Supplementary Online Content

Lee M, Cheng CY, Wu YL, Lee JD, Hsu CY, Ovbiagele B. Association between intensity of low-density lipoprotein cholesterol reduction with statin-based therapies and secondary stroke prevention: a meta-analysis of randomized clinical trials. *JAMA Neurol.* Published online February 21, 2022. doi:10.1001/jamaneurol.2021.5578

This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. Study Selection

Legends: Flow of study selection

Title and abstracts review, n= 3328
(Pubmed, n=817; EMBASE, n=722; CENTRAL,
n=1773; Clinicaltrials.gov, n=16)

3291 were excluded because articles with
patients with case-controlled, cross
sectional, observation cohort, review,
duplication

37 articles retrieved for detailed
assessment

26 were excluded due to
    14 no patients with a history of stroke
     6 subgroup of patients had stroke but
       their outcomes not been reported
     3 no recurrent stroke been reported
     3 treatment duration less than 6 months

11 studies were included[1-11]

eFigure 2. Risk of Bias

Legends: Risk of bias for included trials

eFigure 3: MACE

Legends: Relative risk with 95% confidence interval of MACE in more intensive vs less intensive LDL-C lowering with statin-based therapies in patients with stroke

MACE: Major adverse cardiovascular events
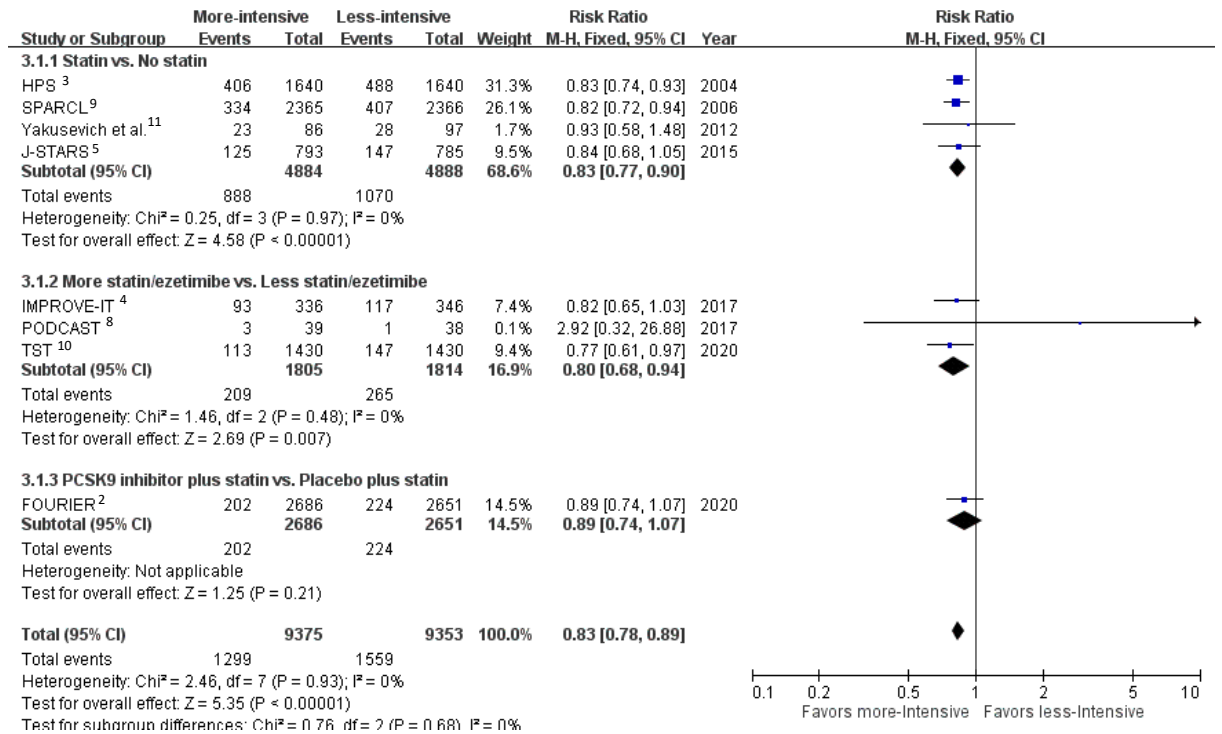
eFigure 4. Recurrent Ischemic Stroke

Legends: Relative risk with 95% confidence interval of recurrent ischemic stroke in more intensive vs less intensive

LDL-C lowering with statin-based therapies in patients with stroke

Study or Subgroup	More-intensive Events	Total	Less-intensive Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year	Risk Ratio M-H, Fixed, 95% CI
4.1.1 Statin vs. No statin								
HPS[3]	100	1640	122	1640	17.0%	0.82 [0.63, 1.06]	2004	
SPARCL[9]	218	2365	274	2366	38.2%	0.80 [0.67, 0.94]	2006	
Yakusevich et al.[11]	12	86	14	97	1.8%	0.97 [0.47, 1.97]	2012	
J-STARS[5]	64	793	67	785	9.4%	0.95 [0.68, 1.31]	2015	
Subtotal (95% CI)		4884		4888	66.5%	0.83 [0.73, 0.94]		
Total events	394		477					
Heterogeneity: Chi² = 1.03, df = 3 (P = 0.79); I² = 0%								
Test for overall effect: Z = 2.91 (P = 0.004)								
4.1.2 More statin/ezetimibe vs. Less statin/ezebimibe								
IMPROVE-IT[4]	23	336	44	346	6.1%	0.54 [0.33, 0.87]	2017	
PODCAST[8]	1	39	1	38	0.1%	0.97 [0.06, 15.02]	2017	
TST[10]	88	1430	109	1430	15.2%	0.81 [0.62, 1.06]	2020	
Subtotal (95% CI)		1805		1814	21.4%	0.73 [0.58, 0.93]		
Total events	112		154					
Heterogeneity: Chi² = 2.11, df = 2 (P = 0.35); I² = 5%								
Test for overall effect: Z = 2.60 (P = 0.009)								
4.1.3 PCSK9 inhibitor plus statin vs. Placebo plus statin								
FOURIER[2]	80	2686	86	2651	12.1%	0.92 [0.68, 1.24]	2020	
Subtotal (95% CI)		2686		2651	12.1%	0.92 [0.68, 1.24]		
Total events	80		86					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.56 (P = 0.58)								
Total (95% CI)		9375		9353	100.0%	0.82 [0.74, 0.91]		
Total events	586		717					
Heterogeneity: Chi² = 4.56, df = 7 (P = 0.71); I² = 0%								
Test for overall effect: Z = 3.75 (P = 0.0002)								
Test for subgroup differences: Chi² = 1.46, df = 2 (P = 0.48), I² = 0%								

