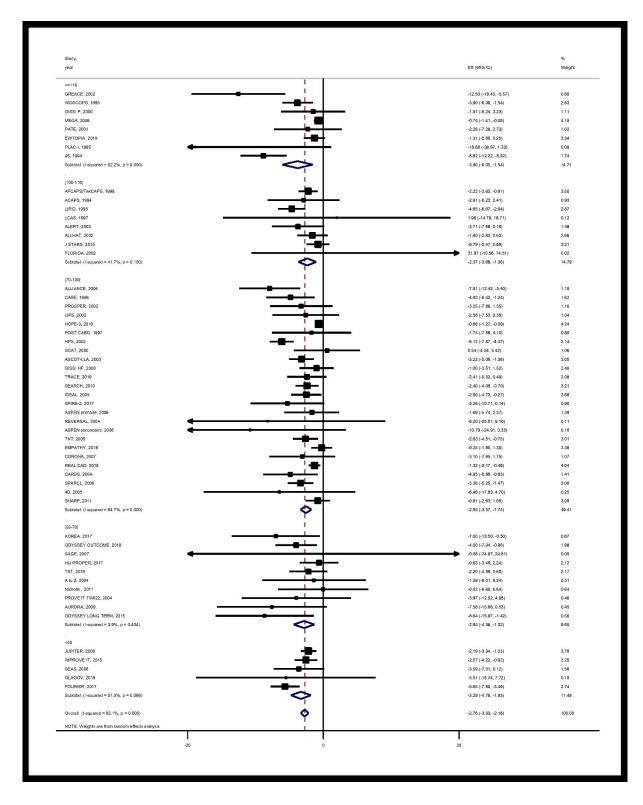
**eFigure 19.** Meta-regression analysis of absolute rate difference (ARD) in myocardial infarction risk by achieved low-density lipoprotein cholesterol (LDL-C) level reduction.

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 metaregression slope of the change in ARD for treatment across increasing levels of achieved LDL-C.

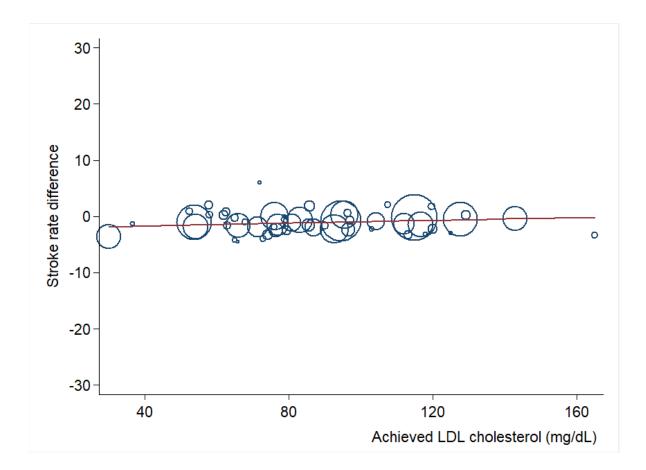


**eFigure 20**. Meta-analysis of myocardial infarction risk stratified by achieved LDL-C levels in the more intensive low-density lipoprotein cholesterol (LDL-C)–lowering arms. Absolute rate difference (ARD) and 95% confidence intervals of more intensive vs less intensive LDL-C lowering therapies and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

