Effect of Intensive and Standard Lipid-Lowering Therapy on the Progression of Stroke in Patients With Coronary Artery Syndromes: A Meta-Analysis of Randomized Controlled Trials

Chengjuan Xie, MD, Mingyu Zhu, MS, Ying Hu, MS, and Kai Wang, MD

Abstract: This meta-analysis demonstrated the effect of intensive versus standard statins on the risk of stroke in patients with coronary artery syndromes (CAS). PubMed, Embase, the Cochrane library, and clinicaltrials.gov were searched, and the retrieved studies were undertaken for randomized controlled trials (RCTs) throughout September 2018. Studies that were designed as RCTs and recruited at least 1000 CAS patients followed up greater than 1 year were eligible for this study. The summary relative risk with the 95% confidence interval was used as an effect estimate and calculated using the random-effects model. Five RCTs comprising a total of 39,612 coronary syndrome patients with reported 1236 stroke events were included in this meta-analysis. The summary result indicated a 14% reduction in the risk of stroke in CAS patients receiving intensive statin therapy as compared to standard statin therapy. The significant differences mainly occurred in mean age ≥60 years (P = 0.007), percentage of males ≥80% (P = 0.011), percentage diabetes mellitus ≥15% (P = 0.018), percentage hypertension ≥50% (P = 0.030), percentage of current smokers <30% (P = 0.011), percentage of prior myocardial infarction ≥50% (P = 0.011), percentage of peripheral arterial disease ≥10% (P = 0.030), patients with stable CAS (P = 0.011), patients using atorvastatin (P = 0.015), follow-up duration ≥3 years (P = 0.011), and study with moderate quality (P = 0.013). Intensive statin therapy should be considered for CAS patients at high risk of stroke events. Further large-scale RCT should be conducted to verify the results of stratified analysis in this study.

Key Words: coronary syndromes, meta-analysis, statin drugs

INTRODUCTION

Stroke is the fifth leading cause of death, accounting for the adult acute onset and long-term disability worldwide. Currently, the burden of stroke in China, Africa, and South America is greater than that in other continents. After stroke, the patients may experience disruptions in their daily functions, causing poor life quality. Several risk factors on the progression of stroke have already been deduced, whereas high residual risk on stroke in patients with coronary artery syndromes (CAS) is yet to be elucidated. Therefore, an additional effective strategy should be used to reduce the residual risk of stroke in CAS patients.

Previous studies demonstrated that CAS patients had a heightened risk of ischemic strokes. Modifiable risk factors should be used for providers and patients through lifestyle and medication management to reduce the risk of stroke. In addition, lipid-lowering therapy has been established for high-risk patients, and achieving low-density lipoprotein <70 mg/mL was associated with additional benefit in patients with ischemic heart disease or equivalent high-risk status. Several meta-analyses have demonstrated the additional benefits of intensive lipid-lowering therapy, whereas the potential benefits of intensive versus standard statin therapy on the risk of stroke remain inconclusive. Moreover, whether the effects of intensive statin therapy are optimal in CAS patients according to patients’ characteristics are yet unknown. Therefore, the current meta-analysis recruited a total of 39,612 CAS patients from 5 randomized controlled trials (RCTs) was conducted to determine any potential benefit of intensive versus standard statin therapy on the risk of stroke.

METHODS

Data Sources, Search Strategy, and Selection Criteria

This review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement issued in 2009. The studies that were designed as RCTs and evaluated the therapeutic effect of intensive versus standard statin therapy on stroke were eligible for this meta-analysis, without restrictions placed on the
publication language and status. We systematically searched PubMed, Embase, the Cochrane library, and clinicaltrials.gov for RCTs that investigated the effect of intensive versus standard lipid-lowering therapy in CAS patients on the risk of stroke, using the following medical search terminology: ("statin" or "HMG-CoA reductase inhibitor" or "atorvastatin" or "simvastatin" or "pravastatin" or "fluvastatin" or "lovastatin" or "rosuvastatin") AND ("intensive" or "high dose") AND "RCTs." Subsequently, the reference lists from the retrieved studies were examined to identify additional potentially eligible studies.