Scale: 0.1 0.2 0.5 1 2 5 10
Favors more-Intensive   Favors less-Intensive

eFigure 5. Myocardial Infarction

Legends: Relative risk with 95% confidence interval of myocardial infarction in more intensive vs less intensive LDL-

C lowering with statin-based therapies in patients with stroke

Study or Subgroup	More-intensive Events	Total	Less-intensive Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
5.1.1 Statin vs No statin							
SPARCL [9]	81	2365	120	2366	36.5%	0.68 [0.51, 0.89]	2006
Yakusevich et al. [11]	7	86	11	97	3.1%	0.72 [0.29, 1.77]	2012
J-STARS [5]	4	793	7	785	2.1%	0.57 [0.17, 1.92]	2015
Subtotal (95% CI)		3244		3248	41.8%	**0.67 [0.52, 0.87]**	
Total events	92		138				
Heterogeneity: Chi² = 0.10, df = 2 (P = 0.95); I² = 0%							
Test for overall effect: Z = 3.01 (P = 0.003)							
5.1.2 More statin/ezetimibe vs Less statin/ezetimibe							
PODCAST [8]	1	39	0	38	0.2%	2.92 [0.12, 69.64]	2017
IMPROVE-IT [4]	51	336	60	346	18.0%	0.88 [0.62, 1.23]	2017
TST [10]	20	1430	31	1430	9.4%	0.65 [0.37, 1.13]	2020
Subtotal (95% CI)		1805		1814	27.6%	**0.81 [0.60, 1.08]**	
Total events	72		91				
Heterogeneity: Chi² = 1.47, df = 2 (P = 0.48); I² = 0%							
Test for overall effect: Z = 1.44 (P = 0.15)							
5.1.3 PCSK9 inhibitor plus statin vs Placebo plus statin							
FOURIER [2]	75	2686	100	2651	30.6%	0.74 [0.55, 0.99]	2020
Subtotal (95% CI)		2686		2651	30.6%	**0.74 [0.55, 0.99]**	
Total events	75		100				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.00 (P = 0.05)							
Total (95% CI)		7735		7713	100.0%	**0.73 [0.62, 0.86]**	
Total events	239		329				
Heterogeneity: Chi² = 2.49, df = 6 (P = 0.87); I² = 0%							
Test for overall effect: Z = 3.81 (P = 0.0001)							
Test for subgroup differences: Chi² = 0.86, df = 2 (P = 0.65), I² = 0%							

Favors more-Intensive   Favors less-Intensive

eFigure 6. All-Cause Mortality

Legends: Relative risk with 95% confidence interval of all-cause mortality in more intensive vs less intensive LDL-C

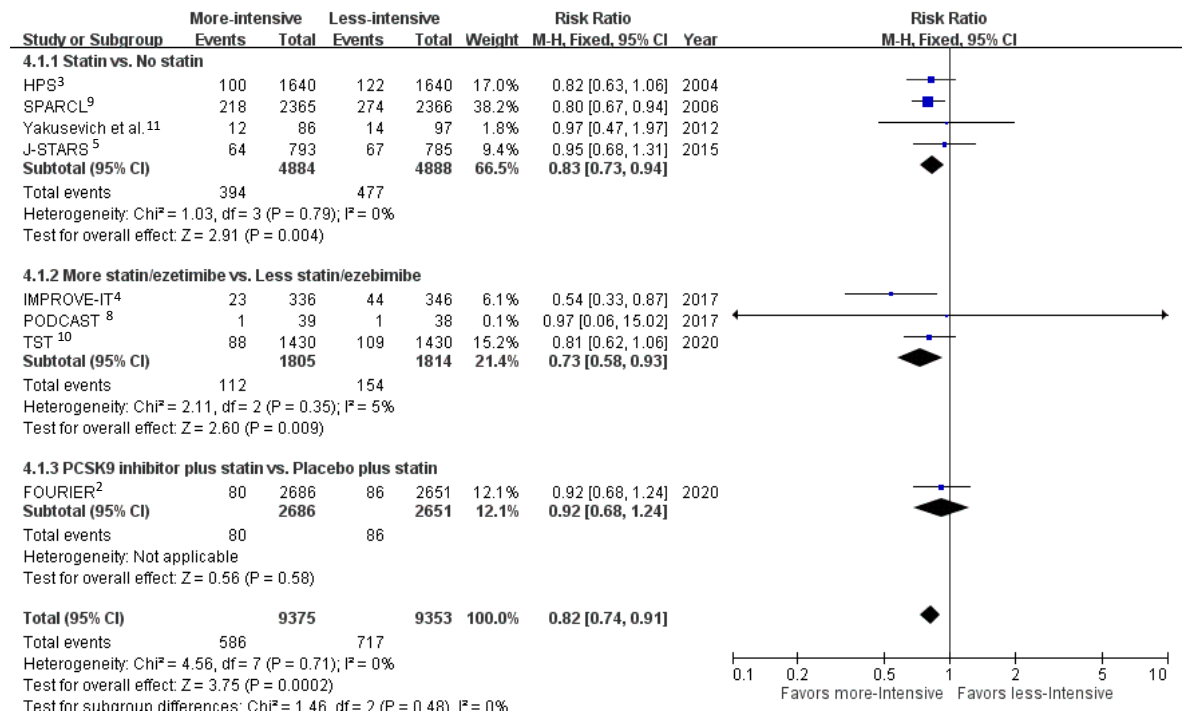lowering with statin-based therapies in patients with stroke

