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Prior statin use and intravenous thrombolysis in acute ischemic stroke: a meta-analysis of cohort studies

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Abstract

Background: There is uncertainty whether prior statin use (PSU) influences the outcomes of intravenous thrombolysis (IVT) in acute ischemic stroke (AIS). Therefore, we conducted a systematic meta-analysis of published clinical trials to evaluate whether statin use combined with IVT therapy may be useful and safe. *Methods:* Electronic databases were searched for clinical trials that involved outcomes between PSU and nonstatin use (NSU) among stroke patients treated with IVT. Functional outcome measures were 3-month favorable outcome (modified Rankin scale [mRS] 0–2) and 3-month excellent outcome (mRS 0–1). Adverse outcome measures were 3-month all-cause mortality, intracranial hemorrhage (ICH) and symptomatic ICH (sICH). Data were extracted and used to calculate odds ratios (ORs) with 95% confidence intervals (CIs) by Review Manager 5.4 software. *Results:* Eleven studies, totaling 13,745 patients (2,957 for PSU and 10,788 for NSU), met the inclusion criteria. Compared with NSU, PSU was associated with excellent outcome (OR=0.78; 95% CI, 0.70–0.88; p<0.0001), ICH (OR=1.26; 95% CI, 1.07–1.47; p=0.005) and sICH (OR_{NINDS}=1.32; 95% CI, 1.06–1.64; p=0.01), whereas favorable outcome (OR=1.08; 95% CI, 0.86–1.35; p=0.50) and mortality (OR=1.11; 95% CI, 0.97–1.27; p=0.15) showed no significant difference between PSU and NSU. However, after combining the available multivariable data, associations with neither excellent outcomes (adjusted OR=0.92; 95% CI, 0.79–1.07; p=0.28) nor adverse outcomes (ICH: adjusted OR=1.11; 95% CI, 0.96–1.29; p=0.16; sICH: adjusted OR_{NINDS}=1.21; 95% CI, 0.95–1.56; p=0.13) was found.
Conclusions: PSU might neither positively nor negatively affect the outcomes of AIS patients treated by IVT.

Keywords: Statin use, intravenous thrombolysis, acute ischemic stroke, functional outcomes, adverse outcomes, meta-analysis

INTRODUCTION

Acute ischemic stroke (AIS) is a debilitating disease threatening the health of those in high-risk groups. Therefore, improving and perfecting the prevention, treatment and prognosis of AIS has become an important goal among clinical workers worldwide. Despite the rapid development of endovascular thrombectomy[1], intravenous thrombolysis (IVT) with alteplase (recombinant tissue plasminogen activator [rt-PA]) within the time window is still crucial.[2,3] Other means of treatment, are still limited its application.

Since statins (3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase inhibitors) became available in the 1980s, pharmacotherapy with statins has been recommended for the primary and secondary prevention of stroke and coronary heart diseases.[4,5] In addition to lowering lipid levels and reducing the risk of recurrent stroke, previous studies have reported that statins can also improve endothelial function, promote angiogenesis, repair endothelial injury[6], inhibit inflammation and stabilize artery plaques.[7] Despite the beneficial effects, some studies have shown that statins decrease platelet aggregation and thrombogenesis[8], which may be related to symptomatic intracranial hemorrhages (sICH) and exacerbate unfavorable outcomes.[9] Some studies have reported that prior statin use (PSU) was associated with improved functional outcomes[10,11,14,17,18], but these findings have not been consistently replicated.[12,13,15,16,19,20] Some studies have shown that statin use before thrombolysis is associated with adverse outcomes

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such as increased mortality and sICH. Whether it is efficient and safe to combine statins with IVT is still a matter of some controversy.

We conducted a systematic review and meta-analysis to further evaluate whether PSU affects the clinical outcomes in patients treated with IVT.

METHODS

Literature search

We performed a comprehensive literature search of the following electronic databases without language restrictions from their establishment through August 2021: PubMed, EMBASE, the Cochrane Library and the Chinese Medical Journal Network. The following search terms were used: [statin OR hydroxymethylglutaryl-CoA reductase inhibitors] AND [thrombolysis OR tissue plasminogen activator] AND [stroke OR ischemic cerebral infarction]. The reference lists of the appropriate trials were manually searched.

