Combination of Thrombolysis and Statins in Acute Stroke Is Safe

Results of the STARS Randomized Trial (Stroke Treatment With Acute Reperfusion and Simvastatin)

Joan Montaner, MD, PhD; Alejandro Bustamante, MD; Silvia García-Matas, PhD; Maite Martínez-Zabaleta, MD, PhD; Carmen Jiménez, MD, PhD; Javier de la Torre, MD; Francisco R. Rubio, MD, PhD; Tomás Segura, MD, PhD; Jaime Masjuán, MD, PhD; David Cánovas, MD, PhD; Mar Freijo, MD, PhD; Raquel Delgado-Mederos, MD, PhD; Javier Tejada, MD, PhD; Aida Lago, MD, PhD; Yolanda Bravo, MD, PhD; Natália Corbeto, PhD; Dolors Giralt, MSc; Bárbara Vives-Pastor, MD; Anna de Arce, MD; Francisco Moniche, MD, PhD; Pilar Delgado, MD, PhD; Marc Ribó, MD, PhD; on behalf of the STARS Investigators

Background and Purpose—The STARS trial (Stroke Treatment With Acute Reperfusion and Simvastatin) was conducted to demonstrate the efficacy and safety of simvastatin treatment in acute stroke.

Methods—STARS07 was a multicentre, phase IV, prospective, randomized, double-blind, placebo-controlled trial. Patients with Acute ischemic stroke recruited within 12 hours from symptom onset were randomized to oral simvastatin 40 mg or placebo, once daily for 90 days. Primary outcome was proportion of independent patients (modified Rankin Scale score of ≤2) at 90 days. Safety end points were hemorrhagic transformation, hemorrhagic events, death, infections, and serious adverse events.

Results—From April 2009 to March 2014, 104 patients were included. Fifty-five patients received intravenous tissue-type plasminogen activator. No differences were found between treatment arms regarding the primary outcome (adjusted odds ratio, 0.99 [0.35–2.78]; *P*=0.98). Concerning safety, no significant differences were found in the rate of hemorrhagic transformation of any type, nor symptomatic hemorrhagic transformation. There were no differences in other predefined safety outcomes. In post hoc analyses, for patients receiving tissue-type plasminogen activator, a favorable effect for simvastatin treatment was noted with higher proportion of patients experiencing major neurological recovery (adjusted odds ratio, 4.14 [1.18–14.4]; *P*=0.02).

Conclusions—Simvastatin plus tissue-type plasminogen activator combination seems safe in acute stroke, with low rates of bleeding complications. Because of the low recruitment, the STARS trial was underpowered to detect differences in simvastatin efficacy.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01073007.

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Around 40 experimental studies have shown the pleiotropic effects of statins in acute stroke, which might be responsible for neuroprotection.[1] A meta-analysis of statins in experimental stroke has reinforced its effects in the reduction of infarct size and improvement in neurological function, identifying also some conditioners for these neuroprotective

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From the Stroke Unit, Department of Neurology (J.M., M.R.), Neurovascular Research Laboratory, Institut de Recerca-Universitat Autónoma de Barcelona (J.M., A.B., N.C., D.G., P.D.), and Vall d' Hebron Institut d'Oncologia (S.G.-M.), Hospital Universitari Vall d'Hebron, Barcelona, Spain; Neurovascular Unit, Department of Neurology, Hospital Universitario Donostia, Donostia-San Sebastian, Spain (M.M.-Z., A.A.); Department of Neurology, Hospital Universitari Son Espases, Palma de Mallorca, Spain (C.J., B.V.-P.); Stroke Program, Institute of Biomedicine of Seville, Hospital Universitario Virgen del Rocio, Seville, Spain (J.T., F.M.); Department of Neurology, Hospital Universitari de Bellvitge, IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain (F.R.R.); Department of Neurology, Hospital Universitario Virgen de la Victoria, Albacete, Spain (T.S.); Stroke Unit, Department of Neurology, IRYCIS, University Hospital Ramón y Cajal, Madrid, Spain (J.M.); Department of Neurology, Hospital Universitari Parc Tauli, Sabadell, Spain (D.C.); Department of Neurology, Hospital de Basurto, Bilbao, Spain (M.F.); Department of Neurology, Hospital de la Santa Creu i Sant Pau, IIB-Sant Pau, Barcelona, Spain (R.D.-M.); Department of Neurology, Hospital Universitario de León, Spain (J.T.); Stroke Unit, Department of Neurology, Hospital Universitari la Fe, Valencia, Spain (A.L.); and Department of Neurology, Hospital Universitari General Yagüe, Burgos, Spain (Y.B.).

