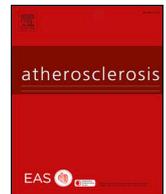




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## Association of statin pretreatment with collateral circulation and final infarct volume in acute ischemic stroke patients: A meta-analysis



Konark Malhotra<sup>a</sup>, Apostolos Safouris<sup>b,c</sup>, Nitin Goyal<sup>d</sup>, Adam Arthur<sup>e</sup>, David S. Liebeskind<sup>f</sup>, Aristeidis H. Katsanos<sup>b,g</sup>, João Sargento-Freitas<sup>h,i</sup>, Marc Ribo<sup>j</sup>, Carlos Molina<sup>j</sup>, Jong-Won Chung<sup>k</sup>, Oh Young Bang<sup>k</sup>, Georgios Magoufis<sup>l</sup>, Ahmad Cheema<sup>e</sup>, Steven J. Shook<sup>m</sup>, Ken Uchino<sup>m</sup>, Andrei V. Alexandrov<sup>d</sup>, Georgios Tsivgoulis<sup>b,d,\*</sup>

<sup>a</sup> Department of Neurology, Charleston Area Medical Center, West Virginia University-Charleston Division, Charleston, WV, USA

<sup>b</sup> Second Department of Neurology, National & Kapodistrian University of Athens, "Attikon" University Hospital, Athens, Greece

<sup>c</sup> Stroke Unit, Metropolitan Hospital, Piraeus, Greece

<sup>d</sup> Department of Neurology, University of Tennessee Health Science Center, Memphis, TN, USA

<sup>e</sup> Department of Neurosurgery, Semmes-Murphey Neurologic and Spine Institute, University of Tennessee Health Science Center, Memphis, TN, USA

<sup>f</sup> Neurovascular Imaging Research Core and UCLA Stroke Center, Department of Neurology, University of California, Los Angeles, CA, USA

<sup>g</sup> Department of Neurology, University of Ioannina School of Medicine, Ioannina, Greece

<sup>h</sup> Department of Neurology, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal

<sup>i</sup> Faculty of Medicine, University of Coimbra, Coimbra, Portugal

<sup>j</sup> Vall D'Hebron Stroke Unit, Hospital Universitari Vall D'Hebron Passeig Vall D'Hebron, Barcelona, Spain

<sup>k</sup> Department of Neurology, Samsung Medical Center, Seoul, South Korea

<sup>l</sup> Department of Interventional Neuroradiology, Metropolitan Hospital, Piraeus, Greece

<sup>m</sup> Department of Neurology, Cleveland Clinic Foundation, Cleveland, OH, USA

### HIGHLIGHTS

- Collateral circulation status and final infarct volume (FIV) are independent outcome predictors after an AIS.
- We evaluated the association of statin pretreatment (SP) on collateral circulation and FIV in AIS patients.
- SP was associated with lower FIV compared to no SP, especially in atherosclerotic AIS.
- A trend towards good collateral scores was observed in the SP group.
- SP appears to be associated with decreased FIV after AIS, possibly due to more favorable collateral circulation.

### ABSTRACT

**Background and aims:** Statin pretreatment (SP) is associated with improved outcomes in acute ischemic stroke (AIS) patients. Collateral circulation status and final infarct volume (FIV) are independent predictors of functional outcome in AIS.

**Methods:** We sought to evaluate the association of SP with collateral circulation and FIV in AIS patients. We used a random-effects model for all the analyses, and pooled standardized mean differences (SMDs) and odds ratios (OR) on the FIV and collateral status according to SP history, respectively.

**Results:** We identified 9 eligible studies (1186 AIS patients). History of SP was associated with lower FIV (SMD = 0.25, 95%CI: 0.07–0.42,  $p = 0.005$ ) compared to negative history of SP. A trend towards good collateral scores was observed in the SP group (OR = 1.45; 95% CI, 0.92–2.29,  $p = 0.11$ ). Subgroup analysis demonstrated reduced FIV among atherosclerotic stroke patients with history of SP (SMD = 0.49; 95% CI, 0.19–0.80,  $p = 0.001$ ).

**Conclusions:** SP appears to be associated with decreased FIV, especially in atherosclerotic AIS.

### 1. Introduction

Statin pretreatment (SP) is associated with favorable clinical

outcomes in acute ischemic stroke (AIS) due to large artery atherosclerosis (LAA) [1]. Pleiotropic properties of statins extend beyond lipid lowering effects, encompassing positive influence on endothelial

\* Corresponding author. Second Department of Neurology, University of Athens, School of Medicine, Athens, Greece, Iras 39, Gerakas Attikis, Athens, 15344, Greece.

