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Comparison of the efficacy and safety of intensive-dose and standard-dose statin treatment for stroke prevention

A meta-analysis

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Abstract

Background: Previous study indicated that high-dose statin treatment might increase the risk of hemorrhagic stroke and adverse reactions. We aim to compare the efficacy and safety of intensive-dose and standard-dose statin treatment for preventing stroke in high-risk patients.

Methods: A thorough search was performed of multiple databases for publications from 1990 to June 2015. We selected the randomized clinical trials comparing standard-dose statin with placebo and intensive-dose statin with standard-dose statin or placebo for the prevention of stroke events in patients. Duplicate independent data extraction and bias assessments were performed. Data were pooled using a fixed-effects model or a random-effects model if significant heterogeneity was present.

Results: For the all stroke incidences, intensive-dose statin treatment compared with placebo treatment and standard-dose statin treatment compared with placebo treatment showed a significant 21% reduction in relative risk (RR) (RR 0.79, 95% confidence interval (CI) [0.71, 0.87], $P < 0.00001$) and an 18% reduction in RR (RR 0.82, 95% CI [0.73, 0.93], $P = 0.002$) in the subgroup without renal transplant recipients and patients undergoing regular hemodialysis separately. For the fatal stroke incidences, intensive-dose statin treatment compared with standard dose or placebo was effective reducing fatal stroke (RR 0.61, 95% CI [0.39, 0.96], $P = 0.03$) and the RR was 1.01 (95% CI [0.85, 1.20], $P = 0.90$) in standard-dose statin treatment compared with placebo.

Conclusion: The results of this meta-analysis suggest that intensive-dose statin treatment might be more favorable for reducing the incidences of all strokes than standard-dose statin treatment, especially for patients older than 65 years in reducing the incidences of all stroke incidences.

Abbreviations: CI = confidence interval, HMG CoA = hydroxymethylglutaryl-CoA, LDL = low-density lipoprotein, RCT = randomized clinical trial, RR = relative risk, ULN = upper limit of normal.

Keywords: intensive statin treatment, meta-analysis, standard statin treatment, stroke

1. Introduction

Currently, cerebrovascular disease is among the major causes of mortality and morbidity worldwide and, as such, confers a substantial burden on society.[1,2] According to statistics, the stroke incidences and mortality rate are increasing in China.[3,4]

Accordingly, it is important to prevent stroke. Hypercholesterolemia and low-density lipoprotein (LDL) cholesterol are the most important controllable factors for preventing the occurrence and recurrence of stroke. Numerous clinical and research studies have demonstrated that inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase (statins) reduce cardiovascular and cerebrovascular mortality and prevent stroke by reducing serum LDL levels; reduced LDL could substantially lower the risk of stroke.[5,6] In recent years, a few large-scale clinical trials have evaluated the efficiency and safety of statins for stroke prevention. Treatment protocols consisting of high-dose or intensive-dose statin treatment to prevent the incidences of stroke were developed by foreign scholars.[7–13] The studies by Waters[13] and Everett[10] showed that intensive-dose treatment was beneficial; the incidences of adverse reactions and hemorrhagic stroke were not significant. Some domestic scholars agreed with this finding.[14] However, the results of a trial by Amarenco et al[7] indicated that high-dose statin treatment might increase the risk of hemorrhagic stroke and adverse reactions. Because of these paradoxical results, there has been increasing attention on the efficacy and safety of intensive-dose statin treatment for stroke prevention. Therefore, we aimed to analyze the efficacy and safety of standard-dose and high-dose statin treatment for stroke prevention and to determine whether high-dose statin treatment could produce the better effect than standard-dose statin treatment. If it does, the high-dose statin treatment should be considered to be the choice of prevention of the stroke.

2. Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement in this study.[15] Ethical approval was not necessary for this meta-analysis because the results in our study for publication only involved de-identified pooled data from individual studies that ethics approval had been received.

2.1. Search strategy

We performed a systematic search of the PubMed, Embase, and Cochrane databases for randomized clinical trials (RCTs) conducted up to June 2015 that compared statins with placebo for the prevention of stroke events without any language restrictions. The following medical subject heading search terms were used in various combinations: hydroxymethylglutaryl-CoA reductase inhibitors (HMG CoA), HMG CoA reductase inhibitor, statin, atorvastatin, fluindostatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin, and rosuvastatin. The primary endpoints of the analysis were all stroke, fatal stroke, and hemorrhagic stroke events; the secondary endpoints were all-cause mortality, death from cancer, myopathy events, musculoskeletal disorders, and rhabdomyolysis disease. The search and data extraction were independently performed by 2 researchers, and differences in opinions were resolved through discussion or consultation with a third researcher. The detail of search strategy was shown in Appendix 1, http://links.lww.com/MD/B295.

2.2. Study selection

Studies were included if they fulfilled the following inclusion criteria: participants age 18 years or older; RCTs; masked assessment of outcomes; and recorded data on stroke events (all stroke, fatal stroke, and hemorrhagic stroke). Trials were also included if they focused on primary or secondary prevention of cardiovascular disease. The first meta-analysis included studies comparing intensive-dose statin treatment with standard-dose statin or placebo treatment; the second meta-analysis included studies that compared standard statin treatment with placebo. Standard treatment was defined as a prescribed daily dose of atorvastatin ≤ 20 mg, simvastatin ≤ 60 mg, or rosuvastatin ≤ 10 mg or any dose of pravastatin, lovastatin, or fluvastatin.[14,16,17] A daily dose that was higher than the standard dose was classified as intensive-dose statin treatment. The quality of the included studies was scored using the Jadad score,[18] which evaluates studies on a scale from 0 to 5 on the appropriateness of the randomization technique, the method for double-blinding and the description of withdrawals and dropouts. Two of us (JW and XY) independently extracted the study information and outcome results.

