

Achieved low-density lipoprotein cholesterol level and stroke risk: A meta-analysis of 23 randomised trials

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Abstract

Aims: Lowering the low-density lipoprotein cholesterol level reduces the risk of stroke, but it has not been clear whether the stroke risk would continuously decrease by lowering low-density lipoprotein cholesterol to a very low level. The purpose of this study was to evaluate the association between achieved low-density lipoprotein cholesterol levels and stroke risk.

Methods and results: A systematic search of MEDLINE, EMBASE and Cochrane Library databases was conducted to identify randomised controlled trials that tested cholesterol-lowering pharmacological therapies and reported both achieved low-density lipoprotein cholesterol levels and stroke outcomes. A meta-regression analysis was conducted to assess the linear association between the achieved low-density lipoprotein cholesterol levels and stroke risk. In addition, we evaluated pooled estimates of low-density lipoprotein cholesterol-lowering effect stratified by achieved low-density lipoprotein cholesterol levels of active arms. A total of 222,149 participants in 23 trials (52 arms of 26 studies) were included. The meta-regression analysis showed that each 1 mmol/L decrease in the achieved low-density lipoprotein cholesterol level (down to 0.78 mmol/L) was associated with a significant reduction of 23.5% (slope 0.235, 95% confidence interval 0.007–0.464, $P=0.044$) in stroke risk. Irrespective of achieved low-density lipoprotein cholesterol levels in the active arms, the effects of lowering the low-density lipoprotein cholesterol level on stroke risk were significant and consistent (test for subgroup difference, $P=0.23$, $I^2=31\%$). However, there was no significant increase in haemorrhagic stroke risk with lower achieved low-density lipoprotein cholesterol levels.

Conclusion: In this meta-analysis of randomised controlled trials, the stroke risk monotonically reduced with lowering of low-density lipoprotein cholesterol to very low levels.

Keywords

Stroke, LDL-cholesterol, statin, PCSK9 inhibitor, meta-analysis

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Introduction

Low-density lipoprotein (LDL)-cholesterol-lowering therapy is effective for the prevention of stroke as well as overall cardiovascular events, and the benefits are proportional to the magnitude of the reduction in LDL-cholesterol level.¹ In clinical practice, rather than the absolute reduction, the achieved LDL-cholesterol level itself could be more practical to guide patients and healthcare providers. A recent meta-analysis of randomised controlled trials (RCTs) demonstrated that the risk of major cardiovascular events reduced with lower achieved LDL-cholesterol levels.² For stroke outcome, in a prior meta-analysis,³ a greater

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difference in LDL-cholesterol level between active and control arms was associated with a greater reduction in stroke risk. However, the meta-analysis was restricted to statin trials and did not evaluate the effect of the achieved LDL-cholesterol level. Therefore, whether stroke risk could be proportionally reduced by achieving a lower LDL-cholesterol level, particularly a very low LDL-cholesterol level, remains unexplored.

This meta-analysis of RCTs evaluated whether a lower achieved LDL-cholesterol level is associated with a lower stroke risk by analysing stroke risk reduction: (a) per 1 mmol/L decrease in achieved LDL-cholesterol level; (b) stratified by achieved LDL-cholesterol levels; and (c) with pharmacological interventions added to background statin therapy to reduce LDL-cholesterol level further.

Methods

Search strategy, selection criteria and quality assessment

In accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,⁴ we searched MEDLINE, EMBASE and the Cochrane Library (January 2002 to May 2017) with the following search terms: pravastatin, lovastatin, atorvastatin, simvastatin, fluvastatin, cerivastatin, rosuvastatin, pitavastatin, HMG-CoA reductase inhibitor, statin, ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, alirocumab, evolocumab or bococizumab. The search was restricted to articles studied with humans and published in the English language. To identify additional trials, we also reviewed references of retrieved articles and earlier meta-analyses. The inclusion criteria were as follows: (a) RCTs; (b) comparison between LDL-cholesterol lowering drugs and placebo or intensive and less intensive LDL-cholesterol-lowering pharmacological therapies; (c) stroke (ischaemic and/or haemorrhagic) endpoint data provided; and (d) at least 5000 person-years to minimise the risk of small study bias. Exclusion criteria were as follows: (a) duplicated publications as exploratory or subgroup analyses and (b) no data on the achieved LDL-cholesterol level. However, studies of subgroup analysis for patients with prior stroke were included in the analysis of secondary stroke prevention trials. Two investigators (JS and WKS) independently reviewed searched abstracts and articles as well as selected eligible studies. Discrepancies were resolved by consensus. A risk of bias of studies included in this meta-analysis was examined using the recommendation of the Cochrane Collaboration (<http://handbook-5-1.cochrane.org/>).

Data extraction and study outcomes

From active (LDL-cholesterol lowering or intensive lowering) and control (placebo or less intensive lowering) arms of each trial, we extracted the following information: (a) annual event rates of any stroke (ischaemic and haemorrhagic stroke), myocardial infarction (MI), cardiovascular mortality, and major adverse cardiovascular event (MACE); (b) baseline and achieved LDL-cholesterol levels; (c) sample size and follow-up duration; and (d) baseline characteristics of age, sex, and vascular risk factor profiles. Details of the data extraction are described in the Supplementary online material.

The primary outcome was any stroke, while secondary outcomes were ischaemic stroke, haemorrhagic stroke, MI, cardiovascular mortality and MACE. Each trial was divided into either primary or secondary stroke prevention trial. If less than 20% of the enrolled population had a prior stroke, we regarded it as a primary stroke prevention trial. The Heart Protection Study (HPS) and the Improved Reduction of Outcomes: Vyturin Efficacy International Trial (IMPROVE-IT) largely enrolled patients without prior stroke history, and thereby they were included as primary stroke prevention trials.^{5,6} However, because these two studies additionally reported detailed event rates in the subgroup of patients with prior stroke, they were also used for the analysis of secondary stroke prevention trials. Although studies of PCSK9 Inhibition and the Reduction of Vascular Events (SPIRE-1 and SPIRE-2) were combined and reported in one article, we regarded it as individual trials because characteristics of the participants were entirely different between the two trials and sufficient information for each trial was available.⁷ To explore an effect of achieved LDL-cholesterol levels further, trials were also categorised into: (a) trials on the achieved LDL-cholesterol levels of active arms (<1.3 mmol/L, 1.3–1.8 mmol/L and >1.8 mmol/L) and (b) trials on non-statin LDL-cholesterol lowering drugs on a background of statin therapy and statin trials.

Statistical analyses

We performed a meta-regression and pooled analyses. Details of the statistical analyses are described in the Supplementary online material.