Shudy. Shudy	ES (95% CI)	% Weight
>=116		
GREACE, 2002	-3.33 (-7.50, 0.83)	0.62
WOSCOPS, 1995	-0.32 (-1.51, 0.88)	3.66
GISSI P. 2000	0.24 (-2.78, 3.25)	1.09
MEGA, 2006	-0.53 (-1.37, 0.31)	4.69
PATE, 2001	-2.99 (-10.70, 4.71)	0.19
EWTOPIA. 2019	-2.26 (-5.39, 0.88)	1.02
PREVEND IT, 2004	1.81 (-2.15, 5.77)	0.68
PLAC-I, 1995	-3.12 (-9.48, 3.25)	0.28
45, 1994	-1.41 (-2.56, -0.27)	3.80
Subtotal (I-squared = 0.0%, p = 0.504)	-0.76 (-1.31, -0.20)	16.03
[100-116]		
AFCAPS/TexCAPS, 1998	-0.18 (-0.81, 0.46)	5.33
ACAPS, 1994	-3.27 (-6.61, 0.07)	0.92
LIPID, 1998	-1.29 (-2.67, 0.09)	3.20
ALERT, 2003	2.08 (-2.20, 6.36)	0.59
ALLHAT, 2002	-0.86 (-2.51, 0.79)	2.61
J STARS, 2015	-2.22 (-7.68, 3.24)	0.38
Subtotal (I-squared = 27.0%, p = 0.232)	-0.70 (-1.54, 0.13)	13.02
[70-100]		
ALLIANCE. 2004	-0.72 (-3.93, 2.50)	0.98
CARE, 1996	-0.72 (-5.95, 2.30) -2.32 (-4.48, -0.15)	1.83
PROSPER, 2002	0.54 (-2.90, 3.98)	0.87
LIPS, 2002	0.39 (-2.50, 5.56)	4.10
HOPE-3, 2016	-0.82 (-1.54, -0.11)	5.08
HPS, 2002	-2.32 (-3.33, -1.31)	4.18
SCAT, 2000	-1.63 (-5.16, 1.90)	0.83
ASCOT-LLA, 2003	-1.92 (-3.59, -0.25)	2.58
GISSI HF, 2008	1.81 (-0.87, 4.48)	1.33
TRACE, 2019	-1.61 (-3.83, 0.61)	1.76
SEARCH, 2010	-0.59 (-1.71, 0.53)	3.86
IDEAL, 2005	-1.06 (-2.72, 0.60)	2.60
SPIRE-2, 2017	-2.45 (-5.43, 0.52)	1.11
ASPEN primaire, 2006	-0.63 (-4.48, 3.23)	0.71
REVERSAL, 2004	-0.04 (-7.41, 7.32)	0.21
ASPEN secondaire, 2006	-1.95 (-9.71, 5.81)	0.19
TNT, 2005	-1.54 (-2.86, -0.22)	3.34
EMPATHY, 2018	-2.42 (-4.41, -0.43)	2.06
CORONA, 2007	-1.88 (-6.16, 2.40)	0.59
REAL CAD, 2018	0.05 (-1.00, 1.10)	4.07
CARDS, 2004	-3.32 (-6.07, -0.57)	1.27
SPARCL, 2006	-3.96 (-8.02, 0.10)	0.65
4D, 2005	6.01 (-0.99, 13.01)	0.23
SHARP. 2011	-1.93 (-3.35, -0.51)	3.09
Subtotal (i-squared = 41.5%, p = 0.018)	-1.16 (-1.67, -0.65)	47.54
(55-70[ KOREA, 2017	-1.00 (-5.38, 3.38)	0.57
ODYSSEY OUTCOME, 2018	-1.00 (-5.36, 3.36) -1.55 (-2.75, -0.35)	3.64
SAGE, 2007	-1.35 (-2.75, -0.35) -4.50 (-13.30, 4.30)	0.15
HJ PROPER, 2017	-0.34 (-3.80, 3.12)	0.86
TST, 2019	-4.20 (-9.69, 1.30)	0.37
A to Z, 2004	-1.66 (-5.12, 1.80)	0.86
Nicholls , 2011	0.72 (-2.46, 3.89)	1.00
PROVE IT TIMI22, 2004	0.16 (-2.86, 3.17)	1.09
AURORA, 2009	0.34 (-3.60, 4.28)	0.69
ODYSSEY LONG TERM, 2015	2.04 (-1.19, 5.27)	0.97
Subtotal (I-squared = 0.0%, p = 0.489)	-0.89 (-1.76, -0.02)	10.20
<55 I		
JUPITER, 2008	-1.83 (-2.97, -0.69)	3.80
IMPROVE IT, 2015	-1.12 (-1.95, -0.28)	4.73
SEAS, 2008	0.87 (-2.96, 4.70)	0.72
GLAGOV. 2016	-1.38 (-7.41, 4.66)	0.31
FOURIER, 2017	-3.60 (-4.79, -2.40)	3.65
Subtotal (I-squared = 69.5%, p = 0.011)	-1.84 (-3.14, -0.54)	13.21
1		
Overall (I-squared = 39.5%, p = 0.002)	-1.10 (-1.45, -0.78)	100.00
NOTE: Weights are from random effects analysis		
-20	0 20	

