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Review Article

High-dose statin therapy and risk of intracerebral hemorrhage: a meta-analysis

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Statin plays a major role in the primary and secondary prevention of cardiovascular disease (CVD). Inconsistent findings in the studies have been observed toward the risk of intracerebral hemorrhage (ICH) using higher dose of statin. To examine this issue, we performed a meta-analysis of randomized controlled trials (RCTs) to assess the association between higher dose of various statins and risk of ICH among patients with CVD. Literature was searched for studies published before June 10, 2015, using electronic database 'PubMed', 'EMBASE', and 'Google Scholar' as well as from many trial databases. The following search terms were used: 'Statin therapy' AND 'Cardiovascular Disease', AND 'Dose' AND 'Intracerebral hemorrhage', AND 'Randomized Controlled Trials' AND 'High Dose Statin'. High dose of statins was defined as atorvastatin 80 mg, simvastatin 80 mg, pravastatin 40 mg, rosuvastatin 20 mg per day. Fixed-effect model was used to estimate the risk ratio (RR) and 95% confidence interval (CI) if heterogeneity was <50%; otherwise, random-effect model was used. Begg's funnel plot was used to assess the publication bias. Seven RCTs involving 31,099 subjects receiving high-dose statin and 31,105 subjects receiving placebo were analyzed in our meta-analysis. A significant risk of ICH was observed in subjects with higher dose of statin (RR = 1.53; 95% CI: 1.16–2.01; $P = 0.002$). There was no difference in all-cause mortality between the two groups (RR = 0.95; 95% CI: 0.86–1.06; $P = 0.36$). No publication bias was observed through Begg's funnel plot. Higher dose of statins was found to be associated with the risk of ICH. Future studies are needed to confirm these findings.

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Key words: intracerebral hemorrhage; cardiovascular disease; high-dose statin; meta-analysis; stroke; mortality

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Introduction

Statins have been recommended by American Heart Association (AHA)/American College of Cardiology (ACC) guidelines (2013), for the prevention of cardiovascular diseases (CVD) (1, 2). Intracerebral hemorrhage (ICH) has been observed to have an inverse relation with serum cholesterol levels (3, 4) with probable reasons being low cholesterol level aggravating arterial muscles necrosis (5) and microaneurysms formation (6).

Two recent studies, Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) (7) (hazard ratio, 1.68; 95% CI: 1.09 to 2.59) and Heart Protection Study (HPS) (8), have shown an increased incidence of ICH following the use of atorvastatin 80 mg and simvastatin 40 mg, respectively. Cochrane review (2009) observed a significant increase in odds of ICH with lipid-lowering medications (OR = 1.72; 95% CI: 1.20 to 2.46) which included SPARCL and HPS trials only (9). These studies had subjects with prior history of CVD. The 'Cholesterol

Treatment Trialists' (CTT) collaboration performed a meta-analysis of 20 clinical trials and observed an insignificant risk of ICH with statin therapy (RR = 1.15; 95% CI: 0.93 to 1.41) (10). Another meta-analysis of 31 randomized controlled trials (RCTs) which included studies of all doses of statins showed no association between statin therapy and risk of ICH (OR = 1.08; 95% CI: 0.88 to 1.32) (11). Hence, concerns arise whether these higher doses are recommended or not. A recent nationwide cohort study (2015) from Taiwan involving 10,96,547 participants without prior history of stroke showed a non-significant association between cumulative statin-stratified doses in highest and lowest quartile with the risk of ICH (hazard ratio, 1.06, 95% CI: 0.94 to 1.19) (12). To the best of our knowledge, there is no study which has explored whether high-dose statins are associated with the risk of ICH. Therefore, the present meta-analysis of RCTs was performed to assess the association between high dose of various statins and risk of ICH among patients with CVD.