The study selection was independently conducted by 2 reviewers, and discrepancies were resolved by discussion until a consensus was achieved. The inclusion criteria of this study were shown as follows: (1) Patients: patients with acute or chronic CAS; (2) Control: standard statin therapy, which defined as daily dose of atorvastatin ≤20 mg, simvastatin ≤60 mg, rosuvastatin ≤10 mg, or any dose of pravastatin, lovastatin, or fluvastatin; (3) Intervention: intensive statin therapy, which defined as daily dose of various statins types were higher than the standard statin therapy; (4) Outcomes: the incidence of stroke in intervention and control groups; (5) Study design: study designed as RCT; (6) Sample size >1000; (7) Follow-up duration >1 year. Study with observational design was excluded because of various uncontrolled biases.

**Data Collection and Quality Assessment**

The following data were collected from the retrieved studies: the study group’s name, publication year, country, sample size, mean age, percentage of male, disease status, percentage of diabetes mellitus (DM), percentage of hypertension, percentage of current smoker, percentage of prior myocardial infarction (MI), percentage of peripheral arterial disease (PAD), intervention, control, follow-up duration, and the prevalence of stroke in each group. The Jadad scale was used to assess the methodological quality as it is the comprehensive quantitative method for assessing the quality of RCTs in a meta-analysis. This score of the scale ranged from 0 to 5 and is based on randomization (1 or 0), concealment of the treatment allocation (1 or 0), blinding (1 or 0), completeness of follow-up (1 or 0), and the use of intention-to-treat analysis (1 or 0). The data collection and quality assessment were performed by 2 reviewers, and inconsistencies were adjudicated independently by referring to the original article.

**Statistical Analysis**

The effect of intensive versus standard statin therapy on the risk of stroke was calculated based on the event numbers occurred in each trial, and the pooled relative risk (RR) with the corresponding 95% confidence interval (CI) was calculated using the random-effects model. The heterogeneity of the therapeutic effect of intensive versus standard statin therapy among the included trials was assessed by $I^2$ and Q statistic, and significant heterogeneity was detected if $I^2 > 50\%$ or $P < 0.10$. Furthermore, sensitivity analysis evaluated the impact of a single study in the overall analysis by sequential removal of individual trials. The univariate meta-regression analyses were conducted based on sample size, mean age, percentage of male, percentage of DM, percentage of hypertension, percentage of current smoker, percentage of prior MI, percentage of PAD, and follow-up duration. Subgroup analyses for stroke were conducted based on sample size, mean age, percentage of male, percentage of DM, percentage of hypertension, percentage of current smoker, percentage of prior MI, percentage of PAD, disease status, and intervention, follow-up duration, and study quality. Also, the ratio of RR and the corresponding 95% CIs between subgroups were calculated using specific RRs and 95% CIs. Publication bias was assessed qualitatively by funnel plot and quantitatively by Egger and Begg tests. The $P$ value for the pooled result was two-sided, and the inspection level was 0.05. All statistical analyses were performed using STATA software (version 10.0; Stata Corporation, College Station, TX).

**RESULTS**

**Search of the Published Literature**

The electronic searches from PubMed, Embase, the Cochrane library, and clinicaltrials.gov retrieved 2630 records, and 2594 were excluded as they were duplicates or irrelevant topics. A total of 36 studies were selected for further evaluations, and 31 studies were excluded because of the following reasons: placebo as the control group (n = 18), study reported same populations (n = 9), and sample size <1000 (n = 4). Subsequently, 5 RCTs fulfilled the inclusion criteria and were selected for the final analysis. No additional eligible study was detected by a manual search of the reference lists of these 5 RCTs. The study selection process is illustrated in Fig. 1, and the baseline characteristics of the included trials are listed in Table 1.

**FIGURE 1.** Schematic representation of the study selection process.
Characteristics of the Included Studies

The included studies involved a total of 39,612 CAS patients and 1236 stroke events. The follow-up duration ranged from 3.0 to 6.7 years, and 4162–12,064 patients were included in each individual trial. All the trials were conducted in multiple centers, and 4 of the included trials were conducted in multicountries. Two trials included patients with the acute CAS, and the remaining 3 studies included patients with stable CAS. Three trials used atorvastatin, and the remaining 2 trials used simvastatin as the intensive therapy. One trial scored a Jadad scale of 5, 2 trials scored 4, and the remaining 2 trials scored 3.

Meta-Analysis and Sensitivity Analysis

After pooling all the included trials, the intensive statin therapy significantly reduced the risk of stroke as compared to standard statin therapy in CAS patients (RR: 0.86; 95% CI: 0.77–0.96; P = 0.008; Fig. 2), and no significant heterogeneity was noted across included trials (I²: 0%; P = 0.742).