# 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 (‰)	Ν	NT (95% CI)	AI	RD (95%CI)	l² (%)	P for trend*
All-cause mortality	935 NA	(559 to 2,833)	-1.07 -0.85	(-1.79 to -0.35)	20 17	
5-9.999 10-14.999 ≥15	NA NA 262	(186 to 443)	-0.86	(-1.88 to 0.17) (-1.91 to 0.19) (-5.39 to -2.26)	0 20	
Overall	708	(503 to 1,193)	-1.41	(-1.99 to -0.84)	32	
Unadjusted analysis Adjusted analysis			-0.83 -0.74	(-1.60 to -0.07) (-1.57 to 0.09)		.03 .08
Cardiovascular mortality	2,105	(462 to 5,814)	-0.48	(-0.78 to -0.17)	0	
5-9.999 10-14.999 ≥15 Overall	1,221 NA 305 1,028	(713 to 4,255) (238 to 424) (756 to 1,605)	-0.82 -0.69 -3.28 -0.97	(-1.40 to -0.24) (-1.49 to 0.12) (-4.21 to -2.36) (-1.32 to -0.62)	0 0 26	
Unadjusted analysis Adjusted analysis			-0.88 -0.87	(-1.33 to -0.43) (-1.37 to -0.38)		<.0001 .001
Myocardial infarction	632	(462 to 999)	-1.58	(-2.16 to -1.00)	44	
5-9.999 10-14.999	343 322	(262 to 499) (239 to 490)	-2.91 -3.11	(-3.82 to -2.00) (-4.18 to -2.04)	27 17	
≥15 Overall	233 352	(160 to 424) (292 to 444)	-4.29 -2.84	(-6.23 to -2.36) (-3.43 to -2.25)	68 63	
Unadjusted analysis Adjusted analysis			-0.29 -0.31	(-0.80 to 0.21) (-0.84 to 0.22)		.25 .24
Stroke <5	1,449	(910 to 3,559)	-0.69	(-1.01 to -0.28)	18	
5-9.999 10-14.999 ≥15 Overall	665 1,006 799 928	(409 to 1,773) (622 to 2,632) (500 to 2,004) (700 to 1,374)	-1.50 -0.99 -1.25 -1.08	(-2.44 to -0.56) (-1.61 to -0.38) (-2.00 to -0.50) (-1.43 to -0.73)	60 0 28 40	
Unadjusted analysis Adjusted analysis			0.17 0.23	(-0.19 to 0.52) (-0.16 to 0.61)		.35 .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