E-mail address: [tsivgoulisgiorg@yahoo.gr](mailto:tsivgoulisgiorg@yahoo.gr) (G. Tsivgoulis).

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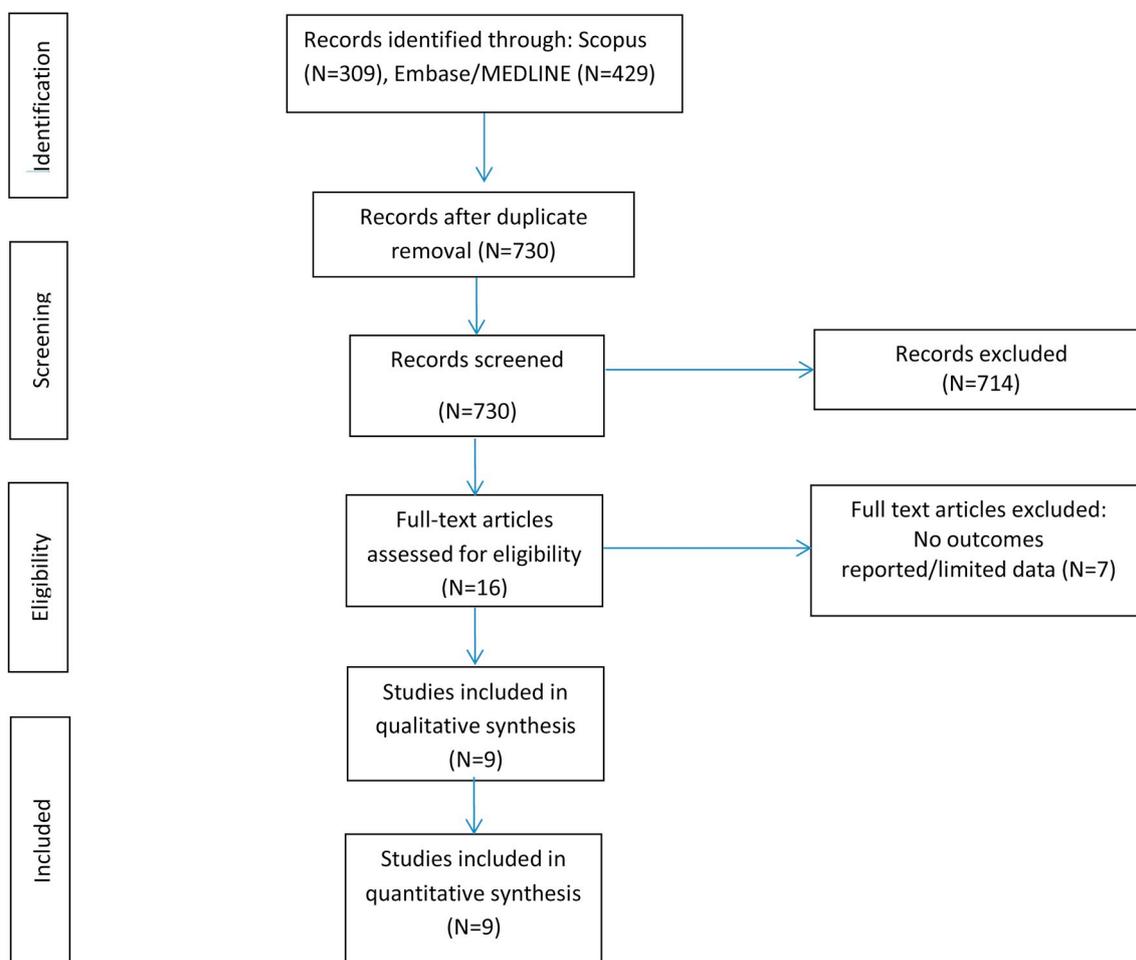


Fig. 1. Flow-chart diagram presenting the selection of eligible studies.

function, cerebral hemodynamics, inflammatory response, platelet function and lipid oxidation [2]. These tissue-level effects further correspond to atherosclerotic plaque stabilization and reduction in stroke recurrence [3]. There are preliminary data showing that SP may be correlated with improved collateralization among AIS patients [4,5]. Moreover, SP have been demonstrated to up-regulate endothelial nitric oxide synthase (eNOS) activity that further enhances collateral perfusion and reduces final infarct volumes (FIV) [6]. Although improved collateral circulation results in reduction of FIV and better clinical outcomes, the potential influence of SP on collateral circulation status and final infarct size has not been determined. In view of these considerations, we performed a systematic review and meta-analysis of available studies reporting FIV or collateral grades based on digital subtraction angiography (DSA) in AIS patients with and without SP.