2.3. Quality assessment

The risk of bias for each study was evaluated based on the guidelines in the Cochrane Handbook for Systematic Reviews. There were 7 parts to the assessment: sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. We valued the impact of the methodological quality of the trials on the results by reviewing the randomization protocols and follow-up procedures adopted in each trial.

2.4. Endpoints

The primary endpoints for both meta-analyses were all stroke incidences, fatal stroke incidences, and hemorrhagic stroke incidences. For the analysis comparing intensive-dose statin treatment to standard-dose statin or placebo, the following secondary endpoints were assessed: death from all causes, myopathy events, musculoskeletal disorders, rhabdomyolysis disease, and creatine kinase >3 or 10 times the upper limit of normal (ULN). The analysis of placebo compared with standard-dose statin treatment assessed death from all causes, death from cancer, and creatine kinase >3 times the ULN.

2.5. Statistical analysis

The dichotomous pooled outcomes were calculated as the relative risk (RR) with the corresponding 95% confidence interval (CI) using the Mantel Haenszel statistical method (fixed-effects model) if no heterogeneity was detected in the studies. We selected the fixed-effects model or a random-effects model according to the Q statistic and I^2 index.[19] If heterogeneity was present ($P < 0.1$, or $I^2 > 50\%$), we used the random-effects model. Evidence for publication and other reporting biases was obtained by visually studying funnel plots. Egger test was applied to determine the symmetry of the funnel plot created to assess for publication and other reporting biases, $P < 0.05$ indicated bias.

All the data analysis was performed using the statistical software Stata 12.0 (Stata Corp, College Station, TX, USA) and Review Manager, version 5.3 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark).

3. Results

3.1. Description of the literature search

The initial database search identified 1836 human studies, and RCTs that were published between 1990 and June 2015. After applying all the exclusion criteria, only 17 RCTs, conducted on 120,970 subjects, were included in the analysis (Fig. 1). Data extracted from the 17 RCTs were included in the meta-analysis (Fig. 1). The first analysis included 7 trials that compared placebo or standard-dose statin treatment with intensive-dose statin treatment. Ten clinical trials comparing standard-dose statin treatment with placebo were included in the second meta-analysis. The characteristics of the included trials and patient can be found in Tables 1 and 2. In total, 70,365 (standard-dose statin/placebo, 35,152/35,213) participants were included in the standard-dose versus placebo analysis and 50,605 (intensive-dose statin/standard-dose statin or placebo, 25,302/25,303) participants were included in the intensive-dose versus standard-dose or placebo analysis. The statin type and dose in each study were described in Table 1. The mean follow-up durations were 4.4 years in the standard-dose statin treatment versus placebo analysis and 4.6 years in the intensive-dose statin treatment versus placebo analysis. The mean serum level of LDL level prior to study initiation was 3.3 mmol/L (125.7 mg/dL) in the standard-dose statin treatment versus placebo analysis and 3.1 mmol/L (119 mg/dL) in the intensive-dose statin treatment versus placebo analysis. All the participants had certain risk factors for stroke, such as diabetes, smoking, previous unstable angina, or cerebrovascular disease. Patients in both meta-analyses were not significantly different in age or gender.
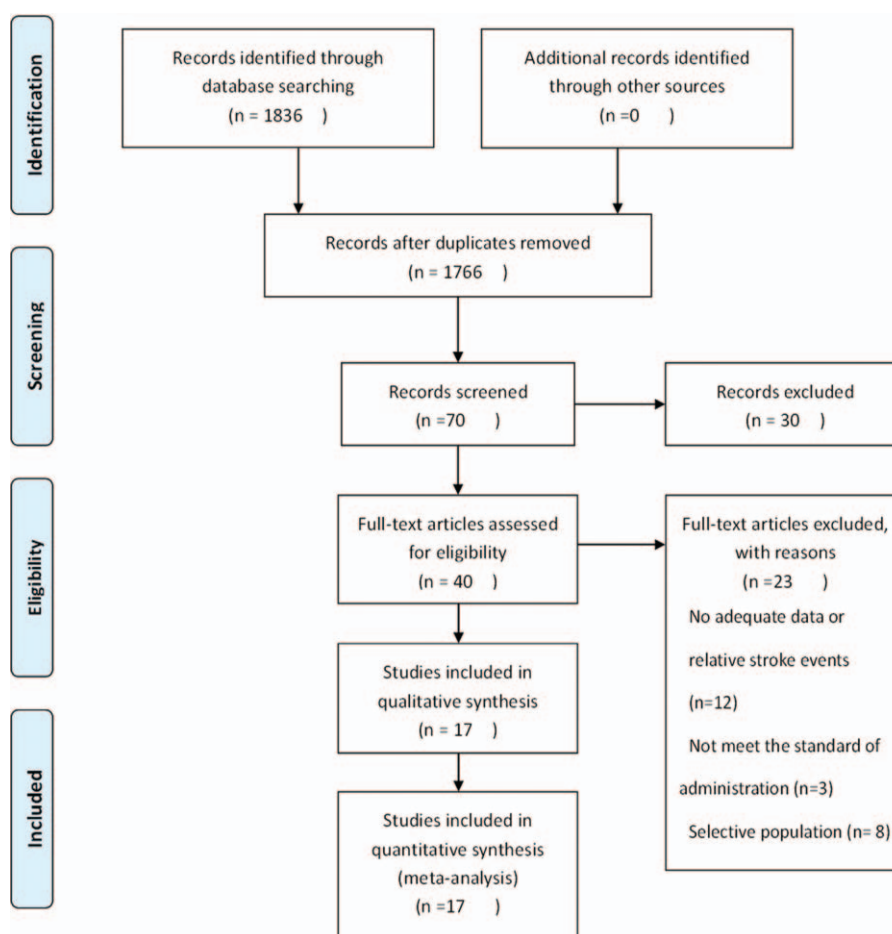
Figure 1. Flow chart of study selection flow diagram adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.