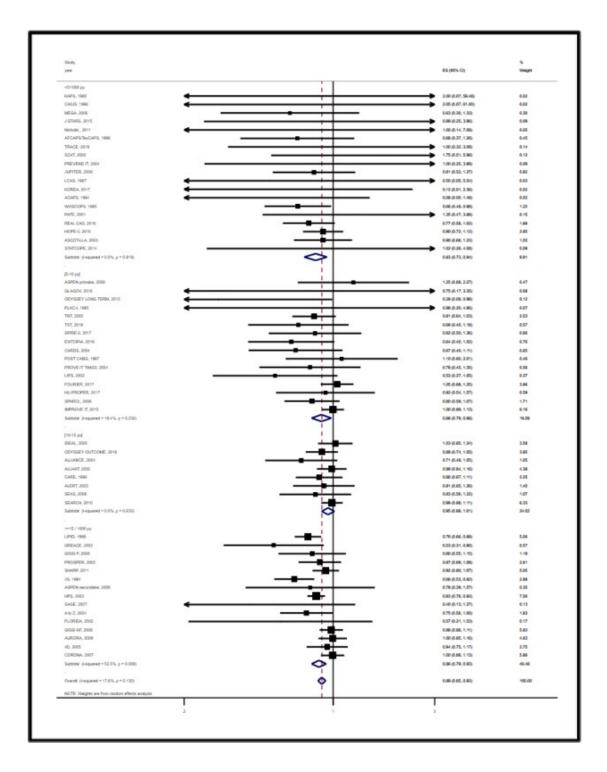
Annual CV mortality rate (‰)	Rate ratio (95% CI)		l² (%)	P for trend*
All-cause mortality				
<5	0.86	(0.80 to 0.94)	4	
5-9.999	0.95	· /	23	
10-14.999	0.97	· /	0	
≥15	0.89	(0.84 to 0.96)	62	
Overall	0.92	(0.89 to 0.95)	36	
Unadjusted analysis	1.01	(0.99 to 1.03)		.33
Adjusted analysis	1.01	(0.99 to 1.02)		.49
Cardiovascular mortality				
<5	0.83	(0.73 to 0.94)	0	
5-9.999	0.88	· ,	19	
10-14.999	0.95	( )	0	
≥15	0.86	( )	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	· · · ·	28	
10-14.999	0.82	````	38	
≥15	0.80	· · · ·	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 1.00)		.013

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

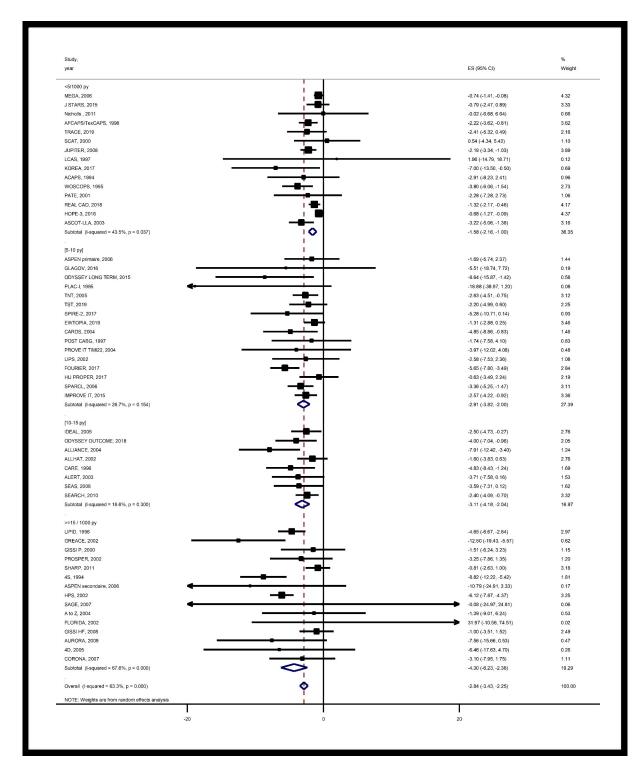
**eFigure 23**. Meta-analysis of all-cause mortality risk stratified by annual CV mortality rates in the less intensive LDL-C lowering arms. Absolute rate difference (ARD) and 95% confidence intervals of more intensive vs less intensive LDL-C lowering therapies and the weight of study data in the meta-analysis.