Study or Subgroup	More-intensive Events	Total	Less-intensive Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
6.1.1 Statin vs. no statin							
SPARCL[9]	216	2365	211	2366	48.2%	1.02 [0.85, 1.23]	2006
Yakusevich et al.[11]	13	86	16	97	3.4%	0.92 [0.47, 1.79]	2012
J-STARS[5]	43	793	35	785	8.0%	1.22 [0.79, 1.88]	2015
Subtotal (95% CI)		3244		3248	59.6%	1.04 [0.89, 1.23]	
Total events	272		262				
Heterogeneity: Chi² = 0.66, df = 2 (P = 0.72); I² = 0%							
Test for overall effect: Z = 0.52 (P = 0.60)							
6.1.2 More statin/ezetimibe vs Less statin/ezetimibe							
IMPROVE-IT[4]	83	336	85	346	19.1%	1.01 [0.77, 1.31]	2017
TST[10]	88	1430	93	1430	21.2%	0.95 [0.71, 1.25]	2020
Subtotal (95% CI)		1766		1776	40.4%	0.97 [0.80, 1.18]	
Total events	171		178				
Heterogeneity: Chi² = 0.10, df = 1 (P = 0.76); I² = 0%							
Test for overall effect: Z = 0.26 (P = 0.79)							
Total (95% CI)		5010		5024	100.0%	1.02 [0.90, 1.15]	
Total events	443		440				
Heterogeneity: Chi² = 1.00, df = 4 (P = 0.91); I² = 0%							
Test for overall effect: Z = 0.25 (P = 0.81)							
Test for subgroup differences: Chi² = 0.29, df = 1 (P = 0.59), I² = 0%							