Methods

Identification of relevant studies

Literature was searched for studies published before June 10, 2015, using electronic database 'PubMed', 'EMBASE', and 'Google Scholar' as well as from many trial databases. The following search terms were used: 'Statin therapy' AND 'Cardiovascular Disease', AND 'Dose' AND 'Intracerebral hemorrhage', AND 'Randomized Controlled Trials' AND 'High Dose Statin'.

Inclusion criteria

For inclusion in the meta-analysis, the following criteria were used: (i) randomized controlled trials, (ii) subjects with age ≥18 years, (iii) blinded outcome assessment, (iv) trials having data on statin dosage and outcome recorded for ICH. High dose of statins was defined as atorvastatin 80 mg, simvastatin 80 mg, pravastatin 40 mg, rosuvastatin 20 mg per day. The major reasons for excluding studies were as follows: (i) other than randomized controlled trials, (ii) publications with duplication or overlapping subjects from the same study, and (iii) comparison between two statins either higher or lower doses. This meta-analysis was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (13).

Data extraction

As per the PRISMA guidelines, each full-text article was checked for eligibility by two authors AKP and PK. These authors independently extracted the following data from the eligible studies: trial name, publication year, number of active group and control subjects included, age, sex, follow-up, incidence of ICH, and all-cause mortality. Disagreements were resolved by discussion among all the authors until consensus was obtained.

Quality assessment

We also examined the methodological quality of every study which is included in our meta-analysis

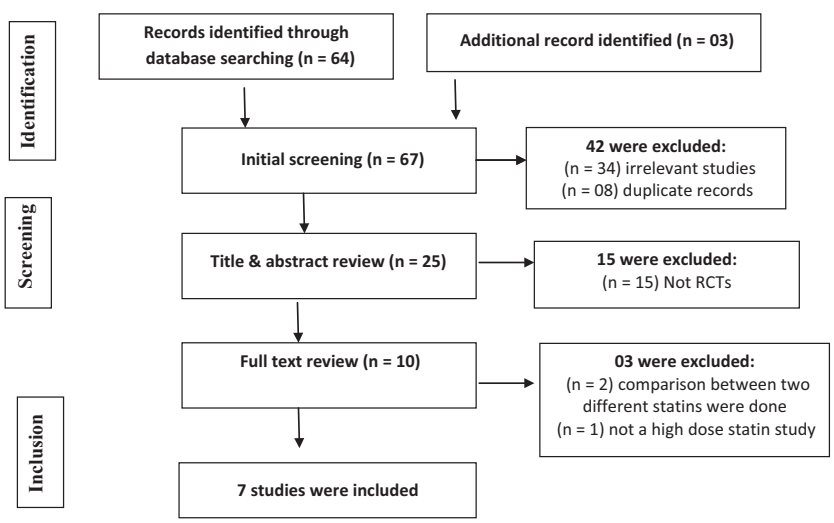

Figure 1. Flow diagram of the selection of studies and specific reasons for exclusion from the present meta-analysis.

by data on random assignment, treatment allocation concealment, group similarity at baseline, eligibility criteria specified, blinding, lost to follow up percentage, and use of intention-to-treat analysis by using Jadad score (14). The quality of included studies was independently assessed by two authors AKP and PK. Inconsistency over the quality scores was resolved by discussion among all the authors, and subsequent agreement was reached.

Statistical analysis

Heterogeneity was assessed by using Cochran's Q statistic and I^2 metric (15). In our study, the I^2 values exceeding 50% and heterogeneity at the 10% level of significance were considered as an indicator of significant heterogeneity. Fixed-effect models were used to estimate the risk ratio (RR) and 95% confidence interval (CI) if heterogeneity was <50%; otherwise, random-effect model was used. Begg's funnel plot was used to assess the potential for publication bias. The software used for carrying out the meta-analysis was Review Manager, version 5.3 (Cochrane Collaboration, Syracuse, NY, USA).