![Figure 2. Intensive versus lipid-lowering therapies on the risk of stroke.](image-url)
Sensitivity analysis indicated that the summary result was not associated with statistical significance after excluding the trial conducted by Treating to New Targets (TNT), which specifically used atorvastatin 10 mg as standard therapy that was associated with a large therapeutic effect between intensive and standard statin therapies (Fig. 3).

Meta-Regression and Subgroup Analyses

Univariate meta-regression analyses demonstrated that sample size ($P = 0.715$; see Figure S1, Supplemental Digital Content 1, http://links.lww.com/JCVP/A438), mean age ($P = 0.488$; see Figure S2, Supplemental Digital Content 1, http://links.lww.com/JCVP/A438), percentage of male ($P = 0.580$; see Figure S3, Supplemental Digital Content 1, http://links.lww.com/JCVP/A438), percentage of DM ($P = 0.461$; see Figure S4, Supplemental Digital Content 1, http://links.lww.com/JCVP/A438), percentage of hypertension ($P = 0.461$; see Figure S5, Supplemental Digital Content 1, http://links.lww.com/JCVP/A438), percentage of current smoker ($P = 0.945$; see Figure S6, Supplemental Digital Content 1, http://links.lww.com/JCVP/A438), percentage of prior MI ($P = 0.480$; see Figure S7, Supplemental Digital Content 1, http://links.lww.com/JCVP/A438), percentage of PAD ($P = 0.584$; see Figure S8, Supplemental Digital Content 1, http://links.lww.com/JCVP/A438), and follow-up duration ($P = 0.586$; see Figure S9, Supplemental Digital Content 1, http://links.lww.com/JCVP/A438) did not play a significant role in the risk of stroke. Subgroup analysis suggested that intensive statin therapy significantly reduced the risk of stroke when the mean age of patients $\geq 60$ years (RR: 0.86; 95% CI: 0.77–0.97; $P = 0.011$), percentage of male $\geq 80\%$ (RR: 0.86; 95% CI: 0.77–0.97; $P = 0.011$), percentage of DM $\geq 15\%$ (RR: 0.78; 95% CI: 0.64–0.96; $P = 0.018$), percentage of hypertension $\geq 50\%$ (RR: 0.78; 95% CI: 0.63–0.98; $P = 0.030$), percentage of current smoker $< 30\%$ (RR: 0.86; 95% CI: 0.77–0.97; $P = 0.011$), percentage of prior MI $\geq 50\%$ (RR: 0.86; 95% CI: 0.77–0.97; $P = 0.011$), percentage of PAD $\geq 10\%$ (RR: 0.78; 95% CI: 0.63–0.98; $P = 0.030$), patients with stable CAS (RR: 0.86; 95% CI: 0.77–0.97; $P = 0.011$), patients received atorvastatin (RR: 0.83; 95% CI: 0.71–0.96; $P = 0.015$), follow-up duration $\geq 3$ years (RR: 0.86; 95% CI: 0.77–0.97; $P = 0.011$), and study with moderate quality (RR: 0.82; 95% CI: 0.70–0.96; $P = 0.013$). However, no significant differences were observed between subgroups based on the predefined factors (Table 2).

Publication Bias

The funnel plot for stroke is shown in Fig. 4, and the Egger ($P = 0.770$) and Begg ($P = 0.806$) test results did not reveal any evidence of publication bias.

**DISCUSSION**

The current meta-analysis investigated the association between intensive statin therapy and long-term stroke risk in CAS patients. The published data from 5 large-scale RCTs involved a total of 39,612 CAS patients and 1236 incident cases of stroke. The pooled result revealed that intensive statin therapy decreased the risk of stroke by 14% in CAS patients as compared to standard statin therapy. However, the therapeutic effect for CAS patients between intensive and standard statin therapies was variable and marginal. Thus, the intensive lipid-lowering therapy was...
preferable to standard lipid-lowering therapy for the treatment of CAS patients with mean age $\geq 60$ years, percentage of male $80\%$, percentage of DM $15\%$, percentage of hypertension $50\%$, percentage of current smoker $30\%$, percentage of prior MI $50\%$, percentage of PAD $10\%$, follow-up duration $3$ years, patients with stable CAS, patients received atorvastatin, and study with moderate quality.