Study,			96
year		ES (95% CI)	Weight
<5/1000 py			
KAPS, 1995	<u>_</u>	1.47 (-6.26, 9.20)	0.52
MEGA, 2006		-1.07 (-2.17, 0.02)	5.87
J STARS, 2015		1.97 (-2.51, 6.44)	1.35
AFCAPS/TexCAPS, 1998	; <b>-</b> ∎	0.17 (-1.26, 1.60)	5.10
TRACE, 2019		-0.56 (-4.33, 3.21)	1.78
SCAT, 2000	i <del></del>	3.80 (-0.84, 8.45)	1.27
PREVEND IT, 2004		1.20 (-2.57, 4.98)	1.77
JUPITER, 2008		-2.90 (-5.34, -0.45)	3.18
LCAS, 1997 KOREA, 2017		-3.69 (-14.03, 6.64) -3.00 (-10.07, 4.07)	0.30
ACAPS, 1994		-5.09 (-9.35, -0.82)	1.46
WOSCOPS, 1995		-1.82 (-3.70, 0.07)	4.14
PATE, 2001		-4.51 (-13.32, 4.30)	0.40
REAL CAD, 2018		-2.17 (-3.92, -0.42)	4.41
HOPE-3, 2016		-0.67 (-2.12, 0.78)	5.06
ASCOT-LLA, 2003		-1.66 (-3.96, 0.64)	3.40
STATCOPE, 2014		-1.76 (-20.29, 16.77)	0.10
Subtotal (I-squared = 20.3%, p = 0.217)	$\diamond$	-1.07 (-1.79, -0.35)	40.72
	1		
[5-10 py] ASREN primarica, 2008	<u> </u>	0.04/14/14 5 201	1.23
ASPEN primaire, 2008 GLAGOV, 2016		0.64 (-4.11, 5.38) -1.38 (-8.52, 5.77)	0.60
ODYSSEY LONG TERM, 2015		-4.71 (-10.11, 0.69)	0.99
PLAC-I, 1995		-12.54 (-27.58, 2.51)	0.14
TNT, 2005	÷.	0.11 (-1.80, 2.01)	4.10
TST, 2019	—— <del>•</del>	-1.00 (-6.27, 4.27)	1.03
SPIRE-2, 2017	— <del></del>	-0.95 (-4.87, 2.98)	1.67
EWTOPIA, 2019		1.83 (-3.50, 7.15)	1.01
CARDS, 2004		-3.96 (-8.20, 0.28)	1.48
POST CABG, 1997		-1.05 (-6.57, 4.47)	0.95
PROVE IT TIMI22, 2004 LIPS, 2002		-5.04 (-10.03, -0.05) -4.15 (-9.68, 1.39)	1.13
FOURIER, 2017		-4.15 (-9.66, 1.39) 0.59 (-1.32, 2.50)	0.94
HIJ PROPER, 2017		-5.49 (-11.39, 0.42)	0.84
SPARCL, 2006		0.44 (-3.06, 3.93)	1.99
IMPROVE IT, 2015	÷.	-0.27 (-2.05, 1.51)	4.35
Subtotal (I-squared = 16.6%, p = 0.263)	0	-0.85 (-1.88, 0.17)	26.54
	1		
[10-15 py] IDEAL, 2005		-0.34 (-2.84, 2.16)	3.10
ODYSSEY OUTCOME, 2018		-0.34 (-2.64, 2.16) -2.19 (-4.18, -0.20)	3.93
ALLIANCE, 2004		-0.99 (-6.87, 4.89)	0.85
ALLHAT, 2002		-0.33 (-3.14, 2.48)	2.68
CARE, 1996		-1.56 (-5.22, 2.09)	1.86
ALERT, 2003		0.98 (-5.15, 7.11)	0.79
SEAS, 2008		0.83 (-6.13, 7.80)	0.62
SEARCH, 2010		-0.14 (-2.27, 1.99)	3.68
Subtotal (I-squared = 0.0%, p = 0.869)	<b>A</b>	-0.86 (-1.91, 0.19)	17.51
=15 / 1000 py			
-=1571000 py _IPID, 1998	<b></b> i	-4.96 (-7.35, -2.56)	3.25
SREACE, 2002		-7.08 (-13.57, -0.60)	0.71
GISSI P, 2000	e+	-3.99 (-10.10, 2.12)	0.79
PROSPER, 2002		-0.61 (-5.80, 4.57)	1.06
SHARP, 2011	<b></b>	0.87 (-3.23, 4.97)	1.56
4S, 1994	<b>_</b> !	-6.15 (-9.57, -2.73)	2.05
ASPEN secondaire, 2006		-0.89 (-15.01, 13.24)	0.16
HPS, 2002		-3.49 (-5.52, -1.46)	3.86
SAGE, 2007		-27.00 (-48.56, -5.43)	0.07
A to Z, 2004		-6.16 (-12.84, 0.51)	0.68
FLORIDA, 2002		-13.58 (-44.27, 17.10)	0.04
GISSI HF, 2008 AURORA, 2009		1.59 (-6.34, 9.51) -5.00 (-18.39, 8.39)	0.49
4D, 2005		-5.83 (-25.23, 13.56)	0.18
CORONA, 2007		-5.33 (-16.50, 5.85)	0.05
Subtotal (I-squared = 20.4%, p = 0.226)		-3.82 (-5.39, -2.26)	15.24
Overall (I-squared = 31.9%, p = 0.013)	•	-1.41 (-1.99, -0.84)	100.00
NOTE: Weights are from random effects 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.