Table 1

Description of selected trials.

Author	Publication year	Treatment comparison, mg/d	Randomized patients (T/C)	Jadad[18] score*
Standard dose[†]				
Knopp et al[26]	2006	Atorvastatin 10 VS placebo	1211/1199	4
Sever et al[28]	2003	Atorvastatin 10 VS placebo	5168/5137	5
Hitman et al[25]	2007	Atorvastatin 10 VS placebo	1429/1412	5
Abedini et al[22]	2009	Fluvastatin 40–80 VS placebo	1050/1052	4
Shepherd et al[12]	2002	Pravastatin 40 VS placebo	2891/2913	5
Margolis et al[20]	2013	Pravastatin 40 VS placebo	7260/7247	4
Wanner et al[29]	2005	Atorvastatin 20 VS placebo	619/636	6
Nakamura et al[27]	2006	Pravastatin 10–20 VS placebo	3866/3966	5
Collins et al[23]	2004	Simvastatin 40 VS placebo	10,269/10,267	5
Fellstrom et al[24]	2009	Rosuvastatin 10 VS placebo	1389/1384	4
Intensive dose[‡]				
Athyros et al[8]	2002	Atorvastatin 10–80 VS placebo	800/800	4
Shepherd et al[21]	2006	Atorvastatin 80 VS 10	4995/5006	4
Amarenco et al[7]	2006	Atorvastatin 80 VS placebo	2365/2366	5
Waters et al[13]	2002	Atorvastatin 80 VS placebo	1538/1548	4
Pedersen et al[11]	2005	Atorvastatin 80 VS simvastatin 20	4439/4449	5
de Lemos et al[9]	2004	Simvastatin 40/80 VS placebo/simvastatin 20	2265/2232	5
Everett et al[10]	2010	Rosuvastatin 20 VS placebo	8901/8901	4

T/C = treatment/control group, VS = versus.
* Ranged from 1 to 5.
† Standard-dose statin treatment compared with placebo treatment.
‡ Intensive-dose statin treatment compared with placebo treatment.

Table 2

Patient characteristics in the included studies.

Author	Treatment comparison, mg/d	LDL, mg/dL	Median follow-up, y	Randomized patients (T/C)	Mean age (T/C)	Male sex (T/C)
Standard dose[*]						
Knopp et al[26]	Atorvastatin 10 VS placebo	179.5	4	1211/1199	61.1/61.0	796/803
Sever et al[28]	Atorvastatin 10 VS placebo	NA	3.3	5168/5137	63.1/63.2	4189/4174
Hitman et al[25]	Atorvastatin 10 VS placebo	115.4	3.9	1429/1412	62[†]	1932[‡]
Abedini et al[22]	Fluvastatin 40–80 VS placebo	157.7	6.7	1050/1052	50[†]	1387[‡]
Shepherd et al[12]	Pravastatin 40 VS placebo	146.2	3.2	2891/2913	75.4/75.3	1396/1408
Margolis et al[20]	Pravastatin 40 VS placebo	145.5	4.8	7260/7247	66[†]	7399[‡]
Wanner et al[29]	Atorvastatin 20 VS placebo	126	4	619/636	65.7/65.7	333/344
Nakamura et al[27]	Pravastatin 10–20 VS placebo	155.8	5.3	3866/3966	58.2/58.4	1227/1248
Collins et al[23]	Simvastatin 40 VS placebo	130.8	4.6	10,269/10,267	65[†]	15,402[‡]
Fellstrom et al[24]	Rosuvastatin 10 VS placebo	99.5	4	1389/1384	64.1/64.3	851/872
Intensive dose[§]						
Athyros et al[8]	Atorvastatin 10–80 VS placebo	180	3	800/800	58/59	624/632
Shepherd et al[21]	Atorvastatin 80 VS 10	97	5	4995/5006	61.2/60.9	4699/4045
Amarenco et al[7]	Atorvastatin 80 VS placebo	133	4.9	2365/2366	63/62.5	1427/1396
Waters et al[13]	Atorvastatin 80 VS placebo	124	0.3	1538/1548	65[†]	2006[‡]
Pedersen et al[11]	Atorvastatin 80 VS simvastatin 20	122	4.8	4439/4449	61.8/61.6	3590/3597
de Lemos et al[9]	Simvastatin 40/80 VS placebo/simvastatin 20	112	4	2265/2232	61/61	1716/1680
Everett et al[10]	Rosuvastatin 20 VS placebo	121.5	1.9	8901/8901	66/66	5475/5526

LDL = low-density lipoprotein, NA = not applicable, T/C = treatment/control group, VS = versus.

[*] Standard-dose statin treatment compared with placebo treatment.

[†] Mean age of all patients.

[‡] Total number of male patients in the treatment and control groups.

[§] Intensive-dose statin treatment compared with placebo treatment.

3.2. Risk of bias

The risk of bias in the studies is summarized in the graphs in Fig. 2; these trials were conducted in different developed countries, such as United States, Greece, and Japan and predominantly in hospitals. Almost no trials were described the allocation method. Most trials reported that the outcome assessment was blinded; only 2 studies[8,20] were considered high risk in this category. Almost all the endpoints were reported in most of the selected trials; thus, we considered the studies with incomplete outcome data to have an unclear or low risk of incidence bias; for other reasons, the risk of bias was characterized as high.