Results

Study selection and characteristics

A total of 1203 articles was searched systemically from MEDLINE, EMBASE and the Cochrane Library (391, 410 and 402, respectively). After excluding duplicated and ineligible reports, a total of 17 articles was included. Six articles were further found by manual

search,^{8–12} comprising a total of 23 articles for our meta-analysis. This provided us with a total of 222,149 participants in 52 arms of 26 studies with 6345 stroke events (Figure 1). Regarding the risk of bias, all trials were at low or unclear risk of bias for most of the assessed domains (see Supplementary online material, Supplementary Figure 1). No significant publication bias was noted from the funnel plot (see Supplementary online material, Supplementary Figure 2). The characteristics of each arm of individual trials are summarised in Table 1. Among the 52 arms, eight arms of four trials were secondary stroke prevention trials exclusively enrolling patients with a stroke history,^{5,6,13,14} while 44 arms of 22 trials (two trials were overlapped with secondary stroke prevention trials) were classified as primary stroke prevention trials.^{5–12,15–28} The primary stroke prevention trial with the highest rate of prior stroke was the active

arm of the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial with 19.5%, and the secondary stroke prevention trial with the lowest rate of prior stroke was the control arm of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial with 68.2%.^{13,27}

Meta-regression analyses for stroke risk

For the annual event rates of any stroke in 44 arms of 22 primary stroke prevention trials (involving 211,871 patients), each 1mmol/L decrease in the achieved LDL-cholesterol level was associated with a significant risk reduction of 19.6% for any stroke events (slope 0.196, 95% confidence interval (CI) 0.034–0.357, $P=0.019$, Table 2 and Figure 2). The achieved LDL-cholesterol level of the included trials ranged from

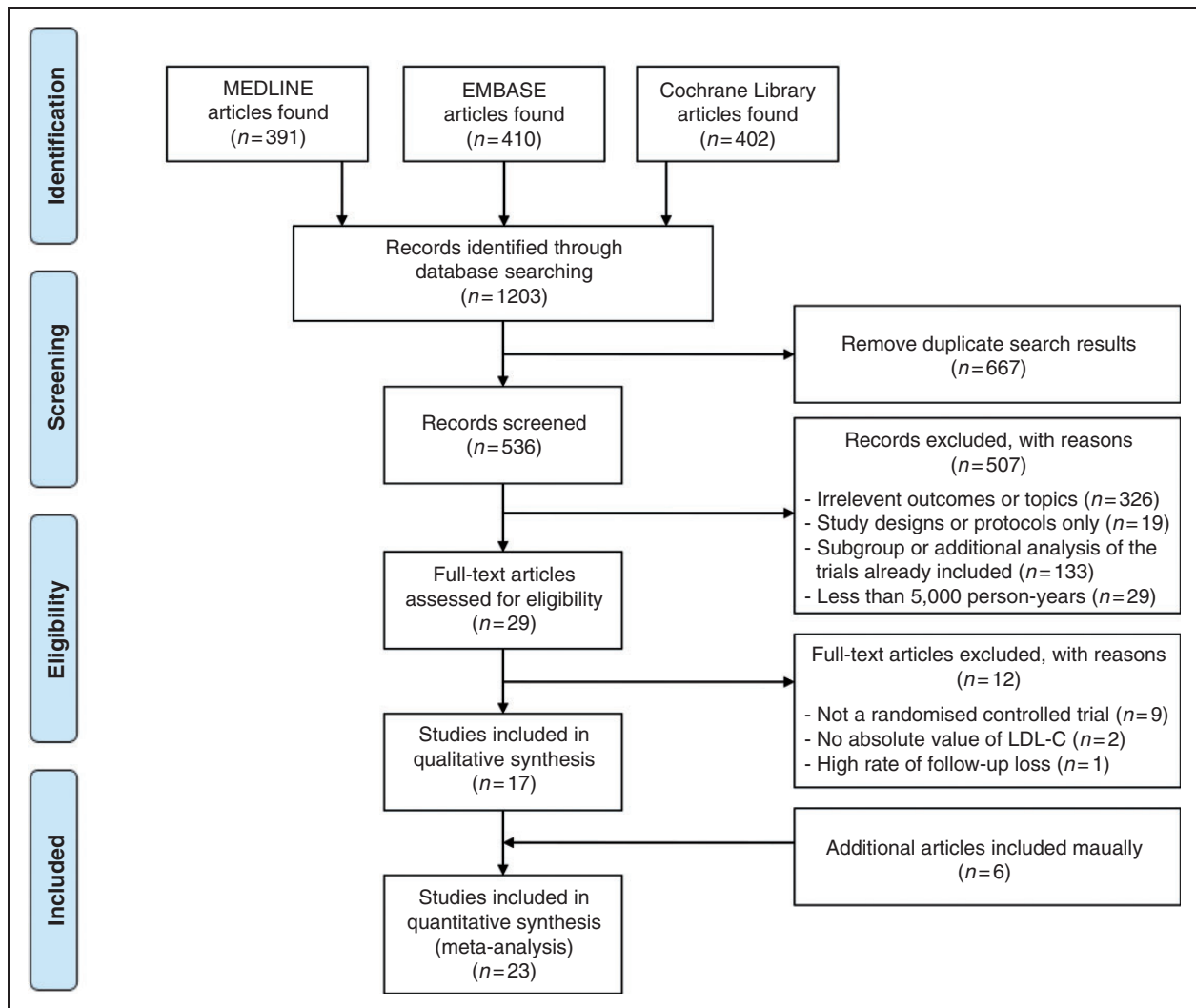


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of included studies.

Table 1. Characteristics of individual trials.