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Correspondence to Joan Montaner, MD, PhD, Neurovascular Research Laboratory, Hospital Universitari Vall d'Hebron, Pg. Vall d'Hebron 119–129, 08035 Barcelona, Spain. E-mail joan.montaner@vhir.org

effects, such as statin type, or its use as pretreatment.[2] In patients with stroke, the benefit of previously being on statin treatment on stroke outcome is well known.[3] To assess whether these benefits might be useful in acute stroke, we conducted a pilot clinical trial, in which patients receiving simvastatin improved significantly by the third day.[4]

Some concerns exist about the use of statins after intravenous thrombolysis. In fact, a meta-analysis has reported an association between statins and increased fatality in studies restricted to tissue-type plasminogen activator (tPA)–treated patients,[5] which together with the increased rates of intracerebral hemorrhage among patients treated with statins in the SPARCL trial (Stroke Prevention by Aggressive Reduction in Cholesterol Levels),[6] call for further evidence about whether the association of statins and tPA may promote hemorrhagic transformation (HT). The STARS trial (Stroke Treatment With Acute Reperfusion and Simvastatin) was conducted to demonstrate the efficacy of simvastatin treatment in acute stroke and the safety of combining it with tPA.

Methods

The STARS trial was a multicentre, phase IV, prospective, randomized, double-blind, placebo-controlled trial carried out in 18 Spanish hospitals. The study protocol was approved by the Spanish National Drug Agency (EudraCT: 2007-005868-26) and by the local Ethics Committee of each center. A detailed list of the inclusion and exclusion criteria is included in Appendix I in the online-only Data Supplement. All participants or relatives gave written informed consent before randomization.

Patients were randomized (1:1) to receive either simvastatin or placebo treatment. A complete description of the randomization process and the study procedures is supported in Appendix II in the online-only Data Supplement. Patients, site investigators, and treating physicians were not informed about treatment allocation. Primary outcome was proportion of patients with good outcome (mRS score, ≤2) 90 days after stroke. Secondary outcomes were NIHSS (National Institutes of Health Stroke Scale) reduction at 90 days and proportion of patients with neurological improvement (decrease in NIHSS score, ≥4) at 7 days. Safety outcomes were symptomatic hemorrhagic transformation according to the ECASS-II criteria (European Cooperative Acute Stroke Study),[7] any HT on follow-up neuroimaging, hemorrhagic events, infections, death, and serious adverse events. Given the high percentage of patients treated with intravenous tPA, as post hoc analyses, we further analyze data on safety and efficacy in this subgroup of patients. In addition, neurological deterioration (increase of the NIHSS ≥4 points) and major neurological improvement (NIHSS score of 0 or decrease in the NIHSS score, ≥8) were assessed at 7 days.

Efficacy analyses were performed by intention-to-treat in patients who completed the follow-up and repeated in patients fulfilling criteria for per-protocol analysis. Given that some patients were missed to follow-up, sensitivity analysis was conducted by assuming the best (mRS≤2) and worst (mRS≤2) primary outcome for these patients as well as the best and the worst possible scenario for simvastatin treatment. Safety analyses were performed in every patient taking any dose of the study medication. Odds ratios (ORs) and 95% confidence intervals were obtained by logistic regression analyses, referred to simvastatin treatment. For safety analyses, crude OR were given, whereas for efficacy analyses, OR were adjusted by age, sex, and baseline NIHSS (adjusted OR). Statistical Package for Social Sciences (SPSS) Software v.17 was used. All analyses were performed blinded to treatment allocation. Details about sample size determination are given in Appendix II in the online-only Data Supplement. This study is registered with ClinicalTrials.gov, number NCT01073007.

Results

From April 2009 to March 2014, 104 patients were included, being randomized to either placebo (54 patients) or simvastatin (50 patients). Figure 1 shows the study flow chart. Median time to first treatment administration was 7.4 hours. Nasogastric tubes were needed in 9 cases. Two patients missed 1 dose of the study medication because of dysphagia and negative reaction to nasogastric tube placement. Demographic data are summarized in the Table.