3.3. All stroke incidences

Intensive-dose statin treatment[7–11,13,21] showed a significant 21% reduction in RR (RR 0.79, 95% CI [0.71, 0.87], $P < 0.00001$; Fig. 3A) for all stroke events. In the high-dose statin treatment group, 2.4% of the patients had a stroke event (616/25,303), 3.1% in the placebo or standard-dose group (781/25,302). There was nonsignificant heterogeneity in the effect estimates ($P = 0.22$; $I^2 = 27\%$). The reduction in RR was much greater in patients older than 65 years (RR 0.52, 95% CI [0.36, 0.74], $P = 0.0003$) than for those younger than 65 years (RR 0.82, 95% CI [0.74, 0.92], $P = 0.0004$; heterogeneity $P = 0.71$; Fig. 3B). The analysis of standard-dose statin treatment[12,20,22–29] compared with placebo showed moderate heterogeneity in the effect estimates ($P = 0.01$; $I^2 = 58\%$). Because there were 3 trials on renal transplant recipients or patients undergoing regular hemodialysis, a subgroup analysis of patients in these trials[22,24,29] was conducted using the random-effects model. The result indicated that standard-dose

statin treatment significantly reduced the incidences of overall stroke (RR 0.82, 95% CI [0.73, 0.93], $P = 0.002$; Figs. 4 and 5), and there was not significant heterogeneity ($I^2 = 40\%$; $P = 0.13$) in the subgroup without renal transplant recipients and patients undergoing regular hemodialysis. The RR was much greater for renal transplant recipients and patients undergoing regular hemodialysis (RR 1.11, 95% CI [0.90, 1.37]). A funnel plot for standard-dose statin treatment versus placebo meta-analysis was shown in Fig. 5. Visual inspection shows no suggestion of publication bias favoring intermittent therapy. The Egger test indicated no statistically significant reporting bias ($P = 0.307$) (Appendix 2. eFig. 1 in the Supplement, http://links.lww.com/MD/B295).

3.4. Fatal stroke and hemorrhagic stroke incidences

Three trial reports included data on the incidences of fatal stroke and hemorrhagic stroke for intensive-dose statin treatment[7,10,13] with 25,619 patients. The meta-analysis using the fixed-effects model showed that high-dose statin treatment versus placebo significantly reduced the incidences of fatal stroke (RR 0.61, 95% CI [0.39, 0.96], $P = 0.03$; Fig. 6A) without heterogeneity among the trials ($I^2 = 0\%$; $P = 0.58$) and achieved a nonsignificant 5% reduction in RR in hemorrhagic stroke (RR 0.95, 95% CI [0.35, 2.55], $P = 0.92$; Fig. 6B).

Seven trials comparing standard-dose statin treatment with placebo provided data on the prevention of fatal stroke events.[12,20,22–25,29] This analysis showed that the increase of RR was not significant (RR 1.01, 95% CI [0.85, 1.20], $P = 0.90$). For the prevention of hemorrhagic stroke, 5 studies[22–24,27,29] were included in the analysis comparing standard-dose statin treatment with placebo. Again, there was a nonsignificant reduction in RR (RR 0.96, 95% CI [0.91, 1.01], $P = 0.13$).
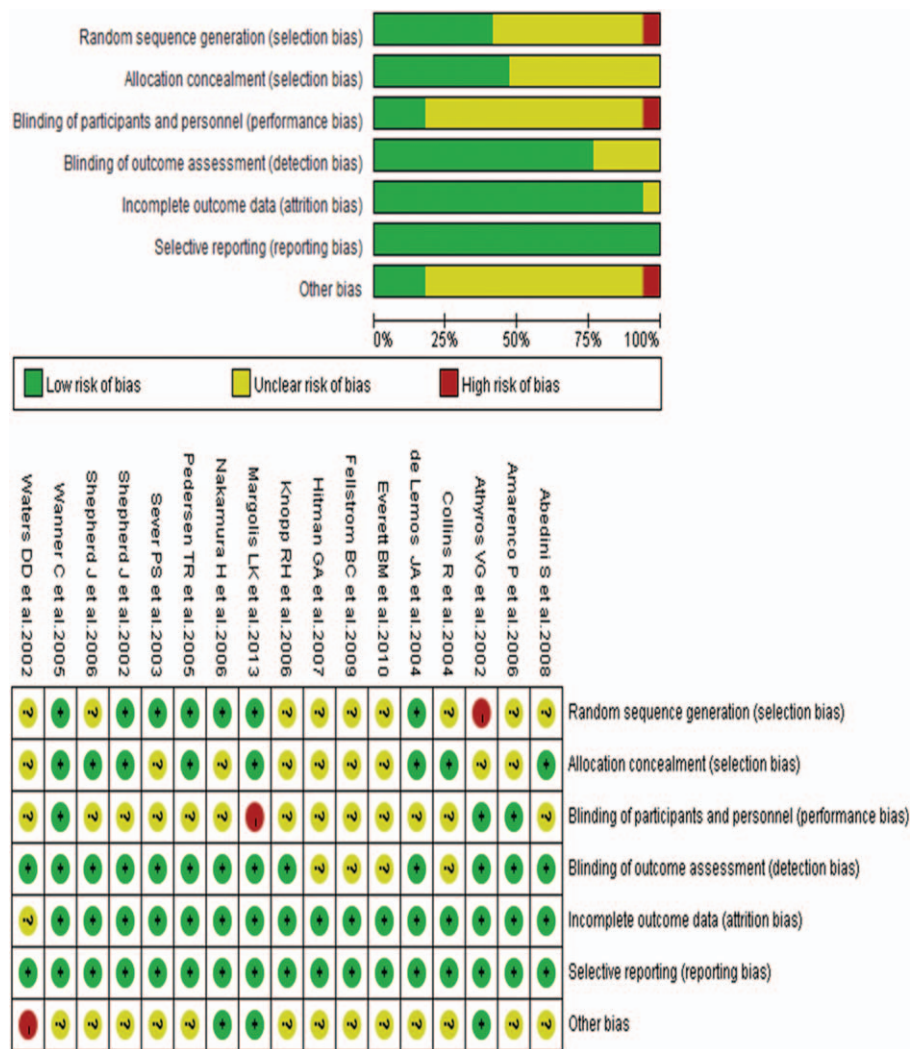
Figure 2. Risk of bias graph and risk of bias summary.