### TABLE 2. Subgroup Analysis

| Variables                  | Subgroups | RR and 95% CI   | $P$   | Heterogeneity (%) | $P$ Value for Heterogeneity | Ratio Between Subgroups | $P$ Value for Ratio Between Subgroups |
|----------------------------|-----------|-----------------|-------|------------------|-----------------------------|-------------------------|---------------------------------------|
| Sample size                | $\geq 10,000$ | 0.85 (0.71–1.02) | 0.075 | 39.3             | 0.199                       | 0.98 (0.75–1.27)         | 0.862                                 |
|                           | $<10,000$  | 0.87 (0.72–1.05) | 0.136 | 0.0              | 0.856                       |                         |                                       |
| Mean age (yr)              | $\geq 60.0$ | 0.86 (0.77–0.96) | 0.007 | 0.0              | 0.620                       | 0.88 (0.48–1.61)         | 0.674                                 |
|                           | $<60.0$    | 0.98 (0.54–1.79) | 0.955 | —                | —                           |                         |                                       |
| Percentage male (%)        | $\geq 80.0$ | 0.86 (0.77–0.97) | 0.011 | 0.0              | 0.437                       | 1.00 (0.67–1.49)         | 1.000                                 |
|                           | $<80.0$    | 0.86 (0.59–1.26) | 0.444 | 0.0              | 0.579                       |                         |                                       |
| Percentage DM (%)          | $\geq 15.0$ | 0.78 (0.64–0.96) | 0.018 | 0.0              | 0.730                       | 0.87 (0.68–1.10)         | 0.242                                 |
|                           | $<15.0$    | 0.90 (0.79–1.02) | 0.105 | 0.0              | 0.718                       |                         |                                       |
| Percentage hypertension (%)| $\geq 50.0$ | 0.78 (0.63–0.98) | 0.030 | 0.0              | 0.428                       | 0.88 (0.68–1.13)         | 0.312                                 |
|                           | $<50.0$    | 0.89 (0.78–1.01) | 0.071 | 0.0              | 0.828                       |                         |                                       |
| Percentage of current smoker (%) | $\geq 30.0$ | 0.86 (0.59–1.26) | 0.444 | 0.0              | 0.579                       | 1.00 (0.67–1.49)         | 1.000                                 |
|                           | $<30.0$    | 0.86 (0.77–0.97) | 0.011 | 0.0              | 0.437                       |                         |                                       |
| Percentage of prior MI (%) | $\geq 50.0$ | 0.86 (0.77–0.97) | 0.011 | 0.0              | 0.437                       | 1.00 (0.67–1.49)         | 1.000                                 |
|                           | $<50.0$    | 0.86 (0.59–1.26) | 0.444 | 0.0              | 0.579                       |                         |                                       |
| Percentage of PAD (%)      | $\geq 10.0$ | 0.78 (0.63–0.98) | 0.030 | 0.0              | 0.428                       | 0.88 (0.68–1.13)         | 0.312                                 |
|                           | $<10.0$    | 0.89 (0.78–1.01) | 0.071 | 0.0              | 0.828                       |                         |                                       |
| Disease status             | Acute CAS | 0.86 (0.59–1.26) | 0.444 | 0.0              | 0.579                       | 1.00 (0.67–1.49)         | 1.000                                 |
|                           | Stable CAS | 0.86 (0.77–0.97) | 0.011 | 0.0              | 0.437                       |                         |                                       |
| Intervention               | Atorvastatin | 0.83 (0.71–0.96) | 0.015 | 0.0              | 0.585                       | 0.92 (0.74–1.14)         | 0.463                                 |
|                           | Simvastatin | 0.90 (0.77–1.05) | 0.192 | 0.0              | 0.577                       |                         |                                       |
| Follow-up duration (yr)    | $\geq 3.0$ | 0.86 (0.77–0.97) | 0.011 | 0.0              | 0.437                       | 1.00 (0.67–1.49)         | 1.000                                 |
|                           | $<3.0$     | 0.86 (0.59–1.26) | 0.444 | 0.0              | 0.579                       |                         |                                       |
| Study quality              | High       | 0.91 (0.78–1.05) | 0.202 | 0.0              | 0.824                       | 1.11 (0.89–1.38)         | 0.347                                 |
|                           | Moderate   | 0.82 (0.70–0.96) | 0.013 | 0.0              | 0.392                       |                         |                                       |