Study, year		ES (95% CI)	% Weigh
<5/1000 py	1		
MEGA, 2006	<b>H</b>	-0.53 (-1.37, 0.31)	4.78
J STARS, 2015	<del>_</del>	-2.22 (-7.68, 3.24)	0.39
Nicholls , 2011		0.72 (-2.46, 3.89)	1.03
AFCAPS/TexCAPS, 1998	i 🖶	-0.18 (-0.81, 0.46)	5.43
TRACE, 2019		-1.61 (-3.83, 0.61)	1.81
SCAT, 2000		-1.63 (-5.16, 1.90)	0.86
PREVEND IT, 2004		1.81 (-2.15, 5.77)	0.70
JUPITER, 2008	-=+	-1.83 (-2.97, -0.69)	3.88
KOREA, 2017	<del>_</del>	-1.00 (-5.38, 3.38)	0.58
ACAPS, 1994		-3.27 (-6.61, 0.07)	0.94
WOSCOPS, 1995		-0.32 (-1.51, 0.88)	3.74
PATE, 2001		-2.99 (-10.70, 4.71)	0.20
REAL CAD, 2018	2 <b>7</b>	0.05 (-1.00, 1.10)	4.16
HOPE-3, 2016	_	-0.82 (-1.54, -0.11)	5.18
ASCOT-LLA, 2003		-1.92 (-3.59, -0.25)	2.64
Subtotal (I-squared = 17.9%, p = 0.253)	P	-0.69 (-1.10, -0.28)	36.32
[5-10 py[			
ASPEN primaire, 2006	<del>_</del>	-0.63 (-4.48, 3.23)	0.73
GLAGOV, 2016		-1.38 (-7.41, 4.66)	0.32
ODYSSEY LONG TERM, 2015	<b>;</b> ∔_∎	2.04 (-1.19, 5.27)	1.00
PLAC-I, 1995		-3.12 (-9.48, 3.25)	0.29
TNT, 2005		-1.54 (-2.86, -0.22)	3.41
TST, 2019		-4.20 (-9.69, 1.30)	0.38
SPIRE-2, 2017		-2.45 (-5.43, 0.52)	1.14
EWTOPIA, 2019	— <del>• !  </del>	-2.26 (-5.39, 0.88)	1.05
CARDS, 2004	— <del>• ;</del>	-3.32 (-6.07, -0.57)	1.30
PROVE IT TIMI22, 2004	- <u>+</u>	0.16 (-2.86, 3.17)	1.12
LIPS, 2002		0.30 (-0.74, 1.34)	4.19
FOURIER, 2017		-3.60 (-4.79, -2.40)	3.73
HIJ PROPER, 2017		-0.34 (-3.80, 3.12)	0.89
SPARCL, 2006 IMPROVE IT, 2015		-3.96 (-8.02, 0.10) -1.12 (-1.95, -0.28)	0.67
IMPROVE IT, 2015 Subtotal (I-squared = 60.0%, p = 0.001)	치	-1.12 (-1.95, -0.28) -1.50 (-2.44, -0.56)	4.82
	Y	-1.30 (-2.44, -0.36)	20.05
[10-15 py]			
IDEAL, 2005		-1.06 (-2.72, 0.60)	2.67
ODYSSEY OUTCOME, 2018	-	-1.55 (-2.75, -0.35)	3.72
ALLIANCE, 2004	P	-0.72 (-3.93, 2.50)	1.01
ALLHAT, 2002		-0.86 (-2.51, 0.79)	2.67
CARE, 1996		-2.32 (-4.48, -0.15)	1.87
ALERT, 2003	-+ <del>  -=</del>	2.08 (-2.20, 6.36)	0.61
SEAS, 2008		0.87 (-2.96, 4.70)	0.74
SEARCH, 2010		-0.59 (-1.71, 0.53)	3.94
Subtotal (I-squared = 0.0%, p = 0.576)	<b>o</b>	-0.99 (-1.61, -0.38)	17.24
>=15 / 1000 m/			
>=15 / 1000 py LIPID, 1998		4.00 / 0.07 0.000	0.07
LIPID, 1998 GREACE, 2002		-1.29 (-2.67, 0.09) -3.33 (-7.50, 0.83)	3.27 0.64
GREACE, 2002 GISSI P, 2000		-3.33 (-7.50, 0.83) 0.24 (-2.78, 3.25)	0.64
GISSI P, 2000 PROSPER, 2002		0.24 (-2.78, 3.25) 0.54 (-2.90, 3.98)	0.89
SHARP, 2011	1	-1.93 (-3.35, -0.51)	3.17
4S, 1994		-1.93 (-3.35, -0.31) -1.41 (-2.56, -0.27)	3.88
ASPEN secondaire, 2006		-1.95 (-9.71, 5.81)	0.20
HPS, 2002		-2.32 (-3.33, -1.31)	4.27
SAGE, 2007		-4.50 (-13.30, 4.30)	0.15
A to Z, 2004	<del></del>	-1.66 (-5.12, 1.80)	0.89
GISSI HF, 2008	<b>↓_</b> ■	1.81 (-0.87, 4.48)	1.36
AURORA, 2009		0.34 (-3.60, 4.28)	0.71
4D, 2005	·	6.01 (-0.99, 13.01)	0.24
CORONA, 2007	<b>e</b> +	-1.88 (-6.16, 2.40)	0.61
Subtotal (I-squared = 27.8%, p = 0.158)	•	-1.25 (-2.00, -0.50)	21.39
	Ĩ		
Overall (I-squared = 40.4%, p = 0.002)	<b></b>	-1.08 (-1.43, -0.73)	100.00
NOTE: Weights are from random effects analysis			
		1	