Study selection and data extraction

Trials included in the meta-analysis were selected based on the following inclusion criteria: (1) Cohort studies; (2) Exclusively AIS patients treated with IVT; (3) Categorized by the outcomes of statin use and (4) Reported on at least one of the outcome measures mentioned below. Trials were excluded from the meta-analysis if (1) They were duplicated publications based on the same data and (2) The full text was not available. Two authors (TN and WW) independently reviewed the titles and abstracts based on the inclusion criteria. If disagreement regarding inclusion or exclusion occurred, we discussed with the other investigators (QD and MHJ). The following data were extracted: first author, year of publication, country where the study was performed, study design, sample size, study population characteristics and clinical outcomes. Data were extracted and entered into Review Manager (version 5.4; Cochrane Collaboration, Oxford, England). Some data in this meta-analysis may differ slightly from the original studies because we standardized outcome definitions for data analysis.

Clinical outcomes

Functional outcome measures were as follows: 3-month favorable outcome (mRS 0–2) and 3-month excellent outcome (mRS 0–1). Adverse outcome measures were 3-month mortality, ICH and sICH. Different studies used different criteria for sICH. To reduce bias, the literature with the same sICH criteria was analyzed. A total of three types of sICH criteria were included: NINDS criteria, SIST-MOST criteria, and ECASS II criteria.

Statistical analysis

Review Manager 5.4 was used to analyze the data. Dichotomous data are reported as ORs with corresponding 95% CIs. Continuous data were reported as the weighted mean difference (WMD). Heterogeneity among trials was assessed by the Q statistic ($P<0.1$ was considered representative of statistically significant heterogeneity), and the I^2 statistic ($I^2>50\%$ was considered representative of statistically significant heterogeneity). Studies with low levels of heterogeneity were combined and calculated using a fixed effect model with the Mantel–Haenszel method. The DerSimonian–Laird random effect model was applied to calculate ORs in instances with significant heterogeneity. Statistical significance was considered at $p<0.05$.

Sensitivity analysis

To confirm the robustness of the results, sensitivity analysis was performed by excluding each study and recalculating the data.

RESULTS

Eligible studies

A flow chart of our study search is shown in Figure 1. Initially, we identified 1,058 potentially relevant articles of which 361 were excluded after excluding duplicates. After reading the titles and abstracts, 672 unrelated, nonhuman and full-text unavailable studies were excluded. The full texts of the remaining 25 articles were identified. Eleven articles that met the inclusion criteria were included in the qualitative analysis and final meta-analysis.

Study characteristics

In total, 13,745 AIS patients treated with IVT were included in the 11 trials: 2,957 patients were prior statin users, 10,788 patients were nonstatin users forming the control. The characteristics of the included studies are presented in Table 1. The PSU group had more vascular risk factors and previous antithrombotic treatment than the nonstatin user (NSU) group. Multivariable analysis was also performed. All the 11 studies were included, regardless of the type, dose or treatment duration of statin therapy, stroke subtypes and lipid levels.