Trial name	Publication year	Group	Intervention	FU duration, years	Randomised patients, n	Mean age, years	Male, %	Baseline LDL-cholesterol level, mmol/L	Achieved LDL-cholesterol level, mmol/L	LDL-cholesterol FU period, m	Annual event rate, %/year				MACE	
											Stroke	Ischaemic stroke	Haemorrhagic stroke	MI		cardiovascular death
ALLHAT-LLT	2002	Active	Pravastatin	4.8	5170	66.4	51.4	3.77	2.87	24	0.88	—	—	1.55	1.15	2.37
		Control	Usual care	4.8	5185*	66.3	51.0	3.77	3.49	24	0.97	—	—	1.73	1.18	2.62
HPS (p)	2002	Active	Simvastatin	5.0	8610*	—	—	—	2.3	Mean	0.64	0.44	0.07	1.69	—	2.33
		Control	Placebo	5.0	8646*	—	—	—	3.2	Mean	0.96	0.66	0.10	2.30	—	3.26
HPS (s)	2002	Active	Simvastatin	4.8	1644*	—	—	—	2.4	Mean	2.14	1.27	0.27	2.17	—	4.31
		Control	Placebo	4.8	1636*	—	—	—	3.4*	Mean	2.16	1.55	0.14	2.78	—	4.94
PROSPER	2002	Active	Pravastatin	3.2	2891	75.4	48.3	3.8	2.5	3	1.46	—	—	3.16	1.46	4.41
		Control	Placebo	3.2	2913	75.3	48.3	3.8	3.79	3	1.41	—	—	3.82	1.68	5.07
ALERT	2003	Active	Fluvastatin	5.1 [†]	1050	49.5	66.8	4.1	3.1	1.4	1.32	—	—	1.31	0.99	—
		Control	Placebo	5.1 [†]	1052	50	65.2	4.1	4.1	1.4	1.29	—	—	1.94	1.27	—
ASCOT-LLA	2003	Active	Atorvastatin	3.3	5168	63.1	81.1	3.4	2.21	6	0.54	—	—	0.60	0.44	1.11
		Control	Placebo	3.3	5137	63.2	81.3	3.4	3.45	6	0.74	—	—	0.94	0.49	1.62
A to Z	2004	Active	Simvastatin	2.0	2265	61	75.8	2.9	1.61	4	0.62	—	—	3.37	1.83	3.99
		Control	Simvastatin	2.0	2232	61	75.0	2.87	3.21	4	0.79	—	—	3.51	2.44	4.30
ALLIANCE	2004	Active	Atorvastatin	4.3	1217	61.1	82.2	3.81	2.46	End	0.67	—	—	1.82	0.82 [‡]	2.48
		Control	None	4.3	1225	61.3	82.3	3.78	2.87	End	0.74	—	—	2.94	1.16 [‡]	3.68
CARDS	2004	Active	Atorvastatin	3.9	1428	61.5	68.1	3.04	1.75	6	0.38	0.29	—	0.59	—	0.97
		Control	Placebo	3.9	1410	61.8	67.9	3.02	3.07	6	0.71	0.56	—	1.11	—	1.82
PROVE-IT	2004	Active	Atorvastatin	2.0	2099	58.1	77.8	2.75	1.61	Median	0.50	—	—	3.30	3.60 [‡]	—
		Control	Pravastatin	2.0	2063	58.3	78.4	2.75	2.46	Median	0.50	—	—	3.70	4.15 [‡]	—
IDEAL	2005	Active	Atorvastatin	4.8	4439	61.8	80.9	3.15	2.01	2.8	0.71	—	—	2.07	1.05	2.78
		Control	Simvastatin	4.8	4449	61.6	80.8	3.14	2.71	2.8	0.81	—	—	2.34	1.02	3.15
TNT	2005	Active	Atorvastatin	4.9	4995	61.2	81.2	2.51	1.99	Mean	0.48	—	0.07	1.41	0.41 [‡]	1.77 [§]
		Control	Atorvastatin	4.9	5006	60.9	80.8	2.54	2.61	Mean	0.63	—	0.07	1.77	0.52 [‡]	2.23 [§]
ASPEN	2006	Active	Atorvastatin	4.0	1211	61.1	65.7	2.93	2.04	End	0.70	—	—	1.01	0.78	1.71
		Control	Placebo	4.0	1199	61	67.0	2.95	2.92	End	0.79	—	—	1.38	0.77	2.17
SPARCL (s)	2006	Active	Atorvastatin	4.9	2365	63	60.3	3.44	1.89	Mean	2.29	1.88	0.47	0.70 [§]	0.67	2.88 [§]
		Control	Placebo	4.9	2366	62.5	59.0	3.46	3.33	Mean	2.68	2.36	0.28	1.04 [§]	0.85	3.51 [§]

(continued)

Table 1. Continued

Trial name	Publication year	Group	Intervention	FU duration, years	Randomised patients, n	Mean age, years	Male, %	Baseline LDL-cholesterol level, mmol/L	Achieved LDL-cholesterol level, mmol/L	LDL-cholesterol FU period, m	Annual event rate, %/year					MACE
											Stroke	Ischaemic stroke	Haemorrhagic stroke	MI	cardiovascular death	
CORONA	2007	Active	Rosuvastatin	2.7	2514	73	76.4	3.54	1.97	3	1.81	1.06	0.22	1.81	7.19	11.40
		Control	Placebo	2.7	2497	73	76.5	3.56	3.57	3	2.02	1.32	0.13	2.19	7.22	12.30
GISSI-HF	2008	Active	Rosuvastatin	3.9	2285	68	76.2	3.16	2.15	12	0.92	—	—	0.68	5.36	1.60
		Control	Placebo	3.9	2289	68	78.6	3.13	3.37	12	0.74	—	—	0.78	5.47	1.52
JUPITER	2008	Active	Rosuvastatin	1.9	8901	66	61.5	2.8	1.42	12	0.18	0.12	0.03	0.17	—	0.45
		Control	Placebo	1.9	8901	66	62.1	2.8	2.85	12	0.34	0.25	0.05	0.37	—	0.85
AURORA	2009	Active	Rosuvastatin	3.2	1389	64.1	61.3	2.59	1.5	3	2.09	1.28	0.56	5.26	7.20	9.20
		Control	Placebo	3.2	1384	64.3	63.0	2.56	2.51	3	1.83	1.24	0.47	5.94	7.30	9.50
SHARP	2011	Active	Simvastatin + Ezetimibe	4.9	4650	62	62.7	2.77	1.69	8–13	0.75	0.50	0.20	0.93	1.58	1.71
IMPROVE-IT (p)	2015	Control	Placebo	4.9	4620	62	62.4	2.78	2.8	8–13	0.93	0.69	0.16	1.02	1.71	1.95
		Active	Simvastatin + Ezetimibe	6.0	8727	—	—	2.46	1.30	12	0.51	0.41	0.10	1.77	0.95	2.77
IMPROVE-IT (s)	2015	Control	Simvastatin + Placebo	6.0	8728	—	—	2.46	1.74	12	0.57	0.48	0.08	2.02	0.96	3.03
		Active	Simvastatin + Ezetimibe	6.0	336	—	—	2.31	1.32	12	1.44	1.14	0.25	2.53	1.88	4.61
J-STARS (s)	2015	Control	Simvastatin + Placebo	6.0	346	—	—	2.23	1.76	12	2.31	2.12	0.14	2.89	1.64	5.64
		Active	Pravastatin	4.9	793	66.1	68.7	3.35	2.67	Mean	2.35	1.60	0.29	0.10	1.11	—
FOURIER	2017	Control	No statin	4.9	785	66.4	69.0	3.35	3.22	Mean	2.47	1.72	0.31	0.18	0.90	—
		Active	Evolocumab + Statin	2.2	13784	62.5	75.4	2.4	0.78	11.2	0.68	0.56	0.10	1.54	0.83	2.87
SPIRE-I	2017	Control	Placebo + Statin	2.2	13780	62.5	75.5	2.4	2.23	11.2	0.86	0.75	0.08	2.11	0.79	3.56
		Active	Bococizumab + Statin	0.6	8408	63.3	73.7	2.43	1.04	3.2	0.33 ^l	—	—	1.70 [#]	0.64	2.59
		Control	Placebo + Statin	0.6	8409	63.3	73.5	2.43	2.51	3.2	0.62 ^l	—	—	1.53 [#]	0.52	2.49