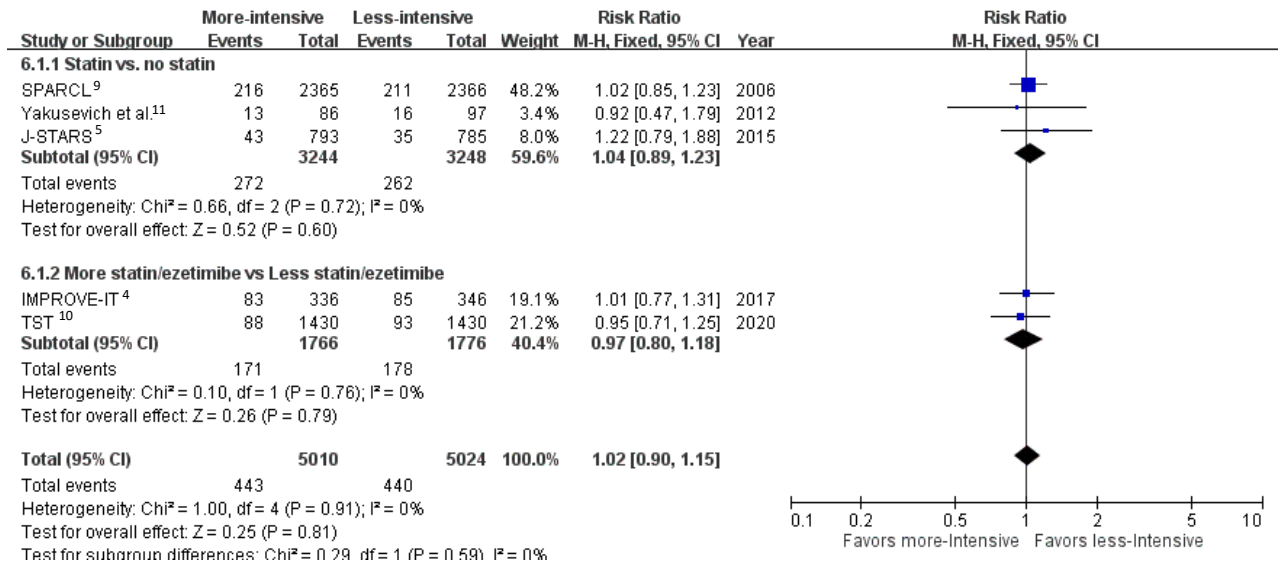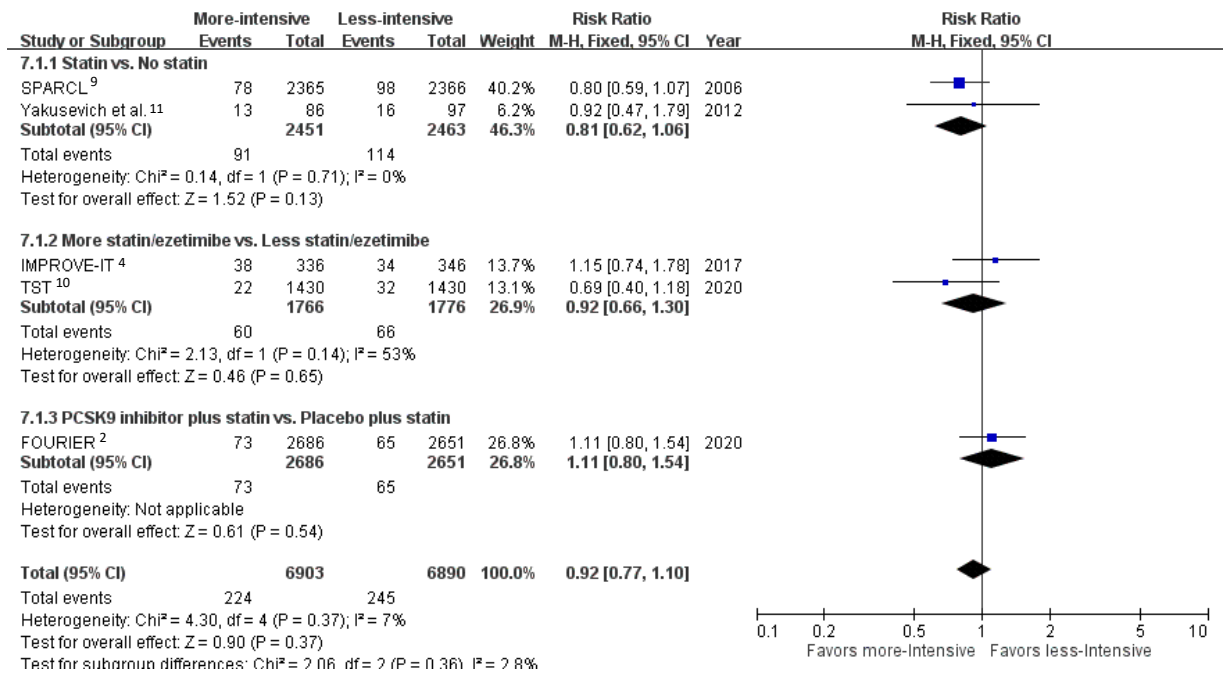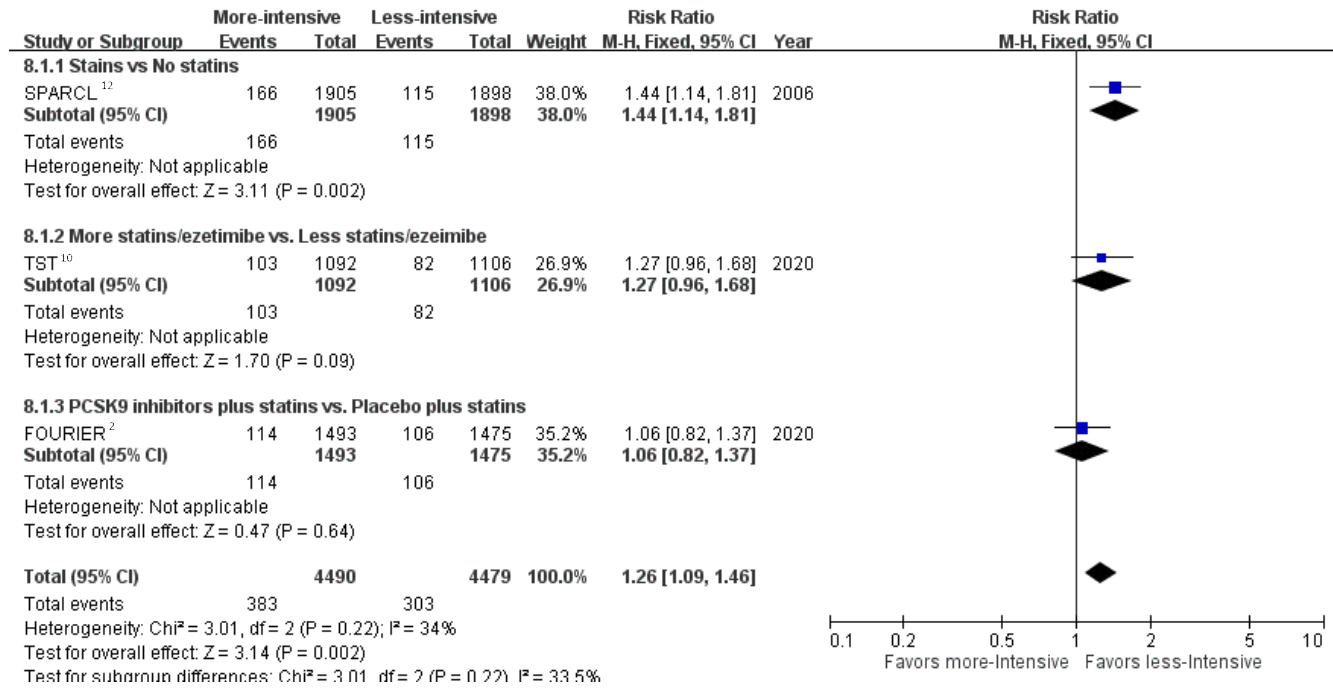## eFigure 7. Cardiovascular Mortality

Legends: Relative risk with 95% confidence interval of cardiovascular mortality in more intensive vs less intensive

LDL-C lowering with statin-based therapies in patients with stroke

Study or Subgroup	More-intensive Events	Total	Less-intensive Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
7.1.1 Statin vs. No statin							
SPARCL [9]	78	2365	98	2366	40.2%	0.80 [0.59, 1.07]	2006
Yakusevich et al. [11]	13	86	16	97	6.2%	0.92 [0.47, 1.79]	2012
Subtotal (95% CI)		2451		2463	46.3%	0.81 [0.62, 1.06]	
Total events	91		114				
Heterogeneity: Chi² = 0.14, df = 1 (P = 0.71); I² = 0%							
Test for overall effect: Z = 1.52 (P = 0.13)							
7.1.2 More statin/ezetimibe vs. Less statin/ezetimibe							
IMPROVE-IT [4]	38	336	34	346	13.7%	1.15 [0.74, 1.78]	2017
TST [10]	22	1430	32	1430	13.1%	0.69 [0.40, 1.18]	2020
Subtotal (95% CI)		1766		1776	26.9%	0.92 [0.66, 1.30]	
Total events	60		66				
Heterogeneity: Chi² = 2.13, df = 1 (P = 0.14); I² = 53%							
Test for overall effect: Z = 0.46 (P = 0.65)							
7.1.3 PCSK9 inhibitor plus statin vs. Placebo plus statin							
FOURIER [2]	73	2686	65	2651	26.8%	1.11 [0.80, 1.54]	2020
Subtotal (95% CI)		2686		2651	26.8%	1.11 [0.80, 1.54]	
Total events	73		65				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.61 (P = 0.54)							
Total (95% CI)		6903		6890	100.0%	0.92 [0.77, 1.10]	
Total events	224		245				
Heterogeneity: Chi² = 4.30, df = 4 (P = 0.37); I² = 7%							
Test for overall effect: Z = 0.90 (P = 0.37)							
Test for subgroup differences: Chi² = 2.06, df = 2 (P = 0.36), I² = 2.8%							