The analysis of adverse reactions to intensive-dose and standard-dose statin treatment showed nonsignificant changes in RR, except for the analysis of creatine kinase level (Table 3; the funnel plots for analysis of adverse reaction for intensive-dose statin treatment is presented in the Appendix 3, http://links.lww.com/MD/B295; the funnel plot for analysis of adverse reaction for standard-dose statin treatment is presented in the Appendix 4, http://links.lww.com/MD/B295).

4. Discussion

The meta-analysis revealed that intensive-dose statins treatment might be more effective than standard-dose statin treatment for the prevention of all strokes and fatal strokes.

The subgroup analysis showed that the treatment with standard-dose statins for the prevention of all stroke events in patients without renal transplant recipients and without undergoing regular hemodialysis resulted in a significant 18% reduction in RR. There was no statistically significant reduction in all stroke incidences when comparing standard-dose statin treatment compared with placebo treatment for renal transplant recipients and patients undergoing regular hemodialysis.

However, for intensive-dose statin instead of standard-dose statin treatment, the RR for all stroke events decreased by 21%. In terms of preventing fatal strokes, intensive-dose statin treatment showed a significant 39% reduction in RR but standard-dose statin treatment did not evoke a significant reduction in RR. Amarenco et al[30] reported similar results regarding these endpoints.

In preventing hemorrhagic stroke, our analysis indicated that the analysis comparing high-dose statin treatment with placebo showed a 5% RR reduction and 4% RR reduction in the standard-dose statin treatment compared with placebo, respectively (Table 4). But the reductions were no statistically significant. The retrospective cohort study by Hackam et al[31] in 2012 reported that statins treatment might not increase the risk of hemorrhagic stroke in the general population. Athyros et al[32] suggested that intensive lipid-lowering treatment had no relation to the increased risk of hemorrhagic stroke, especially for patients with ischemic stroke. Intensive-dose statin treatment decreased not only the risk of recurrent stroke but also the incidences of coronary artery events, which was consistent with previous reports by the statin safety group of the National Lipid Association indicating the safety of statins in preventing
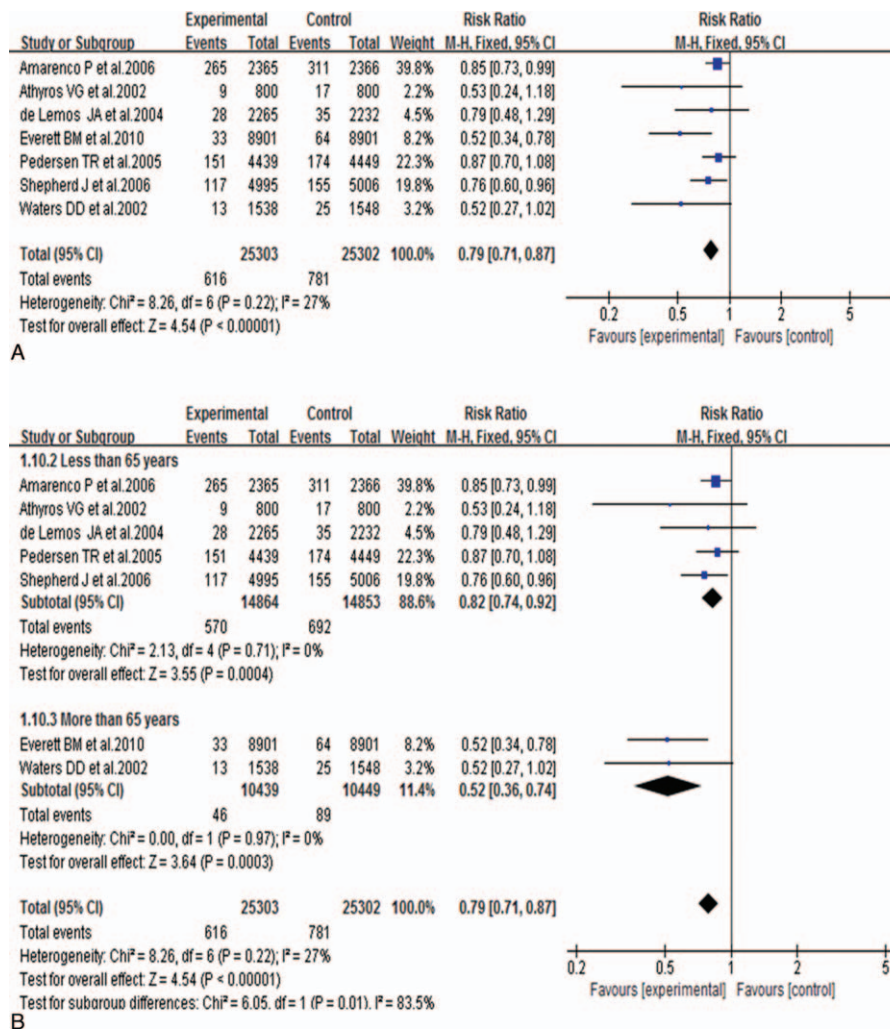
Figure 3A