## 2. Materials and methods

We adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews and meta-analyses [7]. We used the Newcastle-Ottawa Scale to explore sources of bias amongst the included observational studies as previously described [8].

We identified all eligible observational studies that investigated the association of statin pre-treatment (SP) prior to admission with collateral circulation and core infarct volume. Systematic search was conducted in Embase/MEDLINE and Scopus databases from inception to June 17, 2018. Additional manual search included conference abstracts and bibliographies of candidate studies and recent systematic reviews for a comprehensive literature search. The detailed search

algorithm used on MEDLINE search is outlined in [Supplementary Materials](#). No language or other restrictions was imposed. All retrieved studies were independently reviewed by three authors (KM, AS & GT), with any disagreement resolved by consensus. We excluded case series, case reports, or studies not reporting any information on SP. In those studies where the original publication reported evidence of SP stratification, but did not contain all necessary data, we contacted the corresponding authors by e-mail. The quality control and bias identification were performed independently by 2 reviewers (KM, AHK), and disagreements, if any, were resolved by a third tie-breaking evaluator (GT).

The corresponding odds ratios (OR) for good collaterals and standardized mean differences (SMD) to assess final infarct volumes (FIV) in patients with SP *versus* patients without SP were calculated. We also conducted subgroup analyses to evaluate association of SP and FIV among patients with different stroke subtypes. We selected those studies that assessed DSA-based collateral grades according to either the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) or collateral pial circulation (CPC) collateral flow grading classifications. We defined good collaterals as ASITN/SIR grades 3–4 or CPC scores 0–2, as previously described [2,9]. FIV was defined as infarct regions measured using ABC/2 method on available neuroimaging during hospitalization [2].

In all analyses, SMDs and ORs of individual studies were pooled using the random-effects model (DerSimonian Laird). Heterogeneity between studies was evaluated using Cochran Q and  $I^2$  statistics, with  $I^2$  values of  $I^2 > 50\%$  and  $I^2 > 75\%$  indicating substantial and considerable heterogeneity, respectively [10]. Publication bias across individual studies was graphically assessed using a funnel plot, while formal

assessment with Egger's test could not be performed due to the small number of studies (< 10 studies). All statistical analyses were conducted using Review Manager (RevMan) Version 5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

### 3. Results

The systematic search of Embase/MEDLINE and Scopus databases yielded 429 and 309 results respectively. After removing duplicates, the titles and abstracts of the remaining 730 studies were screened and, from the 16 potentially eligible studies, 7 studies were excluded for lack of data availability on either collateral scores or infarct volume stratified by SP status (Supplementary Table I). In the final evaluation of the literature search results, there was no conflict or disagreement between reviewers and the 9 studies that met the protocol's inclusion criteria were included in the meta-analysis (Fig. 1) [2,5,6,9,11–15]. The corresponding authors from 7 studies [2,6,9,11,12,14,15] were contacted to obtain necessary unpublished data for the quantitative analyses. Data on collateral status were available as ASITN/SIR [3,5,9,11,13,14] or CPC [2] classification, whereas FIV data were available from 6 studies [2,6,11–14].

The patient data and study protocols of the included studies comprising a total of 1186 patients are summarized in Table 1 and Supplementary Table II. The risk of bias in the included studies was considered to be moderate, mainly because of the lack of reporting appropriate adjustments for potential confounders in 4 study protocols (Supplementary Table III).

SP was associated with reduced FIV on neuroimaging (SMD = 0.25; 95% CI, 0.07–0.42; Fig. 2A). In studies reporting on collateral status, a trend towards good collateral scores was observed in the SP group (OR = 1.45; 95% CI, 0.92–2.29; Fig. 2B). No evidence of heterogeneity was observed for FIV ( $I^2 = 12%$ ,  $p$  for Cochran Q statistic = 0.34) or good collateral status ( $I^2 = 34%$ ,  $p$  for Cochran Q statistic = 0.17). Inspection of the funnel plot revealed no evidence of asymmetry (Supplementary Fig. I and II).

A subgroup analysis comparing stroke subtypes revealed that SP was associated with reduced FIV among patients with atherosclerotic strokes (3 studies; SMD = 0.49; 95% CI, 0.19–0.80; Fig. 2C). No evidence of heterogeneity was observed ( $I^2 = 0%$ ,  $p$  for Cochran Q statistic = 0.51).

