Am J Transl Res 2020;12(2):463-477
www.ajtr.org /ISSN:1943-8141/AJTR0100829

Original Article

Significant reduction in the LDL cholesterol increases the risk of intracerebral hemorrhage: a systematic review and meta-analysis of 33 randomized controlled trials

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Received August 12, 2019; Accepted December 8, 2019; Epub February 15, 2020; Published February 28, 2020

Abstract: The dose-dependent pleiotropic effects of statin therapy may have unwanted side effects such as increasing the risk of intracerebral hemorrhage (ICH). The relationships among statin therapy, LDL-cholesterol levels, and ICH risk remain controversial. Here, we conduct a systematic review and meta-analysis of dose-dependent statin therapy and ICH risk. Eligible articles were identified by searching MEDLINE from inception up to December 1, 2018. Reference lists of previous meta-analyses were manually searched to retrieve all relevant publications. Statin doses were allocated into one of two groups according to the observed reduction of LDL cholesterol: doses that lowered LDL-cholesterol levels ≥35% were regarded as high-dose statin therapy, whereas those that lowered LDL-cholesterol levels <35% were regarded as low-dose statin therapy. We retrieved 33 studies involving 203,305 subjects. The pooled analysis indicated that high-dose statin treatment significantly increased the risk of ICH [relative risk (RR), 1.35; 95% confidence interval (CI), 1.08-1.68] and reduced the risk of all stroke (RR, 0.85; 95% CI, 0.78-0.92), ischemic stroke (RR, 0.79; 95% CI, 0.72-0.87), and all-cause mortality (RR, 0.94; 95% CI, 0.90-0.98). The analyses did not detect any association between low-dose statin treatment and ICH (RR, 1.05; 95% CI, 0.88-1.25). Low-dose statin therapy significantly reduced the incidence of all stroke (RR, 0.84; 95% CI, 0.79-0.89), ischemic stroke (RR, 0.81; 95% CI, 0.76-0.86), and all-cause mortality (RR, 0.94; 95% CI, 0.92-0.97). Our data indicate that low-dose statin therapy is a safe and effective ICH treatment, whereas high-dose statin therapy is associated with increased ICH risk. Hence, our meta-analysis suggests that the dose-dependent pleiotropic effects of statin therapy are related to the measured reduction in LDL cholesterol.

Keywords: High-dose statin therapy, low-dose statin therapy, intracerebral hemorrhage, meta-analysis

Introduction

Statins are widely used for the primary and secondary prevention cardiovascular diseases [1]. Statins confer dose-dependent reductions in cholesterol levels, but also exhibit dose-dependent pleiotropic effects (vasodilatory, antithrombotic, anti-inflammatory, and antioxidant effects) [2]. The prevailing consensus agrees that reducing LDL cholesterol is beneficial, however, the recommended strategies for achieving this have changed over time [3-6]. The clinical benefit of statin therapy for lowering LDL cholesterol is widely accepted. The Cholesterol Treatment Trialists Collaboration reported that the magnitude of clinical benefit achieved by statin therapy was proportional to the absolute reduction in LDL cholesterol [7].

Intracerebral hemorrhage (ICH) is inversely related to serum cholesterol levels. Low cholesterol levels appear to promote arterial muscle necrosis and microaneurysm formation [8]. Post hoc analyses of the Stroke Prevention by

Aggressive Reduction in Cholesterol Levels (SPARCL) trial and other studies indicated that statin therapy might increase ICH risk [9]. Although the precise definition of intensive reduction in LDL-cholesterol levels remains to be agreed, there are sufficient data to determine whether different statin doses are associated with ICH risk.

This study was performed to evaluate the safety of statin therapy and to guide clinical treatment decisions. We conducted a systematic review and meta-analysis of statin use and patient outcomes after ICH, and assessed the associations between different statin doses and ICH risk.

Materials and methods

Literature search strategy

The methods used in this study are similar to those used in a previous meta-analysis [8]. Eligible articles were identified by searching the MEDLINE database from inception up to December 1, 2018. The following search terms were used: 'statin therapy', 'cardiovascular disease', 'intracerebral hemorrhage', and 'high-dose statin'. The reference lists of previous meta-analyses were manually searched to retrieve all relevant publications. The study employed the criteria and guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [12]. No ethical approval was needed for this study as all data were previously published.

Inclusion and exclusion criteria

The following inclusion criteria were used: (1) original articles reporting randomized controlled trials, case-control studies, or cohort studies; (2) studies comparing intensive reduction of LDL-cholesterol levels with control therapy of lower-dose statins; (3) studies containing data on statin dosage and patient outcomes for ICH. Statin doses that achieved <35% reduction in LDL cholesterol were regarded as low-dose statin therapy, whereas doses that achieved ≥35% reduction in LDL-cholesterol levels were regarded as high-dose statin therapy [10]; (4) studies compared the use of ezetimibe to control therapy according to McKinney [8]; and (5) patients were followed for more than one year. The following exclusion criteria were used: (1) studies lacked data on statin dosage and patient outcomes for ICH; and (2) duplicate publications from the same study.

Data extraction and quality assessment

Three authors independently extracted the following data from eligible studies: study name, publication year, dosage of high-dose statin therapy (active treatment group), dosage of low-dose statin therapy (control group), number of patients, total strokes, ischemic stroke, ICH, all-cause mortality. Disagreements were resolved by discussion with an independent expert. Data on randomization, allocation concealment, comparisons of baseline characteristics, defined eligibility criteria, type of control, blinding (patients, investigators, assessment of vital status), percent lost to follow-up, and use of intention-to-treat analysis were assessed using the Jadad score [8].

Statistical analysis

Relative risk (RR) was used as a measurement of the association between different statin doses and risk of ICH, total strokes, ischemic stroke, and all-cause mortality. We estimated the degree of heterogeneity among the trials using the I^2 test. When significant heterogeneity (I^2>50%) was detected, outcome data were pooled using a random-effects model [11]. Potential publication bias was estimated using Begg's test. Forest plots were generated to analyze and display results. All calculations were performed using STATA (version 11.0).