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Amarenco P et al.2006	265	2365	311	2366	39.8%	0.85 [0.73, 0.99]
Athyros VG et al.2002	9	800	17	800	2.2%	0.53 [0.24, 1.18]
de Lemos JA et al.2004	28	2265	35	2232	4.5%	0.79 [0.48, 1.29]
Everett BM et al.2010	33	8901	64	8901	8.2%	0.52 [0.34, 0.78]
Pedersen TR et al.2005	151	4439	174	4449	22.3%	0.87 [0.70, 1.08]
Shepherd J et al.2006	117	4995	155	5006	19.8%	0.76 [0.60, 0.96]
Waters DD et al.2002	13	1538	25	1548	3.2%	0.52 [0.27, 1.02]
Total (95% CI)		25303		25302	100.0%	0.79 [0.71, 0.87]
Total events	616		781			

Heterogeneity: Chi² = 8.26, df = 6 (P = 0.22); I² = 27%
Test for overall effect: Z = 4.54 (P < 0.00001)

A

Figure 3B

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.10.2 Less than 65 years						
Amarenco P et al.2006	265	2365	311	2366	39.8%	0.85 [0.73, 0.99]
Athyros VG et al.2002	9	800	17	800	2.2%	0.53 [0.24, 1.18]
de Lemos JA et al.2004	28	2265	35	2232	4.5%	0.79 [0.48, 1.29]
Pedersen TR et al.2005	151	4439	174	4449	22.3%	0.87 [0.70, 1.08]
Shepherd J et al.2006	117	4995	155	5006	19.8%	0.76 [0.60, 0.96]
Subtotal (95% CI)		14864		14853	88.6%	0.82 [0.74, 0.92]
Total events	570		692			

Heterogeneity: Chi² = 2.13, df = 4 (P = 0.71); I² = 0%
Test for overall effect: Z = 3.55 (P = 0.0004)

1.10.3 More than 65 years						
Everett BM et al.2010	33	8901	64	8901	8.2%	0.52 [0.34, 0.78]
Waters DD et al.2002	13	1538	25	1548	3.2%	0.52 [0.27, 1.02]
Subtotal (95% CI)		10439		10449	11.4%	0.52 [0.36, 0.74]
Total events	46		89			

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.97); I² = 0%
Test for overall effect: Z = 3.64 (P = 0.0003)

Total (95% CI)		25303		25302	100.0%	0.79 [0.71, 0.87]
Total events	616		781			

Heterogeneity: Chi² = 8.26, df = 6 (P = 0.22); I² = 27%
Test for overall effect: Z = 4.54 (P < 0.00001)
Test for subgroup differences: Chi² = 6.05, df = 1 (P = 0.01), I² = 83.5%

B

Figure 3. Forest plot for overall stroke events. (A) Analyze comparing standard-dose/placebo with intensive-dose statin treatment; (B) Subgroup analyze comparing standard-dose/placebo with high-dose statin treatment.
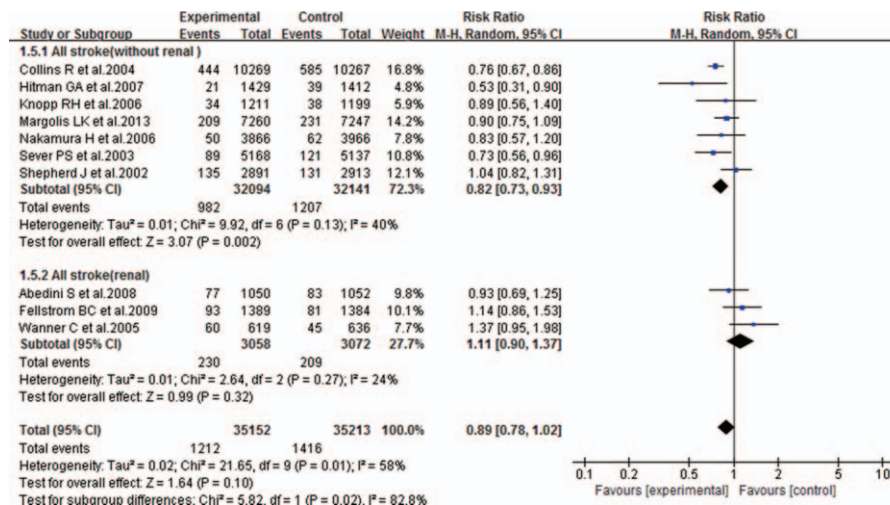
Figure 4

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 All stroke(without renal)						
Collins R et al.2004	444	10269	585	10267	16.8%	0.76 [0.67, 0.86]
Hitman GA et al.2007	21	1429	39	1412	4.8%	0.53 [0.31, 0.90]
Knopp RH et al.2006	34	1211	38	1199	5.9%	0.89 [0.56, 1.40]
Margolis LK et al.2013	209	7260	231	7247	14.2%	0.90 [0.75, 1.09]
Nakamura H et al.2006	50	3866	62	3966	7.8%	0.83 [0.57, 1.20]
Sever PS et al.2003	89	5168	121	5137	10.8%	0.73 [0.56, 0.96]
Shepherd J et al.2002	135	2891	131	2913	12.1%	1.04 [0.82, 1.31]
Subtotal (95% CI)		32094		32141	72.3%	0.82 [0.73, 0.93]
Total events	982		1207			

Heterogeneity: Tau² = 0.01; Chi² = 9.92, df = 6 (P = 0.13); I² = 40%
Test for overall effect: Z = 3.07 (P = 0.002)

1.5.2 All stroke(renal)						
Abedini S et al.2008	77	1050	83	1052	9.8%	0.93 [0.69, 1.25]
Fellstrom BC et al.2009	93	1389	81	1384	10.1%	1.14 [0.86, 1.53]
Wanner C et al.2005	60	619	45	636	7.7%	1.37 [0.95, 1.98]
Subtotal (95% CI)		3058		3072	27.7%	1.11 [0.90, 1.37]
Total events	230		209			