Favors more-Intensive   Favors less-Intensive
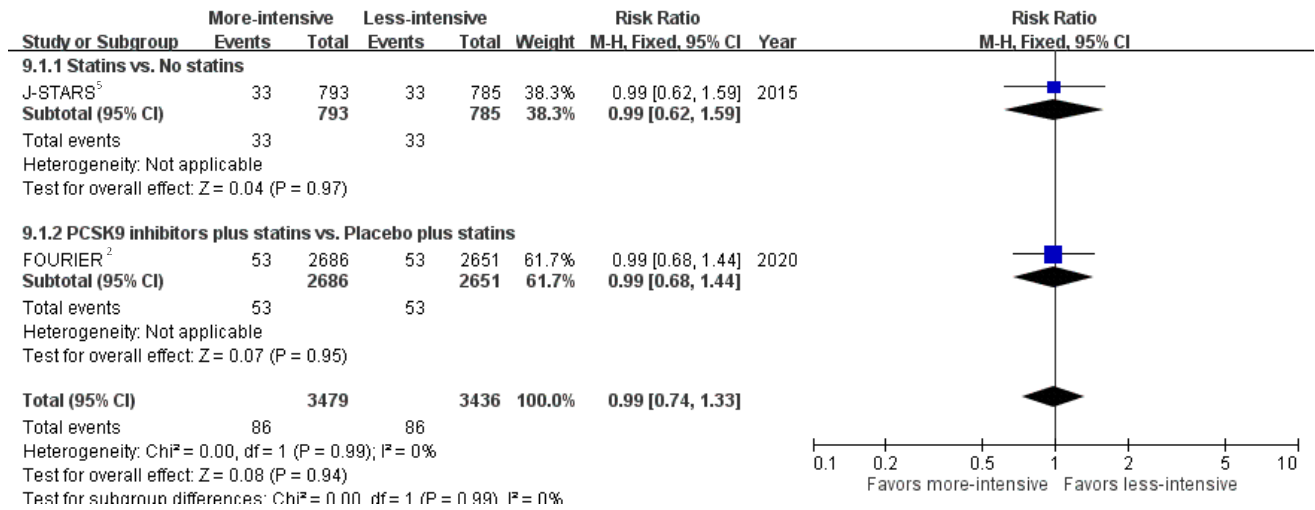
eFigure 8. New-Onset Diabetes

Legends: Relative risk with 95% confidence interval of new-onset diabetes in more intensive vs less intensive LDL-C

lowering with statin-based therapies in patients with stroke

Study or Subgroup	More-intensive Events	Total	Less-intensive Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
8.1.1 Stains vs No statins							
SPARCL [12]	166	1905	115	1898	38.0%	1.44 [1.14, 1.81]	2006
Subtotal (95% CI)		**1905**		**1898**	**38.0%**	**1.44 [1.14, 1.81]**	
Total events	166		115				
Heterogeneity: Not applicable							
Test for overall effect: Z = 3.11 (P = 0.002)							
8.1.2 More statins/ezetimibe vs. Less statins/ezeimibe							
TST [10]	103	1092	82	1106	26.9%	1.27 [0.96, 1.68]	2020
Subtotal (95% CI)		**1092**		**1106**	**26.9%**	**1.27 [0.96, 1.68]**	
Total events	103		82				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.70 (P = 0.09)							
8.1.3 PCSK9 inhibitors plus statins vs. Placebo plus statins							
FOURIER [2]	114	1493	106	1475	35.2%	1.06 [0.82, 1.37]	2020
Subtotal (95% CI)		**1493**		**1475**	**35.2%**	**1.06 [0.82, 1.37]**	
Total events	114		106				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.47 (P = 0.64)							
Total (95% CI)		**4490**		**4479**	**100.0%**	**1.26 [1.09, 1.46]**	
Total events	383		303				
Heterogeneity: Chi² = 3.01, df = 2 (P = 0.22); I² = 34%							
Test for overall effect: Z = 3.14 (P = 0.002)							
Test for subgroup differences: Chi² = 3.01, df = 2 (P = 0.22), I² = 33.5%							