Results

A total of 67 published articles were identified by using the prespecified search strategy. Fig. 1

Table 1 Characteristic of studies included in the meta-analysis

S. No.	Study, year	Type of study	Patient included	Intervention statin (dose in mg)	Active/ control, *n*	Mean age (SD) active/ control, *n*	Sex male, *n* (%) active/ control, *n*	Follow-up (months)	Jadad score (14)
1.	LIPID, 1998 (33)	RCT	Had an acute MI or had a hospital discharge diagnosis of unstable angina between 3 and 36 months before study entry	Pravastatin 40 mg Placebo	4512/4502	62 62	3742 (83) 3756 (83)	72	4
2.	ALLHAT-LLT, 2002 (34)	RCT	Age ≥55 years and stage 1 or 2 hypertension with at least 1 additional CHD risk factor	Pravastatin 40 mg Usual care	5170/5185	66.4 (7.6) 66.3 (7.5)	2659 (51.4) 2645 (51)	57.6	3
3.	PROSPER, 2002 (35)	RCT	Aged 70–82 years were recruited if they had either pre-existing vascular disease (coronary, cerebral, or peripheral) or raised risk of such disease because of smoking, hypertension, or diabetes	Pravastatin 40 mg Placebo	2891/2913	75.4 (3.3) 75.3 (3.4)	1396 (48.3) 1408 (48.3)	63.6	5
4.	A to Z, 2004 (36)	RCT	Age 21–80 years with either non-ST-elevation ACS or ST-elevation MI	Simvastatin 80 mg Simvastatin 20 mg	2265/2232	61 61	1716 (76) 1680 (75)	24	3
5.	TNT, 2005 (37)	RCT	Age 35–75 years who had clinically evident CHD & a history of coronary revascularization	Atorvastatin 80 mg Atorvastatin 10 mg	4995/5006	61.2 (8.8 60.9 (8.8)	4054 (81.2) 4045 (80.8)	58.8	3
6.	SPARCL, 2006 (7)	RCT	Age over 18 years who had had an ischemic or hemorrhagic stroke or a TIA (diagnosed by a neurologist within 30 days after the event) 1–6 months before randomization	Atorvastatin 80 mg Placebo	2365/2366	63 (0.2) 62.5 (0.2)	1427 (60.3) 1396 (59)		4
7.	JUPITER, 2008 (38)	RCT	Male with 50 years of age or older and female with 60 years of age or older not have a history of CVD and if, at the initial screening visit, they had an LDL cholesterol level of less than 130 mg per deciliter and a high-sensitivity C-reactive protein level of 2.0 mg per liter or more	Rosuvastatin 20 mg Placebo	8901/8901	66 66	5475 (61.5) 5526 (62)	22.8	4

SD, standard deviation; RCT, randomized controlled trial; MI, myocardial infarction; CHD, coronary heart disease; ACS, acute coronary syndrome; TIA, transient ischemic attack, CVD, cardiovascular disease.

displays a flowchart of both the retrieved and excluded studies with reasons for exclusion. Of the 67 articles that were retrieved, 34 studies were excluded due to its irrevelency to our interest and eight studies were excluded as they were in duplicate records. As per the inclusion criteria, seven RCTs were included in our meta-analysis. The publication years of the studies included in this meta-analysis ranged from 1998 to 2008. Table 1 gives a summary of the characteristics and methodological quality of all the included studies. Seven RCTs involving 31,099 subjects receiving high-dose statin and 31,105 subjects receiving placebo were analyzed in our meta-analysis.

Risk of ICH

A significant risk of ICH was observed in subjects having high dose of statin (RR = 1.53; 95% CI: 1.16 to 2.01; $P = 0.002$). No significant heterogeneity was observed (chi-square $\chi^2 = 10.01$; $p_{Het} = 0.12$, $I^2 = 40\%$) (Fig. 2). No publication bias was observed through Begg's funnel plot (Fig. 3).

All-cause mortality

There was no difference in all-cause mortality between the high dose of statin and control groups (RR = 0.95; 95% CI: 0.86 to 1.06; $P = 0.36$). A significant heterogeneity was observed ($\chi^2 = 21.04$; $p_{Het} = 0.0002$, $I^2 = 71\%$) (Fig. 4).