(continued)

Table 1. Continued

Trial name	Publication year	Group	Intervention	FU duration, years	Randomised patients, n	Mean age, years	Male, %	Baseline LDL-cholesterol level, mmol/L	Achieved LDL-cholesterol level, mmol/L	LDL-cholesterol FU period, m	Annual event rate, %/year					
											Stroke	Ischaemic stroke	Haemorrhagic stroke	MI death cardiovascular		
SPIRE-2	2017	Active	Bococizumab + Statin	1.0	5312	62.2	65.9	3.47	1.57	3.2	0.48 [§]	–	–	1.73 [#]	0.51	2.66
		Control	Placebo + Statin	1.0	5309	62.6	64.9	3.46	3.53	3.2	0.72 [‡]	–	–	2.26 [#]	0.62	3.57
ODYSSEY OUTCOMES	2018	Active	Alirocumab + Statin	2.8	9462	58	74.7	2.25	0.97	4	0.45	0.42	0.03 ^{**}	3.14	0.91	3.41 ^{††}
		Control	Placebo + Statin	2.8	9462	58	74.9	2.25	2.42	4	0.63	0.57	0.06 ^{**}	3.56	1.02	3.97 ^{††}

ALERT: Assessment of Lescol in Renal Transplantation; ALLHAT-LLT: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ALLIANCE: Aggressive Lipid-Lowering Initiation Abates New Cardiac Events; ASCOT-LLA: Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm; ASPEN: Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus; AURORA: A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Haemodialysis: an Assessment of Survival and Cardiovascular Events; CARDS: Collaborative Atorvastatin Diabetes Study; CORONA: Controlled Rosuvastatin Multinational Trial in Heart Failure; FOURIER: Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk; FU: follow-up; GISSI-HF: Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca; HPS: Heart Protection Study; IDEAL: Incremental Decrease in Endpoints Through Aggressive Lipid; IMPROVE-IT: Improved Reduction of Outcomes: Vytorin Efficacy International Trial; J-STARS: Japan Statin Treatment Against Recurrent Stroke; JUPITER: Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LDL: low-density lipoprotein; ODYSSEY OUTCOME: Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab; PROSPER: Prospective Study of Pravastatin in the Elderly at Risk; PROVE-IT: Pravastatin or Atorvastatin Evaluation and Infection Therapy; SHARP: Study of Heart and Renal Protection; SPARCL: Stroke Prevention by Aggressive Reduction in Cholesterol Levels; SPIRE: Studies of PCSK9 Inhibition and the Reduction of Vascular Events; TNT: treating to new targets; (p): primary; (s): secondary.

*Estimated value.

[†]6.7 Years for stroke outcome.

[‡]Coronary or cardiac mortality.

[§]Including cardiac arrest.

^{||}Non-fatal stroke.

[#]Non-fatal myocardial infarction.

^{**}9451 Subjects of the active group and 9443 subjects of the control group for haemorrhagic stroke outcome.

^{††}Including unstable angina requiring hospitalisation, haemorrhagic stroke not included.

Table 2. Summary of meta-regression analyses on the effect of achieved LDL-cholesterol level.

	All studies			Primary stroke prevention			Secondary stroke prevention		
	No.	Slope (95% CI)	P value	No.	Slope (95% CI)	P value	No.	Slope (95% CI)	P value
Any stroke	52	0.235 (0.007, 0.464)	0.044	44	0.196 (0.034, 0.357)	0.019	8	0.309 (−0.308, 0.648)	0.068
Ischaemic stroke	26	0.286 (−0.019, 0.591)	0.065	18	0.148 (−0.078, 0.375)	0.184	8	0.159 (−0.335, 0.652)	0.461
Haemorrhagic stroke	26	0.011 (−0.068, 0.089)	0.779	18	−0.003 (−0.105, 0.098)	0.943	8	−0.018 (−0.149, 0.113)	0.747
MI	52	−0.083 (−0.520, 0.353)	0.703	44	−0.006 (−0.482, 0.471)	0.981	8	−0.513 (−1.903, 0.878)	0.402
Cardiovascular mortality	44	0.079 (−0.704, 0.861)	0.840	38	0.135 (−0.758, 1.027)	0.761	6	−0.392 (−0.984, 0.201)	0.140
MACE	46	0.268 (−0.713, 1.250)	0.585	40	0.339 (−0.781, 1.458)	0.544	6	0.151 (−1.745, 1.442)	0.805

LDL: low-density lipoprotein; CI: confidence interval; MI: myocardial infarction; MACE: major adverse cardiovascular event.

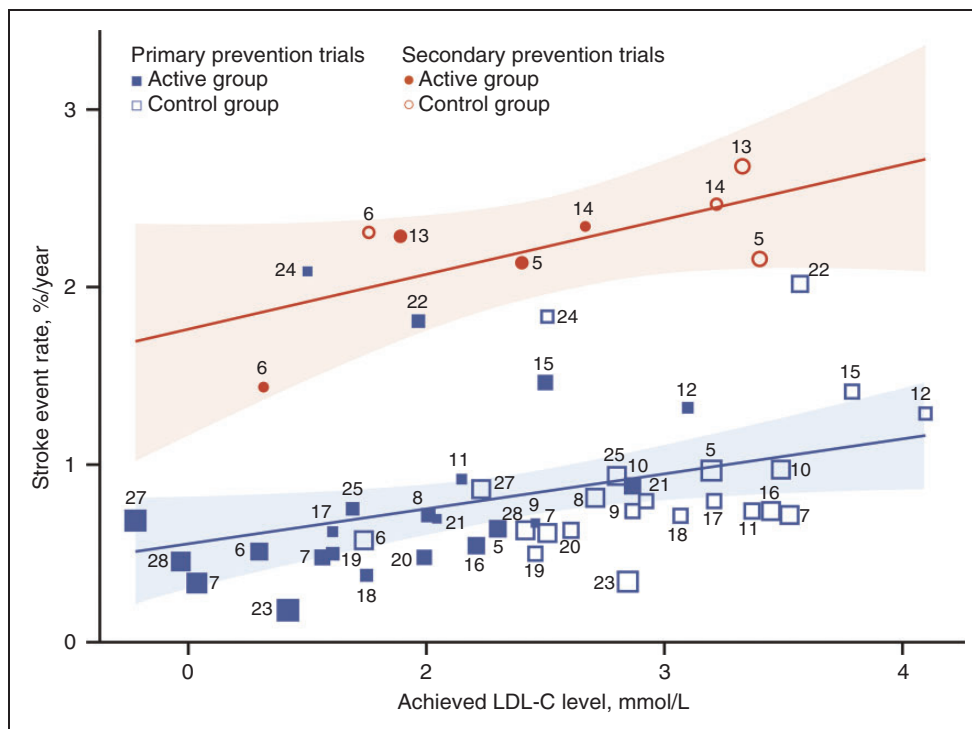


Figure 2. Bubble plot of meta-regression analyses showing significant positive correlations between the achieved low-density lipoprotein (LDL)-cholesterol level and stroke event rate in primary stroke prevention trials. The size of each square on the graph indicates the weight of each trial, which was derived from the inverse of variance of the event rate of each trial. The shaded area indicates the range of the 95% confidence interval.