Heterogeneity: Tau² = 0.01; Chi² = 2.64, df = 2 (P = 0.27); I² = 24%
Test for overall effect: Z = 0.99 (P = 0.32)

Total (95% CI)		35152		35213	100.0%	0.89 [0.78, 1.02]
Total events	1212		1416			

Heterogeneity: Tau² = 0.02; Chi² = 21.65, df = 9 (P = 0.01); I² = 58%
Test for overall effect: Z = 1.64 (P = 0.10)
Test for subgroup differences: Chi² = 5.82, df = 1 (P = 0.02), I² = 82.8%

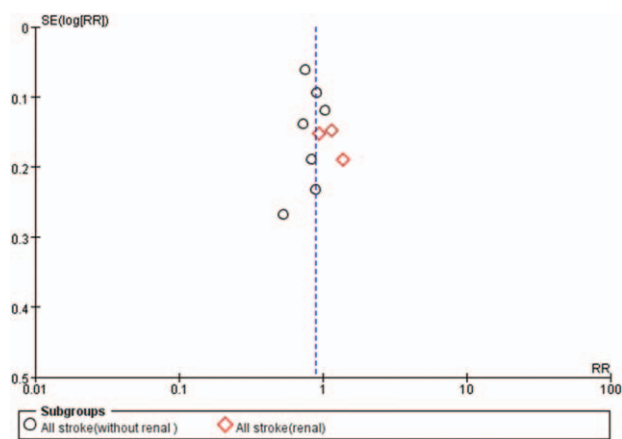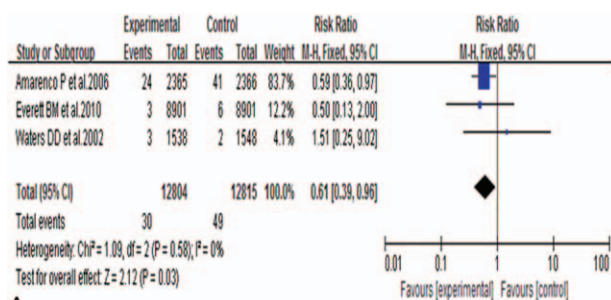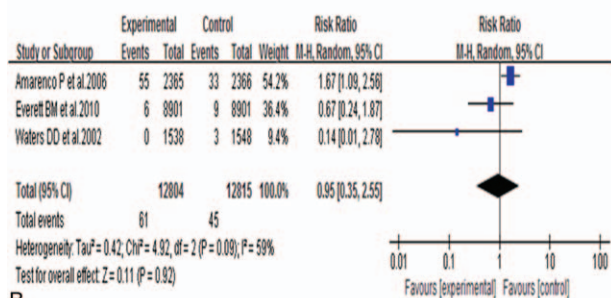**Figure 4.** Forest plot for overall stroke events comparing placebo with standard-dose statin treatment.

Figure 5. Funnel plot for the meta-analysis of overall stroke events comparing placebo with standard-dose statin.

Figure 6. Forest plot comparing standard-dose/placebo with intensive-dose statin treatment. (A) Fatal stroke events; (B) hemorrhagic stroke.

hemorrhagic stroke.[33] However, a meta-analysis by Martinez-Ramirez et al[34] revealed that patients treated with statins who underwent treatment for vein thrombolysis had a significantly greater risk of hemorrhagic stroke, but some studies have reported that statins decrease the incidences of hemorrhagic stroke.[7,30] The number of participants in our analysis comparing high-dose statin treatment for the prevention of hemorrhagic stroke was small, leading to wide CIs. Hackam et al[31] also reported on this endpoint.

The meta-analysis showed that older patients (>65 years) had a significantly lower rate of overall stroke with intensive-dose statin treatment than younger patients (<65 years) (0.44% compared with 3.8%). The analysis comparing intensive-dose statin treatment achieved a significant 21% reduction in RR (RR 0.79, 95% CI [0.71, 0.87], $P < 0.00001$). The RR reduction was much greater for patients older than 65 years (RR 0.52, 95% CI [0.36, 0.74]) than for those younger than 65 years (RR 0.82, 95% CI [0.74, 0.92]) (heterogeneity $P = 0.71$). The results of the secondary prevention of cardiovascular events in the Long-Term Intervention with Pravastatin in Ischemic Disease trial[35] revealed that statin treatment was more effective at preventing stroke in patients older than 65 years, and this was consistent with the findings of Nakaya et al.[36]

The analysis suggested that intensive-dose statin treatment could greatly damage the liver enzymes, with an increased prevalence of alanine aminotransferase or serum aspartate aminotransferase >3 times ULN (RR 5.45, 95% CI [3.81, 7.81], $P < 0.00001$). Previous meta-analysis compared standard statin with placebo for secondary prevention in diabetes patients, or compared statin treatment with placebo for stroke prevention or for the secondary prevention of cardiovascular and cerebrovascular events,[30,37] whereas our analysis compared the efficacy and safety of intensive-dose and standard-dose statin treatment for stroke prevention. Because the inclusion criterion for both comparisons was similar, we could estimate the effect of intensive-dose compared with standard-dose statins.

There are some potential limitations in our study. The definition of stroke was slightly different in some studies, which

Table 3

Results of analysis of adverse reaction.