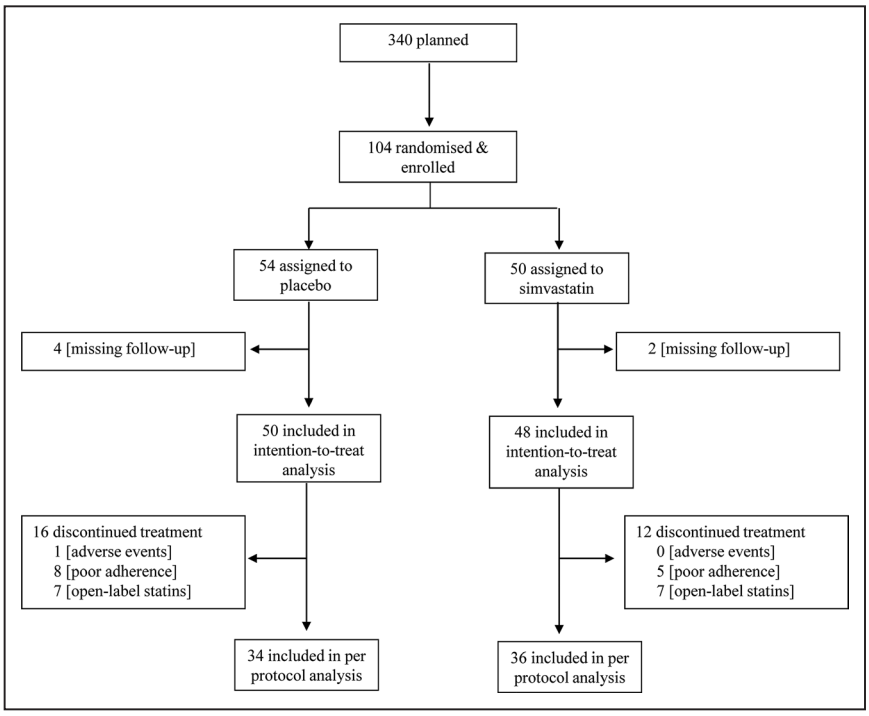

Figure 1. Trial profile.

Table. Baseline Characteristics of the Treatment Groups

	Placebo (n=54)	Simvastatin (n=50)	All (n=104)
Age	75 (57–82)	73.5 (64–82)	74 (62.5–82)
Sex (female; %)	22 (40.7)	26 (52)	48 (46.2)
Smoking (%)	13 (24.1)	10 (20)	23 (22.1)
Hypertension (%)	35 (64.8)	29 (58)	64 (61.5)
Diabetes (%)	7 (13)	10 (20)	17 (16.3)
Dyslipemia (%)	8 (14.8)	7 (14)	15 (14.4)
Atrial fibrillation (%)	3 (24.1)	12 (24)	25 (24)
Previous myocardial infarction (%)	1 (1.9)	2 (4)	3 (2.9)
Previous stroke (%)*	3 (5.6)	4 (8.2)	7 (6.7)
Prestroke mRS			
0 (%)	40 (74.1)	34 (68)	74 (71.2)
1 (%)	14 (25.9)	16 (32)	30 (28.8)
Baseline NIHSS	7 (5–12)	7 (6–11)	7 (6–11.5)
Thrombolysis (%)	28 (51.9)	27 (54)	55 (52.9)
OCSP			
TACI (%)	12 (22.2)	11 (22)	23 (22.1)
PACI (%)	34 (63)	33 (66)	67 (64.4)
LACI (%)	7 (13)	6 (12)	13 (12.5)
POCI (%)	1 (1.9)	0 (0)	1 (1)
TOAST*			
Cardioembolic (%)	24 (46.2)	17 (34.7)	41 (40.6)
Atherothrombotic (%)	8 (15.4)	2 (4.1)	10 (9.9)
Lacunar (%)	4 (7.7)	5 (10.2)	9 (8.9)
Undetermined (%)	15 (28.9)	25 (51)	40 (39.9)
Other determined (%)	1 (1.9)	0 (0)	1 (1)

Data presented as n (%) or median (IQR). LACI indicates lacunar infarct; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OCSP, Oxfordshire Stroke Project classification; PACI, partial anterior circulation infarct; POCI, posterior circulation infarct; TACI, total anterior circulation infarct; and TOAST, Trial of Org 10172 in Acute Stroke Treatment classification.

*Data not available for all the randomized patients.

A total of 33(68.8%) cases in simvastatin arm and 35(70%) in placebo arm achieved the primary outcome, with no differences between treatment arms (adjusted OR, 0.99 [0.35–2.78]; *P*=0.98; Figure 2). Sensitivity analysis did not change these results. There were no significant differences in secondary outcomes, and per-protocol analysis showed similar results (Tables I through II in the online-only Data Supplement). Regarding safety, there were no significant differences in the rate of HT between simvastatin and placebo arms (6 [13.6%] simvastatin versus 8 [17%] placebo; OR, 0.77 [0.24–2.43]; *P*=0.66]. Symptomatic intracranial hemorrhage was diagnosed in 2 cases, both in placebo arm (0 [0%] simvastatin versus 2 [3.7%] placebo; *P*=0.49). There were no differences in other safety concerns except for a trend toward reduced incidence of serious adverse events in simvastatin arm. There were no cases of recurrent stroke or myocardial infarction on 3 months of follow-up. None of the serious adverse events in the simvastatin arm were considered related to the study medication. A complete description of all serious adverse events is available at Appendix III in the online-only Data Supplement.