Favors more-Intensive   Favors less-Intensive

eFigure 9. Cognitive Adverse Events

Legends: Relative risk with 95% confidence interval of cognitive adverse events in more intensive vs less intensive
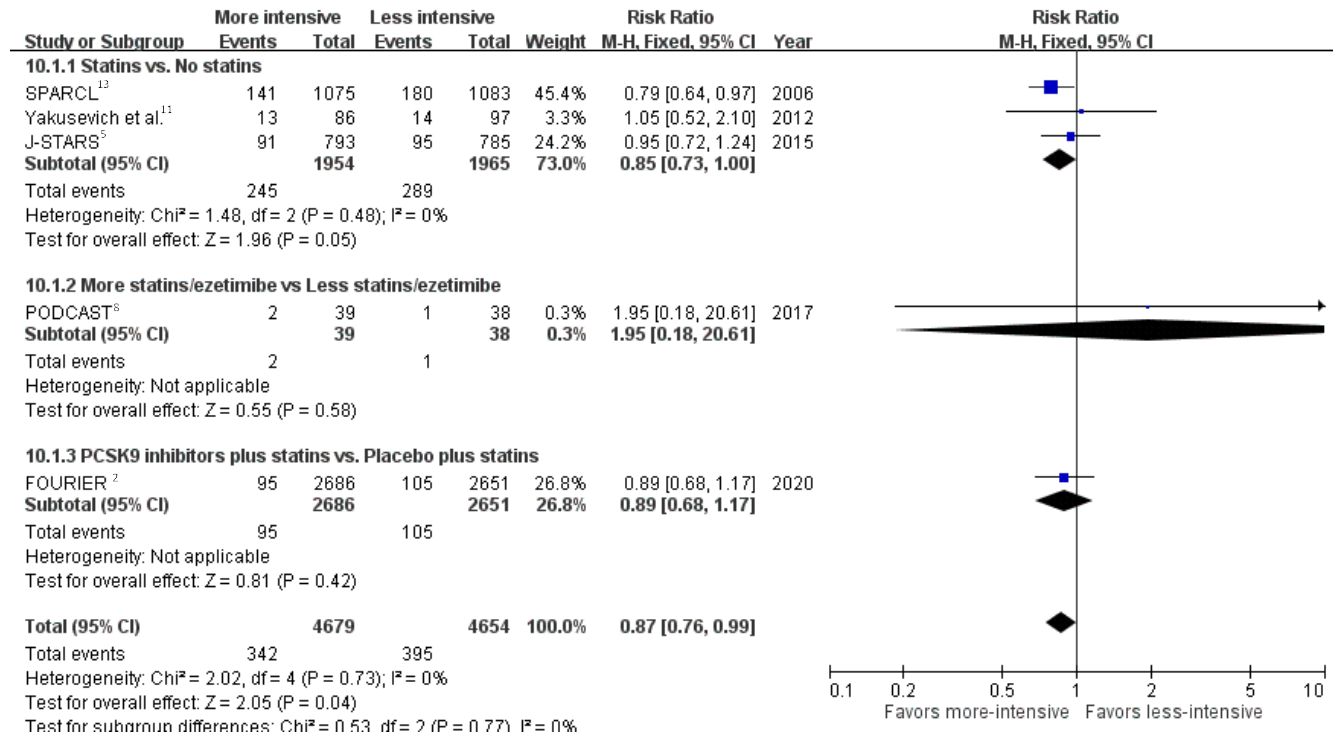
LDL-C lowering with statin-based therapies in patients with stroke

Study or Subgroup	More-intensive Events	Total	Less-intensive Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
9.1.1 Statins vs. No statins							
J-STARS[5]	33	793	33	785	38.3%	0.99 [0.62, 1.59]	2015
Subtotal (95% CI)		793		785	38.3%	**0.99 [0.62, 1.59]**	
Total events	33		33				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.04 (P = 0.97)							
9.1.2 PCSK9 inhibitors plus statins vs. Placebo plus statins							
FOURIER[2]	53	2686	53	2651	61.7%	0.99 [0.68, 1.44]	2020
Subtotal (95% CI)		2686		2651	61.7%	**0.99 [0.68, 1.44]**	
Total events	53		53				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.07 (P = 0.95)							
Total (95% CI)		3479		3436	100.0%	**0.99 [0.74, 1.33]**	
Total events	86		86				
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); I² = 0%							
Test for overall effect: Z = 0.08 (P = 0.94)							
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.99), I² = 0%							

Favors more-intensive   Favors less-intensive

eFigure 10. Recurrent Stroke

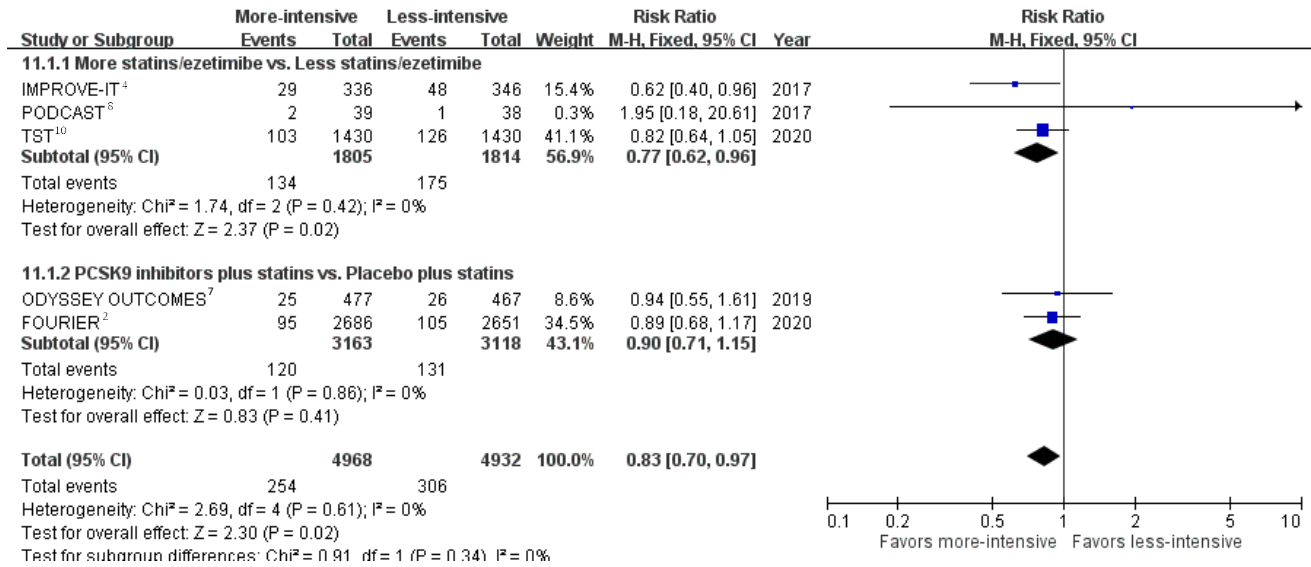Legends: Relative risk with 95% confidence interval of recurrent stroke in more intensive vs less intensive LDL-C

lowering with statin-based therapies in patients with ischemic stroke as an entry event