0.78 mmol/L to 4.10 mmol/L. Analysis restricted to eight arms of four secondary stroke prevention trials provided a steeper regression slope than that observed in the primary stroke prevention trials; however, it did not reach statistical significance (slope 0.309, 95% CI −0.308–0.648, $P=0.068$). When the primary and secondary stroke prevention trials were combined, each 1 mmol/L decrease in the achieved LDL-cholesterol level was associated with a 23.5% reduction in any stroke risk with statistical

significance (slope 0.235, 95% CI 0.007–0.464, $P=0.044$, Table 2 and Figure 3). The significant association was also observed in an adjusted model (slope 0.232, 95% CI 0.060–0.403, $P=0.010$, see Supplementary online material, Supplementary Table 1).

Ischaemic stroke risk was analysed using data from 26 arms of 13 primary or secondary stroke prevention trials, which showed that each 1 mmol/L decrease in the achieved LDL-cholesterol level was associated with a

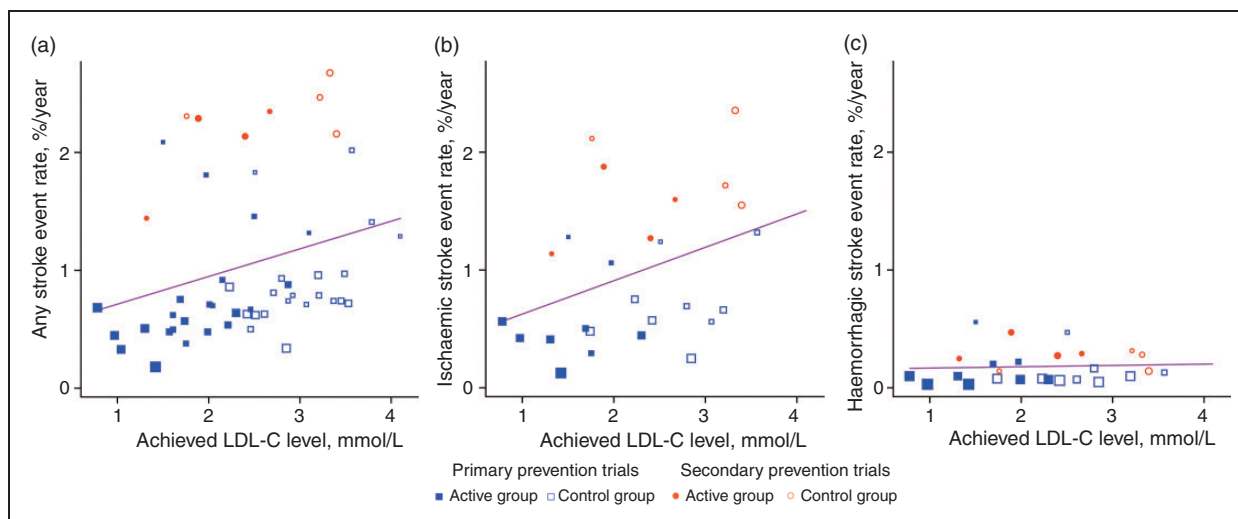


Figure 3. Bubble plots of meta-regression analyses on the effect of achieved low-density lipoprotein (LDL)-cholesterol level on (a) any stroke and (b) ischaemic stroke showing positive correlations. The size of each square on the graph indicates the weight of each trial, which was derived from the inverse of variance of the event rate of each trial.

risk reduction of 28.6% without statistical significance (slope 0.286, 95% CI -0.019 – 0.591 , $P=0.065$).

The annual risk of haemorrhagic stroke obtained from 26 arms of 13 primary or secondary stroke prevention trials was very low (average of 0.18%/year, Figure 3). Noticeably, the risk did not significantly increase with a decrease in the achieved LDL-cholesterol level down to the very low level of 0.78 mmol/L (slope 0.011, 95% CI -0.068 – 0.089 , $P=0.779$). The risk was not increased with the decrease of the achieved LDL-cholesterol level even in the secondary stroke prevention trials.

Pooled analyses for stroke risk

The pooled risk ratios (RRs) for any stroke are presented in Figures 4 and 5. Overall, active arms had a lower risk of any stroke than control arms (RR 0.84, 95% CI 0.78–0.90, $P < 0.001$, see Supplementary online material, Supplementary Figure 3). When the trials were stratified by the achieved LDL-cholesterol level in active arms, the risk reduction with active arms compared with that with control arms was significant. Furthermore, the benefits were consistent irrespective of the achieved LDL-cholesterol levels (test for subgroup difference, $P=0.23$; $I^2=31\%$): the pooled RR was 0.79 (95% CI 0.68–0.91, $P=0.001$) from trials with achieved LDL-cholesterol levels less than 1.3 mmol/L (50 mg/dL); 0.76 (95% CI 0.61–0.93, $P=0.008$) from trials with achieved LDL-cholesterol levels between 1.3 mmol/L and 1.8 mmol/L; and 0.88 (95% CI 0.81–0.96, $P=0.006$) from trials with achieved LDL-cholesterol levels greater than 1.8 mmol/L (70 mg/dL, Figure 4). When stratified by statin trials (average achieved LDL-cholesterol level, active

2.1 mmol/L vs. control 3.1 mmol/L) and non-statin trials (average achieved LDL-cholesterol level, active 1.2 mmol/L vs. control 2.4 mmol/L), stroke risk reduction was significant in the former (RR 0.87, 95% CI 0.79–0.95, $P=0.003$) as well as in the latter (RR 0.79, 95% CI 0.71–0.87, $P < 0.001$, Figure 5).

The risk reduction for ischaemic stroke was significant and consistent irrespective of the achieved LDL-cholesterol levels in active arms (see Supplementary online material, Supplementary Figure 4). The risk reduction with an intervention was also apparent in both statin and non-statin trials.