**FIGURE 4.** Funnel plot.
The quality of the included studies was evaluated using Jadad scale, and data on randomization, blinding, completeness of follow-up, and the use of intention-to-treat analysis were collected from all studies. Of these, 5 trials did not provide the information of concealed treatment allocation, whereas 2 studies did not report the details of randomization. Moreover, the sample size and follow-up duration were restricted to 1000 and 1 year, respectively. Furthermore, the sample size of meta-analysis was calculated, and the power was sufficient to detect the difference between intensive and standard lipid-lowering therapies on the risk of stroke. Therefore, the pooled result of this meta-analysis could reliably demonstrate the therapeutic effect of intensive versus standard lipid-lowering therapies on the risk of stroke in CAS patients.

Recently, several systematic reviews and meta-analyses have illustrated the therapeutic effect of intensive lipid lowering for the prevention of cardiovascular and cerebrovascular outcomes. Wang et al\(^{21}\) indicated that intensive statin therapy was more beneficial in preventing the risk of stroke in elderly patients than the standard statin therapy. Yan et al\(^{22}\) conducted a meta-analysis of 5 RCTs and found that intensive statin therapy was associated with a greater reduction in the serum lipid level and prevention of nonfatal MI, stroke, and coronary revascularization in elderly patients with coronary heart disease. Furthermore, the Cholesterol Treatment Trialists’ collaboration indicated that a reduction in lipid profile was associated with a greater reduction in the risk of heart attack, revascularization, and ischemic stroke.\(^{23}\) Josan et al\(^{24}\) demonstrated that intensive statin therapy further showed a reduction in lipid profile, MI, and stroke risk. Although the above studies provided comprehensive results regarding the therapeutic effects of intensive statin therapy, neither focused on the effect of intensive versus standard statin therapies on the risk of stroke in CAS patients. Moreover, whether the therapeutic effects of intensive versus standard statin therapies differed according to the patients’ characteristics is not elucidated. Therefore, the current quantitative meta-analysis was conducted to provide a comprehensive result about the therapeutic effect of intensive versus standard statin therapies on the risk of stroke in CAS patients.

The summary result of this study suggested that intensive versus standard lipid-lowering therapy was associated with a further reduction in the risk of stroke. Only 1 trial reported similar result, whereas the remaining 4 trials did not reveal any significant reduction in the risk of stroke. The TNT trial recruited 10,001 stable coronary heart disease patients with low-density lipoprotein <130 mg/dL and a follow-up median of 4.9 years. Moreover, the study indicated that the risk of stroke in patients receiving 80 mg of atorvastatin daily was reduced by 24% than those receiving 10 mg daily. Patients receiving 80 mg of atorvastatin exhibit a further reduction in low-density lipoprotein from a baseline of 101 to 77 mg/dL, which could prevent 3.4% major cardiovascular events within the initial 5 years. Furthermore, the benefits of further reduction in low-density lipoprotein level <100 mg/dL extended beyond the coronary heart disease-related vasculature.\(^{39}\) The remaining 4 RCTs did not yield a significant difference between intensive and standard lipid-lowering therapies on the risk of stroke due to the following reasons: (1) these trials were designed composite of cardiovascular and cerebrovascular outcomes as the primary outcome, and the sample size was not sufficient to detect the difference in the risk of stroke; and (2) various standard statin types and doses resulted in diverse therapeutic effects between intensive and standard lipid-lowering therapies.

Subgroup analyses indicated that the significant differences between intensive and standard lipid-lowering therapies on the risk of stroke were contributed by the mean age of patients ≥60 years, percentage of male ≥80%, percentage of DM ≥15%, percentage of hypertension ≥50%, percentage of current smoker <30%, percentage of prior MI ≥50%, percentage of PAD ≥10%, patients with stable CAS, patients who received atorvastatin, follow-up duration ≥3 years, and the study with moderate quality. The reasons for these included (1) elderly, male, DM, hypertension, prior MI, and PAD attributable to increasing periprocedural stroke risk, and further intensive lipid-lowering therapy reduced the risk status and progression of stroke\(^{15,42–46}\); (2) patients with prolonged follow-up duration were correlated with the cumulative morbidity of stroke, which plays a vital role in the weight from overall analysis; (3) the role of percentage of current smoker on the risk of stroke might be associated with coronary syndrome patients receiving clopidogrel, and smoker’s paradox might affect the potential therapeutic effect of intensive and standard lipid-lowering therapies\(^{27}\); (4) patients with stable CAS probably had been treated with dual platelet inhibition treatment for a long period of time, which could affect the progression of stroke; (5) the quality of study was correlated with the balance of characteristics between intensive and standard lipid-lowering therapies that affect the pooled result.