	No. of events (T/C)	No. of participants (T/C)	I², %	RR (95% CI)	Z	P	Rate (T/C), %*
Intensive dose†							
All death	709/755	9869/9847	56	0.90 (0.76–1.07)	1.23	0.22	7.2/7.7
Myopathy	13/18	6804/6815	0	0.72 (0.35–1.47)	0.89	0.37	0.19/0.26
Musculoskeletal disorder	489/529	6019/5982	0	0.96 (0.79–1.17)	0.40	0.69	8.1/8.8
Rhabdomyolysis	8/5	6019/5982	0	1.54 (0.53–4.50)	0.79	0.43	0.13/0.083
ALT or AST > 3 times ULN	191/35	14,064/14,053	50	5.45 (3.81–7.81)	9.25	<0.00001	1.4/0.86
ALT or AST > 10 times ULN	11/1	9069/9047	0	7.59 (1.38–41.59)	2.33	0.02	0.12/0.11
Standard dose‡							
All death	1951/2040	10,067/10,070	0	0.96 (0.91–1.01)	1.53	0.13	19/20
Death from cancer	157/137	4899/4933	0	1.16 (0.92–1.45)	1.25	0.21	3.2/2.8
ALT or AST > 3 times ULN	21/12	2008/2020	58	1.88 (0.57–6.19)	1.03	0.30	1.0/5.9

All the figures (Appendix 3, eFig. 2; Appendix 4, eFig. 3, http://links.lww.com/MD/B295) related to the analysis of adverse reaction were in the accompaniment.

ALT = alanine aminotransferase, AST = serum aspartate aminotransferase, CI = confidence interval, RR = relative risk, T/C = treatment/control group, ULM = upper limit of normal.

* Defined as the ratio of the number of patients with the corresponding events to the total number of patients in the active group.

† Intensive-dose statin treatment compared with placebo treatment.

‡ Standard-dose statin treatment compared with placebo treatment.

Table 4

Results of meta-analysis for all stroke incidences comparing with different dose statin treatments.

	All stroke				Fatal stroke				Hemorrhagic stroke			
	I^2, %	P	RR (95% CI)	Rate (T/C)*, %	I^2, %	P	RR (95% CI)	Rate (T/C)*, %	I^2, %	P	RR (95% CI)	Rate (T/C)*, %
Intensive dose[†]	27	<0.00001	0.79 (0.71, 0.87)	2.4/3.1	0	0.03	0.61 (0.39, 0.96)	0.23/0.38	59	0.92	0.95 (0.35, 2.55)	0.48/0.35
Standard dose[‡]	58	0.10	0.89 (0.78, 1.02)	3.4/4.0	44	0.9	1.01 (0.85, 1.20)	1.1/1.1	0	0.13	0.96 (0.73, 1.25)	0.61/0.64

CI = confidence interval, RR = relative risk, T/C = treatment/control group.

* Defined as the ratio of the number of patients with the corresponding events to the total number of patients in the active group.

† Intensive-dose statin treatment compared with placebo treatment.

‡ Standard-dose statin treatment compared with placebo treatment.

might have been associated with some differences in the populations' baseline risk. The composite endpoint included additional events, which might have leaded to affect the degree of the risk reduction, depending on the effect of statins on such events. For example, the relative reduction of all death events may show that we overestimated the risk reduction for the death events. In the analysis for all stroke events, there are 2 RCTs being intensive-dose statin treatment versus placebo or standard-placebo (Tables 1 and 2), which might also have leaded to affect the degree of the risk reduction.

In addition, during the follow-up periods, the patient's medication standards were not completely consistent; there may be some differences, which might have resulted in smaller or higher risk reductions. Not all patients in the trial group continued taking statins at the end of the follow-up period, or some patients in the placebo group might also receive statins during follow-up in the analysis of intensive-dose statin treatment.[9] Because of the lack of safety data, we could not compare standard-dose and intensive-dose statin treatment for all secondary endpoints in this analysis.

LDL-cholesterol target management is an important part of stroke prevention. For some high-risk patients, the LDL-cholesterol target were difficult to reach, and intensive-dose statin treatment may be necessary.[38,39] Our meta-analysis revealed that intensive-dose statin treatment might be more effective than standard-dose statin treatment for stroke prevention. However, the current Dutch guidelines recommend starting with standard-dose statin; this decision was likely to be driven by economic factors and resource considerations.

The results of the meta-analysis of safety were no statistically significant; except liver enzyme activity, the incidences of safety-related events, such as musculoskeletal disorders, rhabdomyolysis, and death from cancer, were low and not significant for different statin dosages, but this does not mean that intensive-dose statin treatment is safe (Table 3). The Pravastatin in elderly individuals at risk of vascular disease[12] and Cholesterol and Recurrent Events[40] trials suggested that intensive lipid lowering treatment might increase the incidences of death from cancer; however, a recent meta-analysis by Cholesterol Treatment Trialists[41] showed that statin treatment had a nonsignificant relation with death from cancer, and some scholars in China have also claimed that intensive-dose statin treatment is a safe method for preventing strokes.[14,42] It is necessary to obtain more data on the safety of intensive-dose statin treatment to confirm our results.

5. Conclusion

This meta-analysis showed that intensive-dose statin treatment might be more favorable at preventing the incidences of all stroke incidences and fatal stroke incidences than standard-dose statin treatment and especially for patients older than 65 years in reducing the incidences of all stroke incidences, but the safety of intensive-dose statin treatment remains controversial. Patients older than 65 years should receive careful monitoring, and caution should be exercised in treating such patients with statins. Clinicians should pay more attention to the dosage of statins administered to prevent hemorrhagic stroke and other adverse reactions.

Many unknowns should be addressed and resolved: the optimal dose of statins, the risk of death from cancer, and other risks. To substantiate the findings of the analysis and help clinicians better administer statins, it is important to develop more multicentre, double-blind, placebo-controlled, global randomized trials focusing on stroke prevention and the dose–effect relationship.

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