For haemorrhagic stroke risk, active arms showed a greater trend of increased risk than control arms (RR 1.16, 95% CI 0.96–1.40, $P=0.12$, see Supplementary online material, Supplementary Figure 5). However, the pooled RRs stratified by the achieved LDL-cholesterol levels in active arms did not differ significantly (test for subgroup difference, $P=0.92$): the pooled RR was 1.07 (95% CI 0.70–1.65, $P=0.75$) for trials with achieved LDL-cholesterol levels below 1.3 mmol/L (50 mg/dL); 1.16 (95% CI 0.84–1.59, $P=0.38$) for trials with achieved LDL-cholesterol levels between 1.3 mmol/L and 1.8 mmol/L; and 1.21 (95% CI 0.85–1.72, $P=0.30$) for trials with achieved LDL-cholesterol levels over 1.8 mmol/L (70 mg/dL). Besides, no significant difference in the pooled RRs of haemorrhagic stroke was observed between statin and non-statin trials (test for subgroup difference, $P=0.94$).

Other vascular outcome risks

For other vascular event risks, active arms had a lower risk of MI (RR 0.81, 95% CI 0.77–0.85, $P < 0.001$),

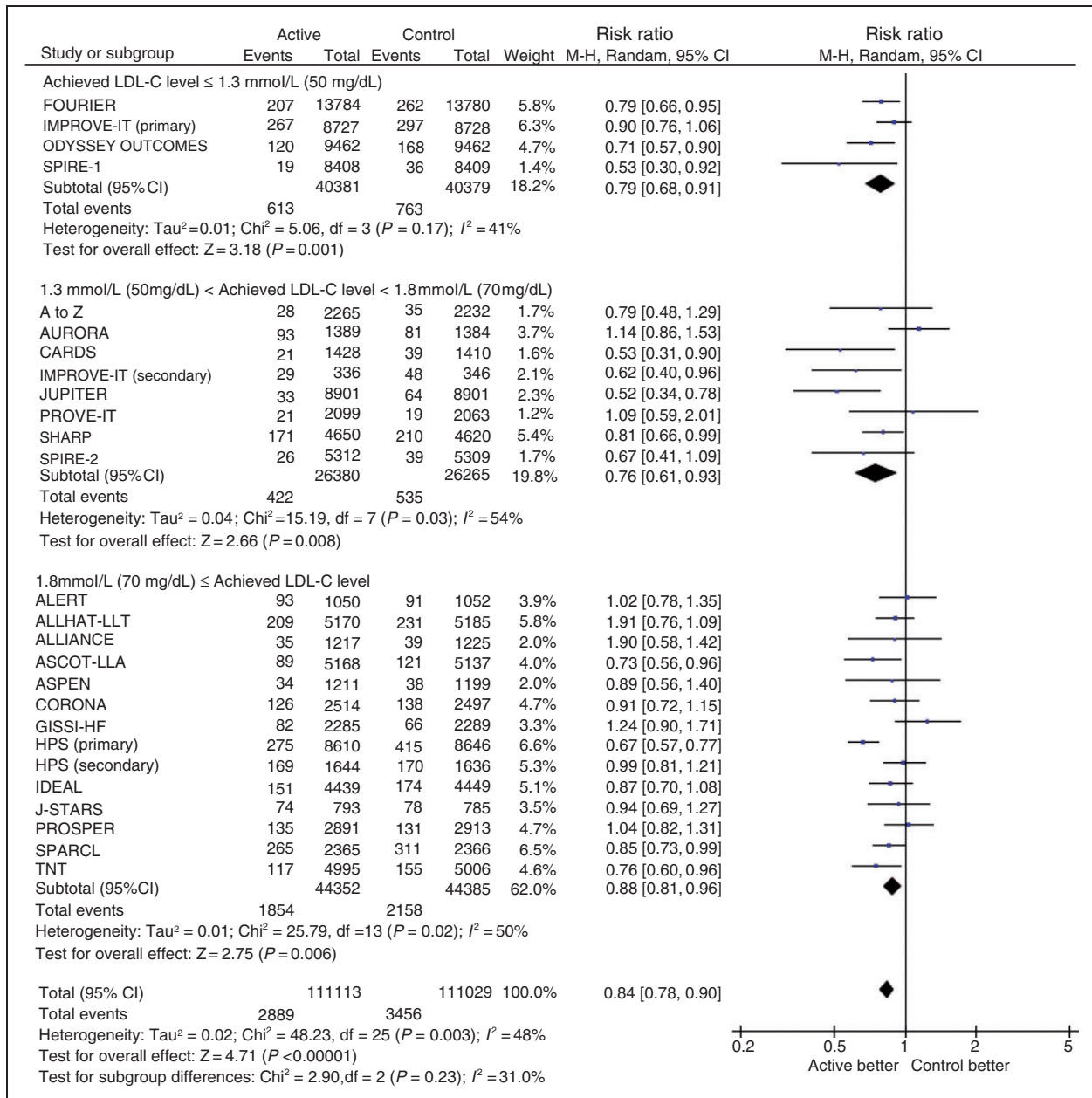


Figure 4. Forest plot showing stroke risk according to the achieved low-density lipoprotein (LDL)-cholesterol level of active arms. Overall estimate is indicated by diamonds.

cardiovascular mortality (RR 0.95, 95% CI 0.92–0.99, $P = 0.02$), and MACE (RR 0.83, 95% CI 0.79–0.88, $P < 0.001$) than control arms (see Supplementary online material, Supplementary Figure 6). However, meta-regression analyses (MI event from 52 arms, cardiovascular mortality from 42 arms, and MACE from 46 arms) showed that there was no significant association between a 1 mmol/L decrease in the achieved LDL-cholesterol level and those event risks (see Supplementary online material, Supplementary Figure 7).