Study or Subgroup	More intensive Events	Total	Less intensive Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
10.1.1 Statins vs. No statins							
SPARCL[13]	141	1075	180	1083	45.4%	0.79 [0.64, 0.97]	2006
Yakusevich et al.[11]	13	86	14	97	3.3%	1.05 [0.52, 2.10]	2012
J-STARS[5]	91	793	95	785	24.2%	0.95 [0.72, 1.24]	2015
Subtotal (95% CI)		1954		1965	73.0%	0.85 [0.73, 1.00]	
Total events	245		289				
Heterogeneity: Chi² = 1.48, df = 2 (P = 0.48); I² = 0%							
Test for overall effect: Z = 1.96 (P = 0.05)							
10.1.2 More statins/ezetimibe vs Less statins/ezetimibe							
PODCAST[8]	2	39	1	38	0.3%	1.95 [0.18, 20.61]	2017
Subtotal (95% CI)		39		38	0.3%	1.95 [0.18, 20.61]	
Total events	2		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.55 (P = 0.58)							
10.1.3 PCSK9 inhibitors plus statins vs. Placebo plus statins							
FOURIER[2]	95	2686	105	2651	26.8%	0.89 [0.68, 1.17]	2020
Subtotal (95% CI)		2686		2651	26.8%	0.89 [0.68, 1.17]	
Total events	95		105				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.81 (P = 0.42)							
Total (95% CI)		4679		4654	100.0%	0.87 [0.76, 0.99]	
Total events	342		395				
Heterogeneity: Chi² = 2.02, df = 4 (P = 0.73); I² = 0%							
Test for overall effect: Z = 2.05 (P = 0.04)							
Test for subgroup differences: Chi² = 0.53, df = 2 (P = 0.77), I² = 0%							

eFigure 11. Recurrent Stroke

Legends: Relative risk with 95% confidence interval of recurrent stroke in more intensive vs less intensive LDL-C

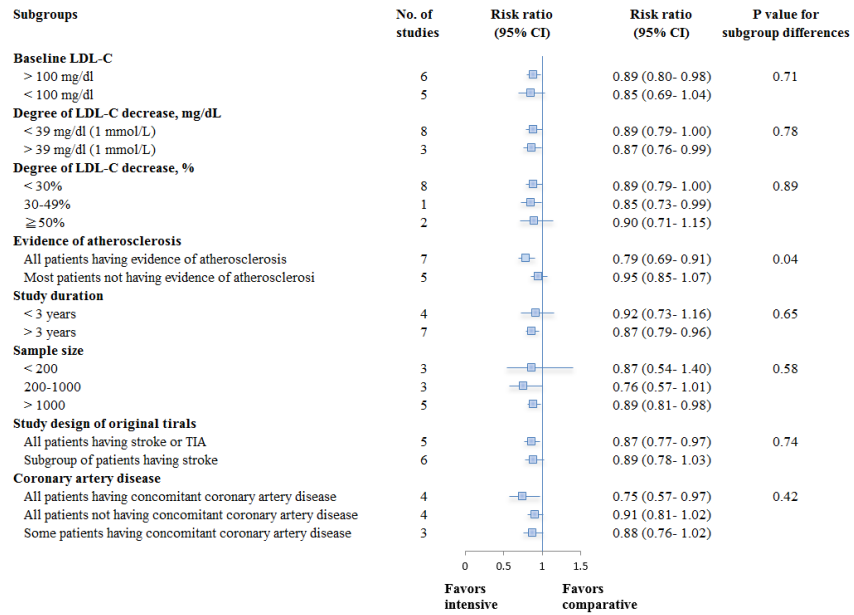lowering with statin-based therapies in patients with stroke and taking statins in both arms

Study or Subgroup	More-intensive Events	Total	Less-intensive Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
11.1.1 More statins/ezetimibe vs. Less statins/ezetimibe							
IMPROVE-IT[4]	29	336	48	346	15.4%	0.62 [0.40, 0.96]	2017
PODCAST[8]	2	39	1	38	0.3%	1.95 [0.18, 20.61]	2017
TST[10]	103	1430	126	1430	41.1%	0.82 [0.64, 1.05]	2020
Subtotal (95% CI)		1805		1814	56.9%	0.77 [0.62, 0.96]	
Total events	134		175				
Heterogeneity: Chi² = 1.74, df = 2 (P = 0.42); I² = 0%							
Test for overall effect: Z = 2.37 (P = 0.02)							
11.1.2 PCSK9 inhibitors plus statins vs. Placebo plus statins							
ODYSSEY OUTCOMES[7]	25	477	26	467	8.6%	0.94 [0.55, 1.61]	2019
FOURIER[2]	95	2686	105	2651	34.5%	0.89 [0.68, 1.17]	2020
Subtotal (95% CI)		3163		3118	43.1%	0.90 [0.71, 1.15]	
Total events	120		131				
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.86); I² = 0%							
Test for overall effect: Z = 0.83 (P = 0.41)							
Total (95% CI)		4968		4932	100.0%	0.83 [0.70, 0.97]	
Total events	254		306				
Heterogeneity: Chi² = 2.69, df = 4 (P = 0.61); I² = 0%							
Test for overall effect: Z = 2.30 (P = 0.02)							
Test for subgroup differences: Chi² = 0.91, df = 1 (P = 0.34), I² = 0%							