Efficacy analyses conducted in the subgroup of patients receiving tPA showed no significant differences in the prespecified end points (Table III in the online-only Data Supplement), but a favorable effect for simvastatin treatment was noted in post hoc analyses, with higher proportion of patients experiencing major neurological recovery (17 [63%] simvastatin versus 8 [32%] placebo; adjusted OR, 4.14 [1.18–14.4]; *P*=0.02).

Discussion

Our study did not show any effect of simvastatin treatment in acute stroke in terms of improvement in neurological or functional outcome. Previous studies have shown a beneficial effect of statin pretreatment,[3] and small clinical trials have shown inconsistent results, with either improved outcomes[4,8] or no effects.[9,10] Our results are limited by the failure to recruit the needed number of patients, with less than one third of those planned. A changing paradigm on statins in cardiovascular diseases, in which finding patients with stroke not on statin therapy could be difficult, represents one of the main causes for that. Moreover, the fact that the role of statins as a secondary prevention therapy has been demonstrated also represent an important cause for the low recruitment rate, as some physicians were not comfortable with the possibility of having patients without statins for the study period. Given the current role of statins in secondary stroke prevention, future trials on patients with stroke might be restricted to the first days after stroke, allowing statins according to the guidelines beyond this point.

One of the main strengths of our study is that it was designed, as suggested by the Stroke Treatment Academy Industry Roundtable (STAIR) recommendations,[11] taking into account the results of the whole evidence on experimental stroke.[2] In fact, simvastatin was the drug associated with higher infarct volume reduction and neurological improvement; pretreatment with statins achieved the biggest infarct reductions; and timing of administration was one of the factors that most influenced the results, features that were taken into account in the design of the STARS trial.

Our study is to our knowledge the first combining statins and tPA in acute stroke. The question of how statins could influence the rates of HT has not been answered by observational studies.[5] Simvastatin initiation in the acute stroke phase is not associated with higher rates of HT, and these safety results are still present when only patients treated with tPA are considered. Regarding symptomatic intracranial hemorrhage, differences were absent in our trial, even with favorable trends to simvastatin therapy. In fact, an increase in the sample size ≤431 patients would be required to demonstrate superiority of simvastatin over placebo. This results altogether might support the design of a future prehospital trial with simvastatin, as a potential neuroprotective role for both ischemic and hemorrhagic stroke, and therefore with the opportunity of being given at the ambulance. Another more restrictive strategy would be to conduct a large trial only in patients receiving

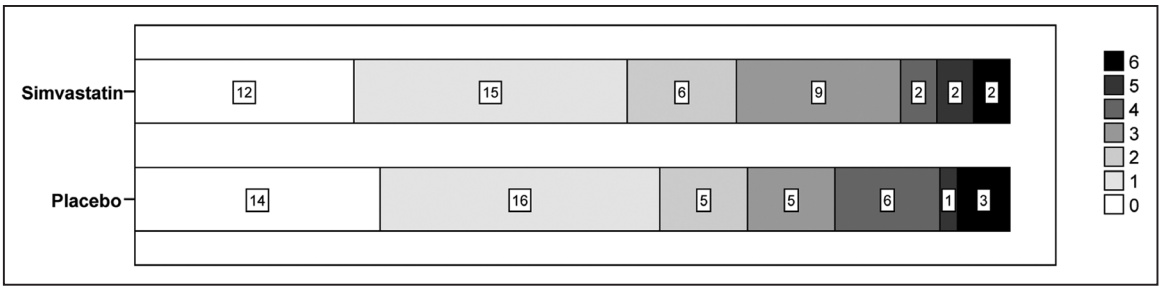

Figure 2. Distribution of the modified Rankin Scale 90 d after stroke. The figure is referred to intention-to-treat analysis. Numbers within the bars represent the number of cases in each score on the modified Rankin scale in simvastatin and placebo arms, ranging from 0 to 6, with 0 indicating no symptoms and 6 indicating death.

reperfusion therapies, which are the ones that seem to benefit in our study. These data, however, should be carefully interpreted, as being based on just 55 patients treated with tPA.

In conclusion, although the STARS trial was underpowered to detect a beneficial effect of simvastatin therapy in acute stroke, the administration of simvastatin combined with tPA in patients with acute stroke seems to be safe and not associated with increased rates of HT. Therefore, this promising combination merits the effort of a large-scale international clinical trial in the near future.

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Disclosures

None.

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