#### 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; l² 16%; Tau² 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) <u>Comparisons with the Navarese' study (Primary and secondary prevention of CVD)</u> <u>published in JAMA 2018²²</u> we did not include :

- the OSLER-1&-2 trials²³ (which compared evolocumab and placebo in 4465 patients due to the short median follow-up (11.1 months)

In Navarese et al's study²², 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 allcause 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) <u>Comparisons with the Chou' study (Primary prevention of CVD)²⁴ published in JAMA 2016</u>, we did not include:

- the 2005 HYRIM trial²⁵ 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 trial²⁶ 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) <u>Comparisons with 2013 Cochrane study (Statins for the primary prevention of</u> <u>cardiovascular disease²⁷</u>; we did not include:

the 1996 CELL trial²⁸: among the 681 subjects randomized "intensive advice" versus
 "usual advice" one-third received pravastatin

- the 2007 METEOR trial²⁶ 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 trial²⁵ 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 trial²⁹ investigating the possibility that statins reduce blood pressure did not report neither death nor clinical events in 253 hypertensive patients.

the 2003 Derosa's trial³⁰ randomized 99 subjects placebo, fluvastatin, orlistat or both
 D) <u>Comparisons with the Wang's meta analysis³¹</u>; we did not include :

- The neutral 2015 ALPS-AMI trial³² 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 trial³³ 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 trial³⁴ that evaluated bococizumab versus placebo during a short follow up period (0.6 year)

- the 2005 HYRIM trial²⁵ 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 trials²³ which compared evolocumab and placebo in 4465 patients due to the short median follow-up (11.1 months)

- the neutral 2013 PEARL study³⁵ (which compared pivastatin versus usual care in 574 Japanese patients with Heart Failure due to coronary artery disease in 27%

- the 2001 BCAPS study³⁶ 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) <u>Comparisons with the Nacis's meta analysis³⁷</u>:

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 trial³⁸ 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 trial³⁹ 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 trial⁴⁰ 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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