Discussion

In this meta-regression analysis, the lower the achieved LDL-cholesterol level, the lesser stroke events occurred with a 23.5% relative risk reduction per 1 mmol/L lowering of LDL-cholesterol level. The association was coherently linear across high LDL-cholesterol to very low LDL-cholesterol levels and consistent across studies of primary and secondary prevention of stroke. Non-statin LDL-cholesterol lowering drugs such as ezetimibe or PCSK9 inhibitors also showed an

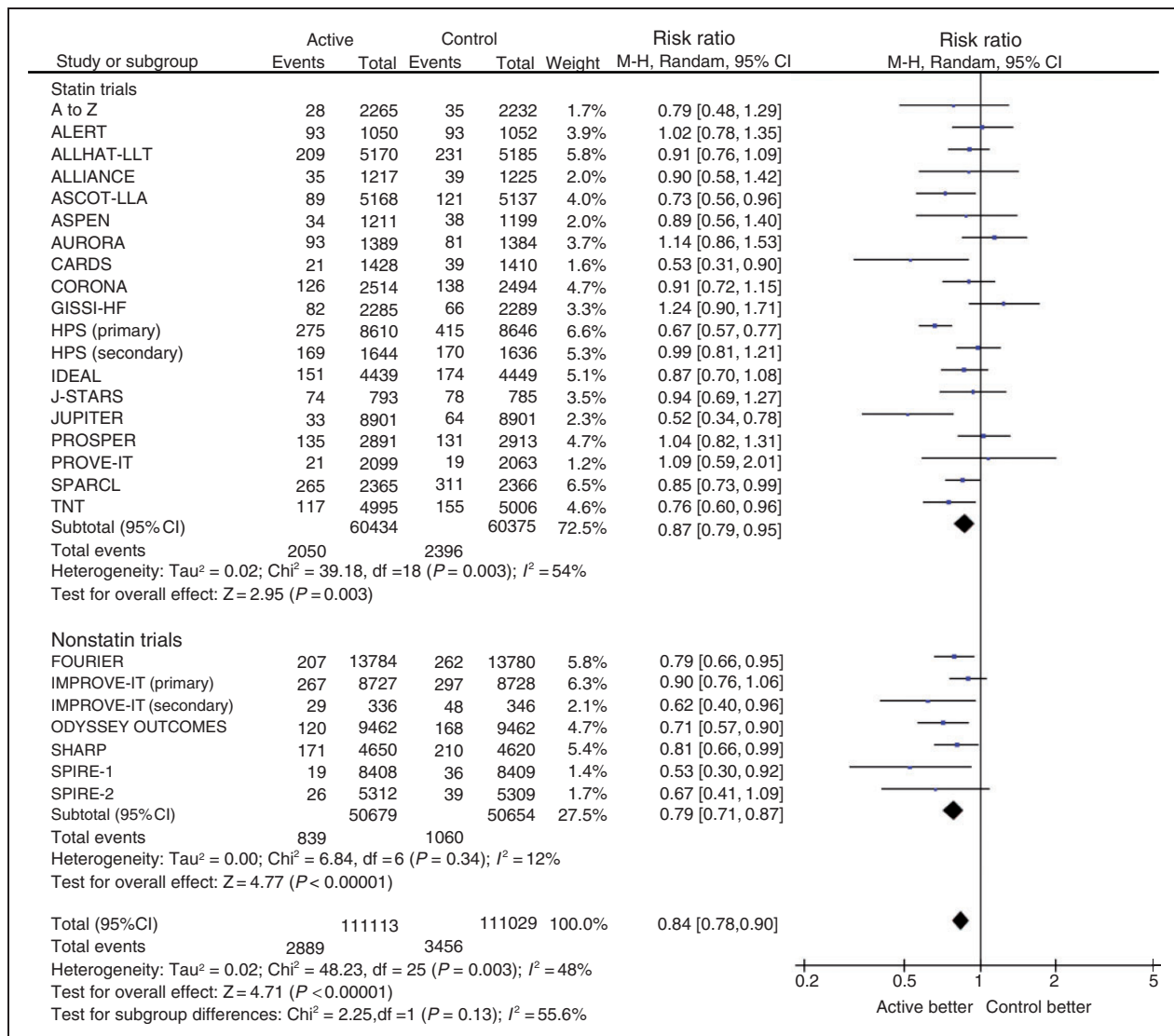


Figure 5. Forest plot showing stroke risk according to low-density lipoprotein (LDL)-cholesterol lowering therapies. Overall estimate is indicated by diamonds.

additional preventive effect for stroke even with the use of statin therapy, implying that the achieved LDL-cholesterol level should be the guidance for the treatment of dyslipidaemia rather than the class of LDL-cholesterol lowering drug. Contrary to our expectation, the hazard of haemorrhagic stroke had no significant association with LDL-cholesterol. These results strongly support the importance of intensive LDL-cholesterol lowering therapy irrespective of the class of LDL-cholesterol lowering drugs for the prevention of stroke.

Statin use in stroke prevention has been debated regarding whether the benefit results from the pleiotropic effect or by lowering the LDL-cholesterol level thoroughly. The primary effect of statin on the prevention of cardiovascular events has been considered to be

attributed to LDL-cholesterol reduction. The Cholesterol Treatment Trialists' collaborators reported that a 1 mmol/L reduction of LDL-cholesterol levels prevented 23% of major coronary events over 5 years.²⁹ However, in addition to the above-mentioned effects, the pleiotropic effect was said to play a key role, which is largely independent of LDL-cholesterol reduction.³⁰ Therefore, the guideline of the American College of Cardiology (ACC) and American Heart Association (AHA) published in 2013 recommended to use a highly potent statin that can combine both effects regardless of baseline LDL-cholesterol level in all high-risk patients. However, the European Society of Cardiology and European Atherosclerosis Society made a different approach in targeting the LDL-cholesterol level according to the individualised risk of each

patient. In 2017, the American Association of Clinical Endocrinologists and American College of Endocrinology opened a new chapter in the management of dyslipidaemia. They proposed a new risk stratification scheme including an extreme risk group and recommended an LDL-cholesterol level under 55 mg/dL as a target for this group. The recently published AHA/ACC guideline does not differ significantly from the previous 2013 guideline of determining statin potency according to the risk of atherosclerotic cardiovascular disease, except the subdivided risk group and some minor changes. However, considering that current guidelines are less well reflecting the evidence from clinical trials, two important questions still remain: what is the threshold of LDL-cholesterol level below which no additional benefit is expected, and is statin therapy enough to achieve the threshold LDL-cholesterol level?

The present meta-regression analysis estimated the lowest LDL-cholesterol level to which the benefit on stroke prevention would persist. The previous meta-analyses had calculated LDL-cholesterol reduction between active and control groups and showed that more between-group reductions in the LDL-cholesterol level lead to less stroke incidence or major cardiovascular events.^{1,3} However, these studies lack an answer to the question on how low the LDL-cholesterol level is beneficial to prevent stroke occurrence. A recent meta-regression study showed a linear association of achieved LDL-cholesterol with the incidence of major coronary events.² However, the lowest level of achieved LDL-cholesterol in the meta-regression analysis was 1.42 mmol/L (53 mg/dL), and stroke outcome was not specifically explored. In contrast, our study showed that the low achieved LDL-cholesterol level itself was related to the stroke risk reduction without a floor effect. Furthermore, the pooled analysis revealed that the significance of the stroke preventive effect was maintained at an LDL-cholesterol level below 1.3 mmol/L (50 mg/dL). This is meaningful because all control groups included in this pooled analysis were receiving statin therapy, and the effect of stroke prevention in a very low LDL-cholesterol level had the same tendency as the meta-regression analysis result. Our results were consistent with the recent data obtained from clinical trials. The FOURIER trial in which the patients with very low achieved LDL-cholesterol levels less than 10 mg/dL showed a 41% lower risk of composite of cardiovascular events including stroke than those with an achieved LDL-cholesterol level of 100 mg/dL without an increased risk of adverse events.