Results

Selection of the clinical trial studies

Our search and selection strategy retrieved 33 clinical trial studies enrolling 203,305 subjects that were included in this systematic review and meta-analysis. Among these trials, 8 random controlled trials (RCTs) compared more-intensive statin therapy (the dose of statins is classified as high- and low-dose statin therapy based on the degree of reduction of LDL cholesterol) with less-intensive statin therapy (these studies are about the effect of different doses of statin, and the dose of statins is classified as low-dose statin therapy based on the degree of reduction of LDL cholesterol)

Table 1. Characteristics of eligible studies

Study	Subgroup	Statin therapy/Control						Follow-up (months)
		Subjects enrolled	All stroke	Ischemic stroke	ICH	Total mortality	Reduction of LDL cholesterol	
ACAPS [25]	Low dose	460/459	0/5	-/-	0/3	1/8	28%/0	34.1
4S [42]	High dose	2221/2223	44/64	29/49	0/2	182/256	35.1%/+1.1%	64.8
CARE [46]	Low dose	2081/2078	54/78	48/64	2/6	180/196	29.5%/2.2%	60
AF-TEXCAPS [44]	Low dose	3304/3301	14/17	1/1	1/0	80/77	23.3%/+5.3%	62.4
LIPID [33]	Low dose	4512/4502	224/272	200/255	17/9	717/888	30%/1.3%	72
CLAPT [22]	Low dose	112/114	0/1	-/-	0/1	0/2	30.4%/11.5%	24
GISSI-P [37]	Low dose	2138/2133	20/19	15/13	1/0	72/88	14.5%/3.3%	23
MIRACL [26]	High dose	1538/1548	12/24	-/-	0/3	64/68	41.9%/+8.9%	4
PATE [19]	Low dose	331/334	11/18	11/15	0/3	14/20	24.5%/18.4%	46.8
ALLHAT-LLT [45]	Low dose	5170/5185	209/231	71/83	17/5	631/641	24.0%/8.2%	57.6
GREACE [35]	High dose	800/800	9/17	-/-	1/1	23/40	46.1%/5.6%	36
HPS [36]	Low dose	10269/10267	444/585	290/409	51/53	1328/1507	32.1%/2.3%	60
PROSPER [31]	Low dose	2891/2913	135/131	91/88	8/10	298/305	34%/0	38.4
ASCOT-LLA [33]	Low dose	5168/5137	89/121	74/95	11/20	185/212	34.6%/2.3%	39.6
ALERT [24]	Low dose	1050/1052	93/91	67/66	10/17	143/138	32.1%/8.2%	61.2
A-to-Z [13]	High dose	2265/2232	28/35	22/31	6/0	130/104	43.8%/30.6%	24
PROVE-IT [14]	High dose	2099/2063	21/19	10/12	4/1	46/66	41.5%/10.4%	24
CARDS [30]	High dose	1428/1410	21/39	9/24	0/0	61/82	39%/+2.6%	46.8
TNT [16]	Low dose	4995/5006	117/155	96/130	16/17	284/282	20.6%/+3.1%	58.5
4D [27]	High dose	619/633	59/44	47/33	5/8	297/320	40.5%/4%	46.8
IDEAL [15]	Low dose	4439/4449	151/174	129/158	6/6	366/374	32.8%/14%	57.6
MEGA [32]	Low dose	3866/3966	50/62	34/46	16/14	55/79	19.1%/6.1%	63.6
SPARCL [43]	High dose	2365/2366	265/311	218/274	55/33	216/211	45.9%/4.5%	58.8
ASPEN [29]	Low dose	1211/1199	34/38	14/15	4/2	70/68	17.7%/1.8%	48
CORONA [38]	High dose	2514/2497	126/145	73/90	15/9	728/759	42%/2%	32.8
BONE [23]	High dose	485/119	1/0	-/-	1/0	0/0	42.1%/0	13
JUPITER [34]	High dose	8901/8901	33/64	23/47	6/9	198/247	50%/0	22.8
GISSI-HF [28]	Low dose	2285/2289	82/66	63/53	11/3	657/644	32%/+7.4%	46.8
AURORA [40]	High dose	13891384	94/81	57/55	25/21	636/660	42%/2%	45.6
SEARCH [17]	Low dose	6031/6033	255/279	233/255	24/25	964/970	16.5%/4.1%	80.4
SHARP [21]	Low dose	4650/4620	171/210	114/157	45/37	1142/1115	30.6%/2.8%	58.8
TIMI [18]	High dose	9067/9077	296/345	236/297	59/43	1215/1231	43%/25%	84
EMPATHY [20]	Low does	2518/2524	30/47	22/41	8/6	41/34	28%/1.9%	37

[13-20], and 25 RCTs compared statin therapy (the dose of statins is classified as high- and low-dose statin therapy based on the degree of reduction of LDL cholesterol) with control (placebo or usual care) [21-46]. The procedure used for literature screening is presented in the Supplementary Figure 1. Measurements of the LDL-cholesterol levels before and after statin therapy and the reduction of LDL cholesterol are presented in **Table 1**. The median duration of follow up among survivors was 46.8 months, ranging from 4 months to 84 months (**Table 1**).

Statin therapy and intracerebral hemorrhage

Combining the two trial types (more-intensive vs. less-intensive therapy and statin vs. control), ICH occurred in 425 subjects (0.46%) in the statin therapy group versus 367 subjects (0.32%) in the control group. Compared with the control group, the statin therapy group had a significantly increased risk of developing ICH (RR, 1.15; 95% CI, 1.00-1.32; **Figure 1A**). Moderate heterogeneity (I^2=22.1%) was detected in these studies. We performed subgroup analysis according to the observed reduction of LDL

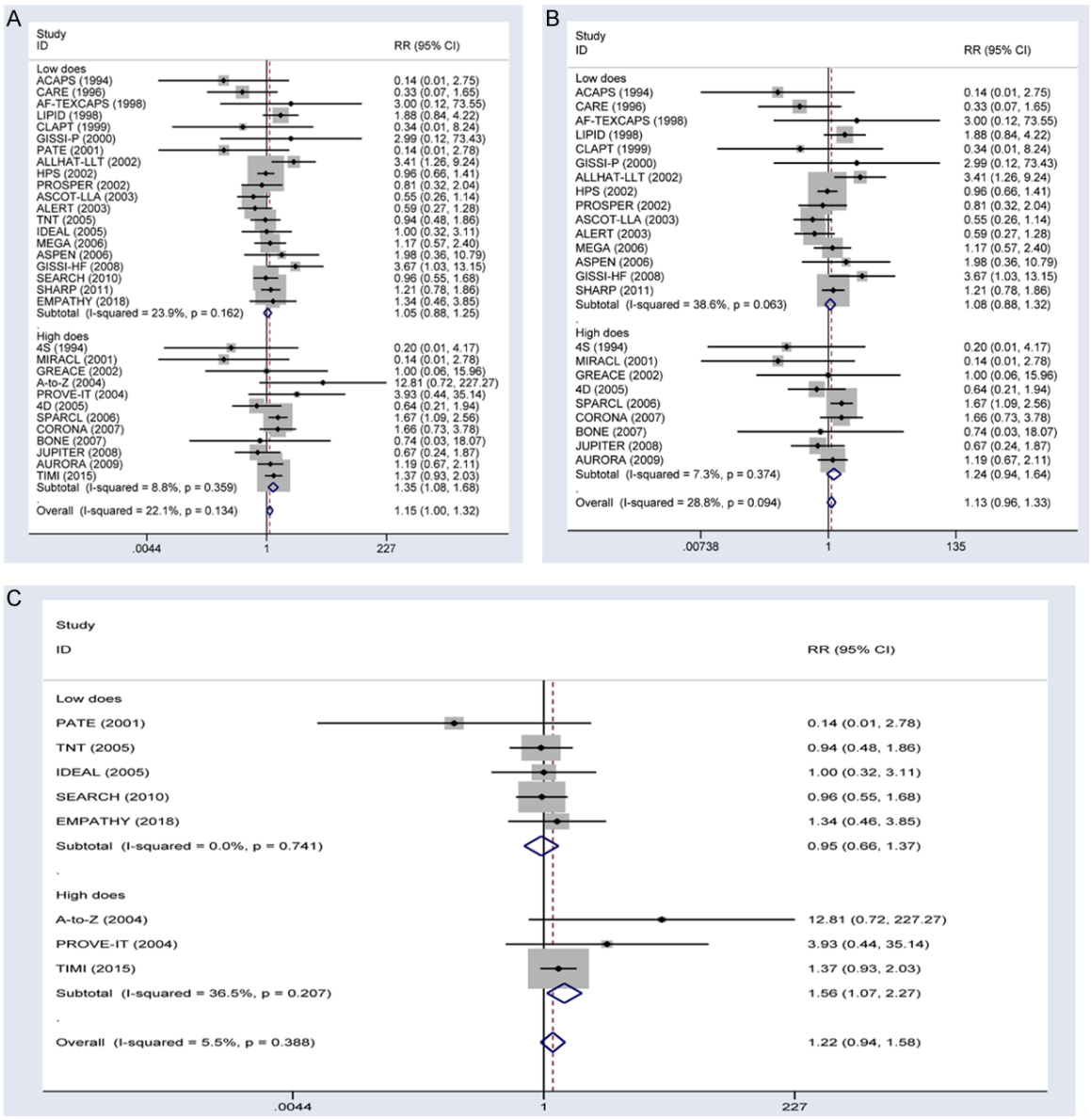

Figure 1. Forest plots showing the effect of statin therapy on ICH risk. A. Effects of all trial type on ICH risk stratified by the reduction in LDL cholesterol. B. Effects of statin vs. control trials on ICH risk stratified by the reduction in LDL cholesterol. C. Effects of more-intensive vs. less-intensive statin therapy trials on ICH risk.

cholesterol in the treatment group (more-intensive therapy or statin therapy) in the two types of as of studies. The frequency of ICH was 0.53% and 0.37% in subjects receiving high-dose and low-dose statin therapy, respectively. Patients taking high-dose statin treatment experienced an increased risk of developing ICH (RR, 1.35; 95% CI, 1.08-1.68). By contrast, low-dose statin treatment was not significantly associated with ICH (RR, 1.05; 95% CI, 0.88-1.25). The power to detect an association of high-dose and low-dose statin therapy with ICH was 88% and 9%, respectively. No heterogeneity was detected among the subgroups, and no significant publication bias was detected in Begg's analysis (**Figure 2**).

Analyses of the 25 RCTs that compared statin therapy with control did not detect any significant association between statin therapy and ICH (RR, 1.13; 95% CI, 0.96-1.33; **Figure 1B**). Moderate heterogeneity (I^2=28.8%) was detected in these studies. Subgroup analyses indicated that high-dose and low-dose statin

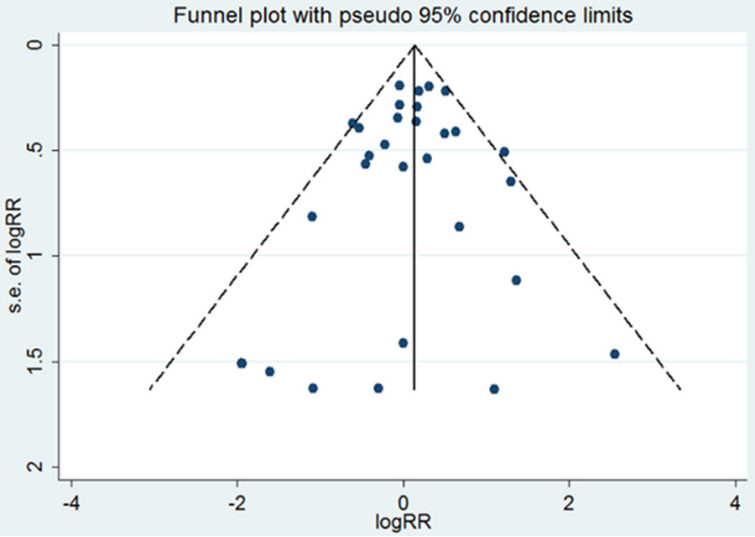

Figure 2. Funnel plot analysis of potential publication bias.

therapy did not significantly affect ICH (for high dose: RR, 1.24, 95% CI, 0.94-1.64; for low dose: RR, 1.08, 95% CI, 0.88-1.32). Analyses of the 8 RCTs that compared more-intensive with less-intensive therapy did not detect any significant association between statin therapy and ICH (RR, 1.22; 95% CI, 0.94-1.58; **Figure 1C**). Moderate heterogeneity (I^2=5.5%) was detected in these studies. Subgroup analysis indicated that low-dose statin therapy had no effect on ICH (RR, 0.95; 95% CI, 0.66-1.37), whereas high-dose statin therapy significantly improved ICH (RR, 1.56; 95% CI, 1.07-2.27) in the subjects.