Discussion

This comprehensive meta-analysis suggests that high dose of statin increases the risk of ICH without any increase in all-cause mortality. We included seven RCTs with 62,204 participants. This association of ICH with high dose of statin was not affected by study design, quality, and publication bias. Although there was indirectness of evidence as the included RCTs had a primary research question of prevention of stroke with statin therapy, it is yet not clear why there is an increased risk of ICH in those who receive high dose of statins. SPARCL trial has cleared that there is no relation of ICH occurrence with LDL cholesterol levels (7, 16), and independent of cholesterol levels, statins may have pleiotropic effect (17–20). There are aggregated hypotheses of statin that may be leading to the loss of integrity of blood vessels [low cholesterol and subsequently leading to arterial muscles necrosis] (5) and microaneurysms formation (6) and causing ICH. Statins may also have mild antithrombotic activity leading to reduced thrombosis by inhibiting platelet aggregation and enhancing fibrinolysis (21–31).

The SPARCL trial being the representative evidence of high-dose statin and risk of ICH is further substantiated by Cochrane review 2009 (9). The post hoc analysis of SPARCL trial observed

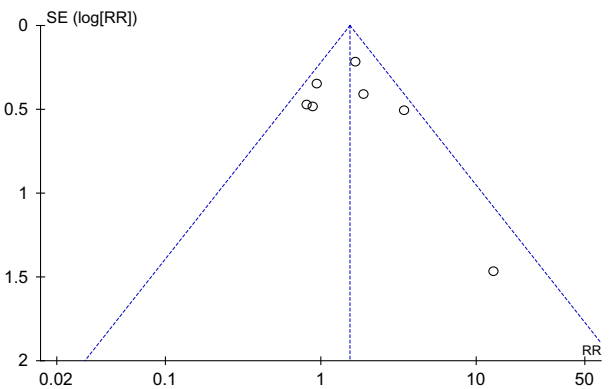

Figure 3. Funnel plot for publication bias.

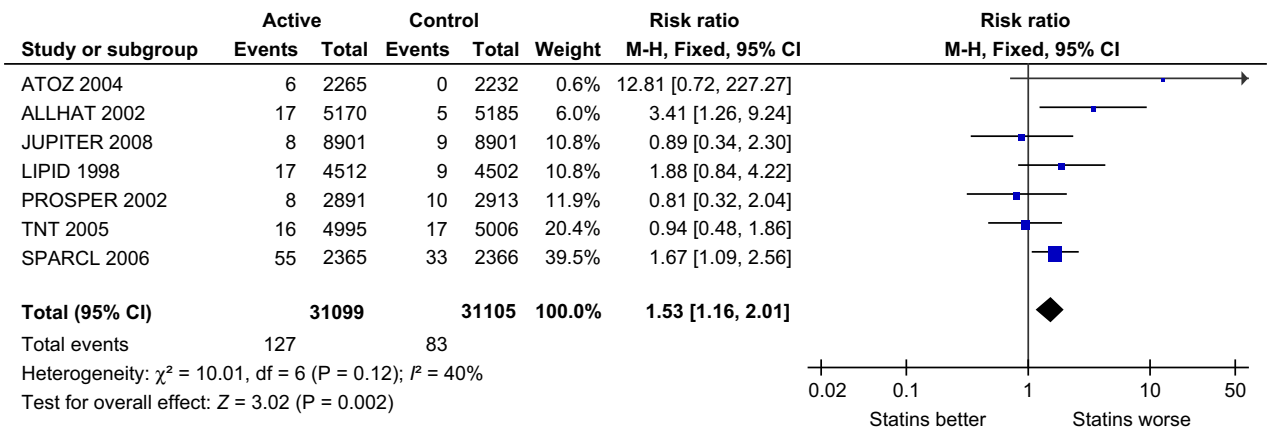

Figure 2. Forest plots for the use of high dose of statins and risk of ICH.