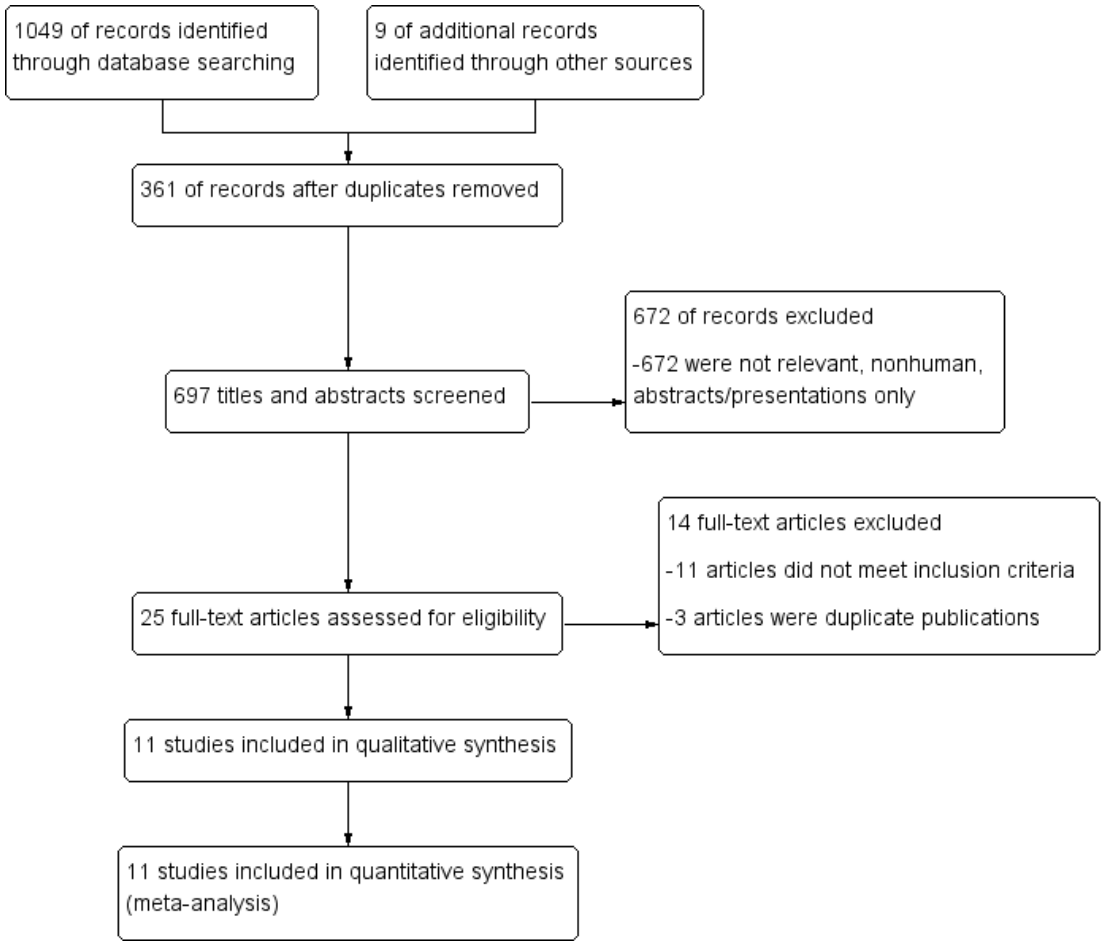


Fig. 1. Flow chart of the search process

The Newcastle–Ottawa Scale (NOS) was adopted to assess methodological quality. The NOS ranges from 0 to 9, with scores of 0–4 indicating low quality and scores of 5–9 indicating high quality. The scores of the included trials ranged from 6 to 9, meaning that the trials were high-quality studies (Table 1).

Functional outcomes

1 Favorable outcome: 3-month mRS of 0–2

Seven articles[10-12,14,15,18,20] provided data for the analysis of favorable outcome. The NSU group had a mildly higher rate of favorable outcome than the PSU group (51.3% vs. 51.0%, respectively). Meta-analysis of these studies showed that there was no difference between the two groups (OR=1.08; 95% CI, 0.86–1.35; p=0.50) (Figure 2A). Four studies[10-12,14] provided data appropriate for multivariate analysis. After adjusting for confounding variables, the results remained unchanged. The results indicated no significant association between PSU and NSU (adjusted OR=1.08; 95% CI, 0.54–2.17; p=0.82) (Figure 2B). Random effect models were used in the above analyses because of significant heterogeneity.

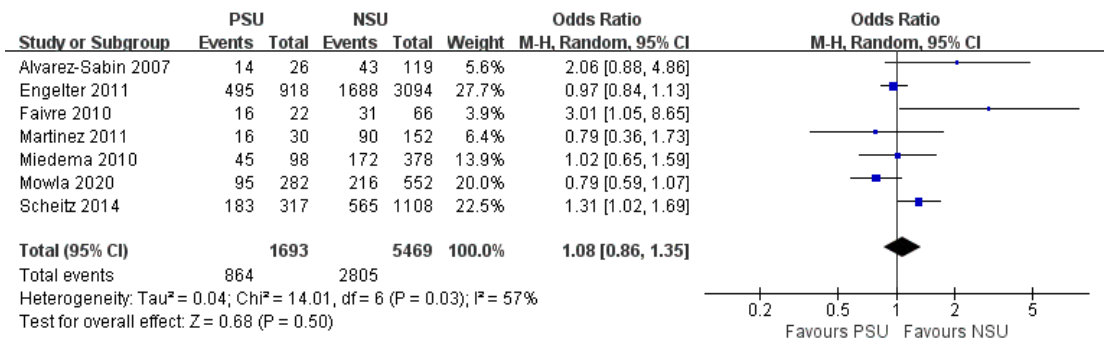
2 Excellent outcome: 3-month mRS of 0–1

Four studies[13,14,16,18] formed the basis for this analysis. No statistically significant heterogeneity was observed (P=0.61; I^2=0%). Meta-analysis of the four studies showed that excellent outcome was significantly more likely in the PSU group than in the NSU group (OR=0.78; 95% CI, 0.70–0.88; p<0.0001) (Fig. 3A). Nevertheless, the result became nonsignificant after excluding confounding variables (adjusted OR=0.92; 95% CI, 0.79–1.07; p=0.28) (Figure 3B). The heterogeneity was not statistically significant (P=0.64; I^2=0%).