Nevertheless, the present meta-analysis has several limitations: (1) the results about the incidence of fatal or nonfatal stroke were not available in 4/5 trials; (2) this study was based on the published studies, and thus, publication bias was inevitable; (3) subgroup analyses were based on multiple factors although only 5 RCTs were included in this meta-analysis. Therefore, the results of subgroup analyses might induce potential multiple comparison biases; (4) the risk of stroke for stratified analyses according to patients’ characteristics in each study was not available as the analysis was based on pooled data, which restricted the results of stratified analyses; (5) the analysis of this study based on RR reduction, whereas the absolute risk reduction was not calculated; (6) this study focused on the treatment effectiveness of intensive versus standard statin therapy on stroke, whereas the safety and cost-effectiveness were not addressed; and (7) patients in mostly trials contained patients from multicountries, and the ethnicity of patients from included trials was not available, which restricted us conducting the treatment effectiveness of intensive versus standard statin therapy according to ethnicity.

**CONCLUSIONS**

In conclusion, this meta-analysis demonstrated the benefit of intensive versus standard lipid-lowering therapies on the risk of stroke. Therefore, intensive statin therapy should be recommended for CAS patients at high risk of stroke. However, large prospective studies are essential to substantiate the results of the stratified analyses in this meta-analysis.
REFERENCES

1. Writing Group M, Mozaffarian D, Benjamin EI, et al; American heart association statistics C; stroke statistics 2016 update: a report from the American Heart Association. Circulation. 2016;133:e38–e360.

2. Kim AS, Johnston SC. Global variation in the relative burden of stroke and ischemic heart disease. Circulation. 2011;124:314–323.

3. Williams LS, Weinberger M, Harris LE, et al. Measuring quality of life in a way that is meaningful to stroke patients. Neurology. 1999;53:1839–1843.

4. Lai SM, Studenski S, Duncan PW, et al. Persisting consequences of stroke measured by the stroke impact scale. Stroke 2002;33:1840–1844.

5. Damush TM, Ofner S, Yu Z, et al. Implementation of a stroke self-management program: a randomized controlled pilot study of veterans with stroke. Transl Behav Med. 2011;1:561–572.

6. Scheers H, Jacobs L, Casas L, et al. Long-term exposure to particulate matter air pollution is a risk factor for stroke: meta-analytical evidence. Stroke 2015;46:3058–3066.

7. Booth J, Connelly L, Lawrence M, et al. Evidence of perceived psychological stress as a risk factor for stroke in adults: a meta-analysis. BMC Neurol. 2015;15:233.

8. Liu FD, Shen XL, Zhao R, et al. Pulse pressure as an independent predictor of stroke: a systematic review and a meta-analysis. Clin Res Cardiol. 2010;105:675–686.

9. Dzhambov AM, Dimitrova DD. Exposure-response relationship between traffic noise and the risk of stroke: a systematic review with meta-analysis. Arch Hig Rada Toksikol. 2016;67:136–151.

10. Sakakibara BM, Kim AJ, Eng JJ. A systematic review and meta-analysis on self-management for improving risk factor control in stroke patients. Int J Behav Med. 2017;24:42–53.

11. Wang J, Wen X, Li W, et al. Risk factors for stroke in the Chinese population: a systematic review and meta-analysis. J Stroke Cerebrovasc Dis. 2017;26:509–517.

12. Li X, Li X, Lin H, et al. Metabolic syndrome and stroke: a meta-analysis of prospective cohort studies. J Clin Neurosci. 2017;40:34–38.

13. McHutchison CA, Backhouse EV, Cvoro V, et al. Education, socioeconomic status, and intelligence in childhood and stroke risk in later life: a meta-analysis. Epidemiology. 2017;28:608–618.

14. Bhatt DL, Eagle KA, Ohman EM, et al. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. JAMA. 2010;304:1350–1357.

15. Witt BJ, Brown RD Jr, Jacobsen SJ, et al. A community-based study of stroke incidence after myocardial infarction. Ann Intern Med. 2005;143:785–792.