0.1 0.2 0.5 1 2 5 10
Favors more-intensive   Favors less-intensive

eFigure 12. Meta-regression

Legends: Meta-regression of included trials to explore the relation between degree of LDL-C lowering and recurrent stroke rate
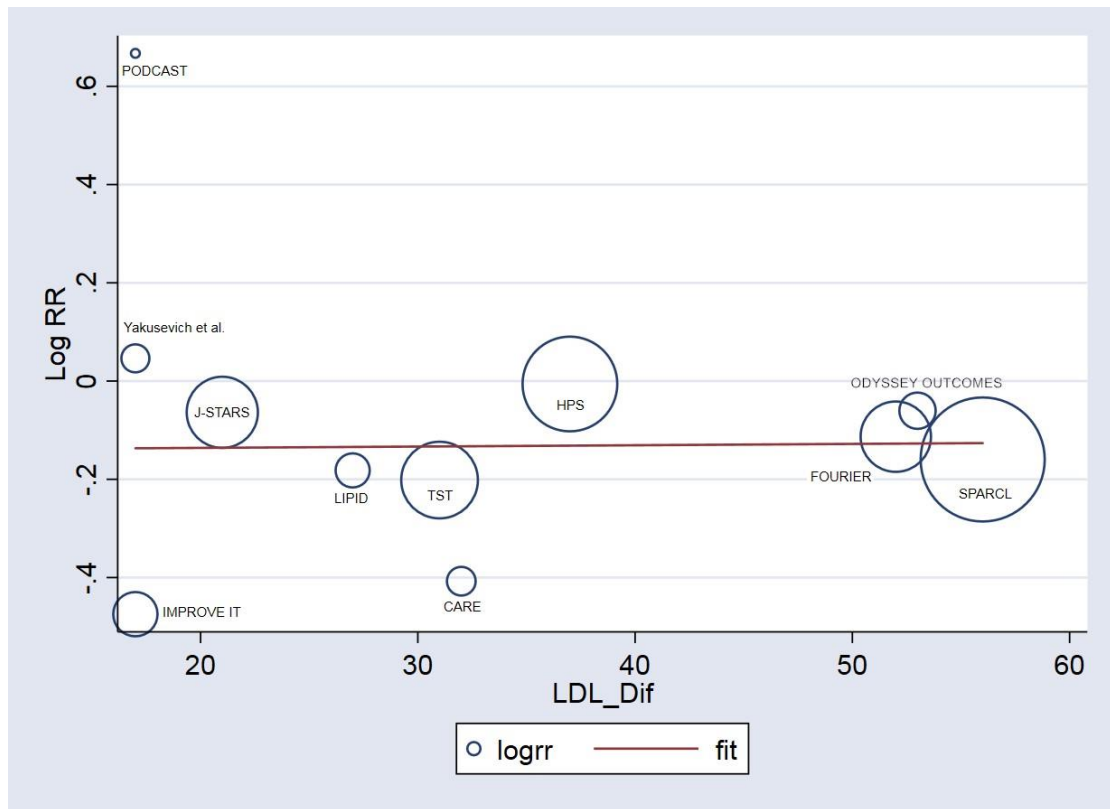
eFigure 13. Subgroup Analyses

Legends: Subgroup analyses based on the characteristics of trials

Subgroups	No. of studies	Risk ratio (95% CI)	Risk ratio (95% CI)	P value for subgroup differences
Baseline LDL-C				
> 100 mg/dl	6		0.89 (0.80- 0.98)	0.71
< 100 mg/dl	5		0.85 (0.69- 1.04)	
Degree of LDL-C decrease, mg/dL				
< 39 mg/dl (1 mmol/L)	8		0.89 (0.79- 1.00)	0.78
> 39 mg/dl (1 mmol/L)	3		0.87 (0.76- 0.99)	
Degree of LDL-C decrease, %				
< 30%	8		0.89 (0.79- 1.00)	0.89
30-49%	1		0.85 (0.73- 0.99)	
≧50%	2		0.90 (0.71- 1.15)	
Evidence of atherosclerosis				
All patients having evidence of atherosclerosis	7		0.79 (0.69- 0.91)	0.04
Most patients not having evidence of atherosclerosi	5		0.95 (0.85- 1.07)	
Study duration				
< 3 years	4		0.92 (0.73- 1.16)	0.65
> 3 years	7		0.87 (0.79- 0.96)	
Sample size				
< 200	3		0.87 (0.54- 1.40)	0.58
200-1000	3		0.76 (0.57- 1.01)	
> 1000	5		0.89 (0.81- 0.98)	
Study design of original tirals				
All patients having stroke or TIA	5		0.87 (0.77- 0.97)	0.74
Subgroup of patients having stroke	6		0.89 (0.78- 1.03)	
Coronary artery disease				
All patients having concomitant coronary artery disease	4		0.75 (0.57- 0.97)	0.42
All patients not having concomitant coronary artery disease	4		0.91 (0.81- 1.02)	
Some patients having concomitant coronary artery disease	3		0.88 (0.76- 1.02)	

Axis: 0   0.5   1   1.5

Favors intensive   Favors comparative

eFigure 14. Publication Bias

Legends: Trim-and-fill analysis for included trials to explore potential publication bias

Filled funnel plot with pseudo 95% confidence limits
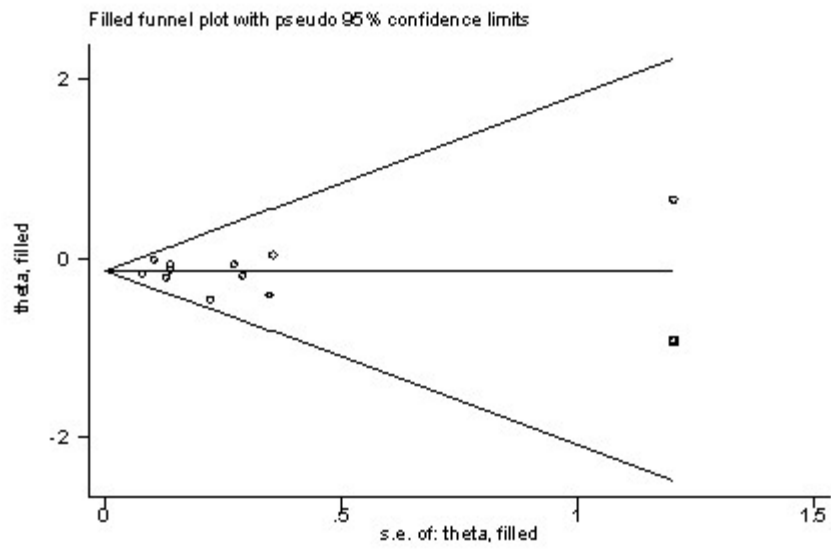
eReferences.

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