Table 1: Characteristics of included trails

	Year	Country	Study design	Sampe size	Mean age	Outcomes	NOS
Alvarez-Sabin *et al*	2007	Spain	Single center	145(PSU=26 NSU=119)	71.9	mRs 0-2, Mortality	6
Makihara *et al*	2009	Japan	Multiple center	600(PSU=67 NSU=533)	72.0	mRS 0-1, Mortality, ICH, sICH	6
Faivre *et al*	2010	France	Single center	88(PSU=22 NSU=66)	63.2	mRS 0-2	6
Miedema *et al*	2010	Netherlands	Single center	476(PSU=98 NSU=378)	69.1	mRS 0-2, Mortality, sICH	7
Martinez *et al*	2011	Spain	Single center	182(PSU=30 NSU=152)	68.3	mRS 0-2, Mortality, ICH, sICH	7
Engelter *et al*	2011	Switzerland	Multiple center	4012(PSU=918 NSU=3094)	68.8	mRS 0-1, mRS 0-2 Mortality , ICH, sICH	8
Rocco *et al*	2012	German	Single center	1018(PSU=209 NSU=809)	69.7	mRS 0-1, Mortality, ICH, sICH	6
Scheitz *et al*	2014	German	Multiple center	1446(PSU=317 NSU=1129)	68.9	mRS 0-2, sICH	6
Tsivgoulis *et al*	2015	Greece	Multiple center	1660(PSU=373 NSU=1287)	67.0	mRS 0-1, Mortality, sICH	9
Minhas *et al*	2018	UK	Multiple center	3284(PSU=615 NSU=2669)	70.2	Mortality, ICH, sICH	8
Mowla *et al*	2020	USA	Single center	834(PSU=282 2AASU=552)	71.1	mRS 0-2, sICH	6

A



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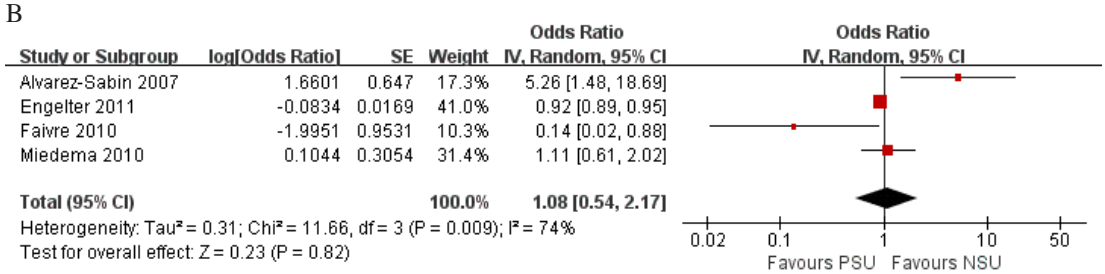
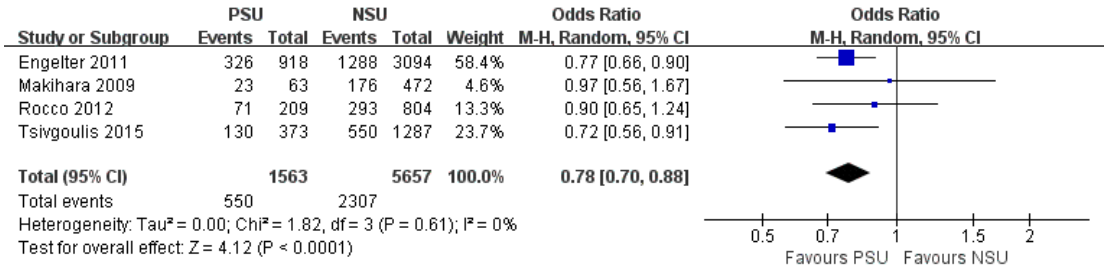


Fig. 2 Effects of PSU on favorable outcome in AIS patients treated by IVT. (A) Univariate analysis. (B) Multivariate analysis.