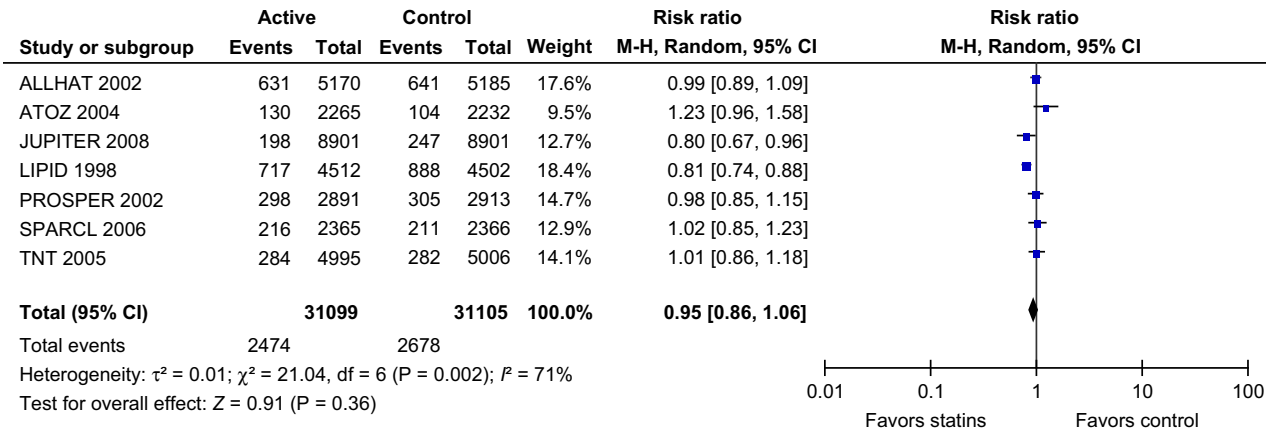

Figure 4. Forest plots for the use of high dose of statins and all-cause mortality.

an increased risk of ICH mainly in elderly male patients with previous history of hemorrhagic stroke and patients with hypertension (7). A nationwide cohort study from Taiwan enrolled patients of ischemic stroke (IS) or transient ischemic attack (TIA) with statin prescribed in-hospital (n = 2019), within 1 year after discharge (intermediate use; n = 2266), 1 year after discharge (late use; n = 2958) and noted crude incidence rate/1000 person-year of 6.8, 5.7 and 6.2, respectively (32). Although not supported by the subsequent meta-analyses, probably these meta-analyses included all studies with varying doses of statins (10, 11). However, our present meta-analysis is restricted to include RCTs with high-dose statin therapy linked with the risk of ICH.

We also noted that there was no difference in all-cause mortality with high dose of statins as compared to control group. This suggests that risk-benefit profile of high-dose statin therapy is not clear, although statin therapy is an accepted modality in abating morbidity and mortality secondary to cardiovascular disease. A recent cohort study having more than one million participants failed to observe an association between cumulative statin use and ICH in subjects without previous history of stroke; however, subgroup analysis demonstrated an increased risk among the non-hypertensive cohort [adjusted hazard ratio (HR) = 1.36; 95% CI = 1.11–1.67] (12). The present meta-analysis must be carefully interpreted because of certain limitations. First, the meta-analysis is not an individual patient's database. Second, the various etiologies of ICH have not been provided in the included RCTs; ICH has multifactorial origin and risk of recurrences. Also, various clinical settings such as prior ICH and ICH not on statin could not be taken into account in analysis because of constraint of such data. Our meta-analysis although with potential limitations showed that high dose of statins may increase the risk of ICH. Therefore, high dose of lipid-lowering medications should be cautiously prescribed with special references to underlying atherosclerotic risk factors and needs a future research for obtaining confirmatory findings.

Conclusion

Higher dose of statins was found to be associated with the risk of ICH. Future studies are needed to confirm these findings.

Acknowledgement

None.

Conflict of interest

No potential conflict of interest.

Funding source

None.

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