Statin therapy and the all stroke rate

Among all trials, the overall stroke rate was 3.2% in the statin therapy group vs. 3.7% in the control group. The statin therapy group had a significantly lower total stroke rate (RR, 0.84; 95% CI, 0.80-0.88; **Figure 3A**) than the control group. Subgroup analyses indicated that the total numbers of strokes were significantly lower in the low-dose statin therapy group (RR, 0.84; 95% CI, 0.79-0.89) than the high-dose statin therapy group (RR, 0.85; 95% CI, 0.78-0.92). Statin therapy reduced the risk of all stroke by 16% (RR, 0.84; 95% CI, 0.80-0.89; **Figure 3B**) in the statin vs. control trials and by 16% (RR, 0.85; 95% CI, 0.78-0.93; **Figure 3C**) in the high-dose vs. low-dose statin therapy trials. Subgroup analyses of the statin treatment vs. control trials indicated that the total numbers of strokes were significantly reduced in the low-dose statin therapy group (RR, 0.84; 95% CI, 0.79-0.90) and the high-dose statin therapy group (RR, 0.84; 95% CI, 0.76-0.93). Subgroup analyses of more-intensive versus less-intensive statin therapy trials also indicated that the total numbers of strokes were significantly reduced in the low-dose statin therapy group (RR, 0.84; 95% CI, 0.75-0.94) and the high-dose statin therapy group (RR, 0.86; 95% CI, 0.75-1.00).

Statin therapy and ischemic stroke

Analysis of all trials showed that the rate of ischemic stroke was 2.3% in the statin therapy group vs. 2.8% in the control group. Thus, ischemic stroke was significantly lower in the statin therapy group (RR, 0.80; 95% CI, 0.76-0.85; **Figure 4A**) than in the control group. Subgroup analyses indicated that ischemic stroke was significantly reduced in the low-dose statin therapy group (RR, 0.81; 95% CI, 0.76-0.86; **Figure 4A**) and the high-dose statin therapy group (RR, 0.79; 95% CI, 0.72-0.87; **Figure 4A**). In trials comparing statin therapy with control, statin therapy reduced the risk of all stroke by 20% (RR, 0.80; 95% CI, 0.75-0.86; **Figure 4B**). Subgroup analyses indicated that the total numbers of strokes were significantly reduced in the low-dose statin therapy group (RR, 0.80; 95% CI, 0.74-0.87) and the high-dose statin therapy group (RR, 0.80; 95% CI, 0.71-0.90). In more-intensive versus less-intensive statin therapy trials, statin therapy reduced the risk of all strokes by 18% (RR, 0.81; 95% CI, 0.74-0.89; **Figure 4C**). Subgroup analyses showed that the total numbers of strokes also were significantly reduced in the low-dose statin therapy group (RR, 0.82; 95% CI, 0.73-0.92) and the high-dose statin therapy group (RR, 0.79; 95% CI, 0.67-0.92).

Statin therapy and all-cause mortality

The all-cause mortality rate in all trials was 11.0% in the statin therapy group vs. 11.4% in the control group. Thus, the statin therapy

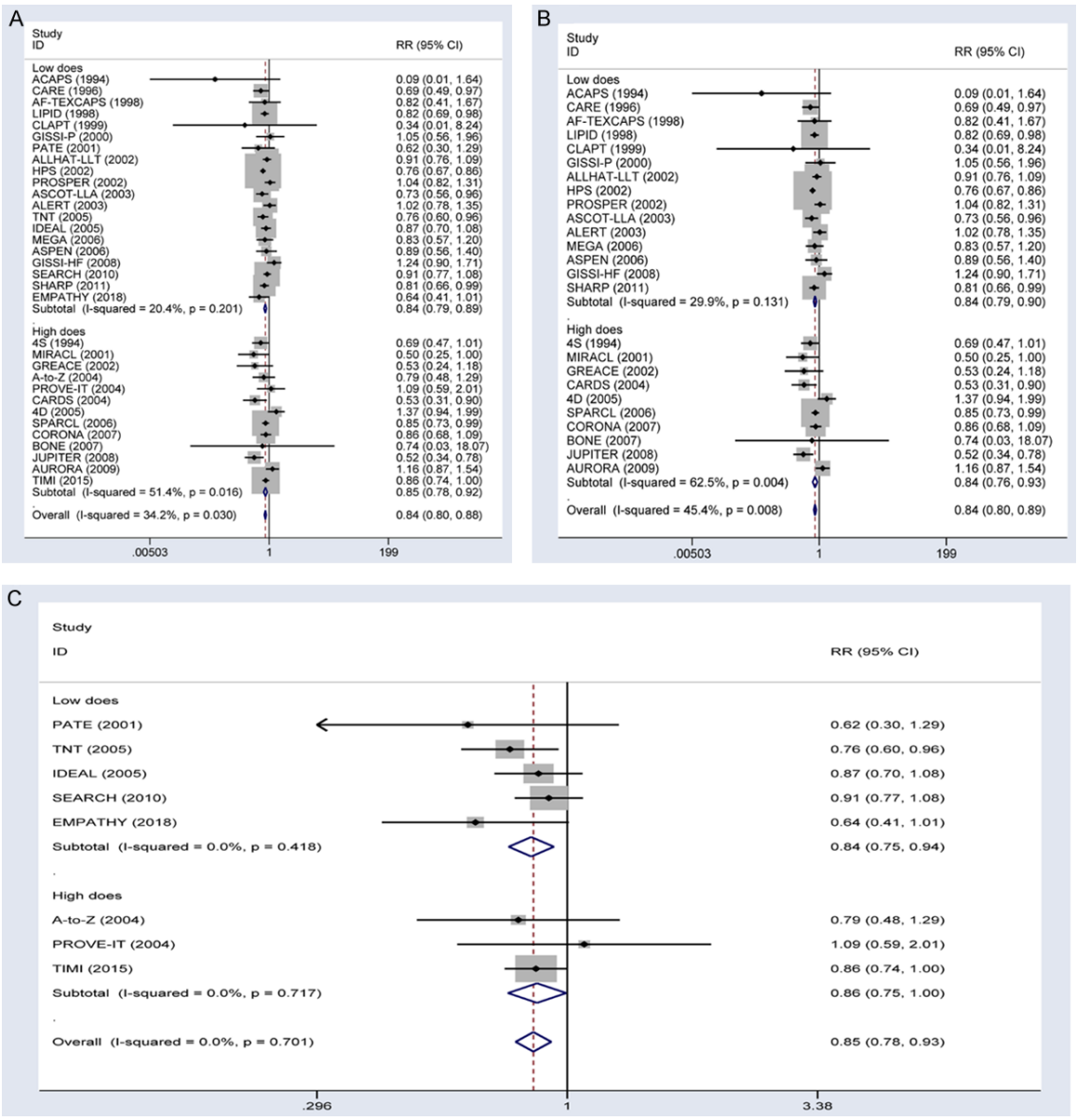

Figure 3. Forest plots showing the use of statin treatment and the risk of all stroke. A. Effects of all type trial on risk of all stroke stratified by the reduction in LDL cholesterol. B. Effects of statin vs. control trials on risk of all stroke stratified by the reduction in LDL cholesterol. C. Effects of more-intensive vs. less-intensive statin therapy trials on risk of all stroke stratified by the reduction in LDL cholesterol.

group exhibited a significant reduction in all-cause mortality (RR, 0.94; 95% CI, 0.92-0.96; **Figure 5A**). Subgroup analyses indicated that all-cause mortality was significantly lower in the low-dose statin therapy (RR, 0.94; 95% CI, 0.92-0.97) and high-dose statin therapy (RR, 0.94; 95% CI, 0.90-0.98) groups than in the control group. In the statin therapy vs. control trials, statin therapy reduced the risk of all-cause mortality by 8% (RR, 0.92; 95% CI, 0.90-0.95; **Figure 5A**). Subgroup analyses indicated that all-cause mortality was significantly reduced in the low-dose statin therapy (RR, 0.93; 95% CI, 0.90-0.96) and high-dose statin therapy (RR, 0.91; 95% CI, 0.87-0.95) groups. In the more-intensive vs. less-intensive therapy trials, there was no significant difference in all-cause mortality between the statin therapy and control groups (RR, 0.99; 95% CI, 0.95-1.04; **Figure 5**). Subgroup analyses indicated that all-cause mortality was not associated with high-dose statin therapy (RR, 0.99; 95% CI,

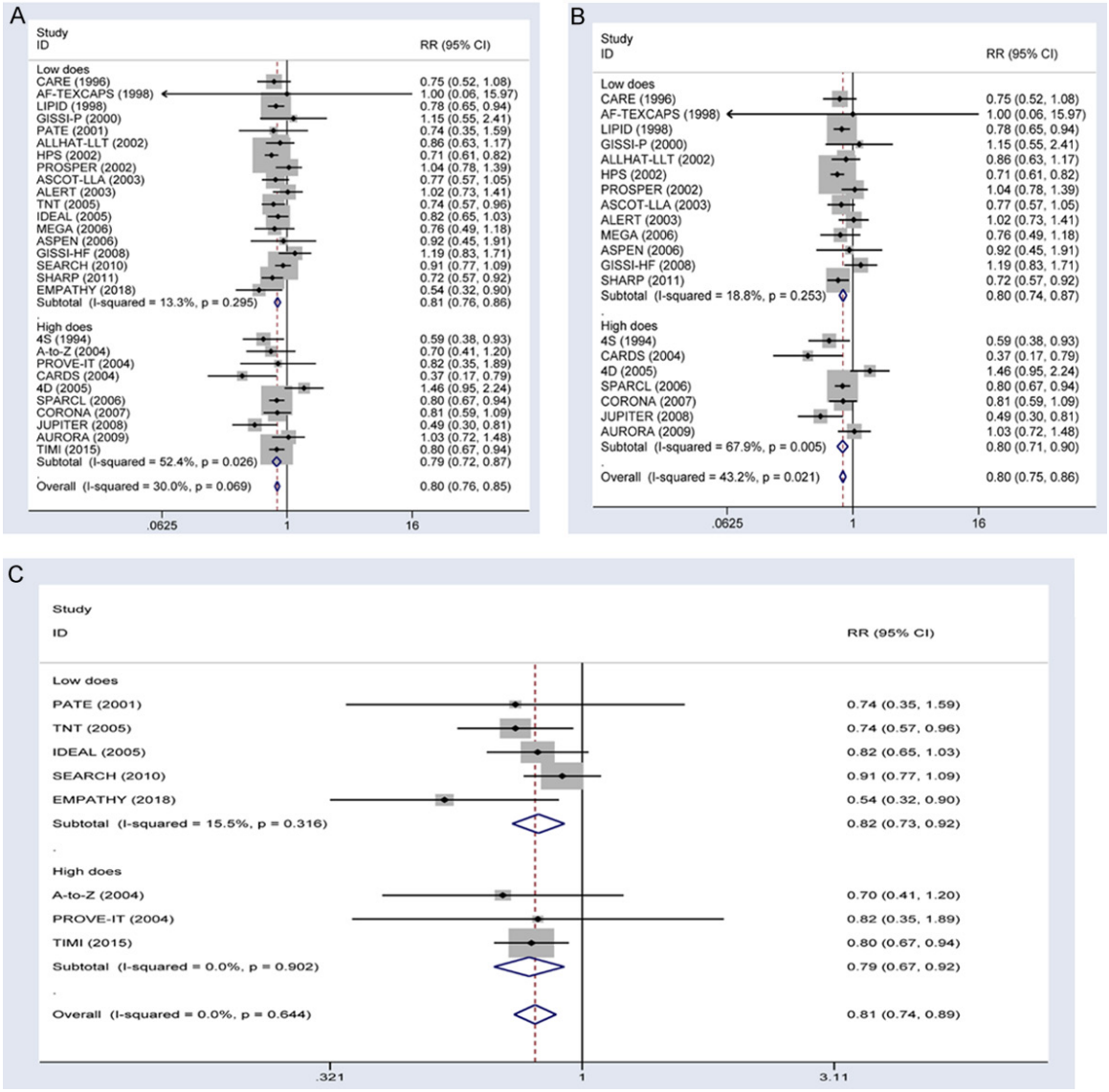

Figure 4. Forest plots showing the use of statin treatment and the risk of ischemic stroke. A. Effects of all type trial on the risk of ischemic stroke stratified by the reduction in LDL cholesterol. B. Effects of statin vs. control trials on risk of ischemic stroke stratified by the reduction in LDL cholesterol. C. Effects of more-intensive vs. less-intensive statin therapy trials on risk of ischemic stroke stratified by the reduction in LDL cholesterol.

0.93-1.06) or low-dose statin therapy (RR, 0.99; 95% CI, 0.93-1.06).

Statin effects on patients with intracerebral hemorrhage

Statins can enhance neurological recovery after ICH in animal models. The beneficial effects appear to be due to endothelial stabilization, anti-inflammatory effects, upregulation of endothelial nitric oxide synthase, and stimulation of neurogenesis and synaptogenesis [47-49] (**Figure 6**). Several retrospective cohort studies have reported that statin therapy after ICH reduced mortality and the risk of recurrent ICH (**Table 2**). Flint et al. [50] analyzed patients admitted to hospital for ICH, and reported that statin use was associated with lower mortality (18.4% vs. 38.7%) and higher likelihood of discharge to home or a rehabilitation facility (51.1% vs. 35.0%) compared to patients who were not treated with a statin, respectively. Patients whose statin therapy was discontinued were less likely to survive to 30 days after ICH than those receiving statin therapy [odds ratio (OR), 0.16; 95% CI, 0.12-0.21; $P<0.001$], and were less likely to be discharged to home or an acute rehabilitation facility than those

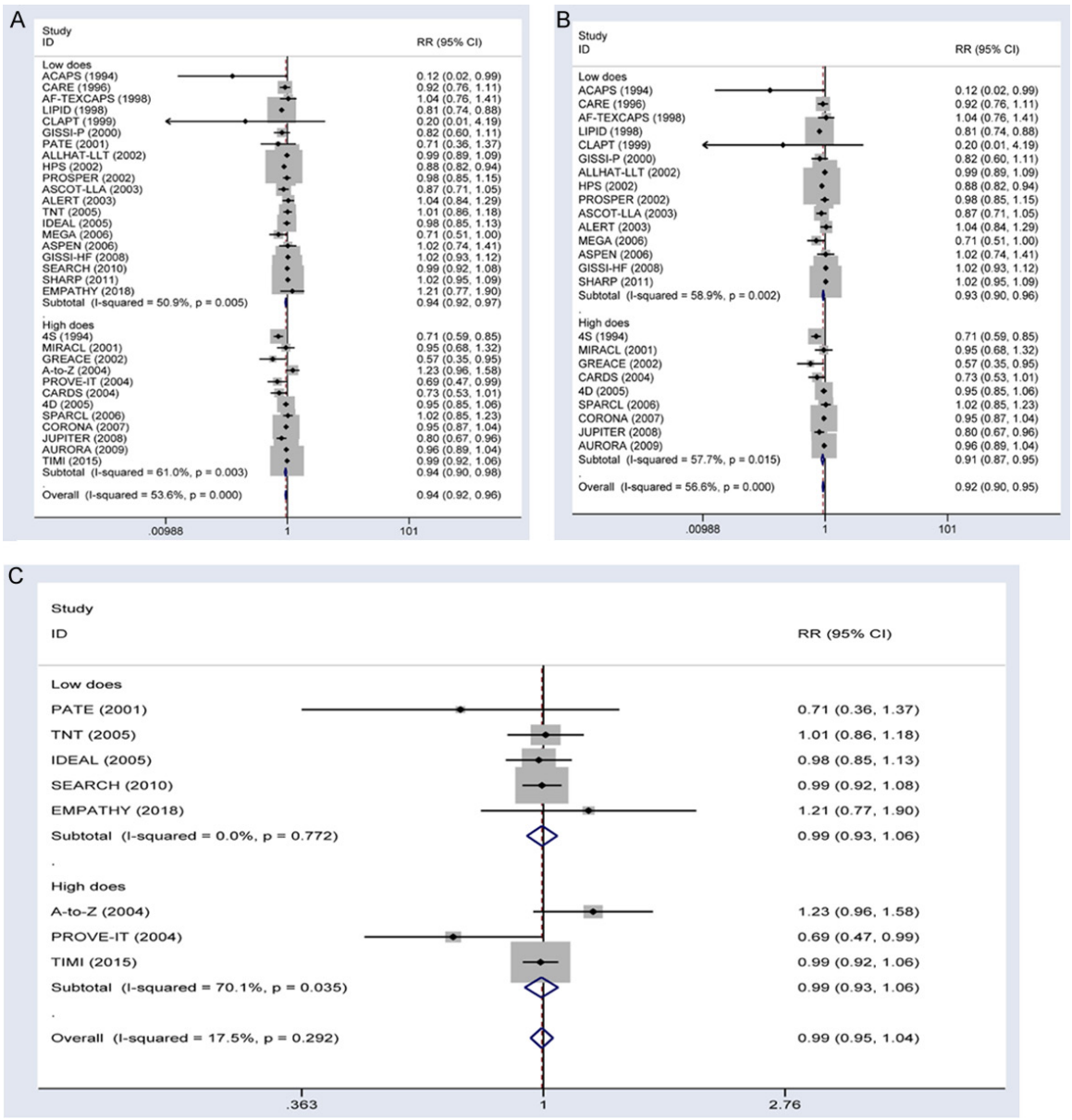

Figure 5. Forest plots showing the use of statin therapy and the risk of all-cause mortality. A. Effects of all type trials on risk of all-cause mortality stratified by the reduction in LDL cholesterol. B. Effects of statin vs. control trials on risk of all-cause mortality stratified by the reduction in LDL cholesterol. C. Effects of more-intensive vs. less-intensive statin therapy trials on risk of all-cause mortality stratified by the reduction in LDL cholesterol.

receiving statin therapy (OR, 0.26; 95% CI, 0.20-0.35; *P*<0.001) [50]. Saliba et al. [51] reported that statin use might be associated with reduced risk of ICH. Retrospective data from the National Health Insurance Research Database of Taiwan also indicated that statin therapy reduced the risk of all-cause mortality in patients with ICH compared with those with ICH who did not received statin therapy, especially for those treated with hydrophilic statins [51, 52].

There are currently no rigorous RCTs that are adequately powered to evaluate the impact of statin therapy on major clinical outcomes following ICH. Patients who appeared to have a better prognosis were more likely to receive continuous or new statin treatment [53]. There is growing evidence from clinical studies that the risk of ICH declines with increasing cholesterol levels. Our meta-analysis demonstrated that high-dose statin therapy that lowered LDL-cholesterol levels by ≥35% slightly increased

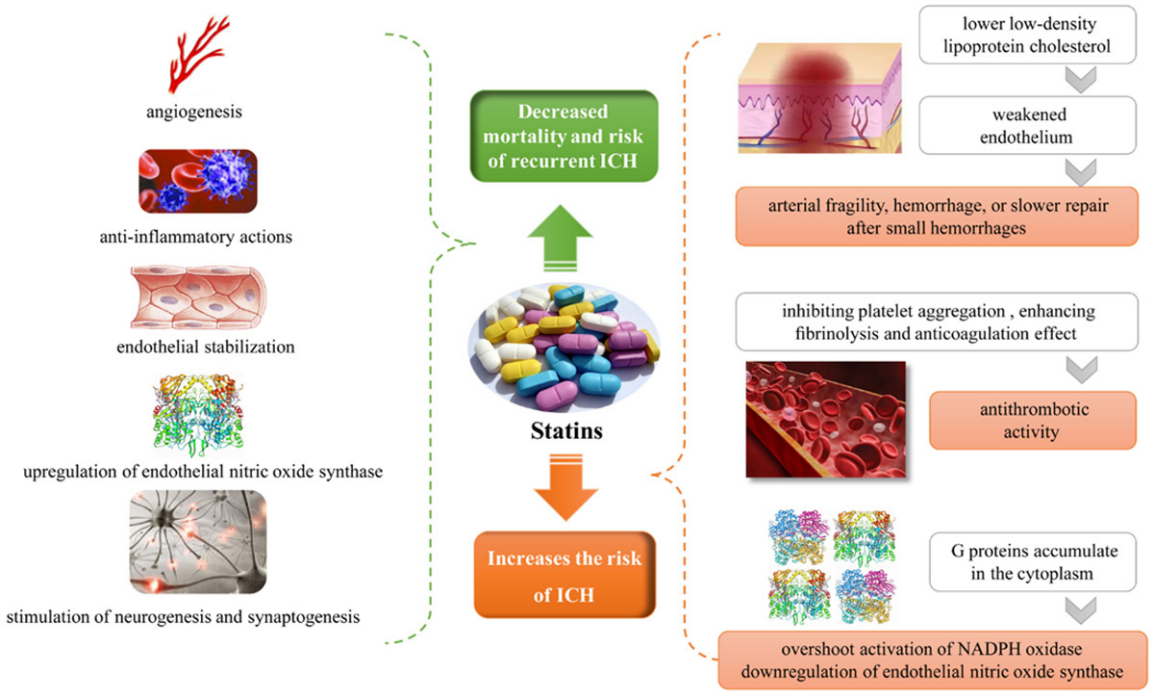

Figure 6. Pleiotropic effects of statin therapy. Statin therapy is beneficial in the treatment of intracerebral hemorrhage (ICH) due to endothelial stabilization, anti-inflammatory effects, upregulation of endothelial nitric oxide synthase, and stimulation of neurogenesis and synaptogenesis [47-49]. The mechanism of statin therapy associated with increased ICH may be due to lower cholesterol levels in a weakened endothelium, which subsequently leads to arterial fragility, hemorrhage, or slower repair after small hemorrhages [57]. Statins may have mild antithrombotic activity and reduce thrombosis by inhibiting platelet aggregation, enhancing fibrinolysis, and affecting anticoagulation [56, 63, 64]. Statin therapy also promotes the accumulation of small G proteins, and activation of small G proteins leads to activation of NADPH oxidase or downregulation of endothelial nitric oxide synthase [65, 66].

Table 2. Studies evaluating statin effects on clinical outcomes in intracerebral hemorrhage

Study	Study design	Number of patients	Statin use	Results
Flint [50]	Retrospective	3481	1194 patients with in-hospital statin use	In-hospital use OR for survival 4.3 (3.5-5.2)
Pan [58]	Retrospective	3218	220 patients with in-hospital statin use	Inpatient use: aOR for good outcome (mRS score of 0-2 at 3 months) 2.3 (1.5-3.4)
Chen [59]	Retrospective	8332	749 patients with statin use within 3 months after ICH	Lower all-cause mortality: aHR, 0.74 (0.60-0.92)
Dowlatshahi [60]	Retrospective	2466	537 with prior statin use	Discontinuation higher rate of poor outcome:mortality: aOR, 1.7 (1.1-2.6)
Tapia-Perez [61]	Retrospective	447	18/63 discontinued	Discontinuation higher risk of death: aHR, 6.9 (2.1-23.1)
Siddiqui [62]	Retrospective	2457	268 discontinued; 423 continued	Continuation lower mortality: aOR, 0.11 (0.03-0.44)
Chung [52]	Retrospective	1416	708 discontinued; 708 continued	Continuation lower mortality: HR, 0.38 (0.26-0.57)
Saliba [51]	Retrospective	1304	75.3% of patients had AAEDD <10 mg/d, 19.0% had AAEDD 0-19.9 mg/d, and 5.7% had AAEDD ≥20 mg/d	Statin use reduced the risk of ICH: 0.62 (0.47-0.81) in those with AAEDD ≥20 mg/d

aOR: adjusted odds ratio; aHR: adjusted hazard ratio; AAEDD: average atorvastatin equivalent daily dose.

the risk of ICH. Our data also indicate that low-level statin therapy and slight reductions in LDL cholesterol confer beneficial effects on patients after ICH. Thus, these data do not indicate that statin use increases the risk of ICH recurrence due to a slight reduction in LDL cholesterol.

Discussion

Several recent high quality meta-analyses show that lower LDL-cholesterol levels were associated with lower rates of major coronary events [7, 54, 55]. However, epidemiological studies

have reported increased rates of hemorrhagic stroke and ICH-related mortality in populations with low cholesterol levels [8]. These inconsistencies among different clinical trials employing different statin doses targeting LDL-cholesterol reductions motivated the current meta-analysis.

Previous meta-analyses of RCTs using standard statin regimens to reduce LDL cholesterol did not report an increased risk of ICH [8, 9, 55]. Studies reported that statins improved patient outcomes after ICH; however, the study enrolled only a small number of patients (9.5%) treated with high-dose statins [50], and the other study did not observe a reduction in lowering of LDL cholesterol [52]. The SPARCL trial, which administered 80 mg of atorvastatin per day to reduce LDL cholesterol by 45.9%, observed an increased the rate of ICH with statin therapy compared with placebo [43]. Although these RCTs were primarily investigating whether statin therapy prevented stroke, it is yet not clear why high-dose statin therapy increased the risk of ICH [56].

Among all trials, high-dose statin therapy increased the risk of ICH and decreased the rates of all stroke, ischemic stroke, and all-cause mortality compared with the control group. Then, combined all types of studies to perform subgroup analysis according to the observed reduction of LDL cholesterol in the treatment group (more-intensive therapy or statin therapy) found that the risk of ICH was increased in the high-dose group (Statin doses that achieved <35% reduction in LDL cholesterol) but not in the low-dose group. Subgroup analysis in different types of studies found that high-dose group increased ICH risk in more-intensive vs. less-intensive therapy types of studies, while high-dose groups had a modest tendency to increase ICH risk in statin vs. control type studies.

Statins have dose-dependent reduction of LDL cholesterol, also have dose-dependent pleiotropic effects including antithrombotic activity. Lower cholesterol levels may weaken endothelial tissue and lead to arterial fragility, hemorrhage, or slower repair after small hemorrhages. Alternatively, potentially weakened endothelium may be more susceptible to microaneurysms, which are the chief pathological finding of cerebral hemorrhages [57]. Statins may have mild antithrombotic activity by inhibiting platelet aggregation and enhancing fibrinolysis [56]. These meta-analyses also indicate that low-dose statin therapy reduced the risk of all stroke, ischemic stroke, and all-cause mortality without increased ICH.

This meta-analysis has some limitations. There are only a limited number of studies investigating the association of statin therapy with ICH, and the relatively small sample size may affect the statistical power for computing associations among high-dose and low-dose statin therapy with ICH. We did not have access to individual patient records, and there may be unreported variables such as a lack of information on blood pressure and type of ICH that affected the ICH incidence in the selected studies. Considering these limitations, our data suggest that high-dose statin therapy significantly increases the risk of ICH compared to the control group. The statin therapy dosage needs to be determined by the measured reduction in LDL cholesterol. Further large randomized controlled studies are required to validate the safety of high-dose statin therapy according to the measured reduction in LDL cholesterol. We provided a comprehensive overview of statin use in patients with ICH, although most of these data originate in patients treated with low-dose statin therapy stratified by the reduction in LDL cholesterol. Hence, dose-dependent pleiotropic effects of statin therapy may be predicted depending on the measured reduction in LDL cholesterol.

Acknowledgements

We thank the families for participating in this research project. This work is supported by clinical medicine science and technology projects of Jiangsu Province (BL2013019), Jiangsu Provincial Health Department Scientific Research Project (Q201412), Suzhou Science and Technology Support Program (SS201429), the innovation program of Jiangsu Province (Q.Z.), and NSFC grants China (Nos. 31271399 and 81472047, 81901632).

Disclosure of conflict of interest

None.

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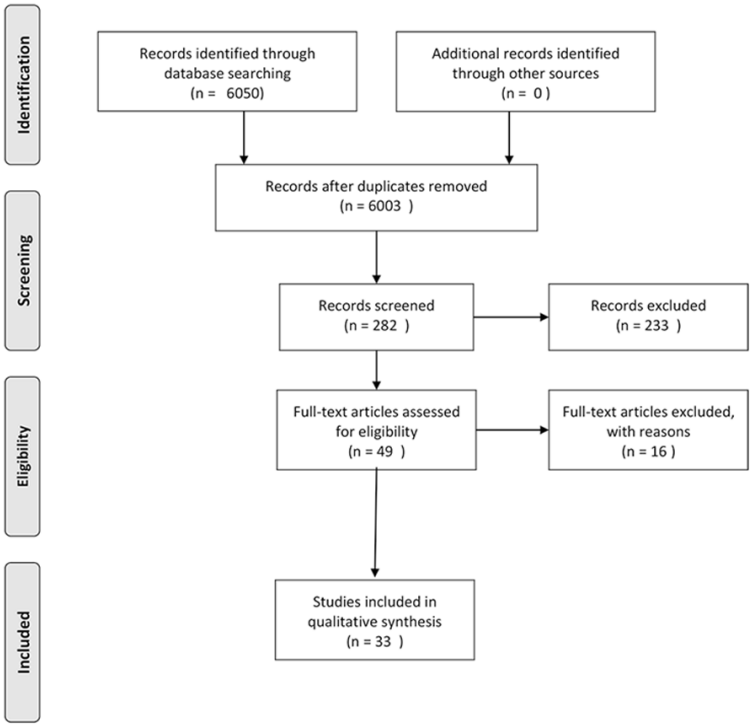

Supplementary Figure 1. Flow chart of study selection.