We also found that non-statin LDL-cholesterol lowering drugs such as ezetimibe or PCSK9 inhibitors are effective for stroke prevention as much as statins are. It implies that lowering of LDL-cholesterol levels

regardless of the pleiotropic effect of statin reduces stroke events. Clinical trials investigating non-statin LDL-cholesterol lowering drugs have supported a similar finding. The IMPROVE-IT trial showed the efficacy of simvastatin–ezetimibe combination therapy which was similar to that seen in previous statin trials, with a similar reduction in cardiovascular events including stroke according to the degree of LDL-cholesterol level lowering.⁶ The aforementioned FOURIER or ODYSSEY OUTCOMES trials also reported a similar trend.^{27,28} In addition, recent meta-analysis showed PCSK9 inhibitors had the highest probability of having the lowest rate of stroke, followed by ezetimibe plus statin and statins. Furthermore, Silverman et al. argued, based on a meta-analysis of MI trials, non-statin LDL-cholesterol lowering therapies were associated with similar cardiovascular risk reduction per decrease in LDL-cholesterol as statin interventions.² In that context, the ACC updated the guidelines that non-statin LDL-cholesterol lowering drugs could be considered optionally in the case of statin failure on maximally tolerated statin therapy. Our results which show the benefit of non-statin LDL-cholesterol-lowering drugs for the prevention of stroke could support this guideline.

Regarding the previous concern for the risk of haemorrhagic stroke, the previous meta-analyses reported that an intense reduction in the LDL-cholesterol level by statins did not increase the incidence of haemorrhagic stroke, whereas others showed the risk was increased without statistical significance.^{1,3} In our analysis, the active group had an increased haemorrhagic stroke risk (see Supplementary online material, Supplementary Figure 5) without statistical significance. However, the haemorrhagic stroke risk was neither statistically significant nor influenced by the achieved LDL-cholesterol level or the type of LDL-cholesterol-lowering therapies. Despite these findings, concern remains because the previous meta-analysis reported a higher risk of haemorrhagic stroke when treated with statin for the secondary stroke prevention population.³ However, in our study, the benefit of lowering LDL-cholesterol on stroke prevention seems greater in the secondary stroke prevention trials than in primary stroke prevention trials, which might be indicated by a significant interaction between primary and secondary prevention studies for the effect of the achieved LDL-cholesterol levels. Therefore, there is no need to hesitate to lower the LDL-cholesterol level even in secondary stroke prevention although the individualised risk of haemorrhagic stroke should be considered.

Unlike a recent meta-analysis of MI trials,² our study demonstrated no significant association between the achieved LDL-cholesterol level and the event rate of cardiovascular outcomes (see Supplementary online

material, Supplementary Figure 7). It might be primarily because a focus made on the enrolment of trials with stroke outcome led the study population to be heterogeneous to the cardiac outcome. To overcome the heterogeneity, we therefore divided the trials into primary MI prevention and non-primary (combined or secondary) MI prevention for our meta-regression analysis. The primary MI prevention group which could be thought of as homogeneous showed a significant positive association between the achieved LDL-cholesterol level and MI event rate ($P=0.008$, see Supplementary online material, Supplementary Figure 8). The second possibility is that the effect of non-statin LDL-cholesterol-lowering drugs could be different from that of statin. Usually, statin produces larger relative risk reduction for MI incidence than that for stroke incidence.¹ Our results also showed a similar trend (21% relative risk reduction for MI and 13% relative risk reduction for stroke in the statin group, see Supplementary online material, Supplementary Figure 9 and Figure 4). However, non-statin LDL-cholesterol lowering drugs produced opposite results (15% relative risk reduction for MI and 21% relative risk reduction for stroke in the statin group, see Supplementary online material, Supplementary Figure 9 and Figure 5). This discrepancy between statins and non-statins on outcomes from different vascular beds should be investigated in the future.

Some limitations of our study should be mentioned. First, subjects of enrolled trials had various cerebrovascular risk factors and clinical characteristics. However, the findings were consistent after adjustment of associated characteristics and the results obtained by different analytical methods and different subgroups showed similar trends, indicating the robustness of our results. Second, all LDL-cholesterol lowering trials for stroke prevention were not included in our meta-analysis. However, for a precise measurement of stroke occurrence, we included highly selective articles published after the year 2002 and trials with more than 5000 person-years. Before the National Cholesterol Education Program Adult Treatment Panel III guideline was announced, the importance of reducing cholesterol was not highlighted so that the studies before the announcement did not have a clear target level for LDL-cholesterol level or intensive medical treatment. In addition, most of the cholesterol-lowering studies at that time were about MI, less focused on stroke, and fewer stroke diagnostic tools were developed such as diffusion-weighted magnetic resonance imaging and had resulted in low diagnostic accuracy and a relatively low event rate of stroke during the study compared with later studies. Third, as mentioned above, some of the subjects in the primary prevention group had a prior stroke. As most of the other trials had a secondary prevention population less than 10%, it could be

considered as the primary prevention of stroke. Fourth, only haemorrhagic stroke was the concern for the adverse effect of the low LDL-cholesterol level. Some studies have reported that low LDL-cholesterol level was associated with an increase in rates of cancer, new onset diabetes, hepatobiliary disorders, and insomnia.¹³ However, haemorrhagic stroke might be the most important complication in the clinical field when using statins on stroke patients.

In conclusion, this meta-analysis demonstrates that lowering of the LDL-cholesterol level reduces stroke events to a very low level. Additional non-statin LDL-cholesterol lowering drugs such as ezetimibe or PCSK9 inhibitors could be used for further reduction of the LDL-cholesterol level to decrease the rate of stroke events.

Author contribution

WKS contributed to the conception and design of the work. JS, WKS, JL, KSH, JWC and HSJ contributed to the data acquisition, analysis and interpretation of data for the work. JS and WKS drafted the manuscript. JL, KSH, GMK and OYB critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work ensuring integrity and accuracy.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: WK Seo received honoraria for lectures from Pfizer, Sanofi-Aventis, Otsuka Korea, Dong-A Pharmaceutical Co., Ltd., Beyer, Daewoong Pharmaceutical Co. Ltd., Daiichi Sankyo Korea Co., Ltd., Boryung Pharmaceutical, study grant from Daiichi Sankyo Korea Co., Ltd. and consulting fee from OBELAB Inc. The other authors declared no conflicting interests.

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