16. Wolf C, Redfem J, Rudd AG, et al. Cluster randomized controlled trial of a patient and general practitioner intervention to improve the management of multiple risk factors after stroke: stop stroke. Stroke. 2010;41:2470–2476.

17. Schmid AA, Andersen J, Kent T, et al. Using intervention mapping to develop and adapt a secondary stroke prevention program in Veterans Health Administration medical centers. Implement Sci. 2010;5:97.

18. Smilde TJ, van Wissen S, Wollersheim H, et al. Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): a prospective, randomised, double-blind trial. Lancet. 2001;357:577–581.

19. O’Keefe JH Jr, Cordain L, Harris WH, et al. Optimal low-density lipoprotein is 50 to 70 mg/dl: lower is better and physiologically normal. J Am Coll Cardiol. 2004;43:2142–2146.

20. Grundy SM, Cleeman JI, Merz CN, et al. National heart L, blood I, American College of cardiology F, American heart A. Implications of recent clinical trials for the National cholesterol education program adult treatment panel III guidelines. Circulation. 2004;110:227–239.

21. Wang J, Chen D, Li DB, et al. Comparison of the efficacy and safety of intensive-dose and standard-dose statin treatment for stroke prevention: a meta-analysis. Medicine (Baltimore). 2016;95:e4950.

22. Yan YL, Qiu B, Hu LJ, et al. Efficacy and safety evaluation of intensive statin therapy in older patients with coronary heart disease: a systematic review and meta-analysis. Eur J Clin Pharmacol. 2013;69:2001–2009.

23. Cholesterol Treatment Trialists C, Baigent C, Blackwell L, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376:1670–1681.

24. Josan K, Majumdar SR, McAlister FA. The efficacy and safety of intensive statin therapy: a meta-analysis of randomized trials. CMAJ. 2008;178:576–584.

25. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6:e1000097.

26. Smith ME, Lee NJ, Haney E, et al. Drug class review: HMG-CoA reductase inhibitors (statins) and fixed-dose combination products containing a statin: final report update 5. Portland, OR: Oreg Health Sci Univ.; 2009.

27. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17:1–12.

28. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177–188.

29. Ader AE, Lu G, Higgins JP. The interpretation of random-effects meta-analysis in decision models. Med Decis Making. 2005;25:646–654.

30. Deeks J, Higgins J, Altman D. Analyzing data and undertaking meta-analyses. In: Higgins J, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions 501. Oxford, UK: The Cochrane Collaboration; 2008. chap 9.

31. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557–560.

32. Tobias A. Assessing the influence of a single study in meta-analysis. Statas Tech Bull. 1999;47:15–17.

33. Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? Stat Med. 2002;21:1559–1573.

34. Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. Lancet. 2011;378:1297–1305.

35. Egger M,Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629–634.

36. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50:1088–1101.

37. Cannon CP, Braunwald E, McCabe CH, et al; Pravastatin or Atorvastatin E, Infection Therapy-Thrombolysis in Myocardial Infarction I. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med. 2004;350:1495–1504.

38. de Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. JAMA. 2004;292:1307–1316.

39. LaRosa JC, Grundy SM, Waters DD, et al. Treating to New Targets I. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005;352:1425–1435.

40. Pedersen TR, Faergeman O, Kastelein J, et al. Incremental Decrease in End Points Through Aggressive Lipid Lowering Study G. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. JAMA. 2005;294:2437–2445.

41. Study of the Effectiveness of Additional Reductions in C, Homocysteine Collaborative G, Armitage J, Bowman L, Wallendausz K, et al. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomised trial. Lancet. 2010;376:1658–1669.

42. Howard G, Roubin GS, Jansen O, et al. Carotid Stenting Trialists C. Association between age and risk of stroke or death from carotid endarterectomy and carotid stenting: a meta-analysis of pooled patient data from four randomised trials. Lancet. 2016;387:1305–1311.

43. Kent DM, Price LL, Ringleb P, et al. Sex-based differences in response to recombinant tissue plasminogen activator in acute ischemic stroke: a pooled analysis of randomized clinical trials. Stroke. 2005;36:62–65.

44. Peters SA, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 33 studies. Diabetes Care. 2004;27:2688–2694.

45. Li YH, Lin GM, Lai CP, et al. The smoker paradox in Asian versus non-Asian patients with percutaneous coronary intervention longer than 6 months follow-up: a collaborative meta-analysis with the ET-CHD registry. Int J Cardiovasc Ther. 2013;68:4544–4548.