A



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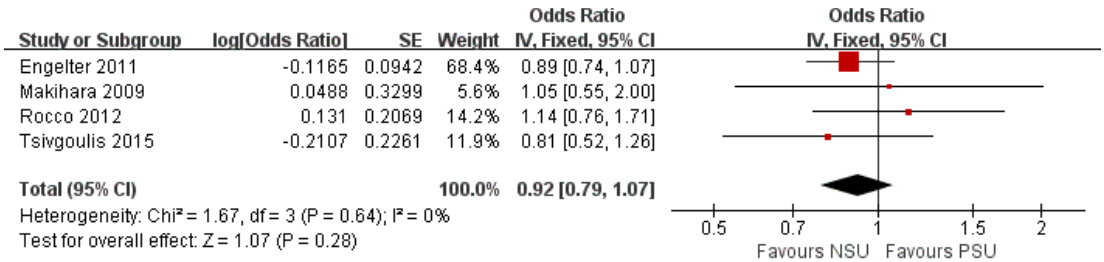


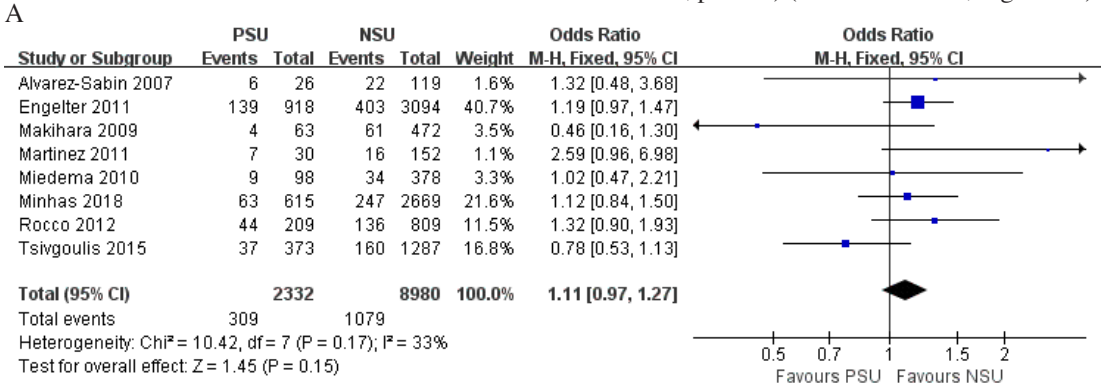
Fig. 3 Effects of PSU on excellent outcome in AIS patients treated by IVT. (A) Univariate analysis. (B) Multivariate analysis.

Adverse outcomes

1 Mortality

Eight trials[10,12-16,18,19] reported data on mortality. Mortality rate in the PSU group was 13.3% (309 of 2,332), while that in the NSU group was 12.4% (1,079 of 8,980). There was no heterogeneity among the studies (P=0.17; I^2=33%), and the data were meta-analyzed using a fixed effect model. The results revealed that PSU therapy was not associated with increased mortality (OR=1.11; 95% CI, 0.97–1.27; p=0.15) (Figure 4A). Multivariate analysis also showed a similar result (adjusted OR=1.06; 95% CI, 0.90–1.27; p=0.48) (4 studies[10,12,14,15]; Figure 4B).

A



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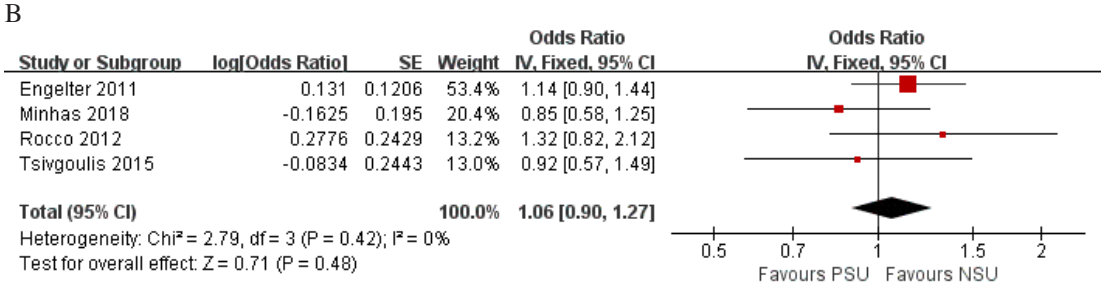
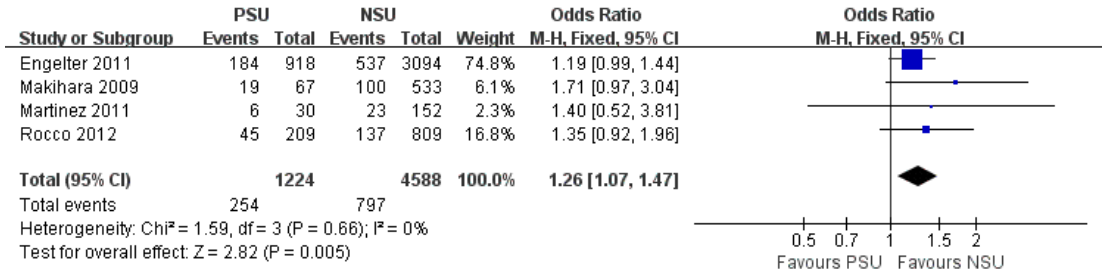


Fig. 4 Effects of PSU on mortality in AIS patients treated by IVT. (A) Univariate analysis. (B) Multivariate analysis.

A



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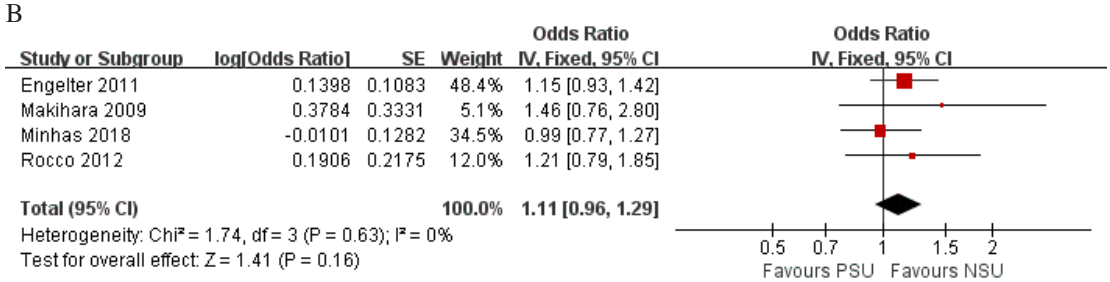


Fig. 5 Effects of PSU on ICH in AIS patients treated by IVT. (A) Univariate analysis. (B) Multivariate analysis.

2 ICH

ICH was reported in four studies.[13,14,16,19] The meta-analysis results showed a statistically significant difference between the two groups (OR=1.26; 95% CI, 1.07–1.47; p=0.005) (Figure 5A). There was no statistically significant heterogeneity among the studies (P=0.66; I^2=0%). However, the multivariate meta-analysis showed no statistical significance (adjusted OR=1.11; 95% CI, 0.96–1.29; p=0.16; Figure 5B) with nonsignificant heterogeneity (P=0.63; I^2=0%).

3 sICH

Nine studies[12–20] reported data for this analysis. Only the sICH meta-analysis based on studies using NINDS criteria had statistical significance (OR_{NINDS}=1.32; 95% CI, 1.06–1.64; p=0.01; Figure 6A1). Multivariate meta-analysis did not show statistical significance (adjusted OR_{NINDS}=1.21; 95% CI, 0.95–1.56; p=0.13; Figure 6B1). Both univariate and multivariate meta-analyses were not statistically significant based on studies using the SIST-MOST and ECASS II criteria for sICH (Figure 6A2, 6A3, 6B2, 6B3).

Publication bias

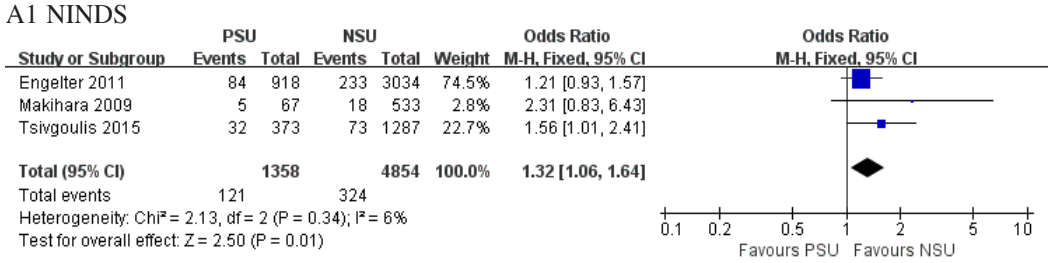
The funnel plots were symmetrical on visual inspection, suggesting low risks of publication biases for each synthesis.

DISCUSSION

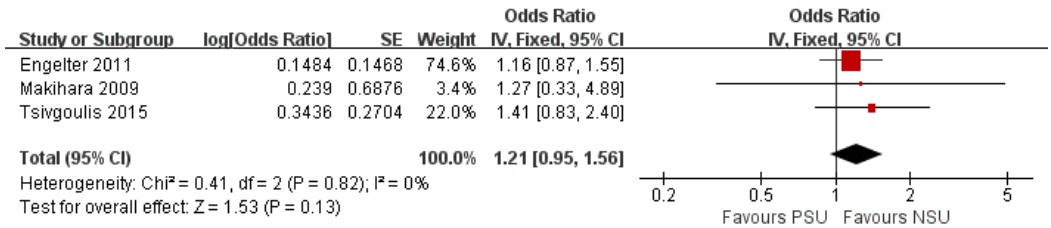
Since statins are widely used to lower lipid levels and stabilize atheromatous plaques, numerous studies have sought to investigate the impacts of statins on AIS. In patients not eligible for IVT, many clinical trials have reported that statins are associated with positive functional outcomes.[21,22] Previous studies[23-25] demonstrated that statin administration significantly reduced infarct volume, edema volume, and neurological deficits. Moreover, statin treatment at stroke onset was also associated with a reduced likelihood of all-cause death at 30 days, 90 days or 1 year after hospital discharge.[26] These data indicated that statins may be effective and safe when applied in the acute phase of stroke.

To date, a few studies have discussed the association of statin treatment in AIS patients treated with IVT. Cappellari *et al*.[27] prospectively collected data from 2,072 stroke patients treated with IVT and reported that statin use in the acute phase was associated with short-term neurologic improvements, 3-month favorable outcome, and a reduced risk of death. Patients who continued with previous treatment using the same type and dose or switched to a higher dose or another type of statin during the acute phase of stroke showed no significant differences in the rate of favorable outcomes and mortality at 90 days compared with patients who started statin treatment in the acute phase.[28] Bruning *et al*.[29] investigated the

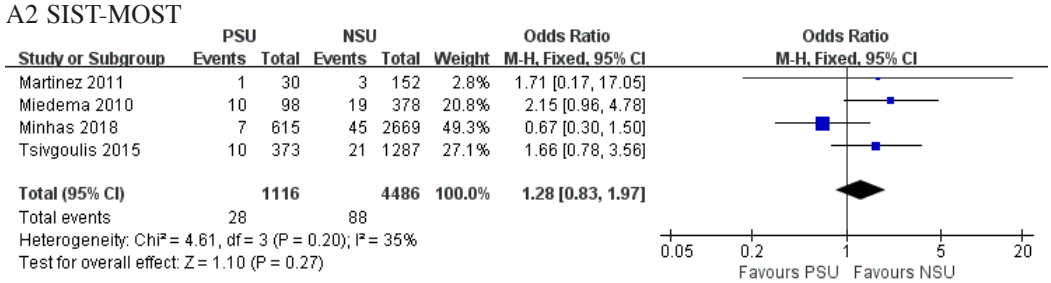
A1 NINDS



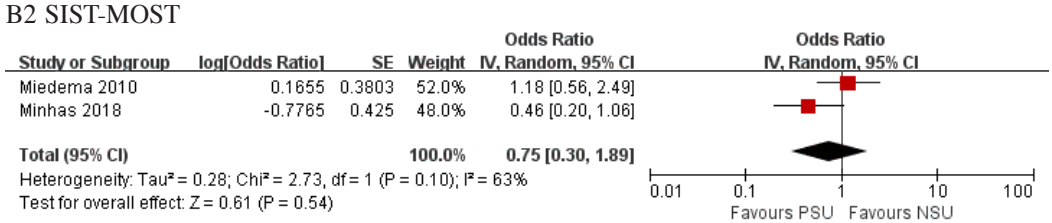
B1 NINDS



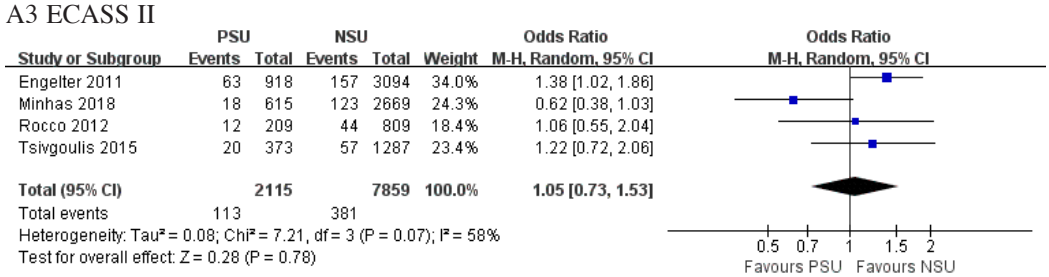
A2 SIST-MOST



B2 SIST-MOST



A3 ECASS II



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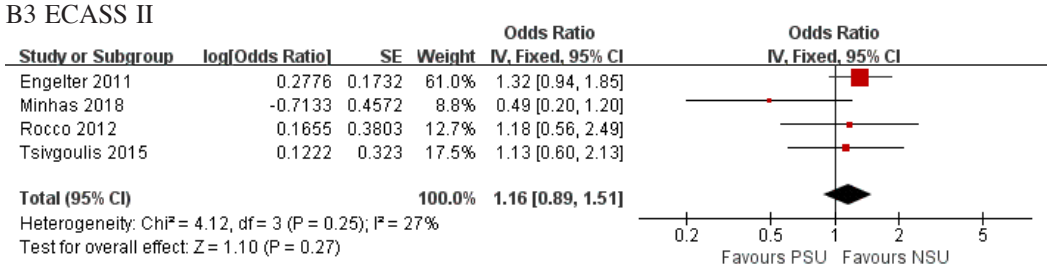

Fig. 6 Effects of PSU on sICH in AIS patients treated by IVT. (A) Univariate analysis. (B) Multivariate analysis (1. NINDS criteria, 2. SIST-MOST criteria, 3. ECASS II criteria).

association between pretreatment with statins or new type or dose adjustments and effects on mortality rate in patients with AIS who received IVT. The PSU group showed a lower rate of in-hospital mortality and 3-month mortality than the group of patients who had no statin treatment during their stay in the hospital. Pretreatment with statins and new adjustments were positively associated with the prognosis of intravenous thrombolyzed stroke patients. These results have suggested a positive effect in the prior statin use.

Among AIS patients, many have risk factors for cerebrovascular diseases such as dyslipidemia, coronary heart disease and previous stroke. As a result, a significant proportion of these patients are under prescription of statins as secondary prevention. If these people experience stroke and need IVT therapy, does prior statin use affect prognosis? Our meta-analysis showed that compared with NSU, PSU was associated with excellent outcome. However, we also presented evidence that PSU increased the risk of bleeding complications. After adjusting for potential confounders, there was neither better functional outcomes nor increased adverse outcomes . The lack of statistical significance with excellent outcome might be explained by the fact that the observed benefits of statin therapy were generated from the effect of statins on stroke severity. The loss of significance with adverse outcomes may be explained by the fact that statin users tended to have more vascular risk factors, which consequently led to poor prognoses.

NINDS criteria[30] is the most widely defined in symptomatic intracranial bleeding, as long as there is neurological dysfunction or clinically suspected bleeding, and CT support is added. Some patients who were not diagnosed with sICH with other criteria were classified as sICH patients based on NINDS criteria. Therefore, sICH is different from other standard results. Based on the meta-analysis findings, we draw a cautious conclusion that PSU does not seem to affect clinical outcomes in AIS patients treated by IVT.

As with other meta-analysis, the present study had limitations. Despite the authors' best efforts to obtain complete data, some studies may have been missed, particularly unpublished studies. In addition, few randomized controlled trials are available at present. In addition, some studies did not provide the results needed for multivariable analysis. When we tried to analyze the outcomes excluding confounding variables, it was inevitable that the sample size was reduced. Finally, the statin dosage, type, or treatment duration, stroke subtypes and lipid levels were not taken into consideration, which may influence the analysis.

In conclusion, our meta-analysis demonstrates that PSU seems neutral with respect to the outcomes in AIS patients treated by IVT. Given the current information, we believe that PSU impose no obvious disadvantages to IVT . Further randomized trials are needed to confirm this.

DISCLOSURE

Conflict of interest: None

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