**Table 1**  
Study design and characteristics of included studies in our meta-analysis.

Study name	Country	Study design, registry	Patients, N	Endpoints	SP +, SP-	Imaging method	Timing from Index Event
Cheng-Ching et al. [14]	United States	Retrospective	91	FIV Collaterals (ASITN/SIR)	32, 58 20, 34	DWI-MRI DSA	< 6 h –
Chung et al. [12]	South Korea	Prospective, STAMINA-MRI	136	FIV	38 <sup>a</sup> , 98	DWI-MRI	< 7 days
Goyal et al. [11]	United States	Retrospective	116	FIV Collaterals (ASITN/SIR)	53, 53 56, 73	FLAIR-MRI DSA	< 14 days –
Lee et al. [5]	International	Retrospective	98	Collaterals	22 <sup>b</sup> , 76	DSA	< 8 h
Liebeskind et al. [9]	International	Prospective, IMS III	331	Collaterals (ASITN/SIR)	98, 178	DSA	–
Safouris et al. [15]	Greece	Prospective	36	Collaterals (ASITN/SIR)	5, 31	DSA	–
Sargento-Frietas et al. [2]	Portugal	Retrospective	118	Collaterals (CPC)	17, 31	DSA	–
Sheth et al. [13]	United States	Retrospective	117	FIV Collaterals (ASITN/SIR)	27, 89 24, 93	DWI-MRI DSA	< 24 h –
Shook et al. [6]	United States	Retrospective	143	FIV	38 <sup>c</sup> , 105	DWI-MRI	< 48 h

SP, statin pretreatment; FIV: final infarct volume; ASITN/SIR: American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology; CPC: collateral pial circulation; MRI: magnetic resonance imaging; DWI-MRI: diffusion weighted sequence of MRI; FLAIR-MRI: fluid attenuated inversion recovery sequence of MRI; DSA: digital subtraction angiography.

<sup>a</sup> Atorvastatin < 40 mg or equivalent dose (n = 22), ≥ 40 mg atorvastatin or equivalent dose (n = 16).

<sup>b</sup> Atorvastatin > 10 mg or equivalent (n = 14), atorvastatin ≤ 10 mg or equivalent (n = 8).

<sup>c</sup> Atorvastatin (n = 24, median dose 20 mg), simvastatin (n = 10, median dose 20 mg), pravastatin (n = 3, median dose 40 mg), and lovastatin (n = 1, dose 20 mg).

### 4. Discussion

To the best of our knowledge, this is the first meta-analysis demonstrating the beneficial effect of SP among AIS patients in regards to reduced infarct volume. Prior studies have demonstrated improved collateral circulation with SP among acute LAA [2] or cardioembolic strokes [4,5]. These beneficial effects are likely attributed to the potential for statins to promote arteriogenesis and augment the eNOS-mediated vasodilation [6]. Among AIS patients with symptomatic intracranial atherosclerotic plaques, SP has been associated with reduced plaque enhancement, stabilization of atherosclerotic plaques, and lower frequency of large cortical ischemic strokes [12]. Our meta-analysis corroborates these results as SP in AIS patients is associated with reduced FIV, potentially secondary to better collateralization. Additionally, our subgroup analysis demonstrated a favorable effect of SP on FIV among patients with atherosclerotic strokes.

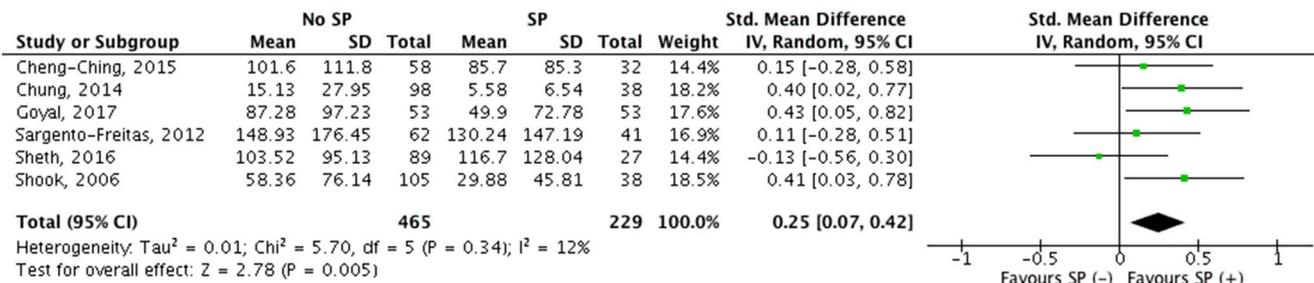
Our study has limitations. First, eligible studies included observational, small-sized cohorts that could have introduced selection bias. Second, data on both the endpoints (FIV and collateral scores) were unavailable in the majority of included studies. Third, statin type and dosage were reported in only 3 of the included studies (Table 1), while the duration of statin pretreatment was not reported in any of the included studies. Therefore, we were not able to perform further analyses on the duration of pretreatment, dosage or intensity of SP with the outcomes of interest. Moreover, in the present meta-analysis, we were unable to control for potential confounders of the collateral status, including metabolic syndrome, hyperuricemia, age and time from stroke onset to presentation [16,17]. Fourth, the evaluation of publication bias using funnel plot inspection was weak, and the possibility of the presence of a small study effect cannot be excluded.

In conclusion, the present meta-analysis adds to the increasing evidence of the beneficial effect of SP in AIS outcomes. SP is associated with reduced infarct volumes, especially in AIS due to LAA. Future prospective observational studies are warranted to confirm these preliminary observations.

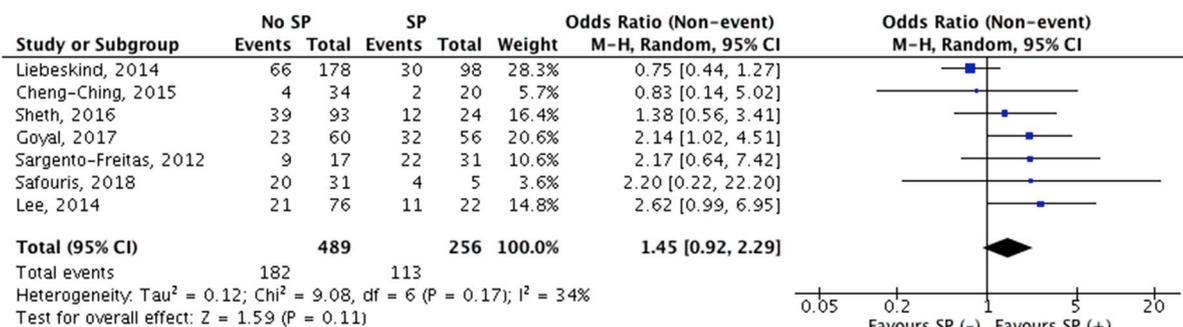
### Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

### A.



### B.



### C.

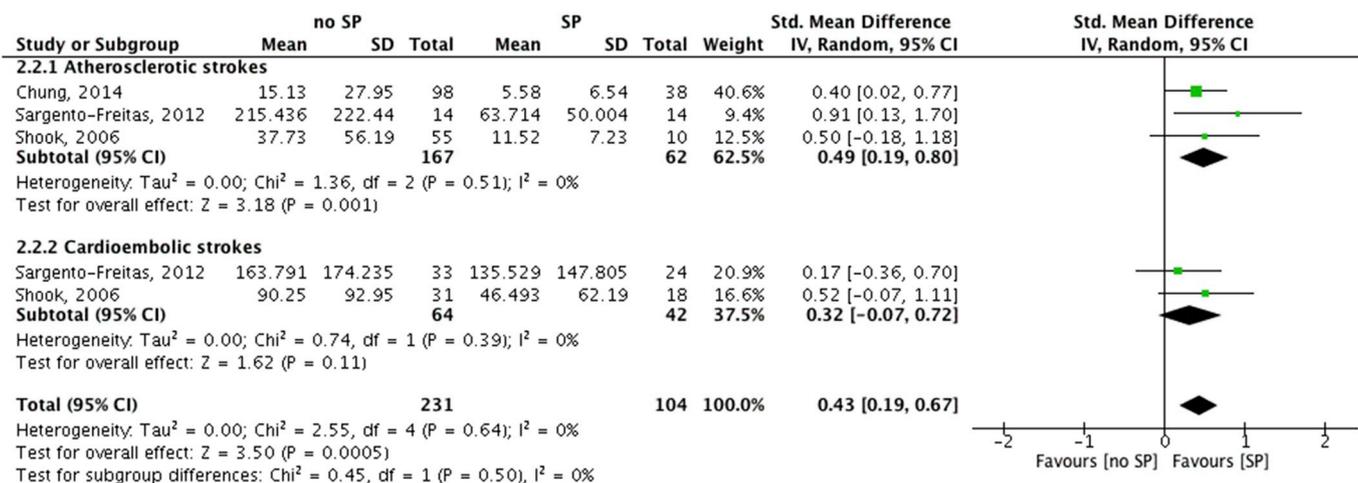


Fig. 2. Forest plots.

Forest plots presenting the association of statin pre-treatment with (A) final infarct volume, (B) good collaterals, and (C) final infarct volume among patients with atherosclerotic or cardioembolic stroke subtypes as subgroup analyses.

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.atherosclerosis.2